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Effect of Mango Kasturi (Mangifera casturi) Bark Extract on the Number of Neutrophils, Monocytes, and Density of Hard Callus After Tooth Extraction of Wistar Rats (*Rattus novergicus*)

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ABSTRACT

Oral and dental health is an integral part of body health that must be maintained. One of the teeth and mouth diseases that most Indonesians suffer from is dental caries and its treatment is tooth extraction. Post-extraction wounds will normally heal on their own, taking 3-4 weeks from the inflammatory phase to the formation of new tissue. Wound healing itself is a complex process because of the bio-cellular activities (neutrophils, monocytes) and biochemistry that occur continuously. Kasturi (Mangifera casturi) is a typical South Kalimantan fruit that contains flavonoids, terpenoids, steroids, and saponins which have antioxidant activity and are potential for the treatment of various diseases including diseases related to inflammation. In this journal review, the authors will identify the effect of the stem bark extract of musk mango (Mangifera casturi) on the number of neutrophils, monocytes, and hard callus density after tooth extraction of Wistar rats (Rattus novergicus) using various literature reviews.

Keywords: teeth, hard callus, castor, monocytes, neutrophils, extraction, rats

INTRODUCTION

Oral and dental health is an integral part of body health that must be maintained. The dental and oral health of the Indonesian people is still far from expectations, according to data from The World Oral Health Report that dental and oral diseases still affect 90% of the Indonesian population. One of the teeth and mouth diseases that most Indonesians suffer from is dental caries. Based on data from Basic Health Research (RISKESDAS) in 2018, the prevalence of dental and oral health problems in the Indonesian community on average shows 57.6% and in South Kalimantan, on average, 59% have high oral health problems and tooth extraction is 31, 3%. This dental and oral health problem results in tooth extraction due to caries, so it requires drugs to accelerate wound healing after tooth extraction (RISKESDAS, 2018).

Dental caries is a hard tissue disease of the teeth characterized by damage that starts from the tooth surface and then extends to the pulp. Based on data from the Indonesian Ministry of Health in the 2013 National Basic Health Research, the prevalence of active caries in Indonesia is 43.4%. South Kalimantan (84.7%) ranks second after Bangka Belitung (86.6%) with the highest caries prevalence in Indonesia (RISKESDAS, 2013; Fachriani, 2016). Tooth extraction is a surgical procedure for removing a part of the tooth that involves bone tissue and soft tissue from the oral cavity. Tooth extraction or tooth extraction is a process of removing a tooth from the alveolus because the tooth cannot be restored. Tooth extraction is an important measure in determining the health status of teeth and mouth. (Fithri, 2017, Yuwono, 2010 and Fachriani et al, 2016).

Post-extraction wounds will normally heal on their own, taking 3-4 weeks from the inflammatory phase to the formation of new tissue. The reaction is usually characterized by cardinal symptoms, namely swelling (tumor), heat (heat), pain (dolor), redness (rubor) and impaired function (functio laesa). In the initial phase of inflammation, the body will release the body's defense cells, namely polymorphonuclear cells (PMN). PMN is the first inflammatory cell to migrate to the wound area and consists mostly of neutrophils. Neutrophils are polymorphonuclear (PMN) leukocytes, representing 50 to 60% of total circulating leukocytes and are the first line of defense against infectious agents or substances that enter the body (Viera, et al 1995).

When inflammation occurs, neutrophils are recruited to the site of infection or injury. Neutrophils have a half-life of 6-7 hours in the blood and have a life span of 1-4 days in connective tissue before the leukocytes are destroyed by apoptosis. Since the first day of migration to the tissue, the number of neutrophils has increased as a form of defense against pathogens. The number of neutrophils will slowly decrease on the 3rd day as the inflammatory process decreases. On the 4th day neutrophils will be destroyed through the process of apoptosis and replaced with macrophages (Abbas et al, 2013; Mescher and Junqueira, 2012; Primadina et al, 2019; Tamara et al, 2015).

Macrophages are mononuclear cells that play a role in phagocytosis of bacteria, clean damaged tissue, and release growth factors and cytokines that play a role in the proliferation phase to the site of inflammation. The process of macrophage infiltration is also stimulated by

lymphocytes. The role of lymphocytes is to release lymphokines which are very influential in the inflammatory process. Lymphokines affect macrophage aggregation and chemotaxis in the wound healing process (Catherin et al, 2012; Gayathriy, 2012; Kumar et al, 2015; Primadina et al, 2019).

The process of healing bones due to wounds occurs through indirect or direct healing. Indirect healing is healing that goes through several processes of callus formation and immediate healing occurs without the formation of callus formations. The calcified callus encloses the two fracture fragments called a union. Bone healing and time to achieve union can be increased by biophysical stimulation or administration of a biological substance. Recent studies on fracture healing mechanisms have produced specific findings regarding important components in fracture healing, one of which is bone morphogenetic proteins (BMPs) (Adjie, 2017).

Wound healing itself is a complex process because of the bio-cellular and biochemical activities that occur continuously. The wound healing process is not only limited to local regeneration processes, but is also influenced by endogenous factors, such as age, nutrition, immunology, drug use, and metabolic conditions (Purnama, 2017). In the process of wound healing, disorders such as infection, hematoma and influence of foreign bodies usually occur. Therefore there needs to be an alternative to herbal plants that are safer to use to help speed up the wound healing process. One of the herbal plants that can be used is Kasturi (Mangifera casturi) (Nurdiantini, 2017; Sukmana, 2017; Yunanda and Tristia, 2016).

Kasturi (Mangifera casturi) is a typical fruit of South Kalimantan, this plant is from the genus Mangifera. The components found in the muskrat plant include flavonoids, terpenoids, steroids, and saponins which have antibacterial activity. Kasturi plants have also been reported to have antioxidant activity and potential for the treatment of various diseases including diseases associated with inflammation. Preliminary and phytochemical tests conducted by Mutikasari and Rosyidah (2008) stated that the bark of the Mangifera casturi tree contains terpenoid compounds that play a role in stimulating fibroblasts. The results of research conducted by Fakhrudin (2013) show that the bark of the musk mango (Mangifera casturi) contains saponins and steroids (Fakhrudin, 2013).

The highest content of secondary metabolites in musk stems is tannins 0.67 mg / 100 gr and terpenoids 0.43 mg / 100 gr. The percentage of tannins in the 8.5% stem bark extract can reach the remaining 3.5% including saponins, steroids, flavonoids, polyphenols, polyacetylene, terpenoids, and diterpenoids (Sukmana, 2017).

Tannins are polyphenolic compounds found in the bark and stems of musk. Tannins are reported to affect in increasing osteoblast activity and suppressing osteoclast activity. Increased activity of osteoblasts by alkaloids and polyphenols such as tannins is due to the induction of IL-1β and BMP-2 expression at the wound site. Secondary substances such as polyphenols in musk mango (Mangifera casturi) can also help repair bone tissue, increase osteoblast activity and suppress osteoclast activity. In a study conducted by Sukmana et al. 2017, it proved that the extract of musk mango stem bark at a concentration of 12.7% was an effective dose to increase the expression of BMP-2 during bone remodeling (Sukmana et al, 2017).

The content of tannin and saponin compounds can also increase macrophage activation to secrete several growth factors that are important in the wound healing phase such as VEGF, PDGF, and TGF. This growth factor is the key needed to stimulate the formation of new blood vessels due to blood vessels that have buds or buds of new vessels which can be called angiogenesis and the formation of large particles with a specific tissue binding mechanism called granulation. In addition, saponins also act as immunomodulators that can stimulate the body's immune system through non-specific immune response mechanisms and through specific immune responses. Previous research has also tested the extract of musk bark with a concentration of 6.35%, 12.7% and 25.4% and it was found that the effective dose of the bark extract was 12.7%, where the increase in expression showed the response of the post wound area. Tooth extraction has improved the formation of new bone faster (Fitrian, 2018, Riana, 2011 and Rahim et al, 2017; Sukmana et al, 2017).

Based on the description above, as an effort to determine alternative therapies for wound healing after tooth extraction, the authors will identify the effect of the bark extract of musk mango (Mangifera casturi) on the number of neutrophils, monocytes, and hard callus density after tooth extraction of Wistar rats (Rattus novergicus) by using various literature reviews.

REVIEW METHOD

The literature review method used is narrative review, which is conducting a study of various articles with the theme of describing the effect of musk mango stem bark extract (Mangifera casturi) on hard callus density with the final result in the form of views / opinions on various articles based on the results of the study conducted.

Search Criteria. Inclusion Criteria

This article is related to the description of the effect of the bark extract of musk mango (Mangifera casturi) on the number of neutrophils, monocytes, and hard callus density after tooth extraction of Wistar rats (Rattus novergicus).

Exclusion Criteria

- The article does not match the research topic.
- Articles published under 2020.

Data source

The data source used in this literature review is secondary data. Secondary data is data obtained not from direct observations in the field. The secondary data source in question is in the form of primary scientific reports contained in articles or journals using the Google Scholar and Science Direct data base relating to research on the description of the effect of musk mango stem bark extract (Mangifera casturi) on hard callus density.

Source selection is based on four aspects, namely: 1. Provenance (evidence), namely aspects of the author's source and evidence support, for example the main source of research; 2.

Objectivity (objectivity), namely whether the perspective idea of the author has many uses or is it detrimental; 3. Persuasiveness (degree of confidence), namely whether the author is included in the official research class; and 4. Value (contributive value), namely whether the author's argument is convincing, and has a significant contribution to the research.

Keywords

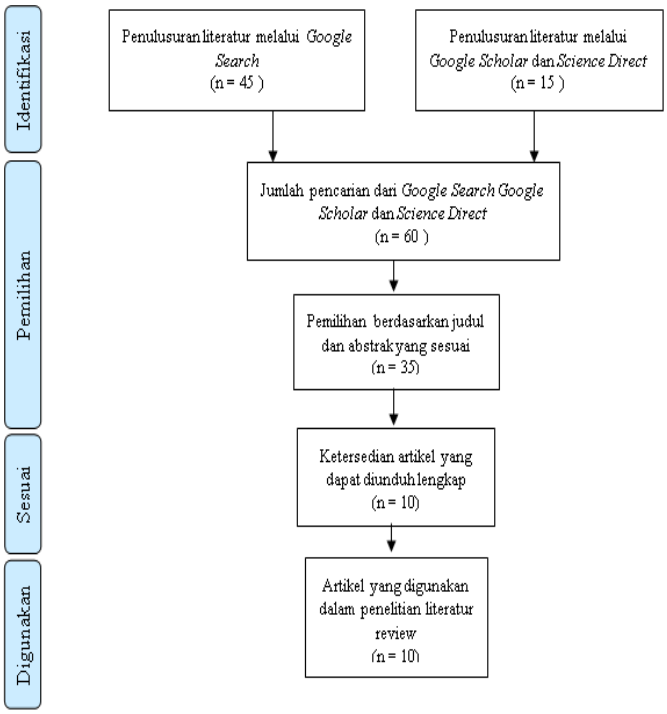
The key words used in this study were the effect of the bark extract of musk mango (Mangifera casturi), hard callus density, neutrophils, monocytes, tooth extraction, Wistar rats (Rattus novergicus).

Search Strategy

Search for published articles on Google Search, Science Direct and Google Scholar using the selected keywords, namely: the effect of the extract of the bark of musk mango (Mangifera casturi), hard callus density. Articles or journals that match the inclusion and exclusion criteria are taken for further analysis. This literature review uses accessible literature published in 2010-2020. Articles that match the inclusion criteria and have the theme of the effect of the bark extract of musk mango (Mangifera casturi) on the number of neutrophils, monocytes, and hard callus density after tooth extraction of Wistar rats (Rattus novergicus) were then reviewed.

Data analysis. Selection Criteria.

Figure 1. Flow of Selection Criteria



Search Procedure

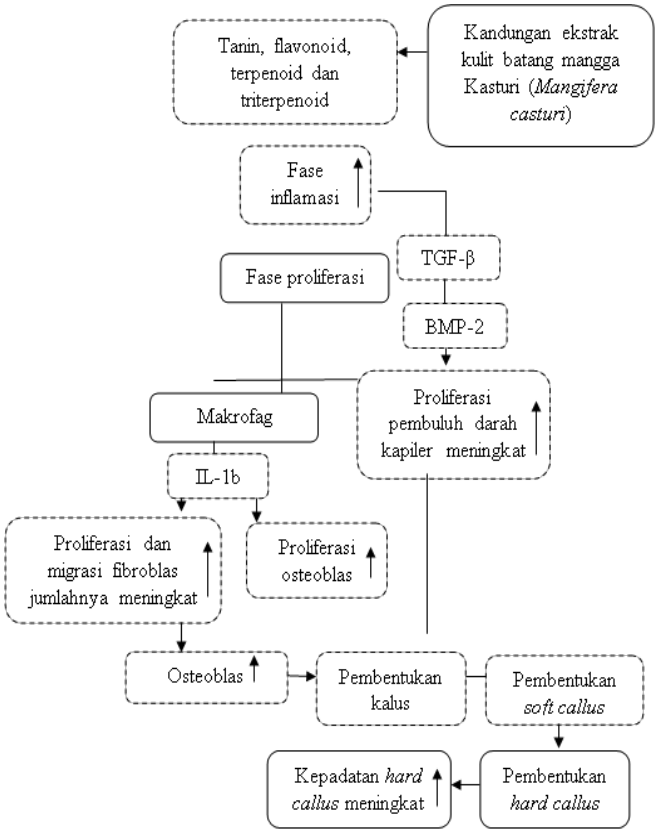
Search procedure using the key word effect of the bark extract of musk mango (Mangifera casturi), hard callus density, neutrophils, monocytes, tooth extraction, Wistar rats (Rattus novergicus)

The first step is to enter keywords in the Google Search search. There are 45 research articles related to the theme under study, then enter the same keywords using the Google Scholar or Science Direct database to get 15 research articles, so that the total number of articles searched for as many as 60 articles. Then the articles were selected according to the research objectives, 35 articles were selected based on the appropriate title and abstract, then there were 10 articles available for complete download and the articles used in this literature review research were selected according to the criteria and research objectives were 10 research articles.

Extract Data

Extracting the data, namely making a summary table of each article following the criteria for literature review by writing the name of the researcher, the year of publication, the title of the study, the results and conclusions.

Figure 2. Theoretical Framework Overview of the Effect of Mango Kasturi (Mangifera casturi) Bark Extract on Hard Callus Density.



Explanation of the Theory Framework

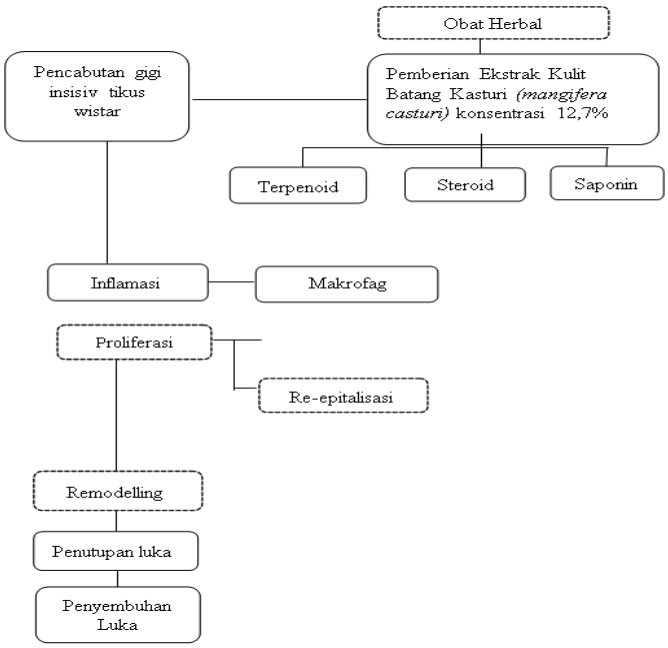
Extract from the bark of musk mango (Mangifera casturi) contains tannins, flavonoids, terpenoids and triterpenoids which have the effect of accelerating the bone remodeling process. The first response to wound healing is inflammation. Blood plugs or hematomas release various signaling factors and angiogenic growth factors that activate inflammatory and repair cells such as fibroblasts, osteoblasts, stem cells and vascular endothelial cells. Interleukin 1 beta acts as an inflammatory cytokine that regulates the immune system. These cytokines are produced by macrophages and other inflammatory cells. IL-1β plays a role in chemotactic effects on other inflammatory cells, stimulation of extracellular matrix synthesis, angiogenesis, recruitment of endogenous fibrogen cells to the injury site, and at the stage of bone resorption. BMP-2 is a member of the TGF-β family released by the extracellular matrix produced by osteoprogenitor, mesenchymal cells, osteoblasts and chondrocytes. BMP-2 induces osteoblast formation via the Smad Dependent Signal Pathway. The formed osteoblasts will stimulate the formation of intercellular material in the form of collagen fibers, alkaline phosphatase (ALP) and osteocalcin. Increasing osteoblast cells through increased osteoprotegerin and decreasing RANKL will reduce the number of osteoclasts originating from hematopoietic progenitors in the injured bone, so that callus formation will increase from soft callus to hard callus.

Description:

: Researched

: Not researched

Figure 3. The theoretical framework of the research on the effect of bark extract of Kasturi (Mangifera casturi) 12.7% concentration on the number of macrophage cells in wistar rats.



Explanation of the Theory Framework

Tooth extraction is an act of removing the tooth from the alveolar bone socket. Tooth extraction is mostly done because of caries, besides caries there are periodontal diseases, supernumerary teeth, impacted teeth, teeth that can no longer be treated with endodontic treatment, teeth that are involved with cysts and tumors, teeth that are involved with jaw fractures. Post-extraction wounds normally experience self-healing in 3-4 weeks starting from the inflammatory phase until the formation of new tissue. Tooth extraction is the last option when the patient's teeth have been damaged and cannot be treated anymore. (Sylvester RN, 2013, Tamara AHJ 2014).

Inflammation is intended as a local response to infection. Inflammation occurs 1–4 days after the wound. This phase is characterized by the infiltration of neutrophil and macrophage cells in the wound tissue. At the infected site, the endothelium releases molecules to attract leukocytes. Simultaneously, polymorphonuclear leukocytes (PMN) are activated and release molecules that cause PMN to collect and limit the endothelium of blood vessels. Inflammation is the emergence of a reaction from the tissue to the presence of an irritant. It is also said that inflammation is a dynamic and unstable process, where the process depends on the type of body tissue. Inflammation can occur starting from sublethal tissue damage and can end with healing. Macrophage cells are the first cellular defense after neutrophil cells whose numbers increase at the onset of injury (Rosa SA, et al. 2018 and Bochud, Kumar, 2015).

Macrophage cells will secrete inflammatory mediators and enzymes to start the next phase, namely the proliferation phase. The proliferation phase occurs 4 to 21 days after the injury, characterized by angiogenesis, collagen deposition, granuloma tissue formation, wound contraction, and epithelialization. The proliferation phase lasts from the fourth to the seventh day, marked by the presence of fibroblasts whose numbers continue to increase during this phase. Fibroblasts are the main factor that dominates wound healing as well as the basic framework or structure to produce collagen. This proliferation phase is also called the fibroplasia phase, because what stands out is the fibroblast proliferation process. This phase lasts from the end of the inflammatory phase to approximately the end of the third week characterized by extracellular matrix deposition, angiogenesis, and epithelialization. Fibroblasts produce extracellular matrix, primary collagen, and fibronectin for cell migration and proliferation. The angiogenesis process also occurs in this phase, which is marked by the formation of new blood vessels and initiation of nerve growth at the end of the wound. At this time, keratinocytes proliferate and migrate from the wound margins to epithelize over the wound surface, providing a natural barrier of defense against external contaminants and infections. The wound edge epithelium consisting of basal cells, detaches from its base and migrates to fill the wound surface. The place is then filled with new cells formed by the mitosis process. This process only stops when the epithelial cells touch each other and cover the entire wound surface. With the closed surface of the wound and with the formation of granulation tissue, the fibroplasia process will stop and the maturation process begins in the remodeling phase (Rosa SA, et al. 2018 and Laut M, et al. 2019).

The maturation phase or the remodeling phase is the phase of wound healing that lasts for a long time (3-6 months or even years). This remodeling phase is the final phase of the soft tissue wound healing process and is sometimes called the wound maturation phase. In this phase there is a change in the shape, density, and strength of the wound. During this process, scar tissue that is pale, thin, limp, and easy to move from the base. You can see the maximum shrinkage of the wound, an increase in wound strength, and a decrease in the number of macrophages and fibroblasts which results in a decrease in the amount of collagen. At the end of this phase the skin can withstand stretches up to 80% of normal skin's ability (Laut M, et al. 2019; Lee, 2017). For the wound healing process, the drug Povidone iodine 10% can be used. Povidone Iodine is an effective local anti-bacterial compound that kills bacteria and spores and is widely used as an antiseptic. The wound healing process can occur naturally through wound healing mechanisms. The wound healing process can be accelerated by treating the wound. In addition, gene therapy techniques have been developed using specific genes for the wound healing process. Development is also carried out on formulas to help the wound healing process, from developing bases and also developing active substances from herbs (Nurdiantini et al, 2017; Purnama, 2017).

Traditional medicine is one of the inheritance of the ancestors or ancestors which is hereditary used in the process of preventing, reducing, eliminating or curing illness, injury and mental illness in humans or animals. Traditional Medicines are ingredients or ingredients in the form of plant ingredients, animal ingredients, mineral substances, galenic preparations or mixtures and these ingredients, which have traditionally been used for treatment based on experience. People think that traditional medicines are made from natural ingredients, are easy to get, are cheap, and traditional medicines are believed to be safer for consumption than synthetic drugs, one of which is the Kasturi plant (Handayani, 2018; Rina, 2012).

The plant from the Mangifera genus that has been researched for its chemical content is Mangifera indica or what is known as mango. The component which is found in the muskrat plant includes flavonoids, terpenoids, steroids, and saponins which have antibacterial activity. The Kasturi plant indicates that the muskie stem contains terpenoid compounds, steroids, and saponins. Several research results indicate that terpenoids, steroids, and saponins have antibacterial activity. Inhibited bacterial growth or bacterial death due to inhibition of protein synthesis, it can be said that terpenoids, steroids and saponins can inhibit bacterial growth by inhibiting protein synthesis (Rahim, 2017).

Tooth extraction is the removal of a tooth or tooth root without pain but with minimal injury to the surrounding tissue and supporting bone. The tooth that is extracted leaving a socket consisting of cortex of bone, is protected by a periodontal ligament with the gingiva as the outermost layer. The socket will fill with blood, later it coagulates to form a blood clot and closes all the sockets from the oral environment. Post-extraction wounds normally heal on their own within 3-4 weeks starting from the inflammatory phase to the formation of new tissue (Tamara AHJ et al, 2014)

The inflammatory phase begins 1-4 days after injury (Silvana RA et al, 2018). When injured, the skin will show signs of inflammation wherein foreign objects from outside the body

can enter through the open wound. Neutrophil cells are the first cellular defenses that increase in number at the onset of injury (Kumar et al, 2015).

In the early phase of inflammation, leukocyte cells, especially tissue neutrophils, will phagocytose the bacteria that enter the body, activation of pro-inflammatory cytokines will cause more neutrophils in the blood to migrate towards the injured organ or tissue due to the signal sent by pro-inflammatory cytokines. . After 48 hours the number of neutrophil cells will decrease because their role is replaced by monocytes that migrate to the area of the lesion and differentiate into macrophages. Neutrophil cells will remain in the injured tissue or organ until the proliferation process occurs, but the numbers are not as many as at the beginning of inflammation, the decrease in neutrophils is a sign of increasing anti-inflammatory cytokines (Avisha et al, 2019).

The proliferation phase occurs 4 to 21 days after the injury, characterized by angiogenesis, collagen deposition, granuloma tissue formation, wound contraction, epithelialization, namely the formation of permeability barriers and re-formation of dermal tissue in injured tissue (Purnama, 2017; Lee et al, 2017) .

The last phase is remodeling which occurs 21 days to 2 years after the injury (Purnama, 2017). The remodeling phase is the longest phase of wound healing in which the process of maturing the ongoing repair of granulation tissue forms a new epithelial layer and increases the tension in the wound. At the end of this phase the skin can withstand stretches up to 80% of normal skin ability (Lee et al, 2017).

For the wound healing process, the drug Povidone iodine 10% can be used. Povidone Iodine is a local anti-bacterial compound that effectively kills bacteria and spores and is widely used for antiseptics (Nurdiantini et al, 2017), another way of 10% Povidone iodine to kill microbes is through amino acid iodination. The presence of this iodine will poison so that it cannot form protein and will cause microorganisms to be destroyed (Rosyidah et al, 2010), but on one hand this material can cause irritation to wounds, change skin color and can cause toxic reactions (Rahmawati and Hanang, 2013)).

Traditional medicine in Indonesia plays a very large role in public health services in Indonesia, so that traditional medicine has the potential to be developed. People think that traditional medicines are made from natural ingredients, are easy to get, are cheap, and traditional medicines are believed to be safer for consumption than synthetic drugs (Handayani, 2018), one of which is the musk plant.

Traditional medicine is considered safer if it is used according to the correctness of the ingredients, the accuracy of the dosage, the accuracy of use, the accuracy of the information, and the accuracy of drug selection for appropriate indications and without abuse so that if it has an effect it will cause neutrophils to go to the area of the tooth extraction and reduce infection so that healing is easy. wounds (Yunanda and Tristia, 2016; Silvana et al, 2018).

REVIEW RESULTS

Searching for data sources published from 2010-2020 obtained results in the form of 11 articles that were deemed appropriate to answer the problem formulation of this literature review. The results of the data obtained from the articles are collected in tabular form on the next page. From the results of this review, the authors obtained several articles relating to the description of the effect of musk mango stem bark extract (Mangifera casturi) on hard callus density according to inclusion and exclusion criteria and are described in Table 1.

Table 1. Data Extraction Results

No	Judul Artikel, Nama Jurnal, Tahun	Hasil	Kesimpulan
1.	Sukmana et al. *The potentiation of mangifera casturi bark extract on interleukin 1β and bone morphogenic protein-2 expressions during bone remodeling after tooth extraction*. Dental Journal. (Majalah Kedokteran Gigi) 2017 March; 50(1): 36–42.	Dosis efektif fraksi kulit batang *Mangifera casturi* untuk menurunkan ekspresi IL-1β selama remodeling tulang setelah pencabutan gigi pada konsentrasi adalah 12,7%. Dosis efektif fraksi kulit batang *Mangifera casturi* untuk meningkatkan ekspresi BMP-2 selama remodeling tulang setelah pencabutan	Dosis efektif fraksi kulit batang *Mangifera casturi* untuk menurunkan ekspresi IL-1β dan meningkatkan ekspresi BMP-2 selama remodeling tulang setelah pencabutan gigi adalah 12,7%.

		gigi pada konsentrasi 12,7%.	
2.	Nuzulia Santi et al. Uji antibakteri infusa kulit batang kasturi (*Mangifera casturi Kosterm*) terhadap bakteri *Escherichia coli* secara in vitro. Jurnal Wahana-Bio Volume XVI Desember 2016.	Berdasarkan hasil penelitian, setiap konsentrasi menghasilkan lebar diameter zona hambat terhadap bakteri *Escherichia coli* yang berbeda-beda. Semakin tinggi konsentrasi maka semakin lebar diameter zona hambat yang terbentuk. Konsentrasi paling menghambat pertumbuhan bakteri E. coli adalah konsentrasi 50%.	Pemberian infusa kulit batang kasturi berpengaruh terhadap daya hambat pertumbuhan bakteri *Escherichia coli*.
3.	Dahlena Ariyani et al. Isolasi senyawa fenolat berkhasiat sitotoksik dari kulit batang	Berdasarkan data spektrum UV-Vis dan IR, senyawa hasil isolasi yaitu senyawa fenolat memiliki sifat sitotoksik	Ekstrak MTC bersifat aktif sitotoksik terhadap BSLT (*Brine*

	kasturi (*Mangifera casturi*). Sains dan Terapan Kimia, Vol.4, No. 2 (Juli 2010), 101-107.	terhadap BSLT (*Brine Shrimp Letality Test*).	*Shrimp Letality Test*).
4.	Budi Prayitno et al. Uji antioksidan dan senyawa terpenoid dari fraksi M-17 ekstrak metilena klorida kulit batang tumbuhan kasturi (*Mangifera casturi*). Jurnal Pharmascience, Vol 3, No. 1, Februari 2016, hal: 32 – 36.	Uji pendahuluan antioksidan dilakukan dengan metode DPPH dan didapatkan bahwa hasil uji memiliki daya penangkal radikal DPPH. Pengukuran daya antioksidan dilakukan dengan mengukur absorbansi DPPH pada spektrometer UV dan dipatkan hasil daya redam senyawa terhadap radikal DPPH sangat lemah.	Hasil uji antioksidan menunjukkan senyawa memiliki daya redam radikal yang lemah, sehingga dapat dikatakan tidak aktif sebagai senyawa antioksidan.
5.	K. Rosyidah et al. Aktivitas	Hasil uji aktivitas antibakteri	Ekstrak fraksi saponin

	antibakteri fraksi saponin dari kulit batang tumbuhan kasturi (*Mangifera casturi*). Alchemy, vol. 1 no 2 2010, hal 53-103.	fraksi saponin dari kulit batang tumbuhan kasturi (*Mangifera casturi*) menunjukkan bahwa aktivitas terhadap *S. aureus* lebih besar dibandingkan terhadap *E.coli*.	pada kulit batang tumbuhan kasturi (*Mangifera casturi*) hambat bakteri *S. aureus* dan *E. coli*.
6.	Destria Indah Sari et al. Karakteristik dan uji stabilitas fisik sediaan edible film ekstrak etanol kulit batang kasturi (*Mangifera casturi Kosterm*) Berbasis Gelatin. Prosiding Seminar Nasional Dan Presentasi Ilmiah	Sediaan edible film ekstrak etanol kulit batang kasturi berbasis gelatin pada konsentrasi 10-20% memberikan karakteristik berupa ketebalan film 0,14 – 0,43 mm; variasi bobot 104,8 – 133,2 mg; daya larut 3–4 mL; waktu melarut 25,25–59,50 detik; kadar air 9,23-22,94%; tensile strength 1,23–3,50	Sediaan edible film ekstrak etanol kulit batang kasturi tidak stabil secara fisik dibandingkan keadaan pada awal penyimpanan.

	Perkembangan Terapi Obat Herbal Pada Penyakit degeneratif. Vol 1 No 1 (2017).	kg/mm2 ; elongasi 66,67–200,11%.	
7.	Sutomo et al. Studi Farmakognostik Dan Uji Parameter Nonspesifik Ekstrak Metanol Kulit Batang Kasturi (*Mangifera casturi Kosterm*.). Jurnal Pharmascience, Vol. 04 , No.01, Februari 2017, hal: 94 – 101.	Hasil identifikasi kimia menunjukkan adanya kesamaan kandungan senyawa pada serbuk dan ekstrak. Identifikasi senyawa kimia terhadap ekstrak didapatkan hasil senyawa golongan alkaloid, flavonoid, fenol, steroid dan terpenoid.	Dalam ekstrak methanol kulit batang Kasturi (*Mangifera casturi*) mengandung senyawa flavonoid, alkaloid, fenol, serta steroid.
8.	Akbar et al. Perbandingan efektivitas antibakteri antara ekstrak metanol kulit batang kasturi dengan	Hasil penelitian ini menunjukan bahwa ekstrak metanol kulit batang kasturi memiliki aktivitas antibakteri terhadap *S.*	Efektivitas antibakteri antara ekstrak metanol kulit batang kasturi dengan

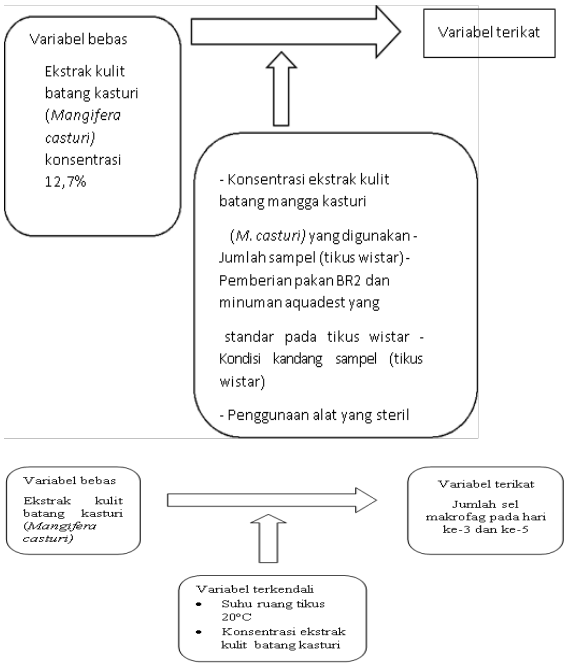
	ampisilin terhadap *Staphylococcus aureus* in vitro. Berkala Kedokteran, Vol.12 No.1, Feb 2016:1-9.	*aureus*. Efek ini disebabkan adanya kandungan terpenoid, steroid, tanin dan saponin. Hasil uji perlakuan ekstrak metanol kulit batang kasturi 25%, dan 37,5% memberikan efek yang sama dengan perlakuan ampisilin.	ampisilin memberikan efek yang sama.
9.	Siddik et al. Perbandingan efektivitas antifungi antara ekstrak metanol kulit batang kasturi dengan ketokonazol 2% terhadap *Candida albicans* in vitro. Berkala Kedokteran, Vol.12, No.2, Sep 2016: 271-	Perlakuan ketokonazol 2% memberikan efek zona hambat sebesar 15 mm, tetapi efek dari ekstrak metanol kulit batang kasturi baru bisa melebihi zona hambat konsentrasi 75% (16 mm). Hasil penelitian ini menunjukan bahwa ekstrak	Ekstrak metanol kulit batang kasturi mempunyai aktivitas antijamur terhadap *C. albicans*.

	278.	metanol kulit batang kasturi mempunyai aktivitas antijamur terhadap *C. albicans*.	
10.	Lia Marliani et al. Penetapan kadar fenolat total dan flavonoid total ekstrak etanol daun, kulit batang dan kulit buah kasturi (*Mangifera casturi*). Prosiding Seminar Nasional Tumbuhan Obat Indonesia Ke-50, Samarinda, 20 – 21 April 2016.	Ekstrak etanol daun kasturi memiliki kadar senyawa fenolat total tertinggi yaitu 18,44 % dan kadar flavonoid total tertinggi sebesar 9,27%. Kadar senyawa fenolat terendah terdapat pada ekstrak etanol kulit batang kasturi yang hanya memiliki kadar senyawa fenolat total sebesar 16% dan untuk kadar senyawa flavonoid terendah terdapat pada ekstrak etanol kulit buah kasturi yaitu sebesar	Kandungan fenolat dan flavonoid tertinggi terdapat pada daun sedangkan kandungan fenolat total terendah terdapat pada kulit batang dan kandungan flavonoid total terendah terdapat pada kulit buah kasturi.

2,098%.

Based on the 10 articles that have been reviewed, it was found that 9 articles (90%) stated that the compound content in the extract of the bark of musk mango (Mangifera casturi) consisting of tannins, flavonoids, terpenoids and triterpenoids effects on the density of hard callus. There is 1 article (10%) that states that the compound content in the extract of the bark of musk mango (Mangifera casturi) consists of flavonoid compounds that do not affect the density of hard callus because they are cytotoxic.

The content of the most compounds in the bark extract of musk mango (Mangifera casturi) is tannins, and the least compound content is flavonoids. Most of the articles state that the compound content in the extract of musk mango stem bark (Mangifera casturi) is indirect in the process of hard callus density and there are articles that state that the compound content of musk mango stem bark has a direct effect on the density of hard callus. The drawbacks of the research articles that the researchers studied were the lack of the number of samples in the study and different analytical tests in each research article.



The research concept framework "The Effect of Kasturi Bark Extract (Mangifera casturi) Concentration of 12.7% on the Number of Macrophage Cells Post Tooth Extraction of Wistar Rats" (Rosdayatri, 2020)

Independent variable:

- Extraction of musk bark (Mangifera casturi)

Dependent variable :

- The number of macrophage cells on the 3rd and 5th day.

Controllable variables:

- The room temperature of the mouse is 20oC
- Concentration of Kasturi bark extract (Mangifera casturi) used.
- Number of samples (wistar rats) 24 with a concentration of 12.7%
- Feeding and drinking samples (Wistar rats)
- The condition of the sample cage (wistar rat)

3.2 Hypothesis

Based on the conceptual framework above, the hypothesis that can be taken:

1. Extract of musk stem bark (Mangifera casturi) with a concentration of 12.7% can increase the number of macrophage cells after tooth extraction of Wistar rats on the 3rd day.
2. Extract of musk stem bark (Mangifera casturi) with a concentration of 12.7% can reduce the number of macrophage cells after tooth extraction of Wistar rats on day 5 which can accelerate wound healing.

Research conceptual framework "Effect of Mango Kasturi (Mangifera Casturi) Bark Extract on the Number of Neutrophils after Tooth Extraction of Wistar Rats (Rattus novergicus)" (Fina, 2020)

Independent variable:
-Pasturi bark extract (Mangifera casturi) concentration of 12.7%
Dependent variable:
- Number of Neutrophil Cells
Controllable variables:
- Concentration of Kasturi Bark Extract (Mangifera casturi) used
- Number of samples (wistar rats)
- Feeding Wistar rats with BR2 and standard aquadest drink
- Condition of sample cage (wistar rat)
- The tools used are sterile

3.2 Hypothesis

Based on the above conceptual framework, the hypothesis that can be drawn by the researchers is that the extract of the bark of muskrat (Mangifera casturi) with a concentration of 12.7% can increase the number of neutrophil cells in Wistar rats on day 1 and can reduce the number of neutrophils in Wistar rats on day 1. 3.

Overview of the Effect of Mango Kasturi (Mangifera casturi) Bark Extract on the Number of Neutrophils and Monocytes

Based on the research of Fina (2020), the extract of the bark of the muskrat (Mangifera casturi) affect the number of neutrophil cells after tooth extraction of the Wistar rat (Rattus norvegicus). The results showed that the group giving castor bark extract had an effect in the form of an increase in the number of neutrophil cells on day 1 and could reduce the number of neutrophil cells on day 3 compared to the 10% Povidone iodine group and the group that was not given any treatment at all (Fina , 2020).

The results of statistical tests on the average number of neutrophil cells on day 1 and day 3 showed that there was a significant difference in the castor bark extract group with negative control and 10% Povidone iodine occurred because the castor stem contained steroids as an anti-inflammatory agent. and saponin content as antibacterial and plays a role in the formation of new bone. Rosyidah et al., 2010 stated that the content of castor stems contains terpenoids, steroids and saponins which function as antibacterials. Steroid compounds function as anti-inflammatory by preventing the formation of prostaglandins by inducing biosynthesis of the phospholipase A2 inhibitor and saponin content which functions to increase the formation of new blood vessels in wounds and stimulate collagen formation in the presence of protein so that it can accelerate the wound healing process (Rosdayatri, 2020).

The results of the statistical test of this study also prove that musk bark extract is better used on the 1st day because on the 1st day the number of neutrophil cells appears to be more than the 3rd day so that if the mussel bark extract is used on the 1st day it can help reduce the number of neutrophil cells on day 3. Following the research by Abbas et al. 2013 which states that neutrophils are inflammatory cells that appear for the first time when inflammation occurs, since the first day they migrate to the tissue, the number of neutrophils will increase as a form of defense against pathogens. The number of neutrophils will decrease on day 3 as the inflammatory process decreases (Fina, 2020).

The results of this study indicated that the castor bark extract had a major effect on the number of neutrophil cells after tooth extraction of Wistar rats compared to the group that was given food only (negative control) and the group that was given 10% Povidone iodine. The increase in the number of neutrophil cells also indicates an increase in macrophage collection activities where macrophages will continue the role of neutrophils in the chronic inflammatory process (Ike, 2012; Fina, 2020).

The inflammatory stage is the body's response stage to clean the wound area from foreign objects, bacteria and dead cells to prepare for the healing process to start. This phase begins, marked by the number of neutrophils around the inflammatory tissue. The decrease in the number of cells that occurs indicates that healing is starting to enter the next stage so that it can accelerate the inflammatory healing process (Lutfiyah et al, 2016). If the inflammation continues, the neutrophil function will be replaced by monocyte cells which will carry out diapedesis from the endothelium to the tissue to become macrophages to carry out phagocytosis (Prasetya et al, 2014).

Based on research by Rosdayatri (2020), it is proven that the extract of the bark of muskrat (Mangifera casturi) with a concentration of 12.7% has an effect on the number of macrophage cells after tooth extraction of Wistar rats (Rattus norvegicus). According to Mills (2016), macrophages are inflammatory cells that have another name, namely monocyt when they are in the vascular area and become macrophages when they migrate to the tissue. The results of Rosdayatri's (2020) study showed that the group giving musk stalk bark extract had an effect in the form of an increase in the number of macrophage cells on the 3rd day and decreased the

number of macrophage cells on the 5th day compared to the 10% Povidone iodine group and the untreated group. at all (Rosdayatri, 2020).

The results of statistical tests in this study that the average number of macrophage cells on the 3rd day was the most or said to have increased on the 3rd day in the Kasturi bark extract group (Mangifera casturi) with a concentration of 12.7% compared to the negative control group and Povidone iodine. 10% because the extract of the bark of the muskrat contains ingredients that make the macrophage cells in the bark extract more influential than other groups. According to Bonardo, 2015 & Nengah, 2016, the increase in the number of macrophages to the site of infection comes from the migration of macrophage cells to the source of stimulation. The increase in the number of macrophages is caused by the acceleration of macrophage proliferation and differentiation characterized by increased macrophage activity, macrophage phagocyte capacity, and interleukin production. The increase in the number of macrophage cells is caused by accelerated proliferation and differentiation of macrophage cells. According to Kumar 2015, macrophage cells can clean damaged tissue, cells and bacteria so that the tissue repair process can be done (Rosdayatri, 2020).

The results of statistical tests on the average number of macrophage cells on the fifth day are at least or can be said to have decreased on the 5th day. According to Setia, 2017 the decrease in the number of macrophage cells on the 5th day indicates that the inflammatory process has been greatly reduced and the post-extraction wound is filled with tissue proliferation. However, the high number of macrophage cells is accompanied by a high average deviation value. This can be caused by the influence of the difference in the amount of trauma on the tooth extraction process of rats so that the response in initiating cells that play a role in the healing process is quite varied. Macrophage cells play a large role in the phagocytosis process as a non-specific immunological process against antigens. According to Hutagalung 2018, the phagocytosis process carried out by macrophage cells will be completed and show a good cure rate. If the inflammatory phase is almost over, the number of macrophage cells in the wound tissue will decrease and the number will decrease on the 5th day. Macrophage cells are the basis for the final stage of the inflammatory response, macrophages act as a key to cell regulation and also mediate changes from the inflammatory phase to the proliferative phase (Ambriyani, 2013).

Overview of the Effect of Mango Kasturi Bark Extract (Mangifera casturi) on Hard Callus Density

Based on the elaboration of previous studies, the researchers found that the extract of the bark of the musk mango (Mangifera casturi) has a direct effect on the process of forming hard callus. Research conducted by Sukmana et al., 2017 states that the extract of the bark of musk mango (Mangifera casturi) contains tannin compounds that can reduce IL-1β expression during bone remodeling and increase BMP-2 expression during bone remodeling, where these two things are very influential in bone density process. Flavonoid compounds can optimize the bone healing process by overcoming oxidative stress in bone fractures, increase osteoblast proliferation, formation a bone trabecular matrix, accelerate wound healing and function as anti-inflammatory. Terpenoid compounds can trigger the proliferation and differentiation of

osteoblasts and mineralization, have an important role in forming phytoestrogen hormones, and increase the proliferation ability of Mesenchymal Stem Cell (MSC) to become deficient in osteoblasts. Triterpenoid compounds act as a therapy for estrogen deficiency and the aging process causes bone loss, can stimulate osteoblast cells to increase bone formation, and the formation of alkaline phosphate which affects bone formation.

The bark of the musk mango (Mangifera casturi) has bioactive compounds such as tannins, flavonoids, terpenoids and triterpenoids which are potential as herbal remedies for hard callus density. The injured bone undergoes a process of regeneration and repair to restore the damaged structure. The first response to wound healing is inflammation. Blood plugs or hematomas release various signaling factors and angiogenic growth factors that activate inflammatory and repair cells such as fibroblasts, osteoblasts, stem cells and vascular endothelial cells. Interleukin 1 beta acts as an inflammatory cytokine that regulates the immune system. These cytokines are produced by macrophages and other inflammatory cells. IL-1β plays a role for chemotactic effects on other inflammatory cells, stimulation of extracellular matrix synthesis, angiogenesis, recruitment of endogenous fibrogen cells to the injury site, and at the stage of bone resorption. BMP-2 is a member of the TGF-β family released by the extracellular matrix produced by osteoprogenitor, mesenchymal cells, osteoblasts and chondrocytes. BMP-2 induces osteoblast formation via the Smad Dependent Signal Pathway. The formed osteoblasts will stimulate the formation of intercellular material in the form of collagen fibers, alkaline phosphatase (ALP) and osteocalcin. Increasing osteoblast cells through increased osteoprotegerin and decreasing RANKL will reduce the number of osteoclasts originating from hematopoietic progenitors in the injured bone, so that callus formation will increase from soft callus to hard callus.

Based on the results of reviews of several articles, the researchers also found that the extract of the stem bark of musk mango (Mangifera casturi) has an indirect effect on the formation process of hard callus. Research conducted by Nuzulia Santi et al, 2016, Akbar et al 2016, and K. Rosyidah, 2010 stated that the extract of the bark of musk mango (Mangifera casturi) has inhibition of the growth of Escherichia coli and Staphylococcus aureus bacteria which can cause inflammation and bone disease. so that it can interfere with the healing process and bone remodeling.

CONCLUSION

The conclusion of this literature review is

1. Extracts of Kasturi mango stem bark (Mangifera casturi) affect the number of neutrophils and monocytes. Based on the research, musk bark extract can reduce the number of neutrophil cells after tooth extraction of male Wistar rats (Rattus norvegicus) on day 3.
2. Based on the research, there is a significant difference between the number of Wistar mouse macrophage cells applied with musk stem bark extract and Wistar mouse macrophage cells treated with 10% povidone iodine on the 3rd and 5th day.

3. Extracts of musk mango stem bark (Mangifera casturi) have a direct and indirect effect on the speed of hard callus formation.
4. Based on the research, the content of tannins, flavonoids, terpenoids and triterpenoids in the extract of the bark of musk mango (Mangifera casturi) affect the number of neutrophils and monocytes and has a direct and indirect effect on the speed of hard callus formation.

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