Effectivity of Temulawak (Curcuma xanthorrhiza roxb.) Extract based Nanotechnology PLGA (Poly-Lactic-Co-Glycolic-Acid) on Diabetic Wound: A Literature Review

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ABSTRACT

Introduction

Impaired wound healing process is one of diabetes mellitus complications. Impaired wound healing process caused by prolonged inflamation, disrupted angiogenesis process and reduced fibroblast proliferation process. Temulawak (Curcuma xanthorrhiza roxb.) extract contains curcumin that serves as an anti-inflammatory and antioxidant ends the inflammatory phase and accelerates the proliferation phase. PLGA (Poly-Lactic-co-Glycolic-Acid) nanoparticle technology is one of innovations to improve the curcumin therapeutic effect by controlling the sustained release, reducing curcumin degradation and increasing bioavailability. This literature review aims to understand the effectivity of Temulawak (Curcuma xanthorrhiza roxb.) extract based Nanotechnology PLGA on Diabetic Wound.

Methods

The review literature and researches was conducted by using several database : 102 article from Science Direct, 15 article from Google Scholar,5 article form ProQuest, 2 article form PubChem, in 2008-2018

Results

PLGA (Poly-Lactic-co-Glycolic-Acid) nanoparticle combined with curcumin (PLGA CC NP) shows great outcome in wound healing. Biphasic pattern of PLGA CC NP drug delivery process controls sustain and gradual release within 8 days without showing any significant cytotoxic effect. Curcumin in PLGA works by inhibiting neutrophil infiltration marked by decrease of Myeloperoxidase enzym and decreased NFkB expression in inflamatory cytokines such as TNFα, IL-1, IL-6, IL-8. Endogenous lactic acid provision with PLGA becomes a potential strategy of sustained supply for accelerating angiogenesis and wound healing process. Lactic Acid in PLGA stimulates collagen syntesis in fibroblast and Vascular Endothelial Growth Factor (VEGF) transcription in endothelial cell.

Conclusion

Temulawak (Curcuma xanthorrhiza roxb.) extract based Nanotechnology PLGA effective for diabetic wound therapeutic agent.

Keywords:
Curcuma; Nanotechnology PLGA; Diabetic Wound

BACKGROUND

Diabetes Mellitus (DM) Type 2 is a group of metabolic disorder which is characterized by abnormalities in glucose levels due to impaired secretion and function of insulin (Yang et al. 2016). This situation triggers an increase of blood glucose concentration or hyperglycemia (Ministry of Health RI, 2014).

In 2014, more than 387 people experienced diabetes and 4.9 million people died from diabetes (Hajna et al. 2016). In Indonesia, people who diagnosed by diabetes mellitus in 2007 was 30.4%, while the undiagnosed was 69.6%. Then in 2013, diagnosed patients with diabetes mellitus was 26.3%, while those who were undiagnosed were 73.7%. The proportion of people with diabetes mellitus increases with age. The proportion of TGT (impaired glucose tolerance) increases with age to the highest at 65-74 years. While the proportion of GDP increases with highest at 55-64 years (Ministry of Health RI, 2014).

Many macro and micro vascular complications can arise from DM, one of them is disruption of the wound healing process (Desta, Li, Chino, & Graves, 2010). The wound healing process runs in a coherent, controlled and complex manner. Normal wound healing process begins with the presence of 1) hemostasis phases, in this phase coagulation process occurs to prevent bleeding; followed by 2) inflammatory phase which is characterized by the clearance of dead cellular debris and pathogens from the wound area; 3) Proliferation phase which characteristic is regenerating the granulation tissue, formating the new blood vessels and re-epitalization. 4) The last phase in the wound healing process is maturation phase which is characterized by tissue remodeling (Kurahashi & Fujii, 2015). However, hyperglycemic conditions in DM conditions can cause disruption of the wound healing process due to prolonged inflammatory process, disruption of the angiogenesis process and reduced fibroblast proliferation process (Chor, Tam, Man, Lun, & Ho, 2011).

Diabetic Wound classified into chronic wound. It has different characteristics in the healing process when compared to the normal wound healing process. Diabetic Wounds healing process undergoes an extension in the inflammatory phase which produces inflammatory mediators of TNF-α, IL-1 β, and MMP-9. This phase also takes place with the process of influx neutrophils characterized by the release of cytotoxic enzymes, free radicals and inflammatory mediators that cause damage to surrounding tissues. Excessive production of free radicals will induce oxidative stress, causing complications in the form of inhibition of tissue remodeling processes (Kant et al. 2014). The prolonged wound healing process causes a higher risk of infection that result in amputation of necrotic limbs (Komelyagina, Kogan, & Antsiferov 2017).

Recently, various approaches have been developed to overcome the problems caused by diabetes mellitus wounds, both traditional and modern way **(Table 1).** There were four types of dressings for diabetic wounds that were approved by FDA, including Bioengineered human skin equivalent, two dermal subtitues, and recombinant human platelet derived growth factor (rhPDGF) (Driver et al., 2015; Wei, Kirsner & Eaglstein, 2016). The mechanism of Human skin equivalent and dermal subtitues are by increasing biomaterial interaction with the wound area, so that healthy wound healing process occurs, while PDGF worked by increasing the stimulation of neutrophil chemotaxis, macrophages, fibroblasts and smooth muscle cells. In addition to the therapies already mentioned, there are also several other types of therapies that are currently used, including artificial dressings, silver dressings, natural dressings, and biomaterials. Recently, these synthetic and natural biomaterials are used as therapeutic agents that accelerate the regeneration of

damaged dermal and epidermal tissues. Natural polymers studied for applications in wounds include polysaccharides (chitosan, chitin, dextran, alginates, chondroitin, and heparin), proteoglycans, and proteins (collagen, gelatin, fibrin, silk fibroin, and keratin). While some synthetic polymers found to be able to be wound healing agents are poly (glycolic acid) (PGA), poly-D, Llactide-co-glycolide (PLGA), poly (vinyl alcohol) (PVA), poly- (lactic acid) (PLA), poly (acrylic acid) (PAA), poly (ε-caprolactone) (PCL), poly (ethylene glycol) (PEG), andpoly (vinylpyrrolidone) (PVP).

In fact, this approach has not been able to provide pleasant *outcomes* (Hamdan et al., 2017). Therefore, an innovation is needed to improve the effectiveness of diabetic wound care that is able to reach the cellular stage.

Table 1. Current Traditional and Modern Approaches Wound Healing

Types of Therapy	Benefit	Weakness	Classification	
			Traditional	Modern
Biomaterial-based dressing (graft and bioengineered skin substitues) (Sun, Siprashvili & Khavari, 2014; MacNeil,2007)	Restore the tissue functional component; restore skin tissue to severe burns and chronic wounds	Reducing tissue vascularization, poor mechanical integrity and immune rejection		X
Cell/growth factor therapy (Borena et al., 2015; Duscher et al., 2016)	*Regenerative strategies* for chronic wounds	Rapid overhaul of growth factor / disruption of stem cell proliferation due to chronic injury		X
Artificial dressing (example: polymer) (Parani, Lokhande, Singh, & Gaharwar, 2016)	Resembling physical and biological components in the original tissue including water content, biocompatibility and biodegradability	Lack of bioactive components		X
Sliver dressing (Pereira & Bartolo, 2016)	Have good, simple and affordable clinical efficacy	Toxic at certain concentrations	X	
Natural Substances (example : herbs, honey, maggots) (Pereira & Bartolo, 2016)	Simple and affordable	Unexpected allergic reactions	X	

Current wound healing methods using natural ingredients is promptly developed, one of them is Temulawak (*Curcuma xanthorrhizaroxb*.). In Indonesia Temulawak (*Curcuma xanthorrhizaroxb.*) also known as Javanese Curcuma. It has bioactive compounds as wound healing properties, including volatile oil, saponins, flavonoids, tannins, curcumin and several other ingredients (Lee, Shim, & Rukayadi, 2008; Pramono & Tuszakka, 2015). Curcumin as bioactive ingredients in Temulawak has been widely used as a treatment agent, because curcumin has properties that are fairly complete as antimicrobial, anti-inflammatory, anti-cancer, anti-diabetic, and anti-hiperlipidemia, anti-oxidant, neuroprotector, anti-allergic and anti-hypercholesterol (Rukayadi and Hwang, 2006; Lee

et al., 2008; Qader et al., 2011; Lim et al., 2005; Peschel et al., 2006). The chemical structure of curcumin is shown in **fig. 1.**

Use of curcumin topical form is one of the finest choice, because (1) low water solubility and extensive first pass metabolism characteristics are capable to increase accessibility, better than given orally (2) able to deliver drugs directly to cells/tissues (3) only requires a small amount to create a therapeutic effect and (4) improve patient compliance by reducing the frequent application doses (Qian, Dai, Zheng, 2009; Zhang, Tsai, &Ramezanli, 2013).

Several studies show that curcumin as Wound healing properties has antioxidant activity and reduce free radicals which are quite strong. These advantages are very appropriate when applied to diabetic wounds, because the inflammatory phase occurs longer than the normal wound healing process. This phenomenon is caused by ongoing neutrophil influx which triggers the production of cytotoxic enzymes, free radicals and inflammatory mediators that cause collateral tissue damage (Mohammad, Pandey, & Tripathi, 2008). Mohanty & Sahoo (2017) conducted the same thing, that the extension of inflammation in diabetic wounds is caused by excessive production of reactive oxygen species (ROS) and instability of the redox reaction to balance ROS production. Based on previous research by Kant et al., (2014) antioxidants and anti-inflammatory possessed by curcumin, can be used as a strategy of diabetic wound healing agent by reducing the inflammatory cytokines expression (TNF-a, IL-1b, and matrix metalloproteinases -9), increases levels of anti-inflammatory cytokines (IL-10) and antioxidant enzymes (superoxide dismutase, catalase and gluthatione peroxidase). In line with research conducted by Merrel et al. (2009) the use of curcumin as a dressing on diabetic wounds can reduce oxidative stress and inflammation characterized by a decrease in IL-6 release.

Not only works in the inflammatory phase, but the benefits of curcumin can also work in other healing phases. Based on research conducted by Sidhu et al. (1999) stated that the use of curcumin orally or topically in diabetic wounds could increase TGF-β1, improve re-epithelialization, neovascularization, improve dermal myofibroblast, fibroblasts and macrophages migration to a wound bed with high collagen content. The results of the study were also supported by the opinion of Kant et al. (2015) which states that the use of curcumin can increase the formation of new blood vessels with an increase in micro vessel density, increase the VEGF and TGF-β1, HIF-1α, SDF-1α, and HO-1 expression and improve neovasculogenesis marked by faster wound closure and better granulation.

However, besides the superiority that has been mentioned, curcumin also has characteristics that reduce curcumin performance, including poor aqueous solubility, low oral bioavailability, chemical instability, inadequate absorption and transmembrane permeation, and rapid metabolism and elimination.

This issue has encouraged researchers in recent years to improve curcumin effective delivery through various strategies such as micellar solubilization, cyclodextrin complexation, crystal modification (metastable polymorphs, salt or co-crystal formation, and amorphization), prodrug strategies and particle size reduction (micronization). But the existing strategy could not show the maximum results (Hussain, Thu, Ng, Khan, & Katas, 2017). Therefore, the innovation is needed for diabetes wound care using curcumin which targets to cell levels, nanotechnology is one of them. Nanotherapeutic approach is able to reduce the material's dimensions until 1-100 nm, within this size the wound healing

process effectiveness would be increased because of the intense interaction between the content of the curcumin and the biological targets (Mordorski, Rosen, & Friedman 2015).

Nanotechnology has good potential development to improve the effectiveness of curcumin, nanotechnology is essentially function as 1) biodegradation prevention in encapsulated cargo 2) Good control and sustained drug release on encapsulated drugs 3) Increases dissolution rate and permeability on low water soluble drug 4) prolongation of plasma half-life and increase pharmacokinetic profile of drug 5) and improve cellular uptake, so that targeting of bioactive molecules can be more efficient (Venkata, Reddy, & Kuppusamy, 2016).

Table 2. Study of Curcumin Application on Diabetic Wound

Trial/Study	Animal Model	Curcumin Regimen	Effect Observed	Refrence
Curcumin enhance wound healing in streptozotocin induced diabetic rats and genetically diabetic mice	STZ Induced diabetic rats and db/db mice	40 mg/kg oral dan 0,1 % topical	Increases TGF-b1, increases epithelialization, neovascularization, improves dermal migration of myofibroblast, fibroblasts and macrophages to a wound bed with high collagen content.	Sidhu et al. (1999)
Curcumin loaded Poly (Ɛ-caprolactone) nanofibers: Diabetic wound dressing	STZ Induced diabetic rats	17% curcumin topically for 10 days	Reducing oxidative and inflammatory stress, characterized by a decrease in IL-6 release	Merrel et al. (2009)
Antioxidant and anti inflamatory potential of curcumin accelerated the cutaneous wound healing in streptozotocin-induced diabetic rats	STZ Induced diabetic rats	0,3 % per days topically for 19 days	Reduces the expression of inflammatory cytokines (TNF-a, IL-1b, and matrix metalloproteinase-9). Increases levels of anti-inflammatory cytokines (IL-10) and antioxidant enzymes (superoxide dismutase, catalase and gluthatione peroxidase)	Kant et al, (2014)
Curcumin induced angiogenesis hasten wound healing in diabetic rats	STZ Induced diabetic rats	0,3 % per days topically for 19 days	increase the formation of new blood vessels with an increase in micro vessel density, increase the VEGF and TGF-β1, HIF-1α, SDF-1α, and HO-1 expression and improve neovasculogenesis marked by faster wound closure and better granulation.	Kant et al, (2015)

METHODS

Search Strategy

Four electronic database such as Science Direct, ProQuest, PubChem, Google Scholar are used to identify topics to be used. The literature search strategy uses several terminology: "*Curcuma xanthorhizzaroxb*.", "Curcuma", "Curcumin", "Diabetic Wound", "Diabetic Wound Healing", "Nanoparticle", "PLGA". The terminology combination aims to provide a broad range of literature search results, not focusing on other specific factors (such as fibroblast proliferation, blood vessels and others) . The purpose of this review literature is to provide a general review of the topics discussed. This review done by several steps, started from identifying relevant articles, longitudinal studies and literature that considered appropriate. The process was carried

out repeatedly by second and third researchers. There are inclusion and exclusion criteria used in the literature review process. Inclusion criteria were: (1) Journal published in 2008-2018, (2) Journal in English, (3) Study of wound healing process (4) Study of Diabetes Mellitus wounds (5) Study of Curcumin (6) Study of Nanoparticles. While the exclusion criteria used are: (1) Journal published not from 2008-2018 (2) The study is not about wound healing process.

124 articles had identified, but 19 articles were the same article. Furthermore, the remaining 105 articles were reidentified based on inclusion and exclusion criteria. The final results of identification, obtained 36 articles that match the inclusion criteria (see **Fig 1.)**

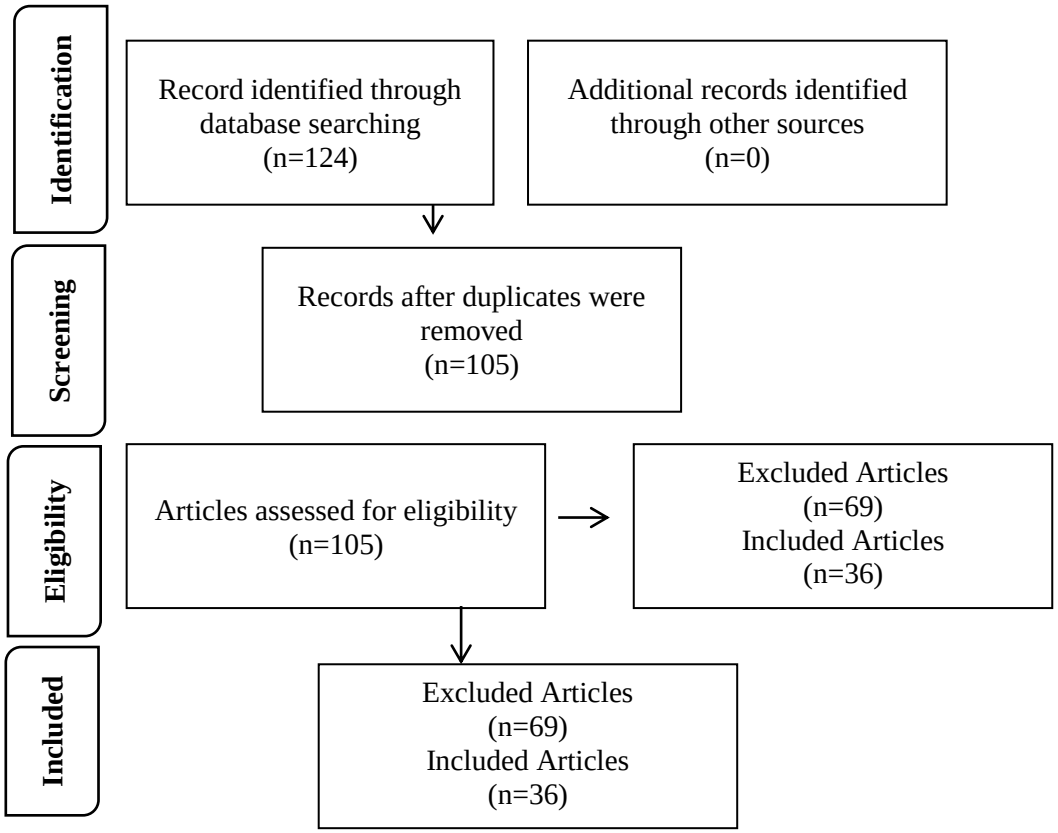

Fig 1. Review and Article Elimination Process

RESULTS

PLGA CC NP Characteristics

Tabel 3. Properties of PLGA-CC and PLGA-NP (Mean ± SD, n=4)

Name	Particle size (nm)	Polydispersity index	Zeta potential (mV)	Encapsulation efficiency (%)
PLGA-CC NP	176.5 ± 7.0	0.105 ± 0.025	−23.2 ± 3.8	89.2 ± 2.5
PLGA NP	150.0 ± 3.2	0.175 ± 0.051	−18.2 ± 2.5	NA

PLGA-CC NP was prepared using emulsification-solvent evaporation technique with PVA (Polyvinyl alcohol) as a stabilizer. Physico chemical properties in the Nanoparticle are

presented in Table 3. Particle size, PDI, zeta potential and efficiency of encapsulation of PLGA CC-NP are 176.5 ± 7.0; 0.105 ± 0.025; -23.2 ± 3.8 and 89.2 ± 2.5.

Profile of Curcumin Release

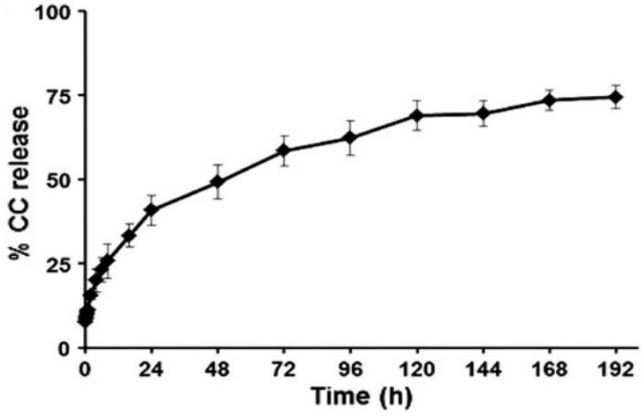

Fig 2. In vitro release of PLGA CC NP (mean± SD) (Chereddy et al., 2013)

Research on the encapsulated drug release from PLGA NP is very important, because limited drug release can reduce availability and efficacy from material formulations. In vitro drug release in PLGA CC is presented in Fig. 2. The curve shows drug release having a biphasic pattern, at the beginning of the release occurred in the first 24 hours with 40.5 ± 4.5% CC compared with PLGA CC NP. Furthermore, drug release occurs sustained from 40.5 ± 4.5% to 75.7 ± 3.4% within 8 days.

PLGA CC NP Accelerates the Wound Healing Process

Effects of CC, PLGA NP and PLGA CC NP on the wound healing process were carried out in rats with full thickness excisional model with treatment using 0.5 mg CC, 1 mg PLGA NP and 1 mg PLGA CC NP. The wound area was monitored for 16 days and animals were sacrificed on days 5 and 10 for histology and biochemical analysis. On day 5 **(Fig. 3a),** the wound treated with PLGA CC NP showed a faster healing process compared to other treatment groups. In the second step, wounds treated only by using CC showed better results compared to PLGA NP. Based on the observations that have been made, the wound that obtained PLGA CC NP treatment had half less wounds area than the one which treated with CC, one third of the area of PLGA NP and the wounds that were not given treatment at all. On day 10 **(Fig. 3b)**, PLGA CC NP showed almost perfect wound closure, while CC and PLGA NP showed 75% wound closure. PLGA NP shows the same potential as CC after the 7th day of the wound care.

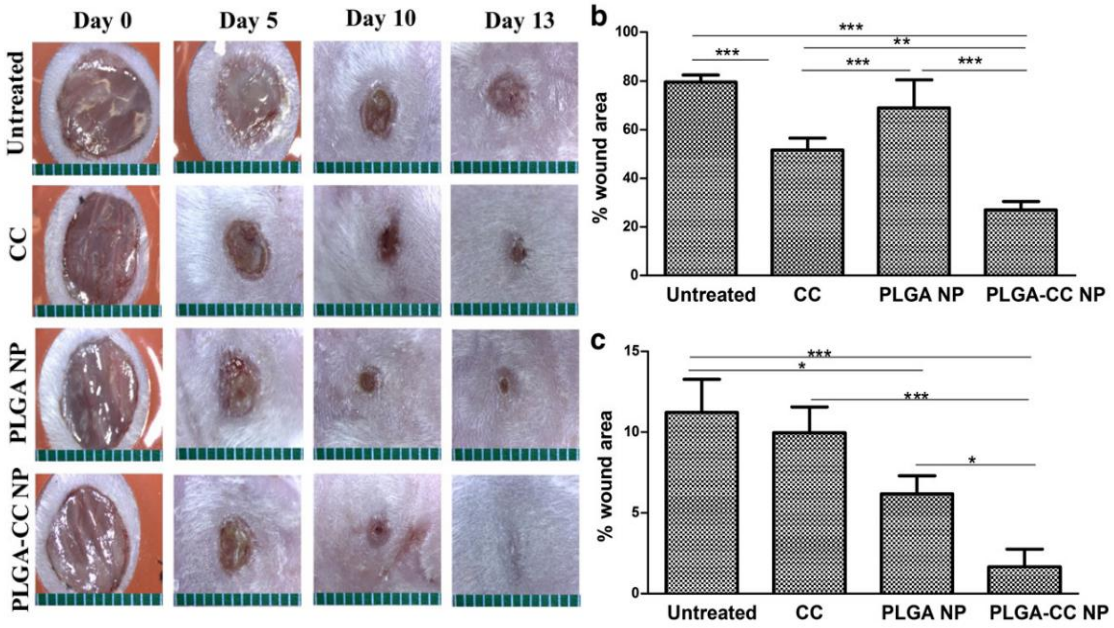

Fig 3. Nanoparticle effects of PLGA Curcumin (PLGA CC NP) in the wound healing process (a) wound in untreated groups, administred with CC, PLGA-NP, and PLGA CC NP. Measuring wounds in mm. Measurement of wound closure using percentage (b) dermal wound area on 5th day (c) the mean value of dermal wound (Chereddy et al. 2013)

PLGA CC NP increases Tissue Re-epithelialization and Granulation

The staining process of incisioned skin was performed using hematoxylin and Eosin (H & E) to obtain general observations on the skin layer and the Masson's Thricome (MT) Stainning Process was used to determine collagen deposition in tissues during the wound healing process. Histology results in wounds that were not treated, obtained CC, PLGA NP and PLGA CC NP treatment on 5^{th} and 10^{th} day were presented in **Fig. 4a.** Group PLGA CC NP shows a significant healing process compared to other groups. On 5^{th} day, in the group that was not obtained treatment and PLGA NP treatment, shows very thin hypocellular epithel, while the group that received CC and PLGA CC NP showed scab formation and epithelium presence. However, in all groups did not show fine dermal layer formation. The observation results on the 10^{th} day, the group that was not obtained treatment showed that there was loose crust in the dermal layer and a few epithelium. Whereas in the PLGA CC NP group showed complete re-epithelialization and a significant increase in connective tissue. When compared with the other treatment groups, the PLGA CC NP group showed higher collagen than MT staining and Sircol collagen assay **(Fig. 4 c and 4d).** Untreated wounds showed collagen with loose reticular formation, while the PLGA CC group showed intact, solid and fused collagen formation. On 10^{th} day, there was an increase in density both in CC and PLGA NP groups compared to the group that did not receive treatment

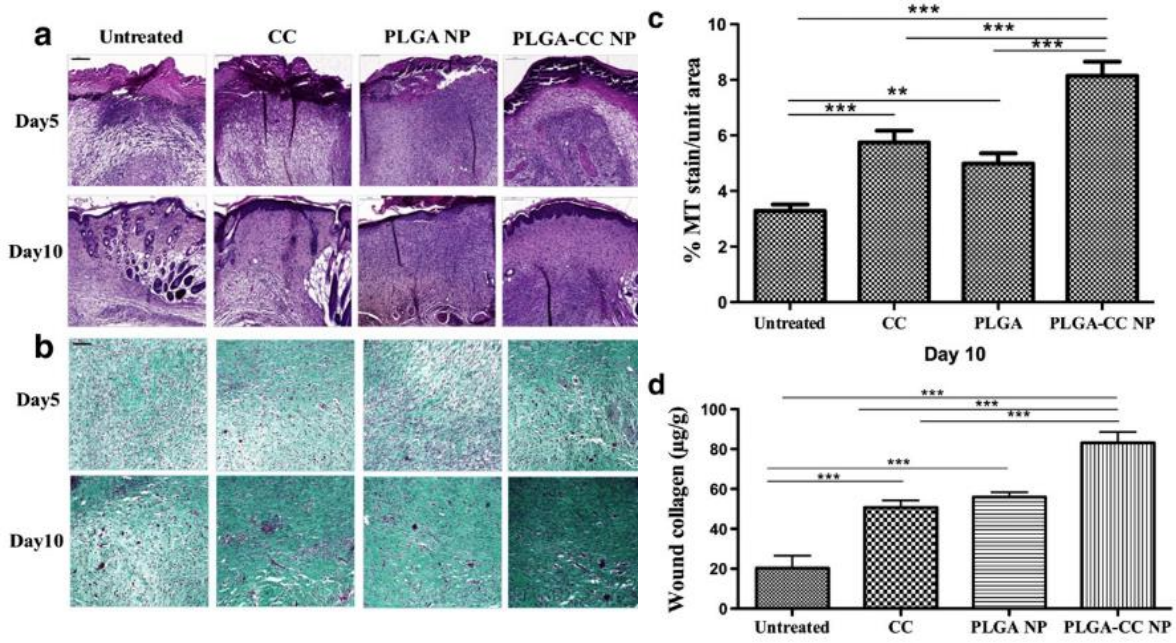

Fig. 4. PLGA CC NP improves re-epitalization and collagen in granulation tissue. (a) stainning process using H & E for general observation of skin layer (b) Mass Trichrome (MT) for collagen. The scale used in all groups was = 200µm (c) the quasi-quantitative estimation of MT stainning on the incision at 10^{th} day, the stainning MT results were seen in all unit areas (d) colometrical analysis of the acid-soluble collagen amount at skin lysate 10 days after wound making (Chereddy et al. 2013)

PLGA CC NP Reduces Myeloperoxidase Activity

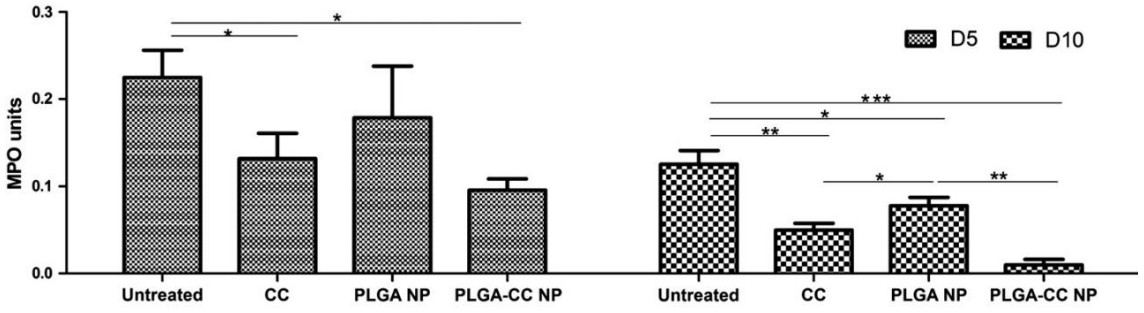

Fig. 5. Myeloperoxidase Inhbition by CC, PLGA NP and PLGA CC NP (Chereddy et al., 2013)

(MPO) is an enzyme present in azurophilic granules in neutrophils and used as a quantitative index of inflammatory infiltration. On the 5th day, there is a significant increase in MPO activity in the wounded group who did not obtain treatment and the group that obtained PLGA NP treatment. Meanwhile, CC and PLGA CC NP groups showed a significant decrease in MPO activity.

DISCUSSION

The mechanism of curcumin and PLGA

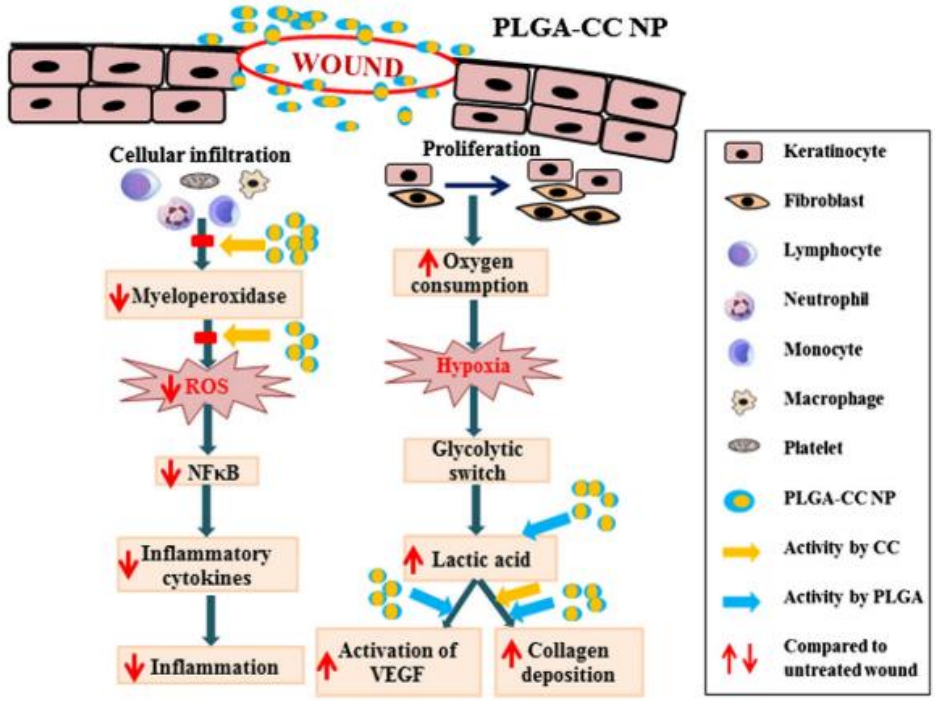

Fig. 1. Mechanism of Work of Curcumin and Lactic Acid in the Wound Healing Process (Chereddy et al. 2013)

PLGA (Nanoparticles*Poly-Lactic-co-Glycolic-Acid*)combined with the use of curcumin (CC) showed fine results in wound healing. PLGA nanoparticles were chosen based on several advantages such as (1) able to compensate for the lack of curcumin, such as poor water

solubility, low photosensitivity and stability; (2) Having a biphasic drug release profile, when 40% initial burst release happened in its first 24 hours, the remaining 40% -75% will be released gradually and sustainably within a period of 8 days; (3)CC, PLGA NP and PLGA CC NP administration does not show a significant cytotoxic effect (Hussain et al., 2017; Parani et al., 2016; Chereddy et al., 2013).

Based on the recent studies, the outcome of wounds treated with PLGA CC NP show a faster healing process compared to other treatment groups. In the second step, wounds treated only by using CC showed better outcome compared to PLGA NP, but PLGA NP showed the same potential as CC after the 7th day of wound care. In line with the results of research conducted by Porporato, Preat, & Thissen (2012) that topical administration of a single PLGA can improve the wound healing process when compared to lactic acid alone.

The inflammatory phase characterized by the production of Reactive Oxygen Species (ROS) has a very important role to fight against microorganisms. But in hyperglycemia, the production of ROS that elongated with high concentration triggers the appearance of oxidative stress which damage the surrounding tissue. In this phase, there is a large amount of neutrophil infiltration in the wound through the respiratory burst process that produces protease, oxygen free radicals and inflammatory mediators such as TNF-a and IL-1 (Yu, Hu, & Peng, 2014). The emergence of these radical substances contributes to the production of Lipid Peroxidase (LPx), DNA damage and enzyme inactivation, including free radical scavenging. Research conducted by Chereddy *et al*., (2013) showed that *Myeloperoxidase enzyme* (MPO) which is often found in neutrophils as a quantitative index of inflammation, showed an activity increase when compared with untreated wounds and PLGA NP on the 5th and 10th day. These results showed that CC was able to inhibit neutrophil infiltration.

In addition, the results of study by Chereddy *et al*., (2013) also showed that the provision of PLGA CC NP was also able to reduce NFkB expression when compared to other treatment groups. NFkB inhibition by PLGA CC NP is considered better if compared with CC alone, Anand et al., (2010) pointed that it is caused by cellular uptake capability of CC NP has higher than CC. NFκB is a transcription factor for various genes that are associated with inflammation, these factors will be activated when excess ROS production occurs (Mohanty&Sahoo, 2017; Morgan & Liu, 2010). Thus, by giving PLGA CC NP, production of proinflammatory gene formation and various kinds of inflammatory cytokines such as TNFα, IL-1, IL-6, IL-8, chemoattractant monocytes and inhibitory migration of proteins can be suppressed (Akbik, Ghadiri, Chrzanowski, &Rohanizadeh, 2014 ; Gupta, 2012; Mohanty et al. 2012).

Hypoxia caused by microcirculation damage, increased use of oxygen by inflammatory cells and increased glycolitic switches activity is one of the metabolic adaptations that aimed to protect cells from damage. The aerobic glycolysis process has an important role in wound healing. Lactic acid produced from this process can trigger the angiogenesis process by increasing the *endhotelial progenitor cells* growth, *procollagen factor* activation and increasing the *extracellular matrix deposition* (Porporato et al, 2012). Lactic acid also stimulates the collagen synthesis process in fibroblasts and Vascular Endothelial Growth Factor (VEGF) transcription in endothelial cells. This process will activate procollagen production and angiogenic factors. Endogenous use of lactic acid using PLGA is one of the strategies to supply lactate on an ongoing basis to achieve the angiogenesis process and a faster wound healing process.

CONCLUSIONS

Advantages of curcumin in Temulawak (*Curcuma xanthorrhiza roxb.*) on PLGA nanotechnology in the form of gradual and sustained drug release and not showing *cytotoxic effect* can be an effective therapeutic agent in diabetic wounds**.** The content of curcumin with PLGA nanoparticles works by inhibiting neutrophil infiltration in the inflammatory phase so that excess ROS production can be reduced and decrease NFκB expression which able to reduce pro inflammatory gene production and various kinds of inflammatory cytokines. In addition, the content of lactic acid in PLGA enables the acceleration process of collagen synthesis and angiogenesis in wounds.

Declarations

Authors' contributions

First author provides the intellectual input and designs, second and third author responsible for the manuscript correction, proof reading, whole correspondence during the paper submission

Competing interests

The authors declare that they have no conflicts of interest.

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