

# Therapeutic Effect of Luteolin in Diabetic Wounds: Minireview

Amnah Asiri

*Department of Bioscience, Faculty of Science, Universiti Teknologi Malaysia, Skudai, Johor, Malaysia*

*email:amnahasiri@graduate.utm.my*

**Abstract:** *Diabetic wounds are a popular health problem affecting 15% of diabetic individuals. Traditional treatment depends on understanding the relationship between diabetes and wound healing mechanisms. Recent studies tend to use natural products that possess active components for treatments. Luteolin is the most common flavonoids found in many medicinal plants. The study has also highlighted the recent advances in the therapeutic effect of luteolin, particularly, on diabetic wounds healing. Luteolin has demonstrated its anti-inflammatory effect through its impact on fibroblast cell proliferation and migration. Further studies are highly recommended to focus on luteolin as an anti-inflammatory agent in human diabetic wounds healing.*

**Keywords:** *Luteolin; Diabetes; Wounds, Healing.*

## 1. INTRODUCTION:

Diabetes is a metabolic disorder affecting more than 422 million people worldwide (1). The World Health Organization (WHO) report predicts that diabetes will be the seventh major cause of death in 2030 (2). Diabetes declines the glucose metabolism, leading to hyperglycemia (3). Hyperglycemia can cause a dysfunction of the peripheral organs such as atherosclerosis, peripheral artery disease, retinopathy, nephropathy, neuropathy, and impaired wound healing (4).

The main problem for individuals with diabetes is impaired or delayed healing of wounds, leading to chronic non-medicated wounds which are considered as the most common diabetic complication (1). Diabetic wounds are estimated to occur in 15% of individuals with diabetes. Leg or foot ulcers are the major type of diabetic wounds (2) which are considered as the main risk factor for injury, foot deformation or amputation (4). Amputation is accompanied by an increase in mortality rates of 16.7% at 1 year and over 50% at 5 years (5). The mortality rate of diabetic ulcers patients exceeds the most common types of cancer (4). Diabetes prevalence continues to increase in general, contributing to an increasing cost of health care (5). About 2.5% - 15% of annual health budgets worldwide are consumed on diabetes and diabetic wounds (2).

## 2. NORMAL WOUND HEALING

Wounds are classified according to various methods; such as etiology, location, injury type, exhibited symptoms, wound depth, tissue loss, clinical appearance and physiology of wound healing (6).

Based on the wound creation cause, wounds are classified into *open* and *closed* wounds (7). In the open wounds, blood escapes the body and bleeding is visible (such as incised,

laceration, puncture, penetration and gunshot wounds) whereas the close wounds, blood escapes into circulatory system and remains in the body (such as contusion, bruises, hematomas, blood tumor or crush injury) (6).

Regarding the basis of potential of wound healing, the wounds are referred to *acute* and *chronic* wounds (8). Acute wounds (such as cuts, injuries, burns and bruises) are generally healed easily without any issues whereas chronic wounds (such as skin ulcers and calluses) take more than 12 weeks to heal (2).

On the basis of origin source, the wounds stratified into *external* and *internal*. External wounds are not usually noticed by diabetic subjects due to peripheral neuropathy, while internal wounds cause microbial infection to skin and surrounding tissues (2).

Regardless of the type of wound, the normal healing process is performed through four extremely programmed phases: hemostasis, inflammation, proliferation and remodeling (9), Fig. 1. This biological process contributes to different cell types and growth factors. Cytokines also play vital functions at each phase to regulate progress smooth cascade healing (1). These four phases occur in a linear way forward under normal circumstances (5).

#### *Hemostasis Phase:*

This phase starts by blood loss and microbes invasion to the affected wounded zone (2). Leakage of the blood components leads to fibroblast formation, that works as a scaffold to penetrate the cells (1). In conjunction with platelet induction, signaling agents are released and activated the neutrophils and macrophages (5).

#### *Inflammation Phase:*

Neutrophils are the initial cells that reach the injury site to clean and deteriorate external materials, harmed cells and microorganisms (1). Neutrophils release chemokines responsible for the recruitment of monocytes spread from peripheral blood to the site of the wound. Monocytes combine that distinguish in macrophages and dendritic cells, alongside F4/80+ resident tissue macrophages (5). The macrophages clean foreign materials and pathogens along with growth factors and other cytokines such as IL-12, IL-1 $\beta$ , IL-6, TNF $\alpha$ , and iNOS (2).

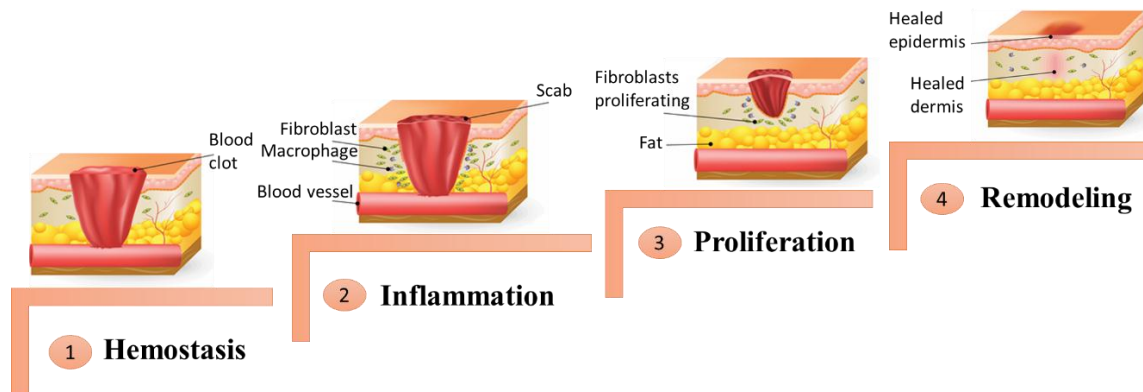
#### *Proliferation phase:*

This phase is recognized by the migration and proliferation of various cells types, involving endothelial cells, fibroblasts, and keratinocytes responsible of angiogenesis, formation of granular tissue, deposition of extracellular matrix, contraction of wound, and re-epithelization (1, 5).

#### *Remodeling phase:*

The neovessels quantity decreases and most of the cells either leave the wound or undergo apoptosis, leaving a develop avascular environment with few cells. Additionally, collagen of type III is progressively changed by stronger collagen type I, that leads to increasing the strength of tensile in scar tissues up to 80% of uninjured skin (1, 5).

Figure 1. Normal wound healing process (10)



Many factors may interrupt the healing process at any stage leading impaired healing wound in the ordinary recovery (6, 9). These factors include aging, malnutrition, medications, infection, ischemia or hypoxia (6, 11).

The most concern wounds that can alter the normal physiological functions such as diabetes, obesity, stress, vascular diseases, and other environmental conditions (2). These wounds are often in a condition of pathological inflammation belong to a postponed, incomplete, or uncoordinated healing process (9).

### 3. DIABETIC WOUNDS

Although wound healing is a normal biological process, this process is very different in diabetics subjects because these wounds are very difficult to heal (12).

Diabetes disease postpones the healing because it damages each phase of wound healing, resulting in a delayed, incomplete, or uncoordinated healing process (2). The negative consequences of this delaying healing are increased in amputations of lower limb, increased health care costs, and shorter life expectancy (4).

Patients with diabetes suffer from poor compensatory responses through the main phases of inflammation, angiogenesis, and re-epithelialization due to several exclusive contributing factors for diabetes mellitus (4).

The inflammatory phase is manifested by high levels of proinflammatory cytokines, proteases, and reactive oxygen species (13), as well as cellular dysfunctions (1) which is related with an obstruction in the formation of mature granulation tissue and reduction of wound tensile strength. These outcomes may belong to blood vessels ischemia (2).

In addition, re-epithelialization is delayed in diabetic wounds because of impaired keratinocyte and fibroblast function as a sequence of hyperglycemia and advanced glycation end-products (AGEs) accumulation, and the epigenetic regulation (5).

The mechanistic insight of the effect of diabetes on delayed wound healing process is summarized through immune cells, activation of molecular signaling pathways (5), molecular involvement, poor growth factor production (2), dysfunction of macrophage and neutrophils (14), production of pro-inflammatory cytokines, angiogenic response failure, vascular complications (13), impaired keratinocytes and fibroblast migration and proliferation (15).

### 4. TREATMENT OF DIABETIC WOUNDS

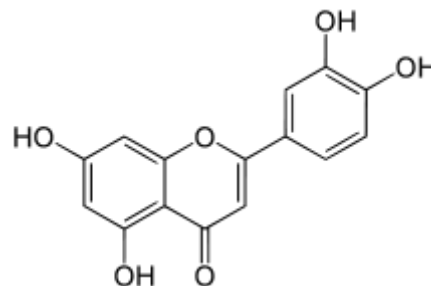
Present treatment for diabetic wounds depends on understanding the relationship between diabetes and wound healing mechanisms. Traditional treatment strategies include pressure

offloading, sharp tissue removal, antibiotic management, and reconstructive surgery to restore blood flow (16). These medications aim at wound closure rather than treat the pathophysiology of the wound, leading to the fluctuation of healing process, prolonged healing period, and recurrence of the wound, causing treatment failure and amputation (1). There is a growing attitude in recent studies to use natural products and herbal extracts that possess active components for treatments (17). Nature has offered the phytochemicals as protective and curative agents against various diseases most likely because of the presence of active compounds (18). One of the most of phytochemicals is flavonoids which are grouped into different classes according to their chemical compositions, including flavones, flavanones, anthocyanidins, flavonols, isoflavones, and catechins (19). Flavones, a class of flavonoids, are widely known to be responsible for many pharmacological actions (20). One of the commonest flavonoids is luteolin that is found in many medicinal plants (21). Luteolin has been proven to use it for traditional medicine to treat various diseases (22). In traditional Chinese medicine, luteolin-rich plants were used to treat diseases such as high blood pressure, disorders of inflammation, and cancers (19). In traditional Iranian and Brazilian medicines, has been utilized to treat diseases associated with inflammation (20).

#### *Chemical Composition and Sources of Luteolin*

Luteolin formula is  $C_{15}H_{10}O_6$  and its structure is [3',4',5,7-tetrahydroxy flavone] (19, 22). It comprises one oxygen, two benzene rings, hydroxyl groups and double bonds which are crucial for luteolin pharmacology (18). Luteolin structure is presented in Fig. 2. Derivatives of Lutein include luteolin-7-*O*-glucoside, luteolin-8-*C*- $\beta$ -glucopyranoside, luteolin-7-*O*- $\beta$ -rutinoside, flavone-*O*-glycoside, luteolin-8- $\beta$ -d-glucopyranoside, luteolin 7-*O*-rutinoside and esculetin (21).

Figure. 2. Chemical structure of luteolin (18).



Luteolin and its derivatives were extracted from various natural plants (21). Luteolin is predominantly found in fruits and vegetables; such as celery, chrysanthemum flowers, carrots, sweet bell peppers, broccoli, onion leaves, parsley (19), honey, pollen (22), apple skins, cabbages, peppers (18), thyme, peppermint, basil, and artichoke (20).

#### *Bioavailability, Absorption and Toxicity of Luteolin*

HPLC and spectral methods are used to isolate and measure the content of luteolin in many plant materials and edible staffs (18).

The bioavailability of luteolin is very low and its oral absorption is similar in duodenum and jejunum, but it is greater in the colon and ileum (21).

Toxicity of dietary luteolin is unlikely to reach toxicity concentration because the oral absorption of luteolin is about 15% (21, 23). If luteolin and its derivatives reach the concentration of toxicity, it may damage cells because of its effect on the endocrine system.

This is probably due to the oestrogenic activity of the luteolin and its affinity to the antagonize activation of progesterone receptor (23).

### *Therapeutic Effect of Luteolin*

Multiple mechanisms may underlie luteolin's actions (24): (1) through an antioxidant function (2) inhibition the ROS-generating oxidases (3) inhibition the enzymes that catalyze oxidation (4) enhancing the endogenous antioxidants such as catalase (CAT), superoxide dismutase (SOD), glutathione-S-transferase (GST), and glutathione reductase (GR).

Luteolin exhibits various biological properties such as anti-oxidant, anti-inflammatory, anticancer, anti-diabetic, anti-microbial, and anti-allergy agent (19). It has been reported to have chemotherapeutic, cardioprotective and neuroprotective properties (20).

Therapeutic actions of luteolin act through diverse signaling pathways. It can initiate the apoptosis pathway, cell cycle capture, stifling cell survival signaling, anti-angiogenesis, anti-metastasis, mitigating and hindering cytochrome P450 and focusing on epidermal, platelet derived, insulin-like and fibroblast development factors (18).

Few published studies have shown the wound healing activity of luteolin. The earlier study was carried out in 2013. Lodhi and Singhai investigated the wound healing effect of flavonoid-rich fraction and luteolin extracted from *Martynia annua* Linn. on streptozotocin-induced diabetic rats. The authors found that wound contraction percent was significantly greater in luteolin treatment groups at ( $P < 0.01$ ). Matured collagen fibers and fibroblasts with better angiogenesis were histopathological noticed. Their study suggested that flavonoid fraction and luteolin may enhance wound healing ability in diabetic rats, due to scavenging activity of free-radical in the *Martynia* plant (9).

Another *in vitro* study was done in 2017, Bayrami et al. studied the activity of luteolin on wound healing. The study finding showed that luteolin treated groups showed a significantly scratch contraction ( $p < 0.01$ ) compared to the control group. Luteolin significantly improved the live population of 3T3 fibroblast cells ( $98.9 \pm 4.9$ ) and population of cells in G2M phase ( $32.2 \pm 1.6$ ) of the cell cycle compared to the control group. Their study suggested that luteolin has a property of wound healing because it effects on the fibroblast cell proliferation and migration (15).

In a recent study was also conducted in 2017, Ozay and his colleagues studied the effects of luteolin ointments on the healing of incision and excision wounds in both diabetic and non-diabetic rats. Luteolin ointments showed an improvement in wound healing of skin tissue in non-diabetic as well as diabetic wounds. Ozay et al. observed that the best wound healing activity was (97.6%) in the incision wounds and (96.1%) in the excision wounds when these wounds were treated with luteolin ointment on day 14 (25).

## **5. CONCLUSION**

In this review, we focused on a potential anti-inflammatory activity of luteolin on diabetic wound since luteolin has demonstrated its anti-inflammatory effect. This study recommended the researchers to focus on this point and manipulate this compound for a potential wounds healing in diabetic patients. Further studies to investigate the effects of luteolin loaded with nanoparticles is highly recommended to study the bioactivity of luteolin on diabetes wound healing process.

### *Acknowledgments*

The author would like to acknowledge the Saudi Arabian Cultural Mission (SACM) for their support

## 6. REFERENCES

- [1] Cho H, Blatchley MR, Duh EJ, Gerecht S (2018) Acellular and cellular approaches to improve diabetic wound healing. *Advanced Drug Delivery Reviews*
- [2] Patel S, Srivastava S, Singh MR, Singh D (2019) Mechanistic insight into diabetic wounds: Pathogenesis, molecular targets and treatment strategies to pace wound healing. *Biomedicine & Pharmacotherapy* 112:108615
- [3] Abe M, Kovcsdy CP, Kalantar-Zadeh K (2019) Glucose Homeostasis and the Burnt-Out Diabetes Phenomenon in Patients with Kidney Disease. *Endocrine Disorders in Kidney Disease*. Springer, pp 27-38
- [4] Ozdemir D, Feinberg MW (2019) MicroRNAs in diabetic wound healing: Pathophysiology and therapeutic opportunities. *Trends in Cardiovascular Medicine* 29:131-137
- [5] den Dekker A, Davis FM, Kunkel SL, Gallagher KA (2019) Targeting epigenetic mechanisms in diabetic wound healing. *Translational Research* 204:39-50
- [6] Sabale P, Bhimani B, Prajapati C, Sabale V (2012) An overview of medicinal plants as wound healers. *Journal of Applied Pharmaceutical Science* 2:143-150
- [7] Nagori BP, Solanki R (2011) Role of medicinal plants in wound healing. *Research Journal of Medicinal Plant* 5:392-405
- [8] Harper D, Young A, McNaught C-E (2014) The physiology of wound healing. *Surgery (Oxford)* 32:445-450
- [9] Lodhi S, Singhai AK (2013) Wound healing effect of flavonoid rich fraction and luteolin isolated from *Martynia annua* Linn. on streptozotocin induced diabetic rats. *Asian Pacific Journal of Tropical Medicine* 6:253-259
- [10] Garg S, Garg A, Shukla A, Dev SK, Kumar M (2018) A review on Nano-therapeutic drug delivery carriers for effective wound treatment strategies. *Asian Journal of Pharmacy and Pharmacology* 4:90-101
- [11] Guo S, DiPietro LA (2010) Factors Affecting Wound Healing. *Journal of Dental Research* 89:219-229
- [12] Becker DL, Thrasivoulou C, Phillips ARJ (2012) Connexins in wound healing; perspectives in diabetic patients. *Biochimica et Biophysica Acta (BBA) - Biomembranes* 1818:2068-2075
- [13] Alavi A, Sibbald RG, Mayer D, Goodman L, Botros M, Armstrong DG, Woo K, Boeni T, Ayello EA, Kirsner RS (2014) Diabetic foot ulcers: Part I. Pathophysiology and prevention. *Journal of the American Academy of Dermatology* 70:1. e1-1. e18
- [14] Okizaki S-i, Ito Y, Hosono K, Oba K, Ohkubo H, Amano H, Shichiri M, Majima M (2015) Suppressed recruitment of alternatively activated macrophages reduces TGF- $\beta$ 1 and impairs wound healing in streptozotocin-induced diabetic mice. *Biomedicine & Pharmacotherapy* 70:317-325
- [15] Bayrami Z, Khalighi-Sigaroodi F, Rahimi R, Farzaei M, Hodjat M, Baeri M, Rahimifard M, Navaei-Nigjeh M, Abdollahi M (2017) In vitro wound healing activity of luteolin. *Research Journal of Pharmacognosy* 4:7-7
- [16] Alexiadou K, Doupis J (2012) Management of diabetic foot ulcers. *Diabetes therapy : research, treatment and education of diabetes and related disorders* 3:4-4
- [17] Khalil WK, Ahmed KA, Park MH, Kim YT, Park HH, Abdel-Wahhab MA (2008) The inhibitory effects of garlic and *Panax ginseng* extract standardized with ginsenoside Rg3 on the genotoxicity, biochemical, and histological changes induced by ethylenediaminetetraacetic acid in male rats. *Archives of toxicology* 82:183-195

- [18] Ahmed S, Khan H, Fratantonio D, Hasan MM, Sharifi S, Fathi N, Ullah H, Rastrelli L (2019) Apoptosis induced by luteolin in breast cancer: Mechanistic and therapeutic perspectives. *Phytomedicine* 152883
- [19] Imran M, Rauf A, Abu-Izneid T, et al. (2019) Luteolin, a flavonoid, as an anticancer agent: A review. *Biomedicine & Pharmacotherapy* 112:108612
- [20] Aziz N, Kim M-Y, Cho JY (2018) Anti-inflammatory effects of luteolin: A review of in vitro, in vivo, and in silico studies. *Journal of Ethnopharmacology* 225:342-358
- [21] Nabavi SF, Braidly N, Gortzi O, Sobarzo-Sanchez E, Daglia M, Skalicka-Woźniak K, Nabavi SM (2015) Luteolin as an anti-inflammatory and neuroprotective agent: A brief review. *Brain Research Bulletin* 119:1-11
- [22] Wang Q, Zhao L, Zhao H, Liu X, Gao L, Cheng N, Cao W (2019) Complexation of luteolin with lead (II): Spectroscopy characterization and theoretical researches. *Journal of Inorganic Biochemistry* 193:25-30
- [23] Nordeen SK, Bona BJ, Jones DN, Lambert JR, Jackson TA (2013) Endocrine disrupting activities of the flavonoid nutraceuticals luteolin and quercetin. *Hormones and Cancer* 4:293-300
- [24] Lin Y, Shi R, Wang X, Shen H-M (2008) Luteolin, a flavonoid with potential for cancer prevention and therapy. *Current cancer drug targets* 8:634-646
- [25] Ozay Y, Guzel S, Halil Erdogdu I, Yildirim Z, Pehlivanoglu B, Aydın Turk B, Darcan S (2018) Evaluation of the Wound Healing Properties of Luteolin Ointments on Excision and Incision Wound Models in Diabetic and Non-Diabetic Rats.