THE MECHANISM OF *FICUS DELTOIDEA* EXTRACT IN AFFECTING THE HEALING OF CHRONIC DIABETIC WOUND *IN VITRO*

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DEDICATION

This dissertation is dedicated to my father, who taught me that education can brighten your future. It is also dedicated to my mother, who taught me that humbleness is priceless so be humble in your life. To my dear siblings who encouraged and helped me at any critical situation. To my lovely spouse for her love and patience. To my cute children Hina, Zohaib and Sana and nephews Afshan and Raihan

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ABSTRACT

Non-healing wound is a serious complication of diabetes mellitus. Untreated chronic diabetic wound negatively impacts human life and increases the risk of mortality and morbidity. *F. deltoidea*, locally known as Mas Cotek in Malaysia, has been recognised as a significant source of antioxidant, anti-inflammatory, and anti-bacterial components. The current study was designed to evaluate the extract and fractions of *F. deltoidea* for cytotoxicity and wound healing activity under normal and hyperglycaemic conditions via *in vitro* study on Human Fibroblast Cells (HSF1184). The extraction and fractionation process was carried out on *F. deltoidea* dried leaves to obtain the ethanolic extract, chloroform and aqueous fraction. Then, the MTT assay was conducted to determine the cytotoxicity effect of the extract and fractions on HSF1184 cells. Meanwhile, the scratch assay was performed to investigate the wound healing activities for the different concentrations of the *F. deltoidea* extract and fractions. The MTT assay results revealed that the cytotoxicity was increased in a dose-dependent manner. The IC_{50} value was recorded for ethanolic extract (144.54 µg/mL), chloroform fraction (128.82 µg/mL) and aqueous fraction (162.18 µg/mL) under normal conditions. The IC_{50} value for the cells treated under hyperglycaemic conditions was observed at (138.03 µg/mL, 120.22 µg/mL 158.48 µg/mL) in an orderly manner for the three samples. The chloroform fraction was more toxic based on the IC_{50} value amongst all the treated samples in both conditions. Nonetheless, the results obtained from scratch assay showed that the ethanolic extract (80 µg/mL) and aqueous fraction (40 µg/mL) exerted their stimulatory effects on HSF1184 cells and significantly ($*p < 0.05$), ($**p < 0.01$) increased the cell migration rate at 18, 20, 22 and 24 hours in normal condition. The same concentrations for ethanolic extract and aqueous fraction were also statistically significant ($*p < 0.05$), ($**p < 0.01$) in terms of HSF1184 cell migration rate under the hyperglycaemic conditions at 22 and 24 hours. However, compared to normal conditions, the cell migration rate was slower under the hyperglycaemic microenvironment as the wound gaps were not fully closed after 24 hours. However, when compared to its control group, the treated group resulted in better migration activity. Meanwhile, the chloroform fraction has no stimulatory effect against HSF1184 in terms of cell migration under normal hyperglycaemic conditions. Taken together, from the findings it is concluded that the ethanolic extract and aqueous fraction significantly exerted their wound healing effect and significantly induced wound healing under normal and hyperglycaemic conditions. Therefore, the ethanolic extract and aqueous fractions need to investigate for further *in vitro* wound healing studies on other cell line such as keratinocytes and also *in vivo* animal model.

ABSTRAK

Luka yang tidak sembuh adalah komplikasi serius diabetes melitus. Luka diabetes kronik yang tidak dirawat memberi kesan negatif terhadap kehidupan manusia dan meningkatkan risiko kematian dan morbiditi. *F. deltoidea*, yang dikenali sebagai Mas Cotek di Malaysia, telah diakui sebagai sumber komponen antioksidan, anti-radang, dan anti-bakteria yang penting. Kajian semasa direka untuk menilai ekstrak dan fraksi *F. deltoidea* untuk aktiviti kesitotoksikan dan penyembuhan luka di bawah keadaan normal dan hiperglisemia melalui kajian *in vitro* mengenai Sel Fibroblas Manusia (HSF1184). Proses pengekstrakan dan pemeringkatan dilakukan pada daun kering *F. deltoidea* untuk mendapatkan ekstrak etanol, kloroform dan fraksi akueus. Kemudian, ujian MTT dijalankan untuk mengetahui kesan kesitotoksikan ekstrak dan fraksi pada sel HSF1184. Sementara itu, asai calaran dilakukan untuk menyiasat aktiviti penyembuhan luka pada kepekatan ekstrak dan fraksi *F. deltoidea* yang berbeza. Hasil ujian MTT menunjukkan bahawa kesitotoksikan meningkat dengan cara yang bergantung pada dos. Nilai IC_{50} dicatat untuk ekstrak etanol (144.54 µg/mL), fraksi kloroform (128.82 µg/mL) dan fraksi akueus (162.18 µg/mL) dalam keadaan normal. Nilai IC_{50} untuk sel yang dirawat dalam keadaan hiperglisemia diperhatikan pada (138.03 µg/mL, 120.22 µg/mL 158.48 µg/mL) secara teratur bagi ketiga-tiga sampel. Fraksi kloroform lebih toksik berdasarkan nilai IC_{50} di antara semua sampel yang dirawat dalam kedua-dua keadaan. Walaupun begitu, hasil yang diperoleh daripada ujian awal menunjukkan bahawa ekstrak etanol (80 µg/mL) dan fraksi akueus (40 µg/mL) memberikan kesan perangsangan pada sel HSF1184 dan secara signifikan (* p <0.05), (** p <0.01) meningkatkan kadar migrasi sel pada 18, 20, 22 dan 24 jam dalam keadaan normal. Kepekatan yang sama untuk ekstrak etanol dan fraksi akueus juga signifikan secara statistik (* p <0.05), (** p <0.01) dari segi kadar migrasi sel HSF1184 di bawah keadaan hiperglisemia pada 22 dan 24 jam. Namun, apabila dibandingkan dengan keadaan normal, kadar migrasi sel lebih perlahan di bawah lingkungan mikro hiperglisemia kerana celah luka tidak ditutup sepenuhnya setelah 24 jam. Namun, jika dibandingkan dengan kumpulan kawalannya, kumpulan yang dirawat menghasilkan aktiviti migrasi yang lebih baik. Sementara itu, fraksi kloroform tidak mempunyai kesan perangsangan terhadap HSF1184 dari segi migrasi sel dalam keadaan hiperglisemia normal. Secara keseluruhannya, berdasarkan hasil kajian ini, dapat disimpulkan bahawa ekstrak etanol dan fraksi akueus memberikan kesan penyembuhan luka secara signifikan dan mendorong penyembuhan luka secara signifikan dalam keadaan normal dan hiperglisemia. Oleh itu, ekstrak etanol dan fraksi akueus perlu disiasat untuk kajian penyembuhan luka *in vitro* lebih lanjut pada garis sel lain seperti keratinosit dan juga model haiwan *in vivo*.

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LIST OF ABBREVIATIONS

AD	-	Anno Domini
ADA	-	American Diabetes Association
AGEs	-	Advance Glycation End products
AIDS	-	Acquired Immune Deficiency Syndrome
DMEM	-	Dulbecco's Modified Eagle Medium
ECM	-	Extracellular Matrix
FGF	-	Fibroblast Growth Factor
GDM	-	Gestational Diabetes Miletus
HPLC	-	High-Performance Liquid Chromatography
HSF	-	Human Skin Fibroblast
IDDM	-	Insulin Dependent Diabetes Mellitus
IL	-	Interleukin
LC	-	Liquide Chromatography
LDL	-	Low-Density Lipoprotein
TPA	-	12-O-tetradecanoylphorbol 13-acetate
TPC	-	Total Phenolic Content
TFC	-	Total Flavonoid Content
DMSO	-	Dimethyl Sulfoxide
FBS	-	Fatal Bovine Serum
PBS	-	Phosphate Buffer Saline
SD	-	Standard Deviation
SPSS	-	Statistical Package for the Social Sciences
IC_{50}	-	Half-maximal inhibitory concentration
DM	-	Diabetes Mellitus
NMR	-	Nuclear Magnetic Resonance
HDF	-	Human Dermal Fibroblast
WRL68	-	Normal Liver Cell Line
HUVECs	-	Human Umbilical Vein Endothelial Cells
SH-SY5Y	-	Human Neuroblastoma Cell Line

DNA	-	Deoxyribonucleic Acid
JNK	-	C-jun N-terminal kinase
FTIR	-	Fourier Transform Infra-Red
MMP	-	Matrix Metalloproteinase
MODY	-	Maturity-Onset Diabetes of the young
MS	-	Mass Spectrometry
MTT	-	3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide
MYR	-	Malaysian Ringgit
NDDG	-	National Diabetes Data Group
NIDDM	-	Non-Insulin Dependent Diabetes Mellitus
PDGF	-	Platelets Derived Growth Factor
RAGE	-	Receptor for Advance Glycation End products
ROS	-	Reactive Oxygen Species
STZ	-	Streptozotocin
T1DM	-	Type One Diabetes Mellitus
TGF	-	Transforming Growth Factor
TIMP	-	Tissue Inhibitor Metalloproteinase
TNF	-	Tissue Necrotic Factor
VEGF	-	Vascular Endothelial Growth Factor
WHO	-	World Health Organization
IGT	-	Impaired Glucose Tolerance

LIST OF SYMBOLS

°C	-	Degree Celsius
%	-	Per cent
<	-	Less than
>	-	Greater than
α	-	Alpha
β	-	Beta
µg	-	Microgram
µL	-	Microlitre
g	-	gram
h	-	Hour
Kg	-	Kilogram
mg	-	milligram
mL	-	Millilitre
mm	-	millimetre
mM	-	millimole
nm	-	nanometre

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CHAPTER 1

INTRODUCTION

1.1 Background Study

Diabetes is a combination of metabolic disorders characterised by high blood glucose levels associated with carbohydrate, fat and protein metabolism (Alberti and Zimmet, 1998; Thomas and Philipson, 2015). Diabetes can be divided into four main types. Type 1 diabetes mellitus is characterised by no or inadequate production of insulin due to the autoimmune destruction of pancreatic beta-cells (Gavin *et al.*, 1997; Tan *et al.*, 2019). On the other hand, type 2 diabetes mellitus is mainly caused by environmental and genetic factors related to insulin and beta-cell dysfunction (Corrine *et al.*, 2020). The third type of diabetes, gestational diabetes mellitus (GDM), refers to carbohydrate intolerance during pregnancy (Mirghani Dirar and Doupis, 2017). Last but not least, the "other specific types" of diabetes take place due to specific causes such as pancreatic disease, endocrine disorders, monogenic defects of beta cells function and insulin action, drugs, chemicals, and infections (Association, 2010; Solis-Herrera *et al.*, 2018). This chronic disease has influenced more than 463 million world population, with approximately 20% of them developed diabetic wounds throughout the disease period (Patel *et al.*, 2019). It is also well known that diabetes can damage vital organs and bring severe complications such as cardiovascular diseases, neuropathy, nephropathy, and risk of chronic non-healing wounds (Association, 2014; Rekha *et al.*, 2018).

Disruption of the tissue or skin barrier by loss of continuity and integrity is referred to as wounds (Lazarus *et al.*, 1994; Shankar *et al.*, 2014). Wounds can be divided into two types, i.e., acute and chronic wounds (Shankar *et al.*, 2014; Whitney, 2005). At the time of injury, it is crucial for the skin to re-establish the function through rapid regeneration and gap-filling, which is generally known as a wound healing process (Landén *et al.*, 2016). The process of wound healing is a dynamic

interdisciplinary procedure involving many molecular and cellular events such as the removal of fibrin-fibronectin, the formation of new blood vessels, and contraction of the wound (El-Bahy *et al.*, 2018). This process is comprised of four interrelated and overlapping phases, namely haemostasis, inflammation, proliferation, and tissue remodelling (Malone-Povolny *et al.*, 2019). For normal wound healing, coordination is necessary among various cell types to re-establish their normal function by coordinating keratinocytes re-epithelialisation and the reconstruction of the dermis by fibroblasts (Schmidt and Horsley, 2013).

The wound that does not pursue a deliberate arrangement of healing and takes more time to recover is referred to as a chronic wound (Järbrink *et al.*, 2017; Lazarus *et al.*, 1994). Chronic wound tends to be trapped in one or more stages of wound healing. For instance, chronic wounds frequently remain in the inflammatory phase for a long time (Cho *et al.*, 2019; Eaglstein and Falanga, 1997; Eming *et al.*, 2014). Chronic wounds can be categorised as diabetic ulcers, vascular leg ulcers, and pressure ulcers (Nunan *et al.*, 2014; Whitney, 2005). Moreover, diabetes is one of the most noticeable factors responsible for wound healing impairment (Tsourdi *et al.*, 2013). Additionally, diabetic patients tend to develop chronic wounds (also known as diabetic ulcers) due to elevated blood glucose, destructive blood circulation, infection, and prolonged inflammation (Greenhalgh, 2003; Guo and Dipietro, 2010). The molecular mechanism delay the healing of chronic diabetic wounds is a complex process, and the aetiology is still poorly understood (Patel *et al.*, 2019).

Chronic diabetic wounds are reported to be difficult to cure properly. Hence, for successful wound treatment, it is crucial to identify the aetiology and local systemic factors of chronic diabetic wounds that may be responsible for poor wound healing (Werdin *et al.*, 2009). Currently, various approaches for the treatment of chronic diabetic wounds such as infection treatment, hyperglycaemic control, wound debridement, wound dressing, hyperbaric oxygen therapy, skin grafts and bioengineered skin, negative pressure wound therapy and growth factors have been introduced and applied clinically (Rekha *et al.*, 2018; Yazdanpanah *et al.*, 2015). It should be noted that several wound healing treating agents (creams, ointment and

emulsions) are derived from natural remedies (Oguntibeju, 2019; Pereira and Bartolo, 2016).

Many plants have been experimentally used in traditional medicine to treat skin ailments, such as wounds and injuries (Abdulla *et al.*, 2010). Several plants, such as *Centella asiatica, Moringa oleifera, Piper betel, Curcuma aromatica* and *Ficus deltoidea*, have been reported elsewhere for their use in the treatment of wounds in Malaysia (Agyare *et al.*, 2016). *F. deltoidea,* locally known as Mas cotek or Misletoe fig, is an evergreen shrub found in Malaysia with large spoon-shaped leaves and bear spherical to round-shaped fruit (Hanafi *et al.*, 2017). Several studies have shown the importance of *F. deltoidea* is a significant source of antioxidants and a variety of phytochemical compounds, such as polyphenol, flavonoids and tannins (Abrahim *et al.*, 2018; Misbah *et al.*, 2013). The anti-inflammatory, antioxidant, antinociceptive, and wound healing activity of *F. deltoidea* has been studied through *in vivo* and *in vitro* approaches. Such studies have shown that the extract of *F. deltoidea* contains significant amounts of antioxidants, the capability of reducing inflammatory reactions and improving dermal healing (Abdulla *et al.*, 2010; Abdullah *et al.*, 2009; Abrahim *et al.*, 2018; Misbah *et al.*, 2013; Mustaffa *et al.*, 2015; Sulaiman *et al.*, 2008; Zakaria *et al.*, 2012). An attempt is being made to study the efficacy of *F. deltoidea* leaves extract and fractions via *in vitro* wound healing activities under normal and hyperglycaemic microenvironment.

1.2 Problem Statement

Non- healing wounds are the most frustrating complications caused by diabetes mellitus that can consequently increase the risk of mortality and morbidity (Hwang *et al.*, 2017). The complications of diabetes mellitus lead to numerous infections, particularly foot ulcer infections (Sindhu, 2018). Approximately 19-34 % of diabetic patients are expected to be affected by diabetic foot ulcers in their lifespan (Everett and Mathioudakis, 2018). Different treatment strategies such as pressure offloading, tissue debridement, antibiotics, skin grafting and growth factors have been used to overcome this non-healing issue (Cho *et al.*, 2019; Patel *et al.*, 2019). Despite their

promising effects on diabetic wound healing, these treatments show variations in healing effects, including extended healing time, short half-life, high cost, increased tolerance to bacteria, and potential cancer risk (Cho *et al.*, 2019; Pereira and Bártolo, 2016). It indicates that there is still a crucial need to develop such treatment approaches that accelerate the healing of chronic diabetic wounds.

Several studies have been reported that herbal medicine can be used to treat diabetic wounds (Teplicki *et al.*, 2018; Tiwary *et al.*, 2015). It is believed that the medicinal plant has fewer side effects and less toxic as compared to conventional therapeutic agents (Oguntibeju, 2019). The utilisation of plant extracts with a known anti-inflammatory, antioxidant, antimicrobial, and wound healing activities may be an alternative in diabetic wound treatment. *F. deltoidea,* for an example, has several significant pharmacological properties, such as anti-inflammatory, antioxidant, antidiabetic, anticancer, and wound healing activity (Abdulla *et al.*, 2010; Abrahim *et al.*, 2018; Hanafi *et al.*, 2017; Misbah *et al.*, 2013). This plant belongs to the *Moraceae* family and can be grown in Malaysia weather (Rosnah *et al.*, 2015). The effect of *F.deltoidea* leaves crude extract was evaluated previously via *in vivo* animal model and *in vitro* study for wound healing activity under normal conditions (Abdulla *et al.*, 2010; Mustaffa *et al.*, 2015). To date, however, no study has been found to evaluate the leaves crude extract and fractions of *F. deltoidea* under a hyperglycaemic microenvironment. A hyperglycaemic microenvironment is an *in vitro* study used to mimic the microenvironment of diabetes mellitus. For this purpose, the current research is to highlight the efficacy of *F. deltoidea* leaves crude extract and fractions for the cells viability and wound healing activity via *in vitro* study on Human Skin Fibroblast (HSF1184) cells under normal and hyperglycaemic microenvironment for potential biomedical applications.

1.3 Research Objectives

The objectives of this study as following:

(a) To extract and fractionate *F. deltoidea* leaves by using 80% ethanol and chloroform as a solvent and aqueous.

(b) To determine the cytotoxicity of *F. deltoidea* plant extract and fractions on Human Skin Fibroblast (HSF1184) cell line under normal and hyperglycaemic conditions

(c) To investigate the potential wound healing activity of *F. deltoidea* plant extract and fractions on Human Skin Fibroblast (HSF1184) cell line via scratch assay under normal and hyperglycaemic conditions.

1.4 Scope of the Study

This study focuses on identifying the potential of *F. deltoidea* extract and fractions in affecting the closing of the wound gap under normal and hyperglycaemic microenvironment without causing the toxicity effects towards the cells. The research started with extracting the *F. deltoidea* dried leaves using 80% ethanol as a solvent. The ethanolic crude extract is then partitioned in different solvents (chloroform, aqueous) based on increasing polarity to get the sample's fractions. The Human Skin Fibroblast (HSF1184) cell line was subculture using DMEM media and stored for further use. The ethanolic extract, chloroform and aqueous fractions were tested for the cytotoxic activity using MTT assay under normal and hyperglycaemic microenvironment. Finally, the wound healing activity was studied using scratch assay under normal and hyperglycaemic microenvironment.

1.5 Significance of the Study

Diabetes is responsible for cellular and molecular abnormalities of connective tissues such as tensile strength, low elasticity, loss of integrity and collagen content reduction (Rodrigues *et al.*, 2019). In diabetic patients, all these abnormalities can produce impaired and non-healing skin complications. The non-healing complications of wound affects the individual, socially and economically (Pereira and Bartolo, 2016). Improved treatment of non-healing wounds could significantly decrease associated healthcare costs.

The significance of this study is to understand the potential of *F. deltoidea* extract and fractions in affecting the wound healing activity under normal and hyperglycemic microenvironments. The outcome of this study provides the potential migratory effect of HSF1184 cells treated with *F. deltoidea* leaves extract and fraction under normal and hyperglycaemic conditions. Apart from being inexpensive, abundant, and non-toxic to cells in culture, the use of *F.deltoidea* as a diabetic wound treatment needs further warrant.

REFERENCES

A'attiyyah, A., Ghazali, W. A. S. W., Ali, N. A. M., Ponnuraj, K. T., Mohamad, S., and Azlina, A. (2018). 'Phytochemical properties and traditional uses of selected medicinal plants in Malaysia: A review'. *Journal of Biomedical and Clinical Sciences (JBCS), 2*(2), 14-25.

Abdulla, M. A., Ahmed, K. A.-A., Abu-Luhoom, F. M., and Muhanid, M. (2010). 'Role of Ficus deltoidea extract in the enhancement of wound healing in experimental rats'. *Biomedical Research, 21*(3), 241-245.

Abdullah, Z., Hussain, K., Ismail, Z., and Ali, R. M. (2009). 'Anti-inflammatory activity of standardised extracts of leaves of three varieties of Ficus deltoidea'. *International Journal of Pharmaceutical and Clinical Research, 1*(3), 100-105.

Abrahim, N. N., Abdul-Rahman, P. S., and Aminudin, N. (2018). 'The antioxidant activities, cytotoxic properties, and identification of water-soluble compounds of Ficus deltoidea leaves'. *PeerJ, 6*, 1-20.

Abu Bakar, A. R., Ripen, A. M., Merican, A. F., and Mohamad, S. B. (2019). 'Enzymatic inhibitory activity of Ficus deltoidea leaf extract on matrix metalloproteinase-2, 8 and 9'. *Natural product research, 33*(12), 1765-1768.

Abubakar, A. R., and Haque, M. (2020). 'Preparation of Medicinal Plants: Basic Extraction and Fractionation Procedures for Experimental Purposes'. *Journal of pharmacy & bioallied sciences, 12*(1), 1-10.

Adam, Z., Khamis, S., Ismail, A., and Hamid, M. (2010). 'Inhibitory properties of Ficus deltoidea on α-glucosidase activity'. *Research Journal of Medicinal Plant, 4*(2), 61-75.

Adam, Z., Khamis, S., Ismail, A., and Hamid, M. (2012). 'Ficus deltoidea: A potential alternative medicine for diabetes mellitus'. *Evidence-Based Complementary and Alternative Medicine, 2012*, 1-12.

Addis, R., Cruciani, S., Santaniello, S., Bellu, E., Sarais, G., Ventura, C., Maioli, M., and Pintore, G. (2020). 'Fibroblast Proliferation and Migration in Wound Healing by Phytochemicals: Evidence for a Novel Synergic Outcome'. *International Journal of Medical Sciences, 17*(8), 1030-1042.

Adetutu, A., Morgan, W. A., and Corcoran, O. (2011). 'Ethnopharmacological survey and in vitro evaluation of wound-healing plants used in South-western Nigeria'. *Journal of Ethnopharmacology, 137*(1), 50-56.

Agyare, C., Bekoe, E. O., Boakye, Y. D., Dapaah, S. O., Appiah, T., and Bekoe, S. O. (2016). Medicinal plants and natural products with demonstrated wound healing properties. In V. Alexandrescu (Ed.), *Wound Healing: New insights into Ancient Challenges* (pp. 483-530). London: InTech.

Ahmad Khan, M. S., and Ahmad, I. (2019). Chapter 1 - Herbal Medicine: Current Trends and Future Prospects. In M. S. Ahmad Khan, I. Ahmad and D. Chattopadhyay (Eds.), *New Look to Phytomedicine* (pp. 3-13): Academic Press.

Ahmad, V. N., and Amin, I. M. (2017). 'Anti-oral ulcer activity of Ficus deltoidea leaves extract on animal model'. *Pertanika J Sci Technol, 25*(S), 41-52.

Ahmed, A. M. (2002). 'History of diabetes mellitus'. *Saudi medical journal, 23*(4), 373-378.

Akhir, N. A. M., Chua, L. S., Majid, F. A. A., and Sarmidi, M. R. (2011). 'Cytotoxicity of aqueous and ethanolic extracts of Ficus deltoidea on human ovarian carcinoma cell line'. *Journal of Advances in Medicine and Medical Research, 1*(4), 397-409.

Alamgir, A. (2018). *Therapeutic Use of Medicinal Plants and Their Extracts: Volume 1*. Cham,: Springer.

Alberti, K. G. M. M., and Zimmet, P. Z. (1998). 'Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation'. *Diabetic medicine, 15*(7), 539-553.

Alwahid, A. A., Yusoff, W. M. W., Nor, N. S. M., and Ibrahim, N. (2015) Cytotoxicity and phytochemical analyses of Orthosiphon stamineus leaves and flower extracts. *AIP Conference Proceedings*. 15-16 September. Selangor, Malaysia, AIP Publishing LLC 030010.

Amiera, Z., Nihayah, M., Wahida, I. F., and Rajab, N. (2014). 'Phytochemical characteristic and uterotonic effect of aqueous extract of'. *Pak J Biol Sci, 17*(9), 1046-1051.

Arora, M. (2013). 'Cell culture media: a review'. *Mater Methods, 3*(175), 1-29

Ashraf, K., Halim, H., Lim, S. M., Ramasamy, K., and Sultan, S. (2020). 'In vitro antioxidant, antimicrobial and antiproliferative studies of four different extracts of Orthosiphon stamineus, Gynura procumbens and Ficus deltoidea'. *Saudi journal of biological sciences, 27*(1), 417-432.

Association, A. D. (2010). 'Diagnosis and classification of diabetes mellitus'. *Diabetes care, 33*(Supplement 1), 62-69.

Association, A. D. (2014). 'Diagnosis and classification of diabetes mellitus'. *Diabetes care, 37*(Supplement 1), 81-90.

Association, A. D. (2015). '2. Classification and diagnosis of diabetes'. *Diabetes care, 38*(Supplement 1), 8-16.

Au - Pinto, B. I., Au - Cruz, N. D., Au - Lujan, O. R., Au - Propper, C. R., and Au - Kellar, R. S. (2019). 'In Vitro Scratch Assay to Demonstrate Effects of Arsenic on Skin Cell Migration'. *JoVE*(144), 1-11.

Ayob, Z., Abd Samad, A., and Bohari, S. P. M. (2013). 'Cytotoxicity activities in local Justicia gendarussa crude extracts against human cancer cell lines'. *Jurnal Teknologi, 64*(2), 45-52.

Ayuk, S. M., Abrahamse, H., and Houreld, N. N. (2016). 'The Role of Matrix Metalloproteinases in Diabetic Wound Healing in relation to Photobiomodulation'. *Journal of diabetes research, 2016*, 1-9.

Bagchi, D., and Nair, S. (2018). *Nutritional and therapeutic interventions for diabetes and metabolic syndrome* (second edition ed.). Kidlington: John fedor.

Bahuguna, A., Khan, I., Bajpai, V. K., and Kang, S. C. (2017). 'MTT assay to evaluate the cytotoxic potential of a drug'. *Bangladesh Journal of Pharmacology, 12*(2), 115-118.

Bainbridge, P. (2013). 'Wound healing and the role of fibroblasts'. *Journal of wound care, 22*(8), 407-412.

Bakar, A., Izzany, F., Bakar, A., Fadzelly, M., Abdullah, N., Endrini, S., and Rahmat, A. (2018). 'A Review of Malaysian Medicinal Plants with Potential Anti-Inflammatory Activity'. *Advances in pharmacological sciences, 2018*. 1-13.

Balekar, N., Katkam, N. G., Nakpheng, T., Jehtae, K., and Srichana, T. (2012). 'Evaluation of the wound healing potential of Wedelia trilobata (L.) leaves'. *Journal of Ethnopharmacology, 141*(3), 817-824.

Ballesteros, L. F., Teixeira, J. A., and Mussatto, S. I. (2014). 'Selection of the solvent and extraction conditions for maximum recovery of antioxidant phenolic compounds from coffee silverskin'. *Food and bioprocess technology, 7*(5), 1322-1332.

Barku, V. Y., Boye, A., and Ayaba, S. (2013). 'Phytochemical screening and assessment of wound healing activity of the leaves of Anogeissus leiocarpus'. *European Journal of Experimental Biology, 3*(4), 18-25.

Baynes, H. W. (2015). 'Classification, pathophysiology, diagnosis and management of diabetes mellitus'. *J diabetes metab, 6*(5), 1-9.

Baz, B., Riveline, J.-P., and Gautier, J.-F. (2016). 'Gestational diabetes mellitus: definition, aetiological and clinical aspects'. *Eur J Endocrinol, 174*(2), R43-51.

Berlanga-Acosta, J., Schultz, G. S., López-Mola, E., Guillen-Nieto, G., García-Siverio, M., and Herrera-Martínez, L. (2013). 'Glucose toxic effects on granulation tissue productive cells: the diabetics' impaired healing'. *BioMed research international, 2013*, 1-15.

Blakytny, R., and Jude, E. B. (2009). 'Altered molecular mechanisms of diabetic foot ulcers'. *The international journal of lower extremity wounds, 8*(2), 95-104.

Boateng, J. S., Matthews, K. H., Stevens, H. N., and Eccleston, G. M. (2008). 'Wound healing dressings and drug delivery systems: a review'. *Journal of pharmaceutical sciences, 97*(8), 2892-2923.

Boniakowski, A. E., Kimball, A. S., Jacobs, B. N., Kunkel, S. L., and Gallagher, K. A. (2017). 'Macrophage-mediated inflammation in normal and diabetic wound healing'. *The Journal of Immunology, 199*(1), 17-24.

Brereton, M. F., Rohm, M., Shimomura, K., Holland, C., Tornovsky-Babeay, S., Dadon, D., Iberl, M., Chibalina, M. V., Lee, S., Glaser, B., Dor, Y., Rorsman, P., Clark, A., and Ashcroft, F. M. (2016). 'Hyperglycaemia induces metabolic dysfunction and glycogen accumulation in pancreatic β-cells'. *Nature communications, 7*(1), 1-15.

Brunetti, A., Chiefari, E., and Foti, D. (2014). 'Recent advances in the molecular genetics of type 2 diabetes mellitus'. *World journal of diabetes, 5*(2), 128-140.

Buranasin, P., Mizutani, K., Iwasaki, K., Pawaputanon Na Mahasarakham, C., Kido, D., Takeda, K., and Izumi, Y. (2018). 'High glucose-induced oxidative stress impairs proliferation and migration of human gingival fibroblasts'. *PloS one, 13*(8), 1-19

Cañedo-Dorantes, L., and Cañedo-Ayala, M. (2019). 'Skin acute wound healing: a comprehensive review'. *International journal of inflammation, 2019*, 1-15.

Canivell, S., and Gomis, R. (2014). 'Diagnosis and classification of autoimmune diabetes mellitus'. *Autoimmun Rev, 13*(4-5), 403-407.

Care, D. (2018). 'Medical Care in Diabetesd2018'. *Diabetes care, 41*(1), 105-118.

Cerf, M. E. (2013). 'Beta cell dysfunction and insulin resistance'. *Frontiers in endocrinology, 4*(37), 1-12.

Chen, Q., Jin, M., Yang, F., Zhu, J., Xiao, Q., and Zhang, L. (2013). 'Matrix metalloproteinases: inflammatory regulators of cell behaviors in vascular formation and remodeling'. *Mediators of inflammation, 2013*, 1-14.

Cherng, J.-H. (2018). The strategies of natural polysaccharide in wound healing. In k. H. Dogan (Ed.), *Wound Healing-Current Perspectives* (pp. 65 - 80). london: IntechOpen.

Chhabra, S., Chhabra, N., Kaur, A., and Gupta, N. (2017). 'Wound Healing Concepts in Clinical Practice of OMFS'. *Journal of maxillofacial and oral surgery, 16*(4), 403-423.

Cho, H., Blatchley, M. R., Duh, E. J., and Gerecht, S. (2019). 'Acellular and cellular approaches to improve diabetic wound healing'. *Advanced drug delivery reviews, 146*, 267-288.

Choo, C., Sulong, N., Man, F., and Wong, T. (2012). 'Vitexin and isovitexin from the leaves of Ficus deltoidea with in-vivo α-glucosidase inhibition'. *Journal of ethnopharmacology, 142*(3), 776-781.

Corrine , Packer;, Sonani;, B., and Manna, B. (2020, July 15, 2020.). Diabetic Ulcer. from https://www.ncbi.nlm.nih.gov/books/NBK499887/

Das, S., and Baker, A. B. (2016). 'Biomaterials and Nanotherapeutics for Enhancing Skin Wound Healing'. *Frontiers in bioengineering and biotechnology, 4*(82), 1-20.

Demidova-Rice, T. N., Hamblin, M. R., and Herman, I. M. (2012). 'Acute and impaired wound healing: pathophysiology and current methods for drug delivery, part 1: normal and chronic wounds: biology, causes, and approaches to care'. *Advances in skin & wound care, 25*(7), 304-314.

Dennedy, M., Rizza, R., and Dinneen, S. (2016). 'Chapter 38–Classification and Diagnosis of Diabetes Mellitus'. *Endocrinol Adult Pediatr*, *1*(10), 662-671.

Desta, T., Li, J., Chino, T., and Graves, D. T. (2010). 'Altered fibroblast proliferation and apoptosis in diabetic gingival wounds'. *Journal of dental research, 89*(6), 609-614.

Deveci, M., Gilmont, R., Dunham, W., Mudge, B., Smith, D., and Marcelo, C. (2005). 'Glutathione enhances fibroblast collagen contraction and protects keratinocytes from apoptosis in hyperglycaemic culture'. *British Journal of Dermatology, 152*(2), 217-224.

Dhivya, S., Padma, V. V., and Santhini, E. (2015). 'Wound dressings - a review'. *BioMedicine, 5*(4), 22-22.

Dinh, T., Tecilazich, F., Kafanas, A., Doupis, J., Gnardellis, C., Leal, E., Tellechea, A., Pradhan, L., Lyons, T. E., and Giurini, J. M. (2012). 'Mechanisms involved in the development and healing of diabetic foot ulceration'. *Diabetes, 61*(11), 2937-2947.

Dzolin, S., Aris, S. R. S., Ahmad, R., and Zain, M. M. (2010). *Radical scavenging and neurotoxicity of four varieties of Ficus deltoidea.* Paper presented at the 2010 International conference on science and social research (CSSR 2010), 11-15.

Eaglstein, W. H., and Falanga, V. (1997). 'Chronic wounds'. *Surgical Clinics, 77*(3), 689-700.

Ekoé, J.-M. (2019). Diagnosis and Classification of Diabetes Mellitus. In I. Huhtaniemi and L. Martini (Eds.), *Encyclopedia of Endocrine Diseases (Second Edition)* (pp. 105-109). Oxford: Academic Press.

El-Bahy, A. A. Z., Aboulmagd, Y. M., and Zaki, M. (2018). 'Diabetex: a novel approach for diabetic wound healing'. *Life sciences, 207*, 332-339.

Ellis, S., Lin, E. J., and Tartar, D. (2018). 'Immunology of wound healing'. *Current dermatology reports, 7*(4), 350-358.

Eming, S. A., Martin, P., and Tomic-Canic, M. (2014). 'Wound repair and regeneration: mechanisms, signaling, and translation'. *Sci Transl Med, 6*(265), 265-266.

Engelgau, M. M. (2004). 'Diabetes diagnostic criteria and impaired glycemic states: evolving evidence base'. *Clinical Diabetes, 22*(2), 69-70.

Ennis, W. J., and Hill, D. (2016). 'Wound healing: a comprehensive wound assessment and treatment approach'. *Skin Tissue Eng Regen Med, 239*, 75-81.

Enoch, S., and Leaper, D. J. (2008). 'Basic science of wound healing'. *Surgery (Oxford), 26*(2), 31-37.

Ernst, E. (2005). 'The efficacy of herbal medicine–an overview'. *Fundamental & clinical pharmacology, 19*(4), 405-409.

Everett, E., and Mathioudakis, N. (2018). 'Update on management of diabetic foot ulcers'. *Annals of the New York Academy of Sciences, 1411*(1), 153-165.

Fabricant, D. S., and Farnsworth, N. R. (2001). 'The value of plants used in traditional medicine for drug discovery'. *Environ Health Perspect, 109 Suppl 1*(Suppl 1), 69-75.

Falanga, V. (2005). 'Wound healing and its impairment in the diabetic foot'. *The Lancet, 366*(9498), 1736-1743.

Farhana, M. H., Fauzi, P. A., and Lim, H. (2007). 'Market potential for mas cotek (ficus deltoidea) products in selected states in peninsular malaysia'. *Forest Research Institute Malaysia (FRIM),* 132 - 136.

Farrar, D. (2016). 'Hyperglycemia in pregnancy: prevalence, impact, and management challenges'. *International journal of women's health, 8*, 519-527.

Farsi, E., Ahmad, M., Hor, S. Y., Ahamed, M. B. K., Yam, M. F., and Asmawi, M. Z. (2014). 'Standardized extract of Ficus deltoidea stimulates insulin secretion and blocks hepatic glucose production by regulating the expression of glucose-metabolic genes in streptozitocin-induced diabetic rats'. *BMC complementary and alternative medicine, 14*(1), 1-13.

Fatihah, H. N. N., Nashriyah, M., Zaimah, A. R. N., Khairil, M., and Ali, A. M. (2014). 'Leaf morphology and anatomy of 7 varieties of Ficus deltoidea (Moraceae)'. *Turkish Journal of Botany, 38*(4), 677-685.

Fatimah, Z., Mahmood, A., Hapipah, M., Suzita, M., and Salmah, I. (2009). 'Anti-ulcerogenic activity of aqueous extract of Ficus deltoidea against ethanol-induced gastric mucosal injury in rats'. *Research Journal of Medical Sciences, 3*(2), 42-46.

Forouhi, N. G., and Wareham, N. J. (2019). 'Epidemiology of diabetes'. *Medicine, 47*(1), 22-27.

Frykberg, R. G., and Banks, J. (2015). 'Challenges in the treatment of chronic wounds'. *Advances in wound care, 4*(9), 560-582.

Fui, L. W., Lok, M. P. W., Govindasamy, V., Yong, T. K., Lek, T. K., and Das, A. K. (2019). 'Understanding the multifaceted mechanisms of diabetic wound healing and therapeutic application of stem cells conditioned medium in the healing process'. *J Tissue Eng Regen Med, 13*(12), 2218-2233.

Gantwerker, E. A., and Hom, D. B. (2011). 'Skin: histology and physiology of wound healing'. *Facial Plast Surg Clin North Am, 19*(3), 441-453.

Gavin, J. R., Alberti, K., Davidson, M. B., and Defronzo, R. A. (1997). 'Report of the expert committee on the diagnosis and classification of diabetes mellitus'. *Diabetes care, 20*(7), 1183-1197.

Ghosh, P. K., and Gaba, A. (2013). 'Phyto-extracts in wound healing'. *Journal of Pharmacy & Pharmaceutical Sciences, 16*(5), 760-820.

Gkogkolou, P., and Böhm, M. (2012). 'Advanced glycation end products: Key players in skin aging?'. *Dermato-endocrinology, 4*(3), 259-270.

Gonzalez, A. C. d. O., Costa, T. F., Andrade, Z. d. A., and Medrado, A. R. A. P. (2016). 'Wound healing-A literature review'. *Anais brasileiros de dermatologia, 91*(5), 614-620.

Gotsulyak, N. Y., Kosach, V. R., Cherednyk, O. V., Tykhonkova, I. O., and Khoruzhenko, A. I. (2014). 'Optimization of cell motility evaluation in scratch assay'. *Biopolymers and cell*, *30* (3), 223-228.

Greenhalgh, D. G. (2003). 'Wound healing and diabetes mellitus'. *Clinics in plastic surgery, 30*(1), 37-45.

Greydanus, D. E., and Hofmann, A. D. (1979). 'Psychological factors in diabetes mellitus: A review of the literature with emphasis on adolescence'. *American Journal of Diseases of Children, 133*(10), 1061-1066.

Group, N. D. D. (1979). 'Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance'. *diabetes, 28*(12), 1039-1057.

Guo, S., and Dipietro, L. A. (2010). 'Factors Affecting Wound Healing'. *Journal of Dental Research, 89*(3), 219-229.

Hakiman, M., and Maziah, M. (2009). 'Non enzymatic and enzymatic antioxidant activities in aqueous extract of different Ficus deltoidea accessions'. *Journal of Medicinal Plants Research, 3*(3), 120-131.

Halliwell, B. (1995). 'How to characterize an antioxidant: an update'. *Biochemical Society Symposia, 61*, 73-101.

Hanafi, M. M., Afzan, A., Yaakob, H., Aziz, R., Sarmidi, M. R., Wolfender, J.-L., and Prieto, J. M. (2017). 'In vitro pro-apoptotic and anti-migratory effects of Ficus deltoidea L. Plant extracts on the human prostate cancer cell lines PC3'. *Frontiers in pharmacology, 8*, 1-20.

Hariono, M., Yuliani, S. H., Istyastono, E. P., Riswanto, F. D. O., and Adhipandito, C. F. (2018). 'Matrix metalloproteinase 9 (MMP9) in wound healing of diabetic foot ulcer: Molecular target and structure-based drug design'. *Wound Medicine, 22*, 1-13.

Hasham, R., Choi, H.-K., Sarmidi, M. R., and Park, C.-S. (2013). 'Protective effects of a Ficus deltoidea (Mas cotek) extract against UVB-induced photoageing in skin cells'. *Biotechnology and Bioprocess Engineering, 18*(1), 185-193.

Hehenberger, K., Heilborn, J. D., Brismar, K., and Hansson, A. (1998). 'Inhibited proliferation of fibroblasts derived from chronic diabetic wounds and normal dermal fibroblasts treated with high glucose is associated with increased formation of L-lactate'. *Wound repair and regeneration, 6*(2), 135-141.

Ho, B. K., Jasvindar, K., Gurpreet, K., Ambigga, D., Suthahar, A., Cheong, S. M., and Lim, K. H. (2014). 'Prevalence, awareness, treatment and control of diabetes mellitus among the elderly: The 2011 National Health and Morbidity Survey, Malaysia'. *Malaysian family physician : the official journal of the Academy of Family Physicians of Malaysia, 9*(3), 12-19.

Huang, C., Jacobson, K., and Schaller, M. D. (2004). 'A role for JNK-paxillin signaling in cell migration'. *Cell Cycle, 3*(1), 4-6.

Hurtado, M. D., and Vella, A. (2019). 'What is type 2 diabetes?'. *Medicine, 47*(1), 10-15.

Hussein, Z., Taher, S. W., Singh, H. K. G., and Swee, W. C. S. (2015). 'Diabetes care in Malaysia: problems, new models, and solutions'. *Annals of global health, 81*(6), 851-862.

Hwang, D. J., Lee, K. M., Park, M. S., Choi, S. H., Park, J. I., Cho, J. H., Park, K. H., and Woo, S. J. (2017). 'Association between diabetic foot ulcer and diabetic retinopathy'. *PloS one, 12*(4), 1-14.

Ilyanie, Y., Wong, T. W., and Choo, C. Y. (2011). 'Evaluation of hypoglycemic activity and toxicity profiles of the leaves of Ficus deltoidea in rodents'. *Journal of Complementary and Integrative Medicine, 8*(1), 1-16.

Jagadish, M., McNally, M. M., Heidel, R. E., Teffeteller, S., Arnold, J. D., Freeman, M., Stevens, S. L., Grandas, O. H., and Goldman, M. H. (2016). 'Diabetic foot ulcers: the importance of patient comorbidity recognition and total contact casting in successful wound care'. *The American Surgeon, 82*(8), 733-736.

Jain, A. K., Singh, D., Dubey, K., Maurya, R., Mittal, S., and Pandey, A. K. (2018). Chapter 3 - Models and Methods for In Vitro Toxicity. In A. Dhawan and S. Kwon (Eds.), *In Vitro Toxicology* (pp. 45-65): Academic Press.

Jamal, M., Afifah, N., Ahmad, K., and Nafiah, M. A. (2017). 'Phytochemical studies of ficus deltoidea var kunstleri'. *Asian Journal of Chemistry, 29*(7), 1451-1454.

Janis, J. E., and Harrison, B. (2014). 'Wound healing: part I. Basic science'. *Plastic and reconstructive surgery, 133*(2), 199-207.

Järbrink, K., Ni, G., Sönnergren, H., Schmidtchen, A., Pang, C., Bajpai, R., and Car, J. (2017). 'The humanistic and economic burden of chronic wounds: a protocol for a systematic review'. *Systematic reviews, 6*(1), 1-7.

Jeeva, J. S., Sunitha, J., Ananthalakshmi, R., Rajkumari, S., Ramesh, M., and Krishnan, R. (2015). 'Enzymatic antioxidants and its role in oral diseases'. *Journal of pharmacy & bioallied sciences, 7*(Suppl 2), 331-333.

Jhamb, S., Vangaveti, V. N., and Malabu, U. H. (2016). 'Genetic and molecular basis of diabetic foot ulcers: clinical review'. *Journal of tissue viability, 25*(4), 229-236.

Jones, W. P., and Kinghorn, A. D. (2012). 'Extraction of plant secondary metabolites'. *Methods in Molecular Biology, 864*, 341-366.

Kalman, D. S., Schwartz, H. I., Feldman, S., and Krieger, D. R. (2013). 'Efficacy and safety of Elaeis guineensis and Ficus deltoidea leaf extracts in adults with pre-diabetes'. *Nutrition journal, 12*(1), 1-7.

Kamal, M. S. A., Ismail, N. H., Satar, N. A., Azis, N. A., Radjeni, Z., Mohammad Noor, H. S., Kasim, N., and Singh, H. (2019). 'Standardized ethanol-water extract of Ficus deltoidea Angustifolia reduces blood pressure in spontaneously hypertensive rats'. *Clinical and Experimental Hypertension, 41*(5), 444-451.

Kaul, K., Tarr, J. M., Ahmad, S. I., Kohner, E. M., and Chibber, R. (2013). Introduction to diabetes mellitus. In *Diabetes* (pp. 1-11): Springer.

Kharroubi, A. T., and Darwish, H. M. (2015). 'Diabetes mellitus: The epidemic of the century'. *World journal of diabetes, 6*(6), 850-867.

Kiya, K., and Kubo, T. (2019). 'Neurovascular interactions in skin wound healing'. *Neurochemistry international, 125*, 144-150.

Kole, D., Ambady, S., Page, R. L., and Dominko, T. (2014). 'Maintenance of multipotency in human dermal fibroblasts treated with Xenopus laevis egg extract requires exogenous fibroblast growth factor-2'. *Cellular reprogramming, 16*(1), 18-28.

Kruse, C. R., Singh, M., Sørensen, J. A., Eriksson, E., and Nuutila, K. (2016). 'The effect of local hyperglycemia on skin cells in vitro and on wound healing in euglycemic rats'. *Journal of Surgical Research, 206*(2), 418-426.

Kunkemoeller, B., and Kyriakides, T. R. (2017). 'Redox Signaling in Diabetic Wound Healing Regulates Extracellular Matrix Deposition'. *Antioxidants & redox signaling, 27*(12), 823-838.

Kyaw, B. M., Jaerbrink, K., Martinengo, L., Car, J., Harding, K., and Schmidtchen, A. (2018). 'Need for Improved Definition of'. *Acta dermato-venereologica, 98*(1-2), 157-158.

Laios, K., Karamanou, M., Saridaki, Z., and Androutsos, G. (2012). 'Aretaeus of Cappadocia and the first description of diabetes'. *Hormones, 11*(1), 109-113.

Landén, N. X., Li, D., and Ståhle, M. (2016). 'Transition from inflammation to proliferation: a critical step during wound healing'. *Cellular and Molecular Life Sciences, 73*(20), 3861-3885.

Latif, M. A., Ibrahim, F. W., Arshad, S. A., and Hui, C. K. (2019). 'Cytotoxicity, Proliferation and Migration Rate Assessments of Human Dermal Fibroblast Adult Cells using Zingiber zerumbet Extract'. *Sains Malaysiana, 48*(1), 121-127.

Lazarus, G. S., Cooper, D. M., Knighton, D. R., Margolis, D. J., Percoraro, R. E., Rodeheaver, G., and Robson, M. C. (1994). 'Definitions and guidelines for assessment of wounds and evaluation of healing'. *Wound repair and regeneration, 2*(3), 165-170.

Lerman, O. Z., Galiano, R. D., Armour, M., Levine, J. P., and Gurtner, G. C. (2003). 'Cellular dysfunction in the diabetic fibroblast: impairment in migration, vascular endothelial growth factor production, and response to hypoxia'. *The American journal of pathology, 162*(1), 303-312.

Li, P., Ma, Z., Yu, Y., Hu, X., Zhou, Y., and Song, H. (2019). 'FER promotes cell migration via regulating JNK activity'. *Cell proliferation, 52*(5), 1-7.

Lindbladh, I., Svärd, A. A., and Lernmark, Å. (2020). Autoimmune (Type 1) Diabetes. In *The Autoimmune Diseases* (pp. 769-787): Elsevier.

Lip, J. M., Hisham, D. N., Zaidi, J. A., Musa, Y., Ahmad, A., Normah, A., and Sharizan, A. (2009). 'Isolation and identification of moretenol from Ficus deltoidea leaves'. *Journal of Tropical Agriculture and Food Science, 37*(2), 195-201.

Liu, Y., Min, D., Bolton, T., Nubé, V., Twigg, S. M., Yue, D. K., and McLennan, S. V. (2009). 'Increased matrix metalloproteinase-9 predicts poor wound healing in diabetic foot ulcers'. *Diabetes care, 32*(1), 117-119.

Lobmann, R., Ambrosch, A., Schultz, G., Waldmann, K., Schiweck, S., and Lehnert, H. (2002). 'Expression of matrix-metalloproteinases and their inhibitors in the wounds of diabetic and non-diabetic patients'. *Diabetologia, 45*(7), 1011-1016.

Lobo, V., Patil, A., Phatak, A., and Chandra, N. (2010). 'Free radicals, antioxidants and functional foods: Impact on human health'. *Pharmacognosy reviews, 4*(8), 118-126.

Lowell, B. B., and Shulman, G. I. (2005). 'Mitochondrial dysfunction and type 2 diabetes'. *Science, 307*(5708), 384-387.

Malone-Povolny, M. J., Maloney, S. E., and Schoenfisch, M. H. (2019). 'Nitric oxide therapy for diabetic wound healing'. *Advanced healthcare materials, 8*(12), 1-18.

Maraschin, J. d. F. (2013). Classification of Diabetes. In S. I. Ahmad (Ed.), *Diabetes: An Old Disease, a New Insight* (pp. 12-19). New York, NY: Springer New York.

Maroon, J. C., Bost, J. W., and Maroon, A. (2010). 'Natural anti-inflammatory agents for pain relief'. *Surgical neurology international, 1*(80), 1-10.

Martinotti, S., and Ranzato, E. (2019). Scratch wound healing assay. In *Epidermal Cells* (pp. 225-229). New York: Springer.

Martins, V. L., Caley, M., and O'Toole, E. A. (2013). 'Matrix metalloproteinases and epidermal wound repair'. *Cell and tissue research, 351*(2), 255-268.

Mat, N., Rosni, N. A., Ab Rashid, N. Z., Haron, N., Nor, Z. M., Nudin, N. F. H., Yunus, A. G., and Ali, A. M. (2012). 'Leaf morphological variations and heterophylly in Ficus deltoidea Jack (Moraceae)'. *Sains Malaysiana, 41*(5), 527-538.

Mirghani Dirar, A., and Doupis, J. (2017). 'Gestational diabetes from A to Z'. *World journal of diabetes, 8*(12), 489-511.

Misbah, H., Aziz, A. A., and Aminudin, N. (2013). 'Antidiabetic and antioxidant properties of Ficus deltoidea fruit extracts and fractions'. *BMC complementary and alternative medicine, 13*(1), 1-12.

Mohammad, N., Wei, Y. K., and Bakar, N. F. A. (2012). 'Determination of mineral content in the Ficus deltoidea leaves'. *Jurnal Sains Kesihatan Malaysia (Malaysian Journal of Health Sciences), 10*(2), 25-29.

Mohd Hafizudin. Z., Roslina. A., Nor Amna A'liah. M. N., and O, N. R. N. (2019). Transformation of Herbal Industry in Malaysia.

Monsuur, H. N., Boink, M. A., Weijers, E. M., Roffel, S., Breetveld, M., Gefen, A., van den Broek, L. J., and Gibbs, S. (2016). 'Methods to study differences in cell mobility during skin wound healing in vitro'. *Journal of biomechanics, 49*(8), 1381-1387.

Moseley, R., Hilton, J. R., Waddington, R. J., Harding, K. G., Stephens, P., and Thomas, D. W. (2004). 'Comparison of oxidative stress biomarker profiles between acute and chronic wound environments'. *Wound repair and regeneration, 12*(4), 419-429.

Mosmann, T. (1983). 'Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays'. *Journal of immunological methods, 65*(1-2), 55-63.

Mukherjee, S., Chowdhury, Debabrata, Kotcherlakota, Rajesh, Patra, Sujata, B, Vinothkumar, Bhadra, Manika Pal, Sreedhar, Bojja Patra, Chitta Ranjan. (2014). 'Potential theranostics application of bio-synthesized silver nanoparticles (4-in-1 system)'. *Theranostics, 4*(3), 316-335.

Muller, M., Trocme, C., Lardy, B., Morel, F., Halimi, S., and Benhamou, P. Y. (2008). 'Matrix metalloproteinases and diabetic foot ulcers: the ratio of MMP-1 to TIMP-1 is a predictor of wound healing'. *Diabetic medicine : a journal of the British Diabetic Association, 25*(4), 419-426.

Mustaffa, N. A. A. W., Hasham, R., and Sarmidi, M. R. (2015). 'An in vitro study of wound healing activity of Ficus deltoidea leaf extract'. *Jurnal Teknologi, 77*(3), 67-72.

Mustapha, F. I., Azmi, S., Manaf, M. R. A., Hussein, Z., Mahir, J., Ismail, F., Aizuddin, A. N., and Goh, A. (2017). 'What are the direct medical costs of managing Type 2 Diabetes Mellitus in Malaysia'. *Med J Malaysia, 72*(5), 271-277.

Naz, R., Ayub, H., Nawaz, S., Islam, Z. U., Yasmin, T., Bano, A., Wakeel, A., Zia, S., and Roberts, T. H. (2017). 'Antimicrobial activity, toxicity and anti-inflammatory potential of methanolic extracts of four ethnomedicinal plant species from Punjab, Pakistan'. *BMC complementary and alternative medicine, 17*(1), 302-302.

Negut, I., Grumezescu, V., and Grumezescu, A. M. (2018). 'Treatment Strategies for Infected Wounds'. *Molecules (Basel, Switzerland), 23*(9), 1-23.

Nguyen, A. V., and Soulika, A. M. (2019). 'The Dynamics of the Skin's Immune System'. *International journal of molecular sciences, 20*(8), 1-53.

Nguyen, D., Orgill, D., and Murphy, G. (2009). The pathophysiologic basis for wound healing and cutaneous regeneration. In *Biomaterials for treating skin loss* (pp. 25-57): Elsevier.

Nguyen, T. T., Mobashery, S., and Chang, M. (2016). Roles of matrix metalloproteinases in cutaneous wound healing. In V. alexandreascu (Ed.),

Wound Healing: New insights into Ancient Challenges (pp. 37 - 71). Croatia: InTech.

Nostro, A., Germanò, M. P., D'Angelo, V., Marino, A., and Cannatelli, M. A. (2000). 'Extraction methods and bioautography for evaluation of medicinal plant antimicrobial activity'. *Lett Appl Microbiol, 30*(5), 379-384.

Nunan, R., Harding, K. G., and Martin, P. (2014). 'Clinical challenges of chronic wounds: searching for an optimal animal model to recapitulate their complexity'. *Disease models & mechanisms, 7*(11), 1205-1213.

Nurdiana, S., Goh, Y. M., Ahmad, H., Dom, S. M., Azmi, N. S. a., Zin, N. S. N. M., and Ebrahimi, M. (2017). 'Changes in pancreatic histology, insulin secretion and oxidative status in diabetic rats following treatment with Ficus deltoidea and vitexin'. *BMC complementary and alternative medicine, 17*(1), 1-17.

Nurdiana, S., Idzham, A. M., Zanariah, A., and Hakim, M. M. L. (2012). 'Effect of Ficus deltoidea leaves extracts on blood clotting, sperm quality and testosterone level in alloxan-induced male diabetic rats'. *International Journal of Pharmaceutical Sciences Review and Research, 13*(1), 111-114.

Ogbole, O. O., Segun, P. A., and Adeniji, A. J. (2017). 'In vitro cytotoxic activity of medicinal plants from Nigeria ethnomedicine on Rhabdomyosarcoma cancer cell line and HPLC analysis of active extracts'. *BMC complementary and alternative medicine, 17*(1), 1-10.

Oguntibeju, O. O. (2019). 'Medicinal plants and their effects on diabetic wound healing'. *Veterinary world, 12*(5), 653-663.

Okano, Y., Masaki, H., and Sakurai, H. (2002). 'Dysfunction of dermal fibroblasts induced by advanced glycation end-products (AGEs) and the contribution of a nonspecific interaction with cell membrane and AGEs'. *J Dermatol Sci, 29*(3), 171-180.

Omar, M. H., Mullen, W., and Crozier, A. (2011). 'Identification of proanthocyanidin dimers and trimers, flavone C-glycosides, and antioxidants in Ficus deltoidea, a Malaysian herbal tea'. *Journal of agricultural and food chemistry, 59*(4), 1363-1369.

Ong, S., Ling, A., Poospooragi, R., and Moosa, S. (2011). 'Production of Flavonoid compounds in cell cultures of Ficus deltoidea as influenced by medium composition'. *International Journal of Medicinal and Aromatic Plants, 1*(2), 62-74.

Organization, W. H. (1985). *Diabetes Mellitus: Report of a WHO Study Group [meeting held in Geneva from 11 to 16 February 1985]* (No. 9241207272): World Health Organizationo. Document Number)

Ousey, K., Edward, K.-L., and Stephenson, J. (2014). 'Exploring quality of life, physical and psychosocial morbidity for patients with non-infected wounds: a pilot study'. *Wounds UK, 10*(3), 30-34.

Öztürk, F., and Ermertcan, A. T. (2011). 'Wound healing: a new approach to the topical wound care'. *Cutaneous and ocular toxicology, 30*(2), 92-99.

Patel, S., Srivastava, S., Singh, M. R., and Singh, D. (2019). 'Mechanistic insight into diabetic wounds: Pathogenesis, molecular targets and treatment strategies to pace wound healing'. *Biomedicine & Pharmacotherapy, 112*, 108615.

Peppa, M., Stavroulakis, P., and Raptis, S. A. (2009). 'Advanced glycoxidation products and impaired diabetic wound healing'. *Wound Repair and Regeneration, 17*(4), 461-472.

Pereira, R. F., and Bartolo, P. J. (2016). 'Traditional therapies for skin wound healing'. *Advances in wound care, 5*(5), 208-229.

Perez-Favila, A., Martinez-Fierro, M. L., Rodriguez-Lazalde, J. G., Cid-Baez, M. A., Zamudio-Osuna, M. d. J., Martinez-Blanco, M., Mollinedo-Montaño, F. E., Rodriguez-Sanchez, I. P., Castañeda-Miranda, R., and Garza-Veloz, I. (2019). 'Current Therapeutic Strategies in Diabetic Foot Ulcers'. *Medicina, 55*(11), 1-21.

Piñero-Piloña, A., and Raskin, P. (2001). 'Idiopathic Type 1 diabetes'. *Journal of Diabetes and its Complications, 15*(6), 328-335.

Plows, J. F., Stanley, J. L., Baker, P. N., Reynolds, C. M., and Vickers, M. H. (2018). 'The Pathophysiology of Gestational Diabetes Mellitus'. *International journal of molecular sciences, 19*(11), 1-21.

Prasetyono, T. O. (2009). 'General concept of wound healing, revisited'. *Medical Journal of Indonesia, 18*(3), 208-216.

Profyris, C., Tziotzios, C., and Do Vale, I. (2012). 'Cutaneous scarring: Pathophysiology, molecular mechanisms, and scar reduction therapeutics: Part I. The molecular basis of scar formation'. *Journal of the American Academy of Dermatology, 66*(1), 1-10.

Punthakee, Z., Goldenberg, R., and Katz, P. (2018). 'Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome'. *Canadian Journal of Diabetes, 42 Suppl 1*, 10-15.

Qing, C. (2017). 'The molecular biology in wound healing & non-healing wound'. *Chinese journal of traumatology, Zhonghua chuang shang za zhi, 20*(4), 189-193.

Rahim, F. F., Abdulrahman, S. A., Kader Maideen, S. F., and Rashid, A. (2020). 'Prevalence and factors associated with prediabetes and diabetes in fishing communities in penang, Malaysia: A cross-sectional study'. *PloS one, 15*(2), 1-17.

Ramamurthy, S., Kumarappan, C., Dharmalingam, S. R., and Sangeh, J. K. (2014). 'Phytochemical, pharmacological and toxicological properties of Ficus deltoidea: a review of a recent research'. *Annual Research & Review in Biology*, *4*(14), 2357-2371.

Rao, A. (2010). 'How many medicinal plant species in Malay Peninsula?'. *Journal of Tropical Medicinal Plants, 11*(1), 13-26.

Reece, E. A., Leguizamón, G., and Wiznitzer, A. (2009). 'Gestational diabetes: the need for a common ground'. *The Lancet, 373*(9677), 1789-1797.

Reinke, J. M., and Sorg, H. (2012). 'Wound Repair and Regeneration'. *European Surgical Research, 49*(1), 35-43.

Rekha, P.-D., Rao, S. S., Sahana, T. G., and Prabhu, A. (2018). 'Diabetic wound management'. *British journal of community nursing, 23*(Sup9), 16-22.

Reynolds, J. F., Noakes, T. D., Schwellnus, M. P., Windt, A., and Bowerbank, P. (1995). 'Non-steroidal anti-inflammatory drugs fail to enhance healing of acute hamstring injuries treated with physiotherapy'. *S Afr Med J, 85*(6), 517-522.

Riss, T. L., Moravec, R. A., Niles, A. L., Duellman, S., Benink, H. A., Worzella, T. J., and Minor, L. (2016). Cell viability assays. In *Assay Guidance Manual [Internet]*: Eli Lilly & Company and the National Center for Advancing Translational Sciences.

Rizvi, S., Raza, S. T., Rahman, Q., and Mahdi, F. (2016). 'Role of GNB3, NET, KCNJ11, TCF7L2 and GRL genes single nucleotide polymorphism in the risk prediction of type 2 diabetes mellitus'. *3 Biotech, 6*(2), 1-9.

Robards, K., Prenzler, P. D., Tucker, G., Swatsitang, P., and Glover, W. (1999). 'Phenolic compounds and their role in oxidative processes in fruits'. *Food Chemistry, 66*(4), 401-436.

Rodrigues, M., Kosaric, N., Bonham, C. A., and Gurtner, G. C. (2019). 'Wound Healing: A Cellular Perspective'. *Physiological reviews, 99*(1), 665-706.

Rosnah, J., Khandaker, M. M., and Boyce, A. N. (2015). 'Ficus deltoidea: Review on Background and recent pharmacological potential'. *Journal of Agronomy, 14*(4), 310-318.

Saad, B., Azaizeh, H., and Said, O. (2005). 'Tradition and perspectives of Arab herbal medicine: a review'. *Evidence-Based Complementary and Alternative Medicine, 2*(4), 475-479.

Sabino, F., and Auf dem Keller, U. (2015). 'Matrix metalloproteinases in impaired wound healing'. *Metalloproteinases In Medicine, 2*, 1-8.

Sabino, F., Hermes, O., Egli, F. E., Kockmann, T., Schlage, P., Croizat, P., Kizhakkedathu, J. N., Smola, H., and auf dem Keller, U. (2015). 'In vivo assessment of protease dynamics in cutaneous wound healing by degradomics analysis of porcine wound exudates'. *Molecular & Cellular Proteomics, 14*(2), 354-370.

Saeedi, P., Petersohn, I., Salpea, P., Malanda, B., Karuranga, S., Unwin, N., Colagiuri, S., Guariguata, L., Motala, A. A., Ogurtsova, K., Shaw, J. E., Bright, D., and Williams, R. (2019). 'Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition'. *Diabetes Research and Clinical Practice, 157*, 1-10.

Sarker, S. D., Latif, Z., and Gray, A. I. (2006). *Natural product isolation: an overview* (2nd ed. Vol. 20). New Jersey: Human Press.

Schmidt, B. A., and Horsley, V. (2013). 'Intradermal adipocytes mediate fibroblast recruitment during skin wound healing'. *Development (Cambridge, England), 140*(7), 1517-1527.

Schwitzgebel, V. M. (2014). 'Many faces of monogenic diabetes'. *Journal of diabetes investigation, 5*(2), 121-133.

Setji, T. L., Brown, A. J., and Feinglos, M. N. (2005). 'Gestational diabetes mellitus'. *Clinical diabetes, 23*(1), 17-24.

Shadhan, R. M., and Bohari, S. P. M. (2017). 'Effects of Hibiscus sabdariffa Linn. fruit extracts on α-glucosidase enzyme, glucose diffusion and wound healing activities'. *Asian Pacific Journal of Tropical Biomedicine, 7*(5), 466-472.

Shafaei, A., Muslim, N. S., Nassar, Z. D., Aisha, A. F., Majid, A. M. S. A., and Ismail, Z. (2014). 'Antiangiogenic effect of Ficus deltoidea Jack standardised leaf extracts'. *Tropical Journal of Pharmaceutical Research, 13*(5), 761-768.

Shankar, M., Ramesh, B., RoopaKumar, D., and Niranjanbabu, M. (2014). 'Wound healing and its importance - a review'. *Der Pharmacologia Sinica, 1*(1), 24 - 30.

Sindhu, S. (2018). 'An overview on diabetic foot ulcer (DFU): mini review'. *Diabetes Case Rep, 3*(1), 1-3.

Singh, S., Young, A., and McNaught, C.-E. (2017). 'The physiology of wound healing'. *Surgery (Oxford), 35*(9), 473-477.

Skyler, J. S., Bakris, G. L., Bonifacio, E., Darsow, T., Eckel, R. H., Groop, L., Groop, P.-H., Handelsman, Y., Insel, R. A., and Mathieu, C. (2017). 'Differentiation of diabetes by pathophysiology, natural history, and prognosis'. *Diabetes, 66*(2), 241-255.

Soib, H. H., Ware, I., Yaakob, H., Mukrish, H., and Sarmidi, M. R. (2015). 'Antioxidant and anti-cancer actvity of standardized extracts of three varieties of Ficus deltoidea's leaves'. *Jurnal Teknologi (Science & Engineering), 77*(3), 19-25.

Solis-Herrera, C., Triplitt, C., Reasner, C., DeFronzo, R. A., and Cersosimo, E. (2018). Classification of diabetes mellitus. In *Endotext [Internet]*: MDText. com, Inc.

Spanheimer, R. G. (1992). 'Correlation between decreased collagen production in diabetic animals and in cells exposed to diabetic serum: response to insulin'. *Matrix, 12*(2), 101-107.

Stojadinovic, O., Pastar, I., Gordon, K. A., and Tomic-Canic, M. (2012). Physiology and Pathophysiology of Wound Healing in Diabetes. In A. Veves, J. M. Giurini and F. W. LoGerfo (Eds.), *The Diabetic Foot: Medical and Surgical Management* (pp. 127-149). Totowa, NJ: Humana Press.

Sulaiman, M., Hussain, M., Zakaria, Z., Somchit, M., Moin, S., Mohamad, A., and Israf, D. (2008). 'Evaluation of the antinociceptive activity of Ficus deltoidea aqueous extract'. *Fitoterapia, 79*(7-8), 557-561.

Süntar, I., and Yakıncı, Ö. F. (2020). Potential risks of phytonutrients associated with high-dose or long-term use. In *Phytonutrients in Food* (pp. 137-155): Elsevier.

Supparmaniam, K., and Bohari, S. P. M. (2015). 'Effects of Justicia gendarussa ethanolic extract on osteoblastic activity of MC3T3-E1 cell '. *Jurnal Teknologi, 77*(3), 1-6.

Suryati, S., Nurdin, H., Dachriyanus, D., and Lajis, M. N. H. (2011). 'Structure elucidation of antibacterial compound from Ficus deltoidea Jack leaves'. *Indonesian Journal of Chemistry, 11*(1), 67-70.

Tan, S. Y., Wong, J. L. M., Sim, Y. J., Wong, S. S., Elhassan, S. A. M., Tan, S. H., Lim, G. P. L., Tay, N. W. R., Annan, N. C., and Bhattamisra, S. K. (2019). 'Type 1 and 2 diabetes mellitus: A review on current treatment approach and gene therapy as potential intervention'. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 13*(1), 364-372.

Teplicki, E., Ma, Q., Castillo, D. E., Zarei, M., Hustad, A. P., Chen, J., and Li, J. (2018). 'The Effects of Aloe vera on Wound Healing in Cell Proliferation, Migration, and Viability'. *Wounds: a compendium of clinical research and practice, 30*(9), 263-268.

Thibault, V., Bélanger, M., LeBlanc, E., Babin, L., Halpine, S., Greene, B., and Mancuso, M. (2016). 'Factors that could explain the increasing prevalence of type 2 diabetes among adults in a Canadian province: a critical review and analysis'. *Diabetology & Metabolic Syndrome, 8*(1), 1-10.

Thiruvoth, F. M., Mohapatra, D. P., Sivakumar, D. K., Chittoria, R., and Nandhagopal, V. (2015). 'Current concepts in the physiology of adult wound healing'. *Plastic and Aesthetic Research, 2*(5), 250-256.

Thomas, C. C., and Philipson, L. H. (2015). 'Update on diabetes classification'. *Medical Clinics, 99*(1), 1-16.

Tian, M., Qing, C., Niu, Y., Dong, J., Cao, X., Song, F., Ji, X., and Lu, S. (2013). 'Effect of aminoguanidine intervention on neutrophils in diabetes inflammatory cells wound healing'. *Experimental and Clinical Endocrinology & Diabetes, 121*(10), 635-642.

Tian, M., Qing, C., Niu, Y., Dong, J., Cao, X., Song, F., Ji, X., and Lu, S. (2016). 'The relationship between inflammation and impaired wound healing in a diabetic rat burn model'. *Journal of Burn Care & Research, 37*(2), 115-124.

Tiwary, R., Tripathi, J., and Dwivedi, K. (2015). 'Effect of Medicinal Plant on Wound Healing in Diabetics'. *Biomedical and Pharmacology Journal, 4*(1), 189-194.

Tomsone, L., Kruma, Z., and Galoburda, R. (2012). 'Comparison of different solvents and extraction methods for isolation of phenolic compounds from horseradish roots (Armoracia rusticana)'. *World Academy of Science, Engineering and Technology, 64*(4), 903-908.

Tsourdi, E., Barthel, A., Rietzsch, H., Reichel, A., and Bornstein, S. R. (2013). 'Current Aspects in the Pathophysiology and Treatment of Chronic Wounds in Diabetes Mellitus'. *BioMed Research International, 2013*, 1-6.

Ueck, C., Volksdorf, T., Houdek, P., Vidal-y-Sy, S., Sehner, S., Ellinger, B., Lobmann, R., Larena-Avellaneda, A., Reinshagen, K., and Ridderbusch, I. (2017). 'Comparison of in-vitro and ex-vivo wound healing assays for the investigation of diabetic wound healing and demonstration of a beneficial effect of a triterpene extract'. *PloS one, 12*(1), 1-16.

Venter, C., and Niesler, C. (2019). 'Rapid quantification of cellular proliferation and migration using ImageJ'. *BioTechniques, 66*(2), 99-102.

Vijayarathna, S., and Sasidharan, S. (2012). 'Cytotoxicity of methanol extracts of Elaeis guineensis on MCF-7 and Vero cell lines'. *Asian pacific journal of tropical biomedicine, 2*(10), 826-829.

Wachtel-Galor, S., and Benzie, I. F. F. (2011). *Herbal Medicine: An Introduction to Its History, Usage, Regulation, Current Trends, and Research Needs* (2nd ed.). Boca Raton (FL): CRC Press/Taylor & Francis Copyright © 2011 by Taylor and Francis Group, LLC.

Wang, H., Vidyadaran, S., Mohd Moklas, M. A., and Baharuldin, M. T. H. (2017). 'Inhibitory activity of Ficus deltoidea var. trengganuensis aqueous extract on lipopolysaccharide-induced TNF-α production from microglia'. *Evidence-Based Complementary and Alternative Medicine, 2017*, 1-7.

Wang, Q., Cao, X., Zhu, G., Xie, T., Ge, K., and Niu, Y. (2019). 'Blockade of receptor for advanced glycation end products improved essential response of inflammation in diabetic wound healing'. *International Journal of Diabetes in Developing Countries*, 1-7.

Wang, X., and Khalil, R. A. (2018). 'Matrix Metalloproteinases, Vascular Remodeling, and Vascular Disease'. *Advances in pharmacology (San Diego, Calif.), 81*, 241-330.

Wang, Y.-m., Zhao, L.-h., Su, J.-b., Qiao, H.-f., Wang, X.-h., Xu, F., Chen, T., Chen, J.-f., Wu, G., and Wang, X.-q. (2015). 'Glycemic variability in normal glucose tolerance women with the previous gestational diabetes mellitus'. *Diabetology & metabolic syndrome, 7*(1), 1-8.

Werdin, F., Tennenhaus, M., Schaller, H.-E., and Rennekampff, H.-O. (2009). 'Evidence-based management strategies for treatment of chronic wounds'. *Eplasty, 9*, 169-179.

Whitney, J. D. (2005). 'Overview: acute and chronic wounds'. *Nurs Clin North Am, 40*(2), 191-205.

Xiang, J., Wang, S., He, Y., Xu, L., Zhang, S., and Tang, Z. (2019). 'Reasonable Glycemic Control Would Help Wound Healing During the Treatment of Diabetic Foot Ulcers'. *Diabetes therapy : research, treatment and education of diabetes and related disorders, 10*(1), 95-105.

Xu, F., Zhang, C., and Graves, D. T. (2013). 'Abnormal cell responses and role of TNF- α in impaired diabetic wound healing'. *BioMed Research International, 2013*, 1-9.

Xuan, Y. H., Huang, B. B., Tian, H. S., Chi, L. S., Duan, Y. M., Wang, X., Zhu, Z. X., Cai, W. H., Zhu, Y. T., and Wei, T. M. (2014). 'High-glucose inhibits human fibroblast cell migration in wound healing via repression of bFGF-regulating JNK phosphorylation'. *PloS one, 9*(9), 1-14.

Yaacob, A., and Baharuldin, M. T. H. (2018). 'A Review on Ficus deltoidea Medicinal Properties and Its Potential Use as Ergogenic Aids in Athletes'. *Pertanika Journal of Scholarly Research Reviews, 4*(2), 18-28.

Yang, Y., and Chan, L. (2016). 'Monogenic Diabetes: What It Teaches Us on the Common Forms of Type 1 and Type 2 Diabetes'. *Endocrine reviews, 37*(3), 190-222.

Yang, Y., Wu, Y., Zhang, S., and Song, W. (2013). 'High glucose promotes Aβ production by inhibiting APP degradation'. *PloS one, 8*(7), 1-7.

Yazdanpanah, L., Nasiri, M., and Adarvishi, S. (2015). 'Literature review on the management of diabetic foot ulcer'. *World journal of diabetes, 6*(1), 37-53.

Ye, J., Xie, T., Niu, Y., Qiao, L., Tian, M., Qing, C., and Lu, S. (2016). A Potential Mechanism for Diabetic Wound Healing: Cutaneous Environmental Disorders. In V. alexandreascu (Ed.), *Wound Healing: New insights into Ancient Challenges* (pp. 223 - 244). Rijeka, Croatia: IntechOpen.

Zakaria, Z., Hussain, M., Mohamad, A., Abdullah, F., and Sulaiman, M. (2012). 'Anti-inflammatory activity of the aqueous extract of Ficus deltoidea'. *Biological research for nursing, 14*(1), 90-97.

Zhang, Q.-W., Lin, L.-G., and Ye, W.-C. (2018). 'Techniques for extraction and isolation of natural products: a comprehensive review'. *Chinese medicine, 13*, 1-26.

Zhang, X., Stewart, J. A., Jr., Kane, I. D., Massey, E. P., Cashatt, D. O., and Carver, W. E. (2007). 'Effects of elevated glucose levels on interactions of cardiac fibroblasts with the extracellular matrix'. *In Vitro Cell Dev Biol Anim, 43*(8-9), 297-305.

Zhao, R., Liang, H., Clarke, E., Jackson, C., and Xue, M. (2016). 'Inflammation in chronic wounds'. *International journal of molecular sciences, 17*(12), 1-14.

Zhou, K., Ma, Y., and Brogan, M. S. (2015). 'Chronic and non-healing wounds: the story of vascular endothelial growth factor'. *Medical hypotheses, 85*(4), 399-404.

Zhu, P., Yang, C., Chen, L. H., Ren, M., Lao, G. J., and Yan, L. (2011). 'Impairment of human keratinocyte mobility and proliferation by advanced glycation end products-modified BSA'. *Arch Dermatol Res, 303*(5), 339-350.