IN-VITRO WOUND HEALING ACTIVITIES OF *CARICA PAPAYA* LEAVES EXTRACT ON HUMAN SKIN FIBROBLAST CELL LINE

HUSNUL HANANI BINTI SOIB

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Faculty of Engineering
Universiti Teknologi Malaysia

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DEDICATION

Special dedication to my beloved husband, who gives me endless support and understanding, my daughters, parents, and the whole family.

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ABSTRACT

Wound healing is a critical issue that has a significant impact on one's quality of life. It imposed a costly burden on individuals and the healthcare system because it necessitates extended hospitalisation and death in severe cases. With the rising cost of antibiotics and the emergence of bacterial resistance, more medical practitioners are turning to traditional medicine for solutions. *Carica papaya* (*C. papaya*) is a well-known plant with various pharmacological activities, including antioxidant and wound healing properties. However, to date, the lack of scientific evidence has been investigated on the efficiency of the solvents towards *C. papaya* leaves extract as a potential wound healer, its underlying mechanism, and *in silico* approach with the putative phenolic compounds. The present study was aimed to explore *in vitro* wound healing activities of *C. papaya* leaves extract and its fraction on human skin fibroblast cells. The study included cell viability, cell proliferation, scratch assay, and collagen synthesis. Different solvents (methanol, ethanol, aqueous) of crude extracts were screened. The best crude extract of *C. papaya* leaves was further subjected to a bioassay-guided fractionation using the solid-phase extraction method to ascertain the best fraction. Further investigation was conducted to evaluate the possible mechanism involved using the best extract and fraction, including the gene expression analysis by quantitative real-time polymerase chain reaction (qRT-PCR), cell cycle analysis, and MMP-1 production. The best extract and fraction were screened for their phytoconstituents using high performance liquid chromatography (HPLC) whilst *in silico* approach was carried out to assess inhibition of glycogen synthase kinase 3-ß (GSK3-ß), a specific biomarker for wound healing. The results showed that the methanolic extract of *C. papaya* leaves and Fraction 2 (Fr II) possessed a significant antioxidant potential and wound healing properties compared to other extracts and fractions. The methanolic extract and Fr II significantly stimulated the highest migration rate on HSF cells at 15.6 µg/mL ($p \leq 0.05$) after 48 h with no cytotoxicity observed at the highest concentration. The qRT-PCR analysis suggested that wound healing activities of the best extract and fraction were strongly associated with activation of the Wnt/ß-catenin signalling pathway, which involved the upregulated expression of genes AXIN2, TGF-β1, and CTNBB1 after 48 h ($p \leq 0.05$). The results also indicated the raised of MMP-1 synthesis upon treatment as compared to control. Furthermore, cell cycle analysis was significantly increased during the G_2/M phase, indicating that *C. papaya* leaves extract and Fr II gradually reinvigorated cell division for wound closure. HPLC analysis identified phenolic compounds of gallic acid, caffeic acid, *p*-coumaric acid, catechin, and quercetin in various concentrations. Molecular docking results found that quercetin and catechin exhibited the most promising activity among the phenolic compounds detected based on the lowest binding energy and inhibition constant of GSK3-ß than the standard drug, nitrofurazone. The findings suggested that the *C. papaya* leaves extract and its fraction exhibited wound healing by activating the Wnt/ß-catenin-dependent signalling pathway. This work provides a significant endeavour in promoting *C. papaya* as an option to treat wounds.

ABSTRAK

Penyembuhan luka adalah isu kritikal yang memberi kesan yang besar terhadap kualiti hidup seseorang. Ia membebankan individu dan sistem penjagaan kesihatan kerana ia menyebabkan kemasukan ke hospital dan kematian pada kes-kes yang teruk. Dengan kenaikan kos antibiotik dan kemunculan daya tahan menentang bakteria, lebih banyak pengamal perubatan beralih kepada ubat tradisional sebagai penyelesaian. *Carica papaya* (*C. papaya*) adalah sejenis tumbuhan yang terkenal dengan pelbagai aktiviti farmakologi, termasuk sifat antioksidan dan penyembuhan luka. Namun, hingga kini, kekurangan bukti saintifik telah dikaji terhadap keberkesanan pelarut pada ekstrak daun *C. papaya* sebagai penyembuh luka, mekanisma penyembuhan, dan pelekatan dok molekul dengan sebatian fenolik yang berpotensi. Kajian ini bertujuan untuk mengkaji aktiviti penyembuhan luka dari ekstrak daun *C. papaya* dan pecahannya terhadap sel fibroblas kulit manusia. Kajian dijalankan meliputi daya maju sel, percambahan sel, uji calar, dan sintesis kolagen. Ekstrak di dalam pelarut yang berbeza (metanol, etanol, air) telah disaring. Ekstrak mentah terbaik daripada daun seterusnya melalui proses pemeringkatan berpandukan bioasai menggunakan kaedah pengekstrakan fasa pepejal bagi mendapatkan pecahan terbaik. Penyelidikan yang lebih mendalam dilakukan untuk menilai mekanisma yang mungkin dilakukan oleh ekstrak terbaik dan pecahan terbaik, termasuk analisa ekspresi gen dengan kuantitatif masa nyata - tindak balas berantai polimer (qRT-PCR), analisa kitaran sel, dan penghasilan MMP-1. Ekstrak terbaik dan pecahan terbaik diperiksa bagi kandungan fitokimianya menggunakan kromatografi cecair berprestasi tinggi (HPLC) sementara pelekatan dok molekul dilakukan untuk menilai perencatan glikogen sintase kinase 3-ß (GSK3-ß), iaitu biopenanda khusus untuk penyembuhan luka. Hasil kajian menunjukkan bahawa ekstrak metanol daun *C. papaya* dan pecahan 2 (Fr II) memiliki potensi antioksidan dan sifat penyembuhan luka yang tinggi berbanding dengan ekstrak dan pecahan lain. Ekstrak metanol dan Fr II merangsang kadar penghijrahan tertinggi sel HSF pada 15.6 µg/mL ($p \leq 0.05$) selepas 48 jam tanpa kesan sitotoksik pada kepekatan paling tinggi. Analisa qRT-PCR menunjukkan bahawa aktiviti penyembuhan luka oleh ekstrak terbaik dan pecahan terbaik sangat berkaitan dengan pengaktifan mekanisma Wnt/ß-catenin, yang melibatkan ekspresi gen AXIN2, TGF-β1, dan CTNBB1 selepas 48 jam ($p \leq 0.05$). Hasilnya juga menunjukkan peningkatan penghasilan MMP-1 semasa rawatan berbanding dengan pemalar. Selain itu, analisa kitaran sel meningkat dengan ketara semasa fasa G_2/M, menunjukkan bahawa ekstrak daun *C. papaya* dan Fr II secara beransur-ansur meningkatkan pembelahan sel bagi penutupan luka. Analisa HPLC telah mengenal pasti sebatian fenolik iaitu asid galik, asid kafeik, asid *p*-kumirik, katekin, dan kuersetin dalam pelbagai kepekatan. Hasil dok molekul mendapati bahawa kuersetin dan katekin menunjukkan aktiviti yang paling tinggi di antara sebatian fenolik yang dikesan berdasarkan tenaga pelekatan dan kadar perencatan terendah pada GSK3-ß berbanding ubat rujukan, nitrofurazone. Hasil kajian menunjukkan bahawa ekstrak daun *C. papaya* dan pecahannya menunjukkan aktiviti penyembuhan luka melalui pengaktifan isyarat yang bergantung pada mekanisma Wnt/ß-catenin. Kajian ini menunjukkan usaha yang paling penting dalam mempromosikan *C. papaya* sebagai pilihan untuk merawat luka.

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LIST OF ABBREVIATIONS

ACN	–	Acetonitrile
ATCC	–	American Type Culture Collection
AXIN2	–	Axis Inhibition Protein–2
CAM	–	Complementary and Alternative Medicine
CO_2	–	Carbon Dioxide
CTNNB1	–	Catenin Beta–1
DAD	–	Diode Array Detector
DMEM	–	Dulbecco's Modofied Eagle Medium
DMSO	–	Dimethy Sulfoxide
DNA	–	Deoxyribonucleic acid
DPPH	–	1,1–Diphenyl–2–Picrylhydrazyl
ECM	–	Extracellular Matrix
ELISA	–	Enzyme–Linked Immunosorbent Assay
EPP	–	Entry Point Project
ESI	–	Electrospray Ionisation
EtOH	–	Ethanol
FBS	–	Fetal Bovine Serum
FRAP	–	Ferric reducing ability of plasma
G	–	Gap
GAE	–	Gallic Acid Equivalent
GC–MS	–	Gas Chromatography–Mass Spectrometry
GSK3–β	–	Glycogen Synthase Kinase 3–β

HHPE	–	High Hydrostatic Pressure
HPLC	–	High Performance Liquid Chromatography
IC_{50}	–	Concentration to Inhibit 50% of Population
IL	–	Interleukin
LC–MS	–	Liquid Chromatography– Mass Spectrometry
M	–	Mitosis
MeOH	–	Methanol
MIC	–	Minimum Inhibitory Concentration
MMP	–	Matrix Metalloproteinases
MMP–1	–	Matrix Metalloproteinase–1
MTT	–	3–[4, 5–dimethylthiazol–2–yl]–2, 5 diphenyl tetrazolium bromide
NMR	–	Nuclear Magnetic Resonance
OD	–	Optical Density
PBS	–	Phosphate Buffered Saline
PDGF	–	Platelet–Derived Growth Factor
PS	–	Phosphatydylserine
qRT–PCR	–	Quantitative Real Time – Polymerase Chain Reaction
RNA	–	Ribonucleic Acid
ROS	–	Reactive Oxygen Species
SEM	–	Standard Error Mean
SOD	–	Superoxide Dismutase
SPE	–	Solid Phase Extraction
STDEV	–	Standard Deviation
TFC	–	Total Flavonoid Content
TGF–β1	–	Transfroming Growth Factor– β1

TNF – Tumor Necrosis Factor

UAE – Ultrasonic–Assisted Extraction

UV – Ultraviolet

UV/VIS – Ultraviolet–Visible

LIST OF SYMBOLS

A	–	Absorbance
%	–	Percentage
°C	–	Degree of Celsius
>	–	Greater than
<	–	Less than
µg	–	Microgram
µL	–	Microliter
cm		Centimeter
g	–	Gram
ng	–	Nanogram
h	–	Hour
kg	–	Kilogram
mg	–	Milligram
mg/g	–	Milligram per gram
m/z	–	Mass per ratio
min	–	Minutes
mL	–	Mililiter
nm	–	Nanometer
rpm	–	Revolutions per minute

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CHAPTER 1

INTRODUCTION

1.1 Research Background

The incorporation of herbs into modern medical practice boosts the demand for natural goods and plant-based compounds. Due to their considerable effect, botanical ingredients are increasingly being used in wound care practices. Chronic wounds continue to be a challenge in healthcare issues. With the increasing expense of antibiotics and bacterial resistance, many practitioners are turning to traditional medicine for remedies. Traditional herbal medicines have been used for ages and have been regarded as complementary to modern medicines in wound healing. The herbs differ from conventional drugs as they are more dilute and often contain active principles that are chemically and therapeutically related to the main responsible effects. As a result, traditional herbal medicines have shown fewer side effects and are safer than modern treatments (Mushtaq Ahmad et al., 2009). Furthermore, the herbs contain high nutritional values and can cure various ailments due to a combination of compounds with potentially multiple targets of action.

Based on the retrospective analysis conducted by Nussbaum et al. (2018), about 8.2 million people suffered wounds with or without infections and experienced pain and discomfort. It causes a financial burden, prolonged hospitalisation, social isolation, and possibly mortality to the individual, healthcare system, and society (Farooqui et al., 2015). Wound healing is a complex and dynamic process involving complex interactions among cellular structures, tissue layers, and different types of cells. The wound can be interpreted as disrupting the functional continuity of cells and tissues due to physical, chemical, microbial infection, or immunology processes. In general, the wound healing process comprises three distinct phases of inflammation, proliferation, and remodelling. During these stages, a disruption of the typical structure and function of skin and underlying soft tissue has been regenerated. The current application of wound healing treatment involves autograft, allograft, cultured epithelial autograft, and wound dressing (Dreifke et al., 2015). Distinct types of treatment are applied based on the types of wounds, such as acute or chronic wound. The management of wounds always deals with haemostasis, wound cleaning, analgesia, wound closure, and wound dressing. Furthermore, the adaptation of patients to the treatment also varies with age, sex, lifestyle, health status, and wound severity (Ghosh and Gaba, 2013). Furthermore, the fibroblast cell is the most significant cell involved in wound healing. It's a type of mesenchymal cell that plays an important role in skin homeostasis and physiological tissue healing. The cell anchored in the dermis layer of the skin that secretes extracellular matrix components such as collagen, growth factors, cytokines, and matrix proteins (Yoon et al., 2018). It may also multiply, differentiate, and migrate to their full potential, which is critical for wound healing.

Carica papaya Linn. (*C. papaya*), locally called "betik" in Malaysia, is a herbaceous plant from the family Caricaceae. It is widely cultivated in most tropical and subtropical countries like Malaysia, Indonesia, Australia, Brazil, India, and China. This perennial plant can grow in male, female, and hermaphrodite, but only the female plant can produce fruits. The colour of papaya fruit changes from green to reddish-orange when it ripens. The ripe fruit contains a high carotene content compared to the immature fruit, together with a high chlorophyll content (Raaman, 2015). Studies revealed that compounds present in the plant postulate various benefits in therapeutic and pharmacological activities, similar to the leaves of *C. papaya*, which contain secondary metabolites like phenolic, alkaloid, tannin, flavonoid, saponin, and glycoside (Prashant et al., 2011; Ancheta and Acero, 2015).

In addition, the leaves of *C. papaya* are rich in polar compounds, specifically phenolic, which are believed to exert wound healing properties (Rex et al., 2018). Phenolic compounds were proved to increase the expression of antioxidant genes as well as anti-inflammatory which highly correlated with the process of wound recovery (Yang et al., 2016; Kapoor et al., 2004). Various literature studies have reported *in vivo* studies on the effect of *C. papaya* extract for its wound healing properties (Nafiu and Rahman, 2015; Ajani and Ogunbiyi, 2015; Nafiu et al., 2016). For instance, stems, leaves, fruits, roots, seeds and epicarps from *C. papaya*'s plant have shown the wound healing properties by postulating the highest migration rate, fibroblast proliferation, wound contraction and hydroxyproline content after exposure to the *C. papaya*'s treatment. Generally, the wound healing properties have been attributed to its antioxidant, anti-inflammatory, and antimicrobial activities (Ghosh and Gaba, 2013). Additionally, other studies reported that the wound healing process was activated by the modulation of the Wnt/ß-catenin signalling gene (Whyte et al., 2012; Zhang et al., 2018). It is a well-known key player in enhancing the overall healing process by involving tissue regeneration through crosstalk with other signalling pathways (Choi et al., 2022). Therefore, the activation of Wnt/ß-catenin signalling highly promotes cell proliferation, survival and differentiation.

A selective extraction technique has always been challenging. It is an important consideration to ensure that the bioactive compounds that are biologically present in the plants remain preserved (Pandey and Tripathi, 2014). The phytochemical discovery from plant materials can be achieved using an appropriate extraction process. Extraction is a process involving separating a mixture of compounds from non-miscible phases using a specific solvent; therefore, many factors influence the quality (bioactivity) and quantity of the extract, including types of solvents, techniques, and the parts of the plant used (Ncube et al., 2008). The choice of suitable extraction solvent should be fully considered during extracting the bioactive constituents to ensure that the target components are not lost, distorted, or destroyed (Soib et al., 2020a).

Solid phase extraction (SPE) is widely used to extract compounds of interest present even in small amounts and later enhances detection sensitivity. It is one of the most famous techniques used for fractionation and is regularly related to the principle of the solid-liquid extraction method. Other extraction methods are liquid-liquid extraction that uses liquid and gas chromatography that uses gas and liquid (Nickerson and Colon, 2011). Throughout the study, SPE is used to fractionate *C. papaya* leaves extract since the method is more convenient, rapid, sensitive, and it improves analytical recovery, purification and detection (Juhascik and Jenkins, 2009; Duca et al., 2014).

Moreover, it is preferred compared to other methods (e.g., column chromatography) as it is a simple method and readily prepared, where the flow rate of sample downwards to the cartridge is maintained, hence reducing the sample volume and solvent, as well as cost-effective (Mohd Marsin et al., 2007; Ku et al., 2001).

Various studies have considered the approach of bioassay-guided fractionation analysis (Muhammad et al., 2013; Balekar et al., 2013). Bioassay-guided fractionation is a procedure where an extract is chromatographically fractionated and re-fractionated until a pure, biologically active compound is isolated. Each fraction produced during fractionation will be evaluated in a bioassay system, and only the best fraction is selected. The bioassay-guided fractionation method is commonly employed in drug discovery research. It effectively and directly links the analysed extract and targeted compounds using fractionation procedure, followed by biological activity. Many studies have successfully used bioassay-guided fractionation to isolate compounds from the active fraction (Melariri et al., 2011; Nwaehujor et al., 2014; Bayrami et al., 2018; Sarkhail et al., 2020).

1.2 Problem Statements

Although scientific research has shown that the *C. papaya* leaves have wound healing capabilities, prior studies have only focused on the effect of wound healing using a single type of extraction solvent rather than examining the influence of multiple extraction solvents on that characteristic. As a result, the current study sought to assess the quality of several extraction solvents which having different polarities on the biological activities related to wound recovery. Besides, it is unclear if each fraction of *C. papaya* leaves extract can provide a comparable positive impact on wound recovery similar to the crude or if it can work better than the crude extract. Previously, limited findings elaborated the effect of the fractions obtained from SPE method of *C. papaya* leaves extract for wound recovery. Furthermore, the potential marker compounds, mainly phenolic compounds found in *C. papaya* leaves extract with wound healing properties, are uncertain. For these purposes, this research aims to investigate the potential of *C. papaya* leaves extract and its fraction in enhancing wound recovery and to identify putative bioactive compounds for wound healing through *in vitro* testing on human skin fibroblast cell line (Bayrami et al., 2018; Sarkhail et al., 2020).

On the other hand, the discovery of the fundamental components behind the reaction of the *C. papaya* leaves extract and its fraction towards wound recovery is not much reported in previous literature, especially in enhancing wound recovery for wound healing through *in vitro* testing on human skin fibroblast cell line. Previously, *in vivo* studies have been used for the evaluation of wound healing activities. Unfortunately, the exploration of the underlying mechanism exerted by *C. papaya* leaves is still not fully observed. Moreover, there are also limited studies that integrate the biological assessment within *in silico* study from the compounds identified in *C. papaya* leaves. This is a primary attempt to elucidate the findings of the characterised compounds from the best extract and fraction to a specific potential protein involved in wound healing using molecular docking. Thus, this study considers the mechanistic wound healing process postulated by *C. papaya* leaves in elucidating the reaction through virtual screening of the compounds detected with the targeted protein by molecular docking. Thus, this approach provides a better understanding of the molecular and cellular distinctions that could enhance the therapeutic techniques and facilitate new, more effective treatments.

1.3 Objectives of the Study

The main objectives of this research are:

1. To evaluate the wound healing activities and physicochemical characteristics of *C. papaya* leaves extracts and fractions including its total phenolic content, antioxidant capacity, cytotoxicity and proliferative activity, migration and collagen stimulation.

2. To determine the underlying wound healing mechanism of *C. papaya* leaves extract and fraction which targeting on Wnt/ß-catenin pathway.

3. To determine the possible phenolic bioactive compounds from *C. papaya* leaves extract responsible for wound healing properties.

1.4 Hypothesis

It is speculated that the phenolic compounds from *C. papaya* leaves extract and its fraction exhibit the wound healing activities through the activation of Wnt/ß-catenin pathway.

1.5 Scope of the Study

The scopes of this study are listed below:

1. The best extraction solvent for wound healing activities was determined. This scope was conducted using three distinctive extraction solvents: absolute methanol, absolute ethanol, and an aqueous solution. Then, the quality of the extracts was determined through the total phenolic content (TPC), 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging activities, cell cytotoxicity and cell proliferation by (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, and migration effect by scratch assay.

2. Fractionation of the best extract of *C. papaya* leaves was done using the SPE process with varying percentages of methanol and acetonitrile. Five different fractions were collected with the highest polarity to the lowest polarity of the solvent eluent. The obtained fractions were then subjected

to bioassay-guided fractionation to ascertain the best fraction. The fractions were assessed for their biological activities related to the wound healing process, such as TPC, DPPH scavenging activities, cell cytotoxicity and proliferation, migration effects, and collagen synthesis.

3. Next, the investigation of the fundamental mechanism of wound healing activities was carried out following the determination of the best extract and the best fraction. The evaluation centred on mechanisms concerning the migration and proliferation activities, with collagen synthesis such as the cell cycle analysis by a flow cytometer, the production of matrix metalloproteinase-1 (MMP-1) by enzyme-linked immunosorbent assay (ELISA), and the gene expression analysis of transforming growth factor-β1 (TGF-β1), axis inhibition protein 2 (AXIN2), and catenin beta 1 (CTNNB1) by qRT-PCR.

4. The characterisation of the compounds present in the best extract and the best fraction was performed using an instrument called high performance liquid chromatography (HLPC). The HPLC method was used to identify five targeted phenolic compounds encompassing gallic acid, catechin, rutin, *p*-coumaric acid, and quercetin, which are believed to lead to wound healing activities.

5. In addition, the investigation of an *in silico* study for molecular docking using AutoDock 4.2 was performed. The method describes the binding interaction of bioactive phytochemicals from *C. papaya* leaves with a specific potential protein, specifically glycogen synthase kinase 3-ß (GSK3-β), which is critical for wound healing.

1.6 Significance of the Study

C. papaya leaves contain tremendous bioactive compounds that exert various health benefits, including wound healing activities. As extraction solvent is the most critical step in analysing constituents present in botanicals and herbal preparations, the strengths and limitations of different extraction solvents which having different polarities need to be addressed. To the best of current knowledge, this is the first work that demonstrates the effect of different solvents of *C. papaya* leaves extract on wound healing activities using an *in vitro* study on human skin fibroblast cells. The finding strongly suggests that the choice of the excellent solvent during extraction is vital in producing maximum activities of wound healing and speedy recovery. Furthermore, it proved that using a different solvent with different polarities highly affects the extracted compounds and in turns, influence of the quantity and quality of the extracts.

Although other scientific studies reported on the effect of papaya enzymes on wound recovery, the recent study examined bioactive compound-rich fractions, mainly phenolic compounds, on human skin fibroblast cells using SPE. This is the first study that used SPE to fractionate the crude extract from *C. papaya* leaves into several fractions, followed by the evaluation of physicochemical characteristics and the assessment through *in vitro* study. With the advantages of using SPE in concentrating the phytoconstituents present, it provides an initial step for further exploration of the isolation of compounds associated with wound healing and the enrichment of the bioactive compounds. Besides, this work also supports the possible underlying wound healing mechanism exerted by *C. papaya* leaves extract by modulation of the Wnt/ß-catenin pathway. At the end of the study, it is expected to contribute novel fundamental knowledge of wound healing mechanism from *C. papaya*.

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LIST OF PUBLICATIONS

Journal with Impact Factor

1. **Soib, H. H.,** Husin, F., Bakar, M. H. A., Yaakob, H. and and Sarmidi, M. R. (2020). Bio–assay guided of different extraction techniques of *Carica papaya* (Linn.) leaves on *in–vitro* wound healing activities. *Molecules,* 25(3), 517 – 530. https://doi.org/10.3390/molecules25030517. (**Q2, IF: 4.411**)

Indexed Journal

1. **Soib, H. H.,** Yaakob, H., Idris, M. K. H. and Abd Aziz, A. (2020). Effects of extraction solvents on antioxidant and wound healing properties of *Carica papaya* leaves extracts. *Food Research Journal,* 4(Suppl.2), 76–83. 10.26656/fr.2017.4(S2). S03. (**Indexed by SCOPUS**)

2. **Soib, H. H.,** Yaakob, H., Sarmidi, M. R., Rosdi, M. N. M. (2019). Fractionation of aqueous extract of *Ficus Deltoidea* var. *Kunstleri*'s leaves using solid phase extraction method for anticancer activity on DU145 cell line. *Malaysian Journal of Analytical Sciences*. 23(3): 534–547. https://doi.org/10.17576/mjas–2019–2303–18. (**Indexed by SCOPUS**)

3. Husin, F., Yaakob, H., Rashid, S. N. A., Shahar, S., **Soib, H. H.** (2019). Cytotoxicity study and antioxidant activity of crude extracts and spe fractions from *Carica papaya* leaves. *Biocatalysis and Agricultural Biotechnology,* 19(2019), 1–6. https://doi.org/10.1016/j.bcab.2019.101130. (**Indexed by WOS**)

4. Ahmed, N. R., Yaakob, H., Ware, I., **Soib**, **H. H.,** Husin, F., Zaki, I. A. M. (2020). Thermal effect of spray drying process on the quality of *Ficus deltoidea* extract. M*alaysian Journal of Medicine and Health Sciences,* 16 (Supp11), 95–100. (**Indexed by SCOPUS and WOS**)

5. Hashim, N.A., Ya'akob, H., Rosdi, M.N.M., Zainol, N.A., Husin, F., **Soib, H. H. and Norhisham, N. F.** (2020). Antioxidant properties of extracts and SPE fractions from *Annona muricate* leaves. *Food Research Journal,* 4(Suppl.2), 71–75. https://doi.org/10.26656/fr.2017.4(S2).S02. (**Indexed by SCOPUS**)