UNIVERSITI PUTRA MALAYSIA

ANTITUMOUR EFFECTS OF Morinda citrifolia L. FRUIT AND Clinacanthus nutans (Burm. F.) LINDAU LEAF MIXTURES IN LEUKAEMIA-LYMPHOMA BEARING SPRAGUE DAWLEY RATS

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By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Doctor Philosophy

December 2016

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DEDICATION

This Thesis is Dedicated to

My Beloved Parents, Sisters,

Lecturers and Friends

Without Whom, None of My Success Would Be Possible

With Love, Nadia Asyura

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Abstract of thesis prepared to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Doctor of Philosophy

ANTITUMOUR EFFECTS OF MIXTURES OF *Morinda citrifolia* L. FRUIT AND *Clinacanthus nutans* (Burm. F.) LINDAU LEAF EXTRACTS IN LEUKAEMIA-LYMPHOMA BEARING SPRAGUE DAWLEY RATS

By

SAJJARATTUL NURUL NADIA ASYURA MOHAMAD IFFENDI

December 2016

Chairman: Hazilawati Hj. Hamzah, PhD
Faculty: Veterinary Medicine

Morinda citrifolia L. (*M. citrifolia*) fruit known as 'mengkudu' and *Clinacanthus nutans* (Burm. F.) Lindau (*C. nutans*) leaf known as 'rumput belalai gajah', are widely known herbs that have anti-cancer properties. The antitumour effects of the combination of these herbs in leukaemia-lymphoma have never been reported. The aim of this study were to evaluate toxicity of ethanol extracts of *M. citrifolia* fruits and *C. nutans* leaves and the antitumour effects of these ethanol extracts in MNU-induced leukaemia-lymphoma. The antitumour of MNU-induced leukaemia-lymphoma rats was evaluated via haematological and serum biochemical parameters, histopathology, levels of an oxidative stress biomarker (malondialdehyde [MDA]) and antioxidative stress enzymes (glutathione peroxidase [GPx] and superoxide dismutase [SOD], transcription levels of VEGF and COX-2 mRNA in the blood, spleen and lymph nodes and expression levels of VEGF and COX-2 protein in the spleen and lymph nodes. A 14-day acute toxicity was conducted for determination of lethal dose 50 (LD_{50}), followed by a 28-day subacute toxicity study and a 13-week subchronic toxicity study of both extracts. In acute toxicity, rats were divided into four groups, namely, control, 10% DMSO (vehicle) and 2000 mg/kg of body weight of each extract. In the subacute and subchronic toxicities, rats were divided into eight groups including control, 10% DMSO (vehicle), 75 mg/kg body weight, 125 mg/kg body weight and 250 mg/kg body weight of each extract. At the end of the experimental period, blood samples were collected for the hematological and serum biochemical parameters. The liver and kidneys were collected for histopathological analysis. The results showed a single dose (2000 mg/kg of body weight) of ethanol extracts of *M. citrifolia* fruits and *C. nutans* leaf induced no acute toxicity to the male Sprague Dawley rats. The oral administration of 75 mg/kg of *M. citrifolia* fruit and *C. nutans* leaf for 28 and 90 days induced no subacute and subchronic toxicity in male Sprague Dawley rats. Administration of 125 mg/kg of *M. citrifolia* fruit and *C. nutans* leaf for 28 and 90 days induced hepatotoxicity in male Sprague Dawley rats. Administration of 250

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mg/kg of *M. citrifolia* fruit and *C. nutans* leaf for 28 and 90 days induced hepatotoxicity and nephrotoxicity in male Sprague Dawley rats.

In the MNU-induced leukaemia-lymphoma study, a total of 56 rats were divided into seven groups namely control (group A), MNU-induced leukaemia-lymphoma rats (group B), MNU-induced leukaemia-lymphoma rats treated with four different combinations of *M. citrifolia* and *C. nutans* extracts (mixture C [group C], mixture D [group D], mixture E [group E] and mixture F [group F]) and MNU-induced leukaemia-lymphoma rats treated with chemotherapy regimen (CHOP) (group G). Leukaemia-lymphoma was induced using *N*-methyl-*N*-nitrosourea (MNU) which was administered intraperitoneally (i.p) at a dose of 60 mg/kg of body weight for four times in the 2-week period. Mixtures of herbs for treatment of the leukaemia-lymphoma rats were formulated not to exceed 250 mg/kg of body weight per administration. The herbal mixed extracts were given via oral gavage, once daily starting from week 12 post MNU administration until week 24 of the experiment period. Blood samples were collected and analysed on the 18^{th} and 24^{th} weeks of the experiment. Heart, lungs, liver kidneys, lymph nodes and spleen were collected for histopathological evaluation. The results showed the presence of blast cells in the blood smear in both untreated and treated leukaemia-lymphoma rats at week 18^{th} and 24^{th}. Groups B and G had a significant elevation in the number of blast cells from week 18 to week 24. The oral administration of herbal mixtures (groups C, D, E and F) was effective in limiting the degree of leukaemic cells progression. The serum biochemical parameter results showed CK level was significantly increased in groups C, D and F from week 18 to week 24. The LDH level had also significantly increased in groups C and F from week 18 to week 24. Histopathology results showed neoplastic lymphocytes were present in all spleen and lymph nodes of the untreated and treated MNU-induced leukaemia-lymphoma rats. The oral administration of mixtures E and F in MNU-induced leukaemia-lymphoma rats inhibited metastasise of neoplastic lymphocytes to the selected vital organs (liver, lungs, heart and kidneys) as compared to other herbal mixtures and CHOP regimen. Treatment of CHOP regimen in MNU-induced leukaemia-lymphoma rats induced significant liver and spleen fibrosis and necrosis in the testis. However, treatment of herbal mixtures in MNU-induced leukaemia-lymphoma rats induced no fibrosis and necrosis (testis).

The levels of serum MDA in the MNU-induced leukaemia-lymphoma rats treated with all herbal mixtures and CHOP regimen were decreased from week 18 to week 24. The level of serum SOD in MNU-induced leukaemia-lymphoma rats treated with herbal mixtures and CHOP regimen increased from week 18 to week 24. A decrease of serum GPx was observed from week 18 to week 24 in all groups. Administration of MNU-induced leukaemia-lymphoma rats with herbal mixtures succeeded in inhibiting angiogenesis and inflammation in blood, lymph node and spleen compared to untreated MNU-induced leukaemia-lymphoma rats. A down-regulated of VEGF and COX-2 mRNA transcription was observed especially in MNU-induced leukeamia-lymphoma rats treated with mixtures E and F compared to untreated MNU-induced leukeamia-lymphoma. On the other hand, treatment of mixture F succeeded to inhibit COX-2 expression in the lymph nodes of MNU-induced leukaemia-lymphoma rats via immunohistochemistry. A more sensitive result was obtained from Western blot

whereby mixtures E and F were able to decrease VEGF and COX-2 expression in MNU-induced leukeamia-lymphoma rats.

In conclusion, oral administration of 2000 mg/kg of body weight of both extracts in male Sprague Dawley rats induced no acute toxicity. Oral administration of 125 mg/kg of body weight for 29 and 90 days of both extracts induced hepatotoxicity. Oral administration of 250 mg/kg of body weight for 29 and 90 days of both extracts induced hepatotoxicity and nephrotoxicity. Oral administration of herbal extracts (group C, D, E and F) limited leukaemic cell progression in MNU-induced leukaemia-lymphoma rats. Oral administration of mixtures E and F inhibited the metastasise of neoplastic lymphocytes in heart, lungs, liver and kidneys. Oral administration of all herbal mixtures down-regulated the serum MDA level in the MNU-induced leukaemia-lymphoma rats. It also enhanced the production of serum SOD level in the MNU-induced leukaemia-lymphoma rats treated with all herbal mixtures. Oral administration of mixtures E and F was able to down-regulate VEGF and COX-2 transcription and expression in MNU-leukaemia-lymphoma rats.

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Abstrak thesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai mematuhi keperluan untuk Ijazah Doktor Falsafah

KESAN ANTITUMOR CAMPURAN EKSTRAK BUAH *Morinda citrifolia* L. DAN DAUN *Clinacanthus nutans* (Burm. F.) LINDAU TERHADAP MODEL TIKUS SPRAGUE DAWLEY LEUKEMIA-LIMFOMA

Oleh

SAJJARATTUL NURUL NADIA ASYURA MOHAMAD IFFENDI

Disember 2016

Pengerusi: Hazilawati Hj. Hamzah, PhD
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Buah *Morinda citrifolia* L. (*M. citrifolia*) atau dikenali sebagai 'mengkudu' dan daun *Clinacanthus nutans* (Burm. F.) Lindau (*C. nutans*) atau dikenali sebagai 'rumput belalai gajah' adalah tumbuhan herba yang dikenali umum dan mempunyai ciri-ciri anti-kanser. Kesan anti-tumor daripada kombinasi ekstrak-ekstrak ini ke atas leukemia dan limfoma belum lagi dilaporkan. Tujuan bahagian pertama kajian ini dijalankan adalah untuk menilai ketoksikan oral ekstrak etanol buah *M. citrifolia* dan daun *C. nutans* dan kesan anti-tumor kombinasi ekstrak etanol ini ke atas MNU-induksi leukemia-limfoma di dalam tikus Sprague Dawley melalui penilaian hematologi dan biokimia serum, histopatologi, tahap penanda-bio tekanan oksidatif [malondialdehyde] dan enzim tekanan anti-oksidatif (glutation peroksidas) [GSH-Px] dan superoxisida dismutas [SOD], tahap transkripsi mRNA VEGF dan COX-2 di dalam darah, limfa dan nodus limfa dan tahap ekspresi protein VEGF dan COX-2 di dalam darah, limfa dan nodus limfa. Kajian ketokiskan akut selama 14 hari telah dijalankan untuk menilai dos kematian purata (LD_{50}), diikuti dengan kajian 28 hari ketoksikan subakut dan 13 minggu kajian ketoksikan subkronik untuk kedua-dua ekstrak. Di dalam kajian ketoksikan akut, tikus-tikus dibahagikan kepada empat kumpulan iaitu termasuk kawalan, 10% DMSO (pengangkutan) dan 2000 mg/kg daripada berat badan untuk kedua-dua ekstrak. Manakala di dalam kajian ketoksikan subakut, tikus-tikus dibahagikan ke kepada lapan kumpulan iaitu kawalan, 10% DMSO (pengangkutan), 75 mg/kg daripada berat badan, 125 mg/kg daripada berat badan dan 250 mg/kg daripada berat badan untuk kedua-dua ekstrak. Penilaian piawaian toksikologi termasuk kadar kematian, patologi kasar, hematologi, biokimia serum, dan pemeriksaan histopatologi ke atas hati dan buah pinggang telah dilakukan di akhir kajian. Keputusan kajian menunjukkan dos tunggal ekstrak etanol (2000 mg/kg) untuk buah *M. citrifolia* dan daun *C. nutans* tidak mengakibatkan ketoksikan akut ke atas tikus jantan Sprague Dawley. Pemberian oral buah *M. citrifolia* dan daun

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C. nutans pada dos 75 mg/kg daripada berat badan untuk 28 dan 90 hari tidak mengakibatkan ketoksikan subakut dan subkronik ke atas tikus jantan Sprague Dawley. Pemberian oral buah *M. citrifolia* dan daun *C. nutans* pada dos 125 mg/kg daripada berat badan untuk 28 dan 90 hari mengakibatkan hepatotoksisiti ke atas tikus jantan Sprague Dawley. Pemberian oral buah *M. citrifolia* dan daun *C. nutans* pada dos 250 mg/kg daripada berat badan untuk 28 dan 90 hari mengakibatkan hepatotoksisiti dan kenefrotiksikan ke atas tikus jantan Sprague Dawley.

Di dalam kajian MNU-induksi leukemia-limfoma, tikus dibahagi kepada tujuh kumpulan termasuk tikus kawalan (kumpulan A), tikus MNU-induksi leukemia-limfoma (kumpulan B), tikus leukemia-limfoma dirawat dengan empat kombinasi buah *M. citrifolia* dan daun *C. nutans* yang berlainan (kombinasi C [kumpulan C], kombinasi D [kumpulan D], kombinasi E [kumpulan E] dan kombinasi F [kumpulan F]) dan tikus leukemia-limfoma dirawat dengan regimen kimoterapi (CHOP) (kumpulan G). Tikus leukemia-limfoma telah diinduksi dengan menggunakan *N*-metil-*N*-nitrosourea (MNU) secara intraperitoneum (i.p) pada dos 60 mg/kg daripada berat badan, diberi sebanyak empat kali dalam tempoh dua minggu. Ekstrak etanol buah *M. citrifolia* dan daun *C. nutans* tersebut telah diberi secara gavaj oral sekali sehari bermula pada minggu ke-12 sehingga minggu ke-24 setelah MNU-diinduksikan. Sampel darah telah diambil dan dianalisa pada minggu ke-12 dan minggu ke-24. Jantung, paru-paru, hati, buah pinggang, modul limfa dan limfa telah diambil untuk dianalisa dan dinilai dengan lebih lanjut. Keputusan darah menunjukkan kehadiran sel-sel blastik pada minggu ke-12 dan minggu ke-24 di dalam tikus tidak dirawat dan dirawat. Kumpulan B and G mempunyai penaikkan yang ketara dalam nombor sel blastik dari minggu 18 ke 24. Pemberian oral kombinasi herba (kumpulan C, D, E dan F) telah menunjukkan keberkesanan dalam mengawal perkembangan sel-sel leukemia. Keputusan biokimia serum menunjukkan aras CK mempunyai peningkatan yang ketara dari minggu 18 ke 24 di dalam kumpulan C, D dan F. Aras LDH juga menunjukkan peningkatan yang ketara dari minggu 18 ke 24 di dalam kumpulan C dan F. Keputusan histopatologi menunjukkan kehadiran limfosit neoplastik di dalam semua limfa dan nodul limfa pada tikus yang tidak dirawat dan dirawat (kombinasi herbal dan CHOP). Pemberian oral kombinasi E dan F ke atas MNU-induksi leukaemia-lymphoma merencat metastasis limfosit neoplastik ke jantung, paru-paru, hati dan buah pinggang. Rawatan regimen CHOP ke atas tikus MNU-induksi leukaemia-lymphoma menyebabkan fibrosis yang ketara pada hati dan limfa serta nekrosis pada testis. Walau bagaimanapun, rawatan kombinasi herba ke atas tikus MNU-induksi leukaemia-lymphoma tidak mengakibatkan fibrosis dan nekrosis (testis). Tahap serum MDA telah menurun daripada minggu 18 ke minggu 24 di dalam tikus MNU-induksi leukemia-limfoma yang dirawat (kombinasi herba dan regimen CHOP). Tahap serum SOD di dalam tikus MNU-induksi leukemia-limfoma telah menaik daripada minggu 18 ke minggu 24 setelah dirawat dengan kombinasi herba dan regimen CHOP. Penurunan serum GPx telah diperhatikan pada minggu 18 ke minggu 24 dalam kesemua kumpulan tikus. Pemberian oral kombinasi herba kepada tikus MNU-induksi leukemia-limfoma telah bejaya merencat angiogenesis dan keradangan di dalam darah, limfa dan nodus limfa. Penurunan transkripsi mRNA VEGF dan COX-2 telah diperhatikan di dalam kumpulan tikus MNU-induksi leukemia-limfoma yang dirawat dengan kombinasi E dan F apabila dibandingkan dengan tikus MNU-induksi leukemia-limfoma yang tidak dirawat. Selain itu juga,

kombinasi F berjaya merencat ekspresi COX-2 ke atas nodul limfa tikus. MNU-induksi leukemia-limfoma melalui peniliaan immunohistokimia. Keputusan yang lebih tepat dan sensitif diperolehi daripada ujian Western blot di mana kombinasi E and F berjaya merencat ekspresi VEGF dan COX-2 di dalam tikus MNU-induksi leukemia-limfoma.

Secara konklusinya, pemberian dos tunggal (2000 mg/kg daripada berat badan) secara oral ekstrak etanol buah *M. citrifolia* dan daun *C. nutans* pada tidak mengakibatkan ketosikan akut ke atas tikus Sprague Dawley jantan. Pemberian oral ekstrak etanol buah *M. citrifolia* dan daun *C. nutans* pada dos 125 mg/kg daripada berat badan mengakibatkan hepatotoksisiti ke atas tikus Sprague Dawley jantan. Pemberian oral ekstrak etanol buah *M. citrifolia* dan daun *C. nutans* pada dose 250 mg/kg daripada berat badan mengakibatkan hepatotoksisiti dan kenefrotoksikan ke atas tikus Sprague Dawley jantan. Pemberian oral kombinasi herba (kombinasi C, D, E dan F) merencat perkembangan sel-sel leukaemia di dalam tikus MNU-induksi leukemia-limfoma. Pemberian oral kombinasi E dan F merencat metastasis limfosit neoplastic ke dalam jantung, paru-paru, hati dan buah pinggang. Pemberian oral kesemua kombinasi herba menurunkan tahap serum MDA di dalam tikus MNU-induksi leukemia-limfoma. Ia juga meningkatkan penghasilan serum SOD di dalam tikus MNU-induksi leukemia-limfoma. Pemberian oral kombinasi E dan F menurunkan transkripsi dan ekspresi VEGF dan COX-2 di dalam tikus MNU-induksi leukemia-limfoma.

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I certify that a Thesis Examination Committee has met on 22 December 2016 to conduct the final examination of Sajjarattul Nurul Nadia Asyura bt. Mohd Iffendi on her thesis entitled "Antitumour Effects of *Morinda citrifolia* L. Fruit and *Clinacanthus nutans* (Burm.f.) Lindau Leaf Mixtures in Leukaemia Lymphoma Bearing Sprague Dawley Rats" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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LIST OF ABBRREVIATIONS

AMTREC	Animal Metabolism, Toxicology and Reproductive Centre
COX-2	Cylooxygenase-2
CHOP	Cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone
CBC	Complete blood count
GPx	Glutathione Peroxidase
HL	Hodgkin's lymphoma
MDA	Malondialdehyde
MNU	*N*-methyl-*N*-nitrosourea
NHL	Non Hodgkin's lymphoma
SD	Sprague Dawley
SOD	Superoxide dismutase
VEGF	Vascular endothelial growth factor

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CHAPTER 1

INTRODUCTION

Cancer or malignant neoplasm is a group of diseases involving abnormal cells growth with the potential to invade or spread to other parts of the body. It is one of the major health problems in many parts of the world including Malaysia; it is also the second leading cause of death in the United States after heart disease and will become the leading cause of death in the next few years (Siegel *et al*., 2015). According to the National Cancer for Health (2015), 1,658,370 new cancer cases and 589,430 cancer deaths were estimated to occur in the United States in 2015. In Malaysia, cancer cases increased from 32,000 to 38,000 cases between 2008 and 2012 (International Agency of Research on Cancer) [IARC], 2012), and the top leading cancers are breast cancer (18.1%), head and neck cancer (13.2%), colorectal cancer (12.3%), tracheal, bronchial and lung cancers (10.2%), and cervix cancer (4.6%) (National Cancer Registry [NCR], 2012). Leukaemia and lymphoma are also among the top leading cancers in the United States (US). Approximately in every 3 minutes, one person in the US is diagnosed with blood cancer (Leukemia & Lymphoma Society, 2016).

Leukaemia is divided into four groups known as chronic lymphocytic leukaemia (CLL), acute lymphocytic leukaemia (ALL), chronic myeloid leukaemia (CML) and acute myeloid leukaemia (AML) (Bain, 2005) while lymphoma is divided into two main categories known as non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL). Leukaemia and lymphoma are haematopoietic cancers derived from haemopoietic and lymphatic systems (Mughal *et al.,* 2006). Leukaemia is a type of blood cancer caused by the overproduction of abnormal white blood cells (WBCs) in the bone marrow. Abnormal WBCs are unable to carry their normal functions to fight infections. Lymphoma, on the other hand, is cancer that starts in the cells of the lymphatic systems that include lymph nodes, thymus and spleen (Mughal *et al*., 2006). Both cancers are diagnosed by the presence of abnormal cells in the blood circulation and organs, (Sathiya & Muthuchelian, 2009). In 2013, 7.35% people with leukaemia in the United States died because of the disease (Leukaemia-lymphoma Society, 2013). As the seventh most common cancer in Malaysia, 741 to 1162 leukaemia cases were reported between the year 2007 and 2009. According to the National Cancer Registry Report (2007), 322 were females while the remaining 419 were males. As for lymphoma, it was estimated that there were between 761,659 and 841,649 people living with lymphoma worldwide from 2013 to 2014 (Leukamia-Lymphoma Society of United States, 2014).

Cyclooxygenases (COXs) or commonly known as prostaglandin H synthase are members of the myeloperoxidase family. These enzymes are mostly expressed and located in the endoplasmic reticulum and nuclear membrane of cells (Sobolewski *et al.,* 2010). Among COXs, cyclooxygenase-2 (COX-2) is a rate limiting enzyme involved in inflammatory reactions and synthesis of angiogenic prostaglandins (PG), for example prostaglandin-endoperoxidase-2 (PGE2) (Fosslien *et al.,* 2001). Activation of PGE2 induces angiogenesis factors which include vascular endothelial

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growth factor (VEGF) and inflammatory cytokines, particularly tumour necrosis factor (TNF). Overexpression of COX-2 is found in a variety of human malignancies including leukaemia (Egyudova *et al*., 2011) and lymphoma (Wun *et al*., 2004). The first evidence of a strong COX-2 expression was immunohistologically detected in the colorectal carcinoma (Wadell & Loughry, 1983). The immunohistological staining showed marked expression of COX-2 in tumour cells that were surrounded by numerous small vessels (Wadell & Loughry, 1983). Furthermore, expression of VEGF in the same area as of the tumour strongly suggests that overexpression of COX-2 induces angiogenesis (Fosslien *et al.,* 2001). It is shown that the expression of COX-2 is reduced by non-steroidal anti-inflammatory drugs (NSAIDs); however, prolonged use of the drugs could cause adverse gastrointestinal and cardiovascular side effects (Cha *et al*., 2007). Previous *in vitro* study has shown that *M. citrifolia* fruit extract inhibited COX-2 expression in the *Helicobactor pylori*-infected glandular cells (AG) cells. However, there is no report on the effects on the expression of this enzyme on cancel cell lines or patients or animals with cancer. Similar to *M. citrifolia,* the inhibition effects of *C. nutans* on the COX-2 expression have never been studied for both *in vitro* and *in vivo* studies of inflammatory or neoplastic diseases.

Angiogenesis is the growth of new blood vessels from the pre-existing blood vessels. It plays important roles in the pathogenesis of malignant tumour (Prager *et al*., 2012). Tumours require sustenance in the form of nutrients and oxygen as well as the ability to evacuate metabolic wastes and carbon dioxide as normal tissues. Tumour-associated neovasculature plays an important role in sustaining nutrients and oxygen in the microenviroment of the tumour. The development of vasculogenesis during embryogenesis involves the development of new endothelial cells and the sprouting of new vessels from the existing ones. During tumour progression, angiogenesis process is always activated, and it remains on. This process leads to the continuality of new blood vessels production that helps to sustain and expand the growth of the tumour (Hanahan & Folkman, 1996). Vascular endothelial growth factor (VEGF) is involved in the development and growth of new blood vessels during embryonic development, in homeostatic survival of endothelial cells, as well as in physiological and pathological process of cells (Hanahan & Weinberg, 2011). The expression of VEGF can be upregulated via hypoxia and signaling pathway (Ferara, 2004). Ferrara (2004) reported that overexpression of VEGF could lead to carcinogenesis and tumourigenesis. Upregulation of VEGF was discovered in various types of cancer including leukaemia, lymphoma, ovarian cancer, gastrointestinal tract cancer and prostate cancer (Brown *et al*., 1993; Bellamy *et al*., 2001; Duncan *et al*., 2008; Botelho *et al*., 2010; Roorda *et al*., 2012). Blocking of angiogenesis is one of the therapeutic ways in blocking cancer growth. No research has been done on *Morinda citrifolia* fruit and *Clinacanthus nutans* leaf in inhibiting angiogenesis in cancer. However, a study on stress-induced impairment cognitive function, showed low level of VEGF protein in the hypothalamus of restrained rats given *M. citrifolia* fruit juice (Muto *et al*., 2010).

Most herbal plants are rich in beneficial compounds such as fiber, vitamins, flavonoids, alkaloids, sulphur compounds, phytosterols, carotenoids and organic acids, which contribute positively to human health (Mohd Shukri *et al*., 2010). Herbal plants are also rich in antioxidant properties that play important roles in protecting

cells against oxidative stress-induced by diseases (Hertoq *et al*., 1992; WHO, 2003). Herbal plants such as *Morinda citrifolia* and *Clinacanthus nutans* are among the two most popular local plants in Malaysia that are being studied for market potential in the medicinal and pharmaceutical industries. Traditionally, *M. citrifolia* was used to treat bowel disorder by Polynesians (Wang *et al*., 2008) while *C. nutans* was traditionally used to treat Herpes simplex virus infection (Sakdarat *et al*., 2006). *M. citrifolia* is already known for its *in vitro* anti-cancer activity. In the non-small human lung cancer (NCI-H23), human cervical cancer (HeLa and SiHa) and human colorectal cancer cell lines, it exhibited anti-proliferative effects (Kharis *et al*., 2012; Nualsanit *et al*., 2012; Gupta *et al*., 2013). Meanwhile the *in vivo* anti-cancer activity of *M. citrifolia* was discovered in rats with Lewis lung carcinoma (Hirazumi *et al.*, 1994) and mammary tumour (Chew, *et al*., 1999; Clafshenkel *et al.*, 2012). In contrast to *M. citrifolia*, the anti-tumour potential of *C. nutans* has not been extensively explored. Previous study by Yong *et al*. (2013) reported that *C. nutans* extract possessed anti-proliferative effects on selected cancer cell lines. The treatment of *C. nutans* chloroform leaf extract showed the highest anti-proliferative activity on human erythroleukaemia cell lines (K-562) and human Burkitt's lymphoma cell lines (Raji). Meanwhile, aqueous extract of *C. nutans* leaves showed the highest anti-proliferative effects on human cervical cancer (Hela) and K-562 cell lines. Previous mentioned studies investigated the effects of non-mixtures of *M. citrifolia* fruit and *C. nutans* leaf on cancer. Therefore, this study was conducted to determine the toxicity of *M. citrifolia* fruit and *C. nutans* leaf extracts and the antitumour effects of mixtures of *M. citrifolia* fruit and *C. nutans* leaf extracts in MNU-induced leukaemia-lymphoma Sprague Dawley rats.

Research problem:

New cases of leukaemia and lymphoma had increased 10.2 % from 2014 to 2016 (Leukaemia and Lymphoma Society, 2016). The use of chemotherapy drugs had increased the five-year survival rates of leukaemia and lymphoma patients by only 2 % (2004-2010 to 2005-2011) (National Cancer Institute, 2015). Side effects of CHOP regimen in treating leukaemia and lymphoma such as hepatic fibrosis (Lim *et al*., 2010) and low sperm production in men (azoospermic) (Chan *et al*., 2009) have been reported. Thus, this study was conducted to evaluate the effects of mixture of *M. citrifolia* fruit and *C. nutans* leaf in alleviating the side effects of chemotheraphy drugs.

Justification of the study:

The study is conducted to seek alternative treatment for leukaemia-lymphoma.

The present study hypothesised that:

1) A single dose of 2000 mg/kg of ethanol extracts of *M. citrifolia* fruit and *C. nutans* leaf will induce no toxicity in male Sprague Dawley rats.

2) Once daily oral administration of ethanol extracts of *Morinda citrifolia* fruit and *Clinacanthus nutans* leaf at a dose of 75 mg/kg of body weight will induce no toxicity in male Sprague Dawley rats.

3) Once daily oral administration of ethanol extracts of *Morinda citrifolia* fruit and *Clinacanthus nutans* leaf at a dose of 125 mg/kg and 250 mg/kg of body weights will induce toxicity in male Sprague Dawley rats.

4) Mixtures of *M. citrifolia* fruit and *C. nutans* leaf extracts will enhance the anticancer acitivities and reduce leukaemia-lymphoma mestatasised in male MNU-induced leukaemia-lymphoma rats.

The objectives of the present study are:

1) to determine the acute (14 days), subacute (28 days) and subchronic (90 days) toxicity studies of ethanol extracts of *M. citrifolia* fruit and *C. nutans* leaf in male Sprague Dawley rats;

2) to investigate and evaluate the antitumour effects of mixtures of *M. citrifolia* and *C. nutans* in MNU-induced leukaemia-lymphoma Sprague Dawley rats; and

3) to evaluate the oxidative stress biomarker, antioxidative stress enzymes, VEGF and COX-2 in MNU-induced leukaemia-lymphoma rats treated with mixture of *M. citrifolia* and *C. nutans* extracts.

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