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CHEMOPREVENTIVE EFFECTS OF Citrus hystrix LEAF ETHANOLIC EXTRACT ON COLITIS-ASSOCIATED CANCER IN MICE

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By

NUR ILIYANI BINTI MOHD ISHAK

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

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

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October 2020

Chair : Prof. Suhaila Mohamed, PhD
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Inflammatory bowel disease (IBD) is a chronic inflammatory disorder that causes inflammation of the intestine, predominantly in the elderly. Patients with IBD are associated with high risk of colorectal cancer (CRC), namely, colitis associated cancer (CAC). Therefore, fluorouracil (5-FU) is the most prescribed medication for CRC to kill cancer cells and abate the cancer from proliferating. However, patients often develop side effects towards 5-FU. Thus, herbal medicines for CRC that have anti-inflammatory and antioxidant properties may offer safer alternative. This study aims to investigate the efficacy of *Citrus hystrix* leaf extract (CLE) in alleviating CAC.

The CLE extract was subjected to UHPLC/MS/MS while MTT assay was employed to assess the in vitro cytotoxic effect of the CLE. The in vivo study utilized male Balb/c mice that were randomly assorted into six groups (n=12): normal control, tumour control Azoxymethane (AOM)/Dextran Sulfate Sodium (DSS), positive control (Limonin; 50 mg/kg body weight) and treated CLE at 100, 200 and 300 mg/kg body weight. Mice were intraperitoneally injected with AOM (10 mg/kg body weight). A week post-injection of AOM, mice received 2% DSS for 7 days via drinking water, followed by regular drinking water during the recovery period. Treatments were orally administered through drinking water for 17 weeks post-induction with AOM/DSS. The CAC development was monitored via macroscopic, histopathological observations, protein biomarkers, mRNA expression and immunophenotyping analysis.

The UHPLC/MS/MS showed CLE contains taxifolin, hesperidin, diosmin, tangeritin, quercitrin, catechin, isovitexin, apiin, apigenin, isovitexin, rutin, luteolin, torachrysone, pelargonidin, kaempferol, xanthotoxol, and their glucosides. The in vitro study showed that CLE exerted cytotoxic effects on HT-29 cells growth at IC50 = 18.93 µg/mL after 24 hours incubation. CLE also did not cause any cytotoxicity towards normal 3T3 cells. Thus, CLE effect on colitis associated cancer was further investigated in an animal model to see how the body respond to CLE absorption in the body of mice.

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In the animal study, the CLE administration has altered disease activity index (DAI) score, colon shortening, spleen weight and histological damage (colon, kidney, and liver). The CLE treatment alleviated AOM/DSS-induced colitis-associated cancer (CAC) by significantly ($p<0.05$) suppressed the pro-inflammatory (TNF-α, iNOS and PGE2), cell proliferation and cell cycle (β-catenin and Cyclin-D1), oxidative stress (MDA) and colon cancer markers (CCA). These findings were supported with anti-tumour effects of CLE which significantly ($p<0.05$) increased anti-inflammatory (TGF-β1), antioxidant (Nrf2, Sod2, GSH), immune (IFN-γ, CD8a and CD11b) and tumour suppressor (p53) biomarkers. The results also indicated that CLE enhanced tissue healing or regeneration of healthy tissues (Stat3, Myc, CD4, Vegfa, Hif-1α, Caspase-3 and Bcl-2). In addition, the CLE significantly ($p<0.05$) increased T cells (CD4 and CD8) and B cells (CD19) and significantly reduced ($p<0.05$) natural killer cells (CD335) in spleen tissues.

Altogether, this study can conclude that CLE has great potential in attenuating colitis-associated cancer (CAC) in colon cancer induced mice via multiple pathways including inflammation, oxidative stress, antioxidant activity and immunity. CLE also protected colon through the reduction in tumor incidence and histological damage.

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KESAN EKSTRAK DAUN LIMAU PURUT KE ATAS KANSER YANG BERKAITAN DENGAN KOLITIS (CAC) DI DALAM MODEL MENCIT

Oleh

NUR ILIYANI BINTI MOHD ISHAK

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Penyakit radang usus (IBD) adalah penyakit kronik yang menyebabkan keradangan usus, terutamanya pada orang tua. Pesakit dengan IBD dikaitkan dengan risiko kanser kolorektal (CRC), iaitu kanser kolitis (CAC). Oleh itu, fluorouracil (5-FU) adalah ubat yang paling biasa dipreskripsikan untuk merawat CRC bagi membunuh sel-sel kanser dan mengurangkan kanser daripada membiak. Walau bagaimanapun, 5-FU akan membawa kesan sampingan di kalangan pesakit. Oleh itu, ubat-ubatan herba untuk CRC yang mempunyai sifat anti-radang dan antioksidan boleh menawarkan rawatan alternatif yang lebih selamat. Justeru itu, kajian ini dijalankan untuk mengkaji keberkesanan ekstrak daun Citrus hystrix (CLE) dalam meredakan CAC.

Dalam kajian awal in vitro, kesan sitotoksik CLE diuji menggunakan ujian asai 3-(4,5-dimetiltiazol-2-il)-2,5 difenil tetrazolium bromida (MTT). Dalam kajian in vivo, mencit Balb/c jantan dibahagikan secara rawak kepada 6 kumpulan (n=12) mencit setiap kumpulan): kawalan normal, kawalan tumour Azoxymethane (AOM)/ Dextran Sulfate Sodium (DSS), kawalan positif (Limonin, 50 mg/kg berat badan) dan diperlaku ekstrak daun *Citrus hystrix* (CLE) pada kadar 100, 200 dan 300 mg/kg berat badan. Mencit disuntik secara intraperitoneal dengan AOM (10 mg / kg berat badan). Selepas seminggu suntikan AOM diberikan, mencit menerima 2% DSS selama 7 hari melalui air minuman, diikuti oleh air minum biasa untuk tempoh pemulihan. Rawatan ekstrak secara oral diberikan melalui air minuman selama 17 minggu selepas diinduksi oleh AOM/DSS. Pengembangan CAC dipantau melalui analisis makroskopik, histopatologi, ekspresi protein, mRNA dan immunophenotype.

UHPLC/MS/MS menunjukkan CLE mengandungi taxifolin, hesperidin, diosmin, tangeritin, quercitrin, catechin, isovitin, apiin, apigenin, isovitin, rutin, luteolin, torachrysone, pelargonidin, kaempferol, xanthotoxol, dan glukosida mereka. Kajian awal in vitro menunjukkan bahawa CLE memberikan kesan sitotoksik pada pertumbuhan sel HT-29 di IC50 = 18.93 µg / mL selepas pengeraman24 jam. CLE juga

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tidak menunjukkan kesan sitotoksik terhadap sel normal (3T3). Oleh itu, kesan CLE pada kanser yang berkaitan dengan kolitis dikaji lebih lanjut dalam model haiwan untuk melihat bagaimana tubuh bertindak balas terhadap penyerapan CLE dalam model mencit.

Dalam kajian haiwan, CLE menunjukkan perbezaan yang jelas dalam skor aktiviti penyakit (DAI), pemendekan kolon, berat limpa dan histologi antara mencit-mencit AOM/DSS, yang sihat dan kumpulan yang dirawat. Rawatan CLE mengurangkan AOM/DSS akibat kanser berkaitan kolitis (CAC) secara tererti ($p<0.05$) melalui faktor pro-inflamasi (TNF-α, iNOS dan PGE2), proliferasi sel dan kitaran sel (β-catenin dan Cyclin- D1), tekanan oksidatif (MDA) dan penanda kanser kolon (CCA). CLE juga meningkatkan kesan anti-tumour secara tererti ($p<0.05$) melalui faktor anti-inflamasi (TGF-β1), antioksidan (Nrf2, Sod2, GSH), imun (IFN-γ, CD8a dan CD11b) dan penindas tumour (p53). Hasil ini juga menunjukkan bahawa CLE menggalakkan penyembuhan tisu atau regenerasi tisu yang sihat (Stat3, Myc, CD4, Vegfa, Hif-1α, Caspase-3 dan Bcl-2). Di samping itu, CLE secara tererti ($p<0.05$) meningkatkan sel T (CD4 dan CD8) dan sel B (CD19) dan mengurangkan secara tererti ($p<0.05$) sel pembunuh semulajadi (CD335) dalam tisu limpa.

Secara keseluruhannya, kajian ini menyimpulkan ekstrak daun *Citrus hystrix* (CLE) mempunyai potensi besar dalam melemahkan kanser yang berkaitan dengan kolitis (CAC) pada mencit yang diinduksi dengan kanser kolon melalui keradangan, tekanan oksidatif, aktiviti antioksidan dan imuniti. CLE juga melindungi usus besar melalui pengurangan kejadian kanser dan kerosakan histologi.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

ACF	Aberrant crypt foci
AKT	Protein kinase B (PKB)
AOM	Azoxymethane
APC	Adenomatous polyposis coli
ARE	Antioxidant responsive element
ATCC	American type culture collection
BCL-2	B-cell leukemia/lymphoma 2
BRAF	V-raf murine sarcoma viral oncogene homolog B
CA 19-9	Carbohydrate antigen (CA) 19-9
CAC	Colitis-associated cancer
CAF	Cancer-associated fibroblast
CASP3	Caspase 3
CAT	Catalase
CCA	Colon cancer antigen
CD	Chron's disease
CD	Cluster of differentiation
CEA	Carcinoembryonic antigen
CIMP	CpG island methylator phenotype
CIN	Chromosomal instability
CLE	Citrus hystrix leaf extract
CRC	Colorectal cancer
CTC	Computer tomographic colonoscopy
CTL	Cytotoxic T lymphocyte
CTNNB1	Catenin Beta 1

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CXCL	Chemokine (C-X-C motif) ligand
CCDN1	Cyclin-D1
DCBE	Double contrast barium enema
DMEM	Dubecco's modified eagle medium
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
DSS	Dextran sulfate sodium
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
eNOS	Endothelial NOS
ERK	Extracellular-signal-regulated kinase
FBS	Fetal bovine serum
FC	Folin-ciocalteau
FDA	Food and drug administration
FOBT	Fecal occult blood test
FOLFIRI	5-fluorouracil + leucovorin + irinotecan
FOLFOX	5-fluorouracil + leucovorin + oxaliplatin
FS	Flexible sigmoidoscopy
FTIR	Fourier transform infrared
FU	Fluorouracil
GPx	Glutathione peroxidase
GR	Glutathione reductase
GSH	Reduced glutathione
GST	Glutathione S-transferase
H2O2	Hydrogen peroxide
HESI	Heated electrospray positive ionization

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HIF-1α	Hypoxia inducible factor 1, alpha subunit
HPGDH	Hydroxyprostaglandin dehydrogenase
HSP	Heat shock protein
HT-29	Human colon adenocarcinoma cell
IACUC	Institutional animal care and use committee
IBD	Inflammatory bowel disease
IEC	Intestinal epithelial cell
IFN-γ	Interferon gamma
IκB	Inhibitor of κB
IKKβ	Inhibitor of nuclear factor kappa-B kinase subunit beta
IL	Interleukin
IL-1β	Interleukin 1 beta
iNOS	Inducible nitric oxide synthase
iPLA2	Calcium-independent phospholipase A2 activity
JAK	Janus kinase
KEAP1	Kelch Like ECH Associated Protein 1
KRAS	Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
MAM	Methylazoxymethanol
MAPK	Mitogen-activated protein kinase
MCL-1	Myeloid cell leukemia 1
MDA	Malondialdehyde
MDSCs	Myeloid derived suppressor cells
MHC	Major histocompatibility complex
mir-1269a	MicroRNA 1269a
MSI	Microsatellite instability
MTT	[3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide]

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MYC	Myelocytomatosis oncogene
MySCAN	Malaysian Study on Cancer Survival
NC	Normal control
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NK	Natural killer
nNOS	Neuronal NOS
NO	Nitric oxide
NRAS	Neuroblastoma RAS viral oncogene homolog
NRF2	Nuclear factor erythroid 2-related factor 2
O2-	Superoxide
OH●	Hydroxyl radicals
p53	Tumour suppressor gene
PBS	Phosphate-buffered saline
PC	Positive control
PGE2	Prostaglandin E2
PI3K	Phosphoinositide 3-kinase
RNA	Ribonucleic acid
ROS	Reactive oxygen species
SMAD4	Mothers against decapentaplegic homolog 4
SOD	Superoxide dismutase
SOX4	SRY-Box Transcription Factor 4
STAT3	Signal transducer and activator of transcription 3
TC	Tumour control
TCF/LEF	T-cell factor/lymphoid enhancer-binding factor
TCR	T-cell receptor

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TGF-β1	Transforming growth factor beta 1
TH1	Type 1 T helper
TNBS	Trinitrobenzene sulphonic acid
TNF-α	Tumour necrosis factor alpha
TNFR	Tumour necrosis factor receptor
UC	Ulcerative colitis
UHPLC-MS/MS	Ultra-high performance liquid chromatography-tandem mass spectrometry
UV	Ultraviolet
VEGFA	Vascular endothelial growth factor A
WHO	World Health Organization
WT	Wild type

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CHAPTER 1

INTRODUCTION

1.1 Research background

Colorectal cancer (CRC) is one of the top three cancer killers worldwide and is a significant economic drain, especially in low- and middle-income countries (World Health Organization, 2019). CRC is the second most common type of cancer in men (1,026,215 cases or 10.9 % of all cancer cases) and third most common type of cancer in women (823,303 cases or 9.5 % of all cancer cases) (Arnold et al., 2017). CAC is a significant complication of inflammatory bowel disease (IBD). It often progresses from chronically inflamed mucosa to dysplasia and, eventually, colorectal cancer (Axelrad et al., 2016).

Surgery, neoadjuvant chemotherapy, and radiotherapy are the most often used treatments, but they all have many unpleasant and unwanted side effects. Capecitabine (Xeloda), Fluorouracil (5-FU), Irinotecan (Camptosar), Oxaliplatin (Eloxatin), and Trifluridine/tipiracil (Lonsurf) have all been approved by the FDA as chemotherapeutic agents for colorectal cancer. Chemotherapy, however, can result in fatigue, diarrhoea, hair loss, nausea, and vomiting. These results emphasise the critical need for significantly more successful treatment of CRC.

A new effective approach for cancer prevention has been identified in dietary sources as insufficient intake of fruits and vegetables is strongly associated with the risk of CRC. Bioactive compounds (polyphenols or flavonoids) have been investigated for their anticancer properties through their ability to modulate cell signalling pathways and gene regulation involved in cell cycle arrest, differentiation, and apoptosis (Pan et al., 2011). These phytochemicals may be beneficial in the prevention or treatment of colorectal cancer, and when combined with certain medications, they may have additive, synergistic, or antagonistic effects on cancer treatment.

Citrus hystrix leaf extract (CLE) from Malaysia has been shown to possess a variety of biological activities, including antioxidant, free radical scavenging, cytotoxic, anti-inflammatory, and hepatoprotective. (Abirami et al., 2015), cardiovascular protective (Siti et al., 2017), antimicrobial and anti-tumour activities (Panthong et al., 2013; Tunjung et al., 2015). Limonoids have received considerable attention because of their biological functions in in vitro and in vivo study (Zhang et al., 2013). The most abundant limonoid in Citrus fruits, especially limonin and obacunone, showed anti-cancer activities on cancer cell lines (Kim et al., 2013; Shimizu et al., 2015) and prevent the incidence of colonic aberrant crypt foci (ACF) in AOM-induced rat (Tanaka et al., 2000). Most studies on Citrus fruit compounds that helped suppressed

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colon carcinogenesis, is on limonene a common cyclic terpene, but limonene is not present in this Citrus leaf compounds mixture (Kaur & Kaur, 2015).

To the best of our knowledge, there is to date no report on the effect of CLE on colorectal cancer in vivo. This study hypothesizes that dietary CLE has the potential to abate CAC via anti-cancer pathways and mechanisms in a mouse model.

1.2 Justification of the study

Anticancer properties of natural products have increased dramatically over the years. For instance, the National Institutes of Health are acquiring and screening substances from natural products for their medicinal properties. On top of that, most solid tumours being unresponsive to most chemotherapeutic drugs, there's also dose-limiting toxicity and unfavourable side effects in adult use (Hesketh, 2008).

Citrus hystrix appears to have an antitumorigenic and chemoprotective effect on disease. Pre-clinical and clinical studies have found that citrus hystrix appears to have antitumor properties, as well as tolerable side effects. However, up to this point, no evaluation has looked at the effectiveness of the citrus hystrix leaf in treating cancer or the toxicology of the citrus leaf extract on animal study have been done, and thus its mechanism of action has remained unknown. Thus, the action of citrus hystrix may be mediated by a variety of molecules, but the exact signalling network is still unclear. In this project, it was to investigate the chemopreventive activity of citrus hystrix leaf extract and its mechanism.

1.3 Hypothesis of the study

The CLE treatment alleviated AOM/DSS-induced colitis-associated cancer (CAC) via suppression of pro-inflammatory, cell proliferation and cell cycle, oxidative stress, and colon cancer markers. These findings were supported with anti-tumor effects of CLE by activation of anti-inflammatory, antioxidant, immune and tumor suppressor biomarkers. The results also indicated that CLE could enhanced the tissue regeneration process of damages or diseased tissues.

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1.4 General objective

To investigate the chemo-preventive effect of CLE against colitis-associated cancer (CAC) in Balb/c mice.

1.5 Specific objectives

a) to identify the active compounds of CLE.
b) to determine the inhibitory effect of CLE on HT-29 colon cancer cell line.
c) to investigate the preventive effect of CLE in AOM/DSS-induced CAC in Balb/c mice model.
d) to verify the mechanisms involved in AOM/DSS-induced CAC in Balb/c mice model.

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