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INFLUENCE OF CARICA PAPAYA L. CONSUMPTION ON THE LYMPHOCYTE PHENOTYPES IN MALES AND FEMALES

NUR RAMZIAHRAZANAH BINTI JUMAT

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By

NUR RAMZIAHRAZANAH BINTI JUMAT

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

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Master of Science

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Chairman : Associate Prof. Maha Abdullah, PhD

Faculty : Medicine and Health Sciences

The immune system that protects human body from infection consists of innate and adaptive immunity. Cytotoxic immune response specifically provides protection against intracellular pathogens and tumor cells. Natural killer (NK) and cytotoxic $CD8^+$T cells (CTLs) are cells of innate and adaptive immunity, respectively, that participates and play major roles in cytotoxic immune response. Immune-related conditions such as cancer and autoimmune diseases present with gender biasness and may be linked to sex hormones which modulates the immune system. Fruits and vegetables boost the immune response and may also have effect on the endocrine system. The impact of fruits and vegetables on the immune system of the different genders is still unknown. *Carica papaya* is one of the commonly consumed fruits in Malaysia but traditionally implied unsuitable for pregnant women. The current study was carried out to evaluate hormonal changes and alterations in lymphocytes phenotypes from consumption of ripe papaya. Eighteen healthy individuals, (n=9 and female, n=9) were recruited and underwent a four-day controlled diet study. Volunteers were abstained from taking papaya for two days and followed by two days of papaya exposure. Whole blood samples were collected on the third and fifth day of experiment. Lymphocyte subsets distribution, activation, IFN-γ production, cytokine receptors (IL-21R, IL-12Rβ2 and IL-15Rα) expression, CD107a degranulation and NK cell cytotoxicity were performed using flow cytometry. Levels of sex hormones (17β-estradiol, progesterone and testosterone) were also determined and correlated with the

immune profiles. Papaya consumption significantly increased progesterone levels in all the volunteers (p=0.039, n=18) and levels of 17β-estradiol (p=0.036, n=9) and progesterone (p=0.039, n=9) in females. Increased percentage of $CD4^{+}$T cells (p= 0.028, n=18) but reduced percentage of $CD3^{-}CD56^{+}IL\text{-}21R^{+}$ (p=0.031, n=18) following *C. papaya* consumption were generally observed in all volunteers. In females, the percentage of $CD4^{+}$ T (p=0.036, n=9) and $CD8^{+}$ T (p=0.038, n=9) cells were significantly increased and $CD3^{-}CD56^{+}IL\text{-}21R^{+}$ (p=0.035, n=9) cells remained significantly suppressed after papaya consumption. However, these effects were not significant in males. *C. papaya* consumption increased the percentage of $CD4^{+}CD45RA^{-}CD69^{-}$ central/effector memory T cells (p=0.017, n=8) but reduced percentage of $CD8^{+}$ T (p=0.028, n=9) and absolute count of B cells (p=0.021, n=9) in males. Increased percentages of NK cell cytotoxicity when co-cultured with K562 cells were observed for both ½ (p=0.032, n=18) and ¼ (p=0.022, n=18) diluted whole blood when compared in all volunteers after *C. papaya* consumption but not within gender. Correlation analysis showed 17β-estradiol levels in females (n=9) were positively correlated with absolute count of B, $CD4^{+}$ T and $CD3^{+}$ T cells and NK cells producing IFN-ɣ after papaya consumption but negatively associated with percentage of $CD8^{+}$ T cells and $CD4^{+}CD25^{+}$ T cells. In addition, levels of progesterone in females (n=9) were also significantly associated with percentage of $CD4^{+}CD45RA^{+}CD25^{+}$ of late activated effector T cells after *C. papaya* consumption. Testosterone levels in males (n=9) positively correlated with percentage of $CD4^{+}$ T cells but negatively correlated with $CD8^{+}$ T cells count after *C. papaya* consumption. Thus, papaya consumption modulated many immune profiles including cytotoxic responses as a response to changes in the hormone levels.

Abstrak thesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Sarjana Sains

KESAN PENGAMBILAN BETIK TERHADAP FENOTIP SEL IMUN DI ANTARA LELAKI DAN PEREMPUAN

Oleh

NUR RAMZIAHRAZANAH BINTI JUMAT

Jun 2015

Pengerusi **: Prof. Madya Maha Abdullah, PhD**

Fakulti **: Perubatan dan Sains Kesihatan**

Sistem imuniti yang melindungi tubuh manusia daripada serangan jangkitan terdiri daripada sistem imuniti semulajadi dan adaptif. Tindak balas sitosik sel imun menyediakan perlindungan imuniti daripada patogen intrasel dan sel-sel tumor. Sel NK dan sel sitotoksik $CD8^+$ T (CTLs) merupakan sel-sel imun yang masing-masing terlibat dalam imuniti semulajadi dan adaptif yang memainkan peranan penting dalam tindak balas sitotosik. Keadaan yang berkaitan dengan sistem imun seperti kanser dan penyakit autoimun lebih cenderung berlaku terhadap jantina tertentu dan mungkin boleh dipengaruhi oleh hormon seks yang juga dipercayai dapat mengawal sistem imun. Pengambilan buah-buahan dan sayur-sayuran dapat meningkatkan tindak balas sistem imun dan mungkin juga dapat mempunyai kesan terhadap sistem endokrin. Namun begitu, kesan pengambilan buah-buahan dan sayur-sayuran terhadap sistem imuniti masih lagi tidak diketahui. *Carica papaya* merupakan salah satu buah-buahan yang biasanya dijumpai di Malaysia tetapi dipercayai secara tradisi tidak sesuai untuk wanita hamil. Oleh itu, kajian ini telah dijalankan untuk menilai perubahan hormon dan kesan terhadap fenotip sel imun selepas pengambilan betik yang telah masak. Lapan belas individu yang sihat (lelaki, n=9 dan perempuan, n=9) telah terlibat dalam kajian kawalan diet selama empat hari. Para peserta ditegah daripada memakan betik selama dua hari dan seterusnya diikuti dengan dua hari pengambilan betik. Sampel darah kemudian diambil pada hari ketiga dan kelima eksperimen. Ujian terhadap penentuan subset limfosit, pengaktifan limfosit, penghasilan IFN-γ, ekspresi reseptor sitokin (IL-

21R, IL-12Rβ2 dan IL-15Rα), degranulasi CD107a dan tindak balas sitotosik sel NK telah dijalankan menggunakan 'flow cytometry'. Pemerhatian terhadap tahap hormon seks (17β-estradiol, progesteron dan testosteron) juga telah dibuat dan kemudian dikaitkan dengan profil-profil imun yang telah dikaji. Pengambilan betik menyebabkan peningkatan yang ketara terhadap tahap progesteron di kalangan semua peserta (p=0.039, n=18) dan tahap 17β-estradiol (p=0.036, n=9) dan progesteron (p =0,039, n=9) di kalangan subjek perempuan. Peningkatan yang ketara terhadap peratusan sel $CD4^+$ T (p= 0.028, n=18) dan penurunan ketara terhadap peratusan sel $CD3^-CD56^+IL\text{-}21R^+$ (p=0.031, n=18) selepas pengambilan betik dapat diperhatikan secara keseluruhan di kalangan para peseerta. Peningkatan yang ketara juga dapat diperhatikan dalam peratusan sel $CD4^+$ T (p=0.036, n=9) dan $CD8^+$ T (p=0.0038, n=18) tetapi menyebabkan penurunan ketara terhadap peratusan sel $CD3^-CD56^+IL\text{-}21R^+$ (p= 0.035, n=9) di kalangan subjek perempuan tetapi tiada kesan ketara dapat diperhatikan di kalangan peserta lelaki. Pengambilan betik juga dapat meningkatkan peratusan sel $CD4^+CD45RA^-CD69^-$ (p=0.017, n= 8) T efektor/pusat memori tetapi menyebabkan penurunan terhadap peratusan sel $CD8^+$ T (p= 0.028, n=9) dan kiraan mutlak sel B (p= 0.021, n=9) di kalangan peserta lelaki sahaja. Disamping itu, peningkatan ketara terhadap peratusan tindak balas sitotosik sel NK terhadap sel K562 apabila dikulturkan dengan darah yang dicairkan kepada ½ (p=0.032, n=18) dan ¼ (p=0.022, n=18) dapat diperhatikan secara keseluruhan di kalangan para peserta selepas pengambilan betik tetapi tiada perubahan yang ketara dapat dilihat apabila dibandingkan di kalangan peserta lelaki atau perempuan. Analisis korelasi menunjukkan bahawa terdapat hubungan positif yang ketara di antara tahap 17β-estradiol di kalangan peserta perempuan (n= 9) dengan kiraan mutlak sel B, $CD4^+$ T and $CD3^+$ T dan juga peratusan sel $CD3^-CD56^+IFN\text{-}\gamma^+$ tetapi mempunyai hububungan negatif yang ketara terhadap peratusan sel $CD8^+$ T dan $CD4^+CD25^+$ T selepas pengambilan betik. Di samping itu, tahap progesteron di kalangan peserta perempuan (n= 9) juga telah didapati mempunyai hubungan yang signifikan terhadap peratusan sel-sel $CD4^+CD45RA^+CD25^+$ efektor T yang lewat diaktifkan selepas pengambilan betik. Tahap testosteron di kalangan peserta lelaki sahaja didapati mempunyai hubungan positif yang ketara terhadap peratusan sel $CD4^+$ T tetapi mempunyai hubungan negative yang ketara terhadap kiraan mutlak sel $CD8^+$ T. Justeru itu, pengambilan betik dapat disimpulkan bahawa boleh mempengaruhi pelbagai profil sel imun termasuk tindak balas sitotoksik disebabkan oleh perubahan tahap hormon.

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I certified that a Thesis Examination Committee has set on 19 June 2015 to conduct the final examination of Nur Ramziahrazanah binti Jumat on her thesis entitled "Influence of *Carica papaya* L. Consumption on the Lymphocyte Phenotypes in Males and Females" 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 Master of Science.

Members of the Thesis Examination Committee were as follows:

Seow Heng Feng, PhD.
Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
Chairman

Loh Su Peng, PhD.
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Internal Examiner)

Norazmi Mohd Nor, PhD.
Professor
Universiti Sains Malaysia
(External Examiner

ZULKARNAIN ZAINAL, PhD
Professor and Deputy Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 22 September 2015

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

Maha Abdullah, PhD.
Asscociate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairman)

Rosita Jamaluddin, PhD.
Asscociate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

Zainina Seman, MD
Senior Lecturer
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

Wong Nyet Kui, PhD.
Associate Professor
Faculty of Science and Natural Resources
Universiti Malaysia Sabah
(Member)

_____
BUJANG BIN KIM HUAT, PhD
Professor and Dean
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Name of Chairman of Supervisory Committee	: Maha Abdullah, PhD	Name of Member of Supervisory Committee	: Rosita Jamaluddin, PhD
Signature	:	Signature	:
Name of Member of Supervisory Committee	: Wong Nyet Kui, PhD	Name of Member of Supervisory Committee	: Zainina Seman, MD

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AD	Autoimmune diseases
AITD	Autoimmune thyroid disease
APC	Antigen presenting cells
AR	Androgen receptor
BID	BH3-interacting domain
CFSE	Carboxufluorescein succinimidyl ester
CD	Cluster of differentiation
CO_2	Carbon dioxide
CRC	Colorectal cancer
CTL	Cytotoxic T lymphocyte
DISC	Death-inducing signaling complex
DMSO	Dimethyl sulfoxide
EDTA	Ethylenediaminetetraacetic acid
ER	Estrogen receptor
FasL	Fas ligand
FBS	Fetal bovine serum
FVJC	Fruit and vegetables juice concentrate
HIV	Human immunodeficiency virus
IFN-ɣ	Interferon gamma
IL-	Interleukin-
KAR	Killer activating receptors
LAMP-1	Lysosome-associated protein-1
LPS	Lipopolysaccharide
MHC	Major histocompatibility complex
mRNA	Messenger RNA
NK	Natural killer
OC	Oral contraceptives
PAMP	Pathogen-aasociated molecular patterns
PBMC	Peripheral blood mononuclear cells
PBS	Phosphate buffer saline
pH	Power of hydrogen
PMA	Phorbol-12-myristate-13-acetate
PR	Progesterone receptor
PS	Phosphatidylserine
RA	Rheumatoid arthritis
RBC	Red blood cells
RPMI	Roswell Park Memorial Institute
SD	Standard deviation
SLE	Systemic lupus erythematosus
SS	Sjogren's Syndrome
T1D	Type 1 diabetes
T_{CM}	Central memory T cells
TCR	T cell receptor
T_{EM}	Effector memory T cells
TGF-β	Tumor growth factor- beta

Th	Helper T cells
TLR	Toll-like receptor
TME	Tumor microenvironment
TNF	Tumor necrosis factor
Tregs	Regulatory T cells
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

The immune system protects from infection and prevents formation of tumor in the body. In general, the human immune system can be divided into innate and acquired immune system. These systems consist of cells and molecules that interact, regulate and perform unique and redundant functions. Two cell types from the innate and adaptive systems, respectively, play major roles in the killing of virus infected cells and tumors (Segerstrom & Miller, 2004; Fehniger *et al*., 2003).

Natural killer (NK) cells and cytotoxic $CD8^+$ T cells (CTLs) are lymphocyte effector cells that take part in cytotoxic immune cell responses. Cytotoxic immune cell responses are important in order to help the body to fight against intracellular pathogens and tumor cells (Grossman *et al*., 2004). NK cells are a part of innate immune system and do not require prior stimulation for their cytotoxicity. CTLs on the contrary participate in acquired immunity and they require at least three signals for activation via interaction with MHC class I molecule. However, both NK cells and CTLs use similar cytotoxic effector pathways regardless of their differences in recognition and cell signalling pathway (Zaritskaya *et al*., 2010).

"Health and well-being" is a major concern in society especially in this modern era. The younger generation tend to lack awareness of the importance of health and well-being and focus more on appearance that lead to development of unhealthy habits (Kim, 2014). Unhealthy lifestyle habits that normally develop during youth such as lack of exercise and sleep, alcohol consumption, smoking and poor diet are alarming as these may be major contributors that lead to the development of chronic illness such as obesity, cancer, diabetes, cardiovascular disease, hypertension and stroke. These diseases are also associated with a stressed immune system (Dodd *et al*., 2010; WHO Report, 1990).

Consumption of fruits and vegetables is known to boost the immune system (Lampe, 1999). A negative correlation between intake of fruits and vegetables and incidence of chronic diseases such as cancer and atherosclerosis has been reported by various studies. Fruits and vegetables are known to be rich in nutrient such as vitamins, trace minerals, dietary fibre and many other biologically active compounds. These compounds have been proven to have health-enhancing effect. Promoting a healthy lifestyle through direct intake of fruits and vegetables is a cost effective method for disease prevention, reduces usage of expensive drugs and their side effects (Brandt *et al*., 2004). Furthermore, isolating pure compounds from natural products may cause loss in bioactivity or prevent whole food from behaving in the same manner in its original form (Heber, 2004).

Gender is a factor that influences immune function. Sexual dimorphism has been documented in both humoral and cell-mediated immune response in humans. Studies have found that humoral and cell-mediated immune response is more active in females compared to males (Klein, 2000). Thus, females have been reported to have higher immunoglobulin levels and stronger antibody response, which increased resistance to certain infections (Grossman, 1985). Females are able to reject allografts and tumors successfully compared to males (Shames, 2002). However, females are more prone to suffer from autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren syndrome (SS), autoimmune thyroiditis and inflammatory myopathies (Abdou & Rider, 2010). Diseases such as asthma and coronary artery disease have been reported to be higher in males (Ensom, 2000).

Other studies have reported on gender differences in number and activity of NK cells and CTLs. In contrast to the above, NK cells and $CD8^+$ T cells percentage and NK cell activity in men were higher compared to women (Abdullah *et al*., 2012; Uppal *et al*., 2003; Yovel et al., 2000). Thus, it is not surprising that sex hormones affects immune functions (De Leon-Nava *et al*., 2009). Sex hormones are regulated by the neuroendocrine systems and interactions between the immune and neuroendocrine systems have been reported by various studies and are more apparent in conditions such as pregnancy, autoimmune diseases and some infectious diseases.

Carica papaya is a fruit commonly consumed and can easily be found in Malaysia. Many studies have reported on the various medical benefits including immunomodulatory potentials from various components of the plant (Dharmarathna *et al*., 2013; Abdullah *et al*., 2011; Ahmad *et al*., 2011; Otsuki *et al*., 2009). However, there is no clear evidence whether genders respond differently to immunomodulatory factors. Thus, the present study was conducted to evaluate responses in cytotoxic immune cells of healthy volunteers to papaya consumption.

Objectives of this study are:

1. To determine levels of sex hormones in plasma after papaya consumption in healthy males and females.

2. To determine absolute number, activation, and cytokine expression in natural killer (NK) and cytotoxic ($CD\ 8^+$) T cells of healthy males and females after papaya consumption.

3. To determine functional responses of natural killer (NK) and cytotoxic ($CD\ 8^+$) T cells in healthy males and females after papaya consumption.

4. To correlate levels of sex hormones with immune profiles of natural killer (NK) and cytotoxic ($CD\ 8^+$) T cells in the genders after papaya consumption.

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