UNIVERSITI PUTRA MALAYSIA

PROPHYLACTIC AND THERAPEUTIC EFFICACY OF DIETARY Nigella sativa L. SUPPLEMENTATION AGAINST HEPATOPATHY IN RATS INDUCED BY KAVALACTONE AND KAVALACTONE WITH ALCOHOL

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By

MOHAMMED ABDULABBAS HASAN

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

August 2018

DEDICATION

To my lovely country Iraq

To my parents, may God have mercy on them

To my wife "Civil Engineer" Noralhuda, brother, sisters, lovely son "hasan" and daughters "ruqayah and fatemah" whose encourage and gave me the power to achieve my goal

and

To all my sincere teachers, friends who boost me all those past years

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirements for the degree of Doctor of Philosophy

PROPHYLACTIC AND THERAPEUTIC EFFICACY OF DIETARY *Nigella sativa* L. SUPPLEMENTATION AGAINST HEPATOPATHY IN RATS INDUCED BY KAVALACTONE AND KAVALACTONE WITH ALCOHOL

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Chairman : Professor Noordin Mohamed Mustapha, PhD
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Despite having potent psychoactive properties, the hepatotoxic effects of kavalactone (KL) is well documented. It has been banned in Europe and Canada with cautions and advisories by the US FDA. A study was designed to investigate the prophylactic and therapeutic efficacies of dietary *Nigella sativa* (NS) supplementation on the oral sub-acute and sub-chronic toxicity of 800 mg/kg KL with or without alcohol in rats. The idiosyncratic toxicity of KL appears to have an unclear risk-to-benefit ratio**.** Therefore, it is critical to identify and determine any possible adverse side effects of KL products that could potentially lead to toxicity especially when taken with alcohol. Seventy-two, female Sprague-Dawley rats, were divided randomly into two experimental studies, viz; prophylactic and therapeutic efficacy of NS supplementation against KL with or without alcohol. Rats were equally allotted into nine groups comprising six animals each, namely negative control (NCx1), positive control (NCx2), alcohol (EtOH), Nigella sativa (NS), kavalactone (KL) and alcohol plus kavalactone (EtOH+KL) and NS-preventing groups {(NS+KL), (NS+EtOH) and (NS+KL+EtOH)}. The other experimental trial is aimed at investigating the therapeutic effect of NS in treatment and reducing the hepatic lesion progression and establishment, wherein rats were equally assigned into nine groups comprising six animals each, namely control groups {(NCx1), (NCx2), (EtOH), (NS), (KL) and (EtOH+KL)} and NS-treatment groups {(NS+KL), (NS+EtOH) and (NS+KL+EtOH)}. Rats in the NS-preventive groups were given NS at doses of 100 mg/kg (b.w)/per day orally for three consecutive days prior to the onset of hepatotoxicity induction and then with the course of KL (alone or in combination) with EtOH as a prophylactic measure. On the other hand, those in the {(NS+KL), (NS+EtOH) and (NS+KL+EtOH)} treatment groups were given NS at the same dose, together with KL at 800 mg/kg/day (orally) (alone or in combination) with EtOH as a therapeutic measure. The sampling was done at weeks (W0), (W1),

(W2) and (W3) in both experiments as a sub-acute trial and also at weeks (W6), (W9), (W12) and (W14) as a sub-chronic study for both experiments. Exsanguinations were done following euthanasia followed by procurement of the liver at 3rd and 14th weeks post-treatment for the prophylactic and therapeutic study as sub-acute and sub-chronic trials.

Rats receiving KL plus EtOH showed the severest bodyweight changes, clinical signs (abnormal breathing, ataxia, lethargy, loss of appetite and incoordination), oxidative stress, and pathology of the liver (hepatocellular necrosis, hepatocellular hypertrophy with high proliferation of sER). Furthermore, dietary supplementation of NS for almost 14 weeks showed that NS exhibited an anti-oxidative stress effect in the liver as evidenced seen from the low ALT. In response to antioxidant enzymes, especially in preventing groups, an increase in SOD and GSH-Px indirectly has alleviated oxidative stress leading to a much lower MDA. The NS reduces the incidence of hepatopathy especially fatty degeneration, hepatomegaly, sER and peroxisome proliferation for more than 50%. This study demonstrated that dietary supplementation of NS at a dose of 100 mg/kg/day orally, significantly ($p < 0.01$) reduces serum lipid profile together with suppression of oxidative damage and therefore alleviates hepatopathy lesions. Ethanol potentiated the sedative and hypnotic activity of KL and markedly increased the toxicity whereas, KL toxicity is likely due to herbal drug interaction rather than direct liver toxicity from KL alone. Finally, NS is highly efficacious in abating oxidative stress and cellular damage in rats.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

KEBERKESANAN PROFILAKSIS DAN TERAPEUTIK PEMBERIAN SAMPINGAN *Nigella sativa* L. TERHADAP HEPATOPATI TERARUH ALKOHOL DENGAN DAN TANPA KAVALAKTON PADA TIKUS

Oleh

MOHAMMED ABDULABBAS HASAN

Ogos 2018

Pengerusi : Profesor Noordin Mohamed Mustapha, PhD
Fakulti : Perubatan Veterinar

Disebalik sifat psikoatif kuat, kesan hepatotoksik kavalakton (KL) amat diketahui. Ia telah diharamkan di Eropah dan Kanada dengan peringatan mudarat oleh FDA, Amerika Syarikat. Satu kajian telah direka untuk mengkaji keberkesanan profilaksis dan terapeutik pemberian sampingan *Nigella sativa* (NS) terhadap ketoksikan oral sub-akut dan sub-kronik 800 mg/kg KL dengan dan atau tanpa alkohol. Ketoksikan idiosinkrasi KL didapati tiada mempunyai nisbah risiko ke manafaat yang jelas. Dengan itu, adalah kritikal untuk mengenalpasti dan menentukan kesan buruk hasilan KL yang berpotensi kepada ketoksikan terutama bersama alkohol. Sebanyak 72 ekor, tikus Spraque-Dawley betina dibahagikan dua kajian, profilkasis dan terapeutik keberkesanan pemberian NS terhadap KL dengan atau tanpa alkohol. Tikus dibahagikan kepada Sembilan kumpulan mengandungi enam ekor setiap satu seperti berikut: kawalan negatif (NCx1), kawalan positif (NCx2), alkohol (EtOH), Nigella sativa (NS), kavalakton (KL) dan alkohol dengan kavalakton (EtOH+KL) and kumpulan pencegahan-NS {(NS+KL), (NS+EtOH) and (NS+KL+EtOH)}. Satu lagi kajian bertujuan mengkaji kesan terapeutik NS dalam merawat dan mengurangi kerosakan dan pengukuhan lesi hepar, dimana tikus dibahagikan kepada sembilan kumpulan mengandungi enam ekor setiap satu, yakni kawalan negatif (NCx1), kawalan positif (NCx2), alkohol (EtOH), Nigella sativa (NS), kavalakton (KL) dan alkohol dengan kavalakton (EtOH+KL) dan kumpulan terawat-NS {(NS+KL), (NS+EtOH) and (NS+KL+EtOH)}. Tikus dalam kumpulan NS-tercegah menerima NS pada kadar 100 mg/kg berat badan secara oral untuk tiga hari berturut sebelum permulaan aruhan dan kemudian dengan KL (sendirian atau gabungan) dengan EtOH sebagai langkah profilaksis. Sebaliknya, kumpulan rawatan lain {(NS+KL), (NS+EtOH) dan (NS+KL+EtOH)} menerima NS pada kadar yang sama bersamaan dengan KL secara oral pada kadar 800 mg/kg (sendirian atau gabungan) dengan EtOH sebagai langkah terapeutik. Persampelan dilakukan pada minggu (W0), (W1),

(W2) dan (W3) pada kedua-dua kajian sebagai ujian sub-akut dan juga pada minggu (W6), (W9), (W12) dan (W14) sebagai ujian sub-kronik untuk kedua-dua kajian. Sembelihan disusuli dengan pengambilan hati pada minggu ketiga dan empat belas dibuat untuk kedua kajian.

Tikus yang menerima KL bersama EtOH mempunyai berat badan tertinggi, petanda klinikal (keabnormalan bernafas, ataksia, letargi, hilang selera dan ketidakselarasan), tegasan oksidatif dan patologi hepar (necrosis, hipertrofi dengan pemfoliferatan sER). Tambahan lagi, pemberian sampingan harian NS selama hampir 14 minggu menunjukan bahawa NS mempamer kesan tegasan anti-oksidatif pada hati yang terbukti dengan ALT yang rendah. Sebagai gerakbalas kepada enzim anti-oksidaan, terutama pada kumpulan pencegahan, peningkatan SOD dan GSH-Px secara tak langsung telah meredakan tegasan oksidatif yang menjurus kepada MDA yang lebih rendah. Pemberian NS telah mengurangkan hampir 50% kesan hepatopati terutama penjanarosotan lemak, hepatomegali, pemfoliferatan sER dan peroksisom. Kajian ini menunjukan bahawa pemberian NS pada dos 100 mg/kg/hari secara oral secara signifikan ($p<0.01$) merendahkan profil lipid serum bersamaan dengan penindasan kerosakan oksidatif dan dengan itu meredakan lesi hepatopati. Etanol telah memperkasa aktiviti sedative dan hypnosis KL dan dengan ketaranya meningkatkan ketoksikan dimana ketoksikan KL berkemungkinan akibat dari interaksi drug-herba daripada kerosakan langsung hati akibat KL sahaja. Akhir sekali, NS adalah amat mujarab dalam menangani tegasan oksidatif dan sel pada tikus.

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I certify that a Thesis Examination Committee has met on 17 August 2018 to conduct the final examination of Mohammed Abdulabbas Hasan on his thesis entitled "Prophylactic and Therapeutic Efficacy of Dietary *Nigella sativa* L. Supplementation Against Hepatopathy in Rats Induced by Kavalactone and Kavalactone with Alcohol" 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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This thesis was submitted to the Senate of the Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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This is to confirm that:

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LIST OF ABBREVIATIONS

A_B	Absorbance of Blank Control
As	Absorbance of Sample
Ab	Absorbance of Standard Control
ALT	Alanine Aminotransferase
ALD	Alcoholic Liver Disease
ALDH	Aldehyde Dehydrogenase
ALP	Alkaline Phosphatase
Vs	Amount of Sample in The Extract
ACUC	Animal Care and Use Committee
AST	Aspartate Transaminase
BD	Bile Duct
BHT	Butylated Hydroxytoluene
CCL4	Carbon Tetrachloride
CDC	Centers for Disease Control and Prevention
CV	Central Vein
Z_3	Centrilobular, Periacinar, Perivenous Zone
r	Correlation Coefficient
CREA	Creatinine
COX	Cyclooxygenase Enzyme
CYPs	Cytochromes P450 Isozymes
°C	Degree Celsius
DIW	Deionized Water
DNA	Deoxyribonucleic Acid
EtOH	Ethyl Alcohol

Ve	Final Volume of Extract
FDA	Food and Drug Administration
GGT	Gama-Glutamyl Transferase
GSH	Glutathione
G-P_X	Glutathione Peroxidase
GSR	Glutathione Reductase
GST	Glutathione S-Transferases
G	Grams
H&E	Hematoxylin and Eosin
Hb	Hemoglobin
$t_{1/2}$	Half-Life
HA	Hepatic Artery
HHP	Hepatocellular Hypertrophy
HN	Hepatocellular Necrosis
HDL	High-Density Lipoprotein
HPLC	High-Performance Liquid Chromatography
h	Hour
HCL	Hydrochlorous Acid
H_2O_2	Hydrogen Peroxide
KL	Kavalactones (Alpha-Pyrones)
Kg	Kilogram
KCs	Kupffer Cells
LPS	Lipopolysaccharide
L	Liter
MDA	Malondialdehyde
pH	Measurement for Hydrogen Ion Concentration

LD50	Median Lethal Dose
HPO3	Metaphosphoric Acid
µm	Micro Meter
µg	Microgram
µl	Microliter
Z_2	Midzonal
mg	Milligrams
min	Minute
DPX	Mounting Media and Section Adhesive
NAPQI	N-acetyl-p-benzoquinone imine
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
NS	*Nigella Sativa*
NP-SH	Non-Protein Thiol
GSSG	Oxidised Glutathione
O_2	Oxygen
Z_1	Periportal, Outer Zone
$ONOO^-$	Peroxynitrite
PBS	Phosphate Buffer Saline
PUFA	Polyunsaturated Fatty Acids
PV	Portal Vein
$B_{\Delta A}$	Rate of Spontaneous Oxidation of Blank Control
$S_{\Delta A}$	Rate of Spontaneous Oxidation of Sample
RNS	Reactive Nitrogen Species
RONS	Reactive Oxygen and Nitrogen Species
ROS	Reactive Oxygen Species
rER	Rough Endoplasmic Reticulum

RPM	Round Per Minute
Se	Selenium
SS	Sinusoidal Space
sER	Smooth Endoplasmic Reticulum
NaOH	Sodium Hydroxide
Na_2WO_4	Sodium Tungstate
SI	Somatic Index
SPSS	Statistical package For the Social Sciences
H_2SO_4	Sulphuric Acid
SOD	Superoxide Dismutase
$O^{2-}\cdot$	Superoxide Molecules
TBHP	Tert-Butyl Hydroperoxide
TBA	Thiobarbituric Acid
TBARS	Thiobarbituric Acid Reactive Substances
TQ	Thymoquinone
TNF-α	Tissue Necrotizing Factor Alpha
®	Trade Mark
TEM	Transmission Electron Microscopy
UPM	University Putra Malaysia
Vs	Volume of Plasma Sample
Vm	Volume of Total Reactive Mixture
v/v	Volume to Volume
W	Week
WHO	World Health Organization
w/v	Wright to Volume
XO	Xanthine Oxidase

ANOVA	One-Way Analysis of Variance
TEP	1,1,3,3-Tetraethoxypropane
P <0.05	Probability Values of Less Than Alpha 0.05

CHAPTER 1

GENERAL INTRODUCTION

Plants have been traditionally used to treat illnesses and diseases with varying degrees of success. It was only in the 20th century that the awareness on the side-effects of conventional drugs people has led to the search of traditional herbal remedies (Lüde, 2005). However, it should not be forgotten that the use of herbal plants is not without its very own untoward effect which may in severe cases lead to fulminant organ failure or death (Stickel et al., 2003). As natural products, herbs are mainly used as food additives and teas, however, manufactured herbal products are in the form of dietary supplements and drugs. The popularity of phytomedicine has been attributed to the perception that natural medicines are safe, gentle and cost-effective, as well as easily accessible and can be self-prescribed (Abebe, 2002). The danger of such assumption is self-medication of various herbal drugs without a validated medical advice.

Apart from the possible toxic of the parent herbal compounds, contamination (pesticides, heavy metals), their interaction with other drugs (e.g. *Hypericum perforatum*) and adulteration may contribute to toxic effects (De Smet, 2004). In short, injudicious use of phytomedicines could potentially cause serious detrimental effects (De Smet, 2004).

In order to establish an accurate and effective diagnosis of hepatotoxicity, a number of factors must be taken into account such as pattern recognition, anamnesis, awareness of the spectrum of herbal liver injury and botanic identification (Chitturi et al., 2000). Sometimes the hepatotoxic effect does not originate from the intake of a single botanical, but from the combination with other drugs. These interactions may occur through the induction of CYPs (like CYP3A4 or CYP2E1) by other drugs or alcohol, which could lead to enhanced production of toxic herbal metabolites (Stedman, 2002). Conversely, herbal components may also act by inhibiting CYPs, thus eventually causing an accumulation of concomitantly taken drugs. It was demonstrated in an *in vitro* study, that kava, garlic, Ginkgo biloba, and St. John's wort inhibited CYP 2C9, 2C19 and 3A4 (Zou et al., 2002). The occurrence of these interactions are not only limited via CYPs, but may occur via other pathways as well such as, the renal system (licorice–spironolactone), the immune system (Echinacea–corticosteroids, cyclosporine), the cardiac system (herbs containing cardiac glycosides–digoxin), and the clotting system (garlic, ginger, ginkgo–warfarin) (Miller, 1998; Lüde, 2005).

Problem Statement

In many countries mostly those within the Pacific Ocean and Micronesia, kava (*Piper methysticum*, KL) tinctures, extract capsules, teas and dried powders continue to be sold in health food stores, local markets, and kava "cafes" despite a consumer advisory issued by the Food and Drug Administration (FDA), concerning the potential hepatotoxicity of kava products. Therefore, it is critical to identify and determine any possible adverse side effects of KL products that could potentially lead to toxicity especially when taken with other substances like alcohol. Between 1990 and 2001, there were 82 case reports of alleged KL associated liver toxicity and deaths among patients consuming KL extract preparations were documented.

Likewise, in the past few years, about 35 cases of severe liver toxicity associated with KL intake have been reported in Europe and the US, with the occurrence of severe hepatic toxicity possibly related with the consumption of products containing kava. Until this day, KL is still used in religious practices and is of social and economic importance has in religious, social and economic life for too many of the Pacific Island communities. Thus, owing to quite extensive use spilling over beyond the Pacific Ocean and Micronesia, a database on its safety in combination with other compounds and an effective antidote is necessary.

Justifications of the study

One of the reasons for choosing kava in our study was because of its widespread use and popularity, with the general belief that it is safe, an effective anxiolytic, reliable, non-toxic, easily available and affordable, as compared to its synthetic chemical counterparts such as, Valium (diazepam), Xanax (alprazolam), Klonopin (clonazepam), and Ativan (lorazepam). However, there is a paucity of information and literature regarding the hepatotoxic effects of kava, and the hepatotoxicity pathway. Therefore, this study attempted to investigate the hepatotoxic effects of this popular drug. In same time we justify the using of alcohol with Kava in our study by: “Synthetic anxiety drugs such as, Xanax, Valium, Klonopin cannot be consumed with alcohol, as these drugs contain a black-box warning against use with alcohol, as it can be dangerous and potentially fatal. However, kava is widely used among alcoholics because of the belief that it is a “natural” safe alternative to synthetic drugs, and users feel that they can enjoy the benefits of mood alteration, without experiencing any adverse side effects”.

On the other hand, we used NS seeds, as it has been recorded in literature that, it has strong and effective hepatoprotective effects, and possesses antioxidant and antifibrotic properties, and is known to be natural, affordable and very safe, even for long time use.

Hypothesis, Aim and Objectives

Based on documented evidence, it is hypothesised that long-term administration of whole black seeds can provide stronger hepatoprotective activity against KL-induced hepatopathy and alleviated extremely toxicity after combined with EtOH (EtOH+KL) via the anti-oxidative pathway.

Thus, the study is undertaken with the aim of paving an insight into the cellular mechanisms of toxicity of kava and mechanisms of kava toxicity alleviation by NS with the following objectives, to:

i. to investigate the prophylactic and therapeutic efficacies of dietary *Nigella sativa* (NS) supplementation on the oral sub-(acute and chronic) toxicity induced by Kava-Kava.
ii. to analyze the possible protective pathway of NS in abating KL-induced hepatotoxicity in rats.
iii. to assess the extent of KL-induced hepatic damage in rats given KL with or without alcohol supplementation.
iv. to determine the changes in detoxifying enzymes, anti-oxidant and peroxidation status in rats receiving KL with or without alcohol supplementation.

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