UNIVERSITI PUTRA MALAYSIA

ANTI-AGEING PROPERTIES OF EDIBLE BIRD'S NEST ASCERTAINED BY IN VITRO AND IN VIVO STUDIES IN ANIMAL MODEL

HOU ZHIPING

IB 2015 18

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By

HOU ZHIPING

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

August 2015

Specially dedicated to,

My parents, husband and daughter

For their invaluable love, dedication, encouragement and patience

Abstractof thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the Doctor of Philosophy

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August 2015

Chairman: Maznah binti Ismail, PhD
Faculty : Institute of Bioscience

According to the World Health Organization (WHO), the world average life expectancy as at 2014 is 66.26 years, having an average of 64.30 years for males and 68.35 years for females. However, the onset of menopause for women, usually around 50 years, has not been postponed along with increasing longevity, but rather brought forward due to the impacts of environment, diet, and lifestyle. Most women spend approximately one-third of their life span in the postmenopausal phase. Hormonal imbalance during menopausal stage has been linked to increased risks of the fatal diseases including Alzheimer's disease, dementia, stroke, diabetes mellitus, and breast cancer. Hormone replacement therapy (HRT) has been used to restore postmenopausal hormonal levels in order to relieve menopausal problems, but its associated side effects including development of cancers and cardiovascular diseases have necessitated the search for other alternatives such as natural food supplementation.

Edible bird's nest (EBN) from the saliva of swiftlet has been esteemed as a precious food tonic by Chinese people since the Tang dynasty (618AD) because it contains rich amount of bioactive compounds such as water - soluble proteins, carbohydrate, iron, inorganic salt, and fiber, and is reported to traditionally possess anti-ageing, anti - cancer, and immunity - enhancing properties. Evidence-based details of its anti-ageing effects including underlying mechanisms are lacking. In this study, EBN was evaluated for its anti - ageing effects and its potential mechanisms were evaluated. First of all, ovariectomized female Sprague - Dawley rats were fed with EBN (6 %, 3 % and 1.5 % in normal pellet) for 12 weeks, then, cognitive function, metabolic indices (serum estrogen, insulin, liver enzyme, kidney function, lipid profile, and antioxidant markers) and hippocampal sirtuin - 1 protein level were in comparison with non - treated ovariectomized rats were observed, and in some instances it showed better results than estrogen therapy. Additionally, EBN produced better transcriptional regulation of hippocampal anti-oxidant genes and an Alzheimer disease isrelated genes, and hepatic insulin signaling genes. Moreover, EBN and its constituents (lactoferrin and ovotransferrin) attenuated H_2O_2 - induced cytotoxicity, and decreased radical oxygen species through increased scavenging activity, with corresponding transcriptional changes in anti - oxidant and apoptosis - related genes that tended towards neuroprotection.

These data suggested that EBN reduced the risks of neurodegenerative diseases, and may be used as functional ingredient for the prevention of neurodegenerative and metabolism related diseases associated with estrogen deficient ageing.

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

SIFAT ANTI-PENUAAN SARANG BURUNG WALIT DITENTUKAN MELALUI KAJIAN *IN VITRO* DAN MODEL HAIWAN *IN VIVO*

Oleh

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Menurut Pertubuhan Kesihatan Sedunia (WHO), purata jangka hayat manusia di dunia pada 2014 adalah 66.26 tahun, di mana lelaki mempunyai purata 64.3 tahun manakala wanita mempunyai 68.35 tahun. Walau bagaimanapun, permulaan menopaus bagi wanita, biasanya sekitar 50 tahun, tidak ditangguhkan bersama - sama dengan peningkatan umur, tetapi sebaliknya dipercepatkan oleh kesan persekitaran, diet dan gaya hidup. Kebanyakan wanita menghabiskan kira-kira satu pertiga daripada jangka hayat mereka dalam fasa menopaus. Ketidakseimbangan hormon semasa menopaus telah dikaitkan dengan peningkatan risiko penyakit - penyakit kronik termasuk penyakit Alzheimer, nyanyuk, strok, kencing manis, dan kanser payudara. Terapi penggantian hormon (HRT) telah digunakan untuk mengubati masalah putus haid, tetapi kesan sampingan seperti kanser dan penyakit kardiovaskular telah mendorong pencarian alternatif lain seperti suplemen makanan semulajadi.

Sarang burung (EBN) daripada air liur burung walit telah digelarkan sebagai tonik makanan yang berharga oleh orang-orang Cina sejak Dinasti Tang (618AD) kerana ia mengandungi jumlah sebatian bioaktif yang kaya seperti protein larut air, karbohidrat, besi, garam bukan organik, dan serat. Ia juga dilaporkan secara tradisi mempunyai anti - penuaan, anti - kanser, dan sifat - sifat meningkatkan imuniti. Maklumat berasaskan bukti saintifik kesan anti - penuaan termasuk mekanisme kefungsiannya adalah amat sedikit. Dalam kajian ini, kesan anti - penuaan daripada EBN telah dikaji dan mekanisme yang berpotensi juga ditentukan. Pertamanya, tikus Sprague-Dawley betina "yang dibuang ovari" yang diberi makan EBN (1.5 %, 3 %, dan 6% dalam normal pelet) selama 12 minggu menunjukkan fungsi kognitif, indeks metabolik (serum estrogen, insulin, hati fungsi buah pinggang enzymesm, profil lipid, dan penanda antioksidan) dan protein sirtuin – 1 pada hippocampus adalah lebih baik berbanding dengan tikus yang dibuang ovari tanpa makanan EBN, dan dalam keadaan tertentu ia menunjukkan keputusan yang lebih baik berbanding dengan terapi estrogen. Di samping itu, EBN menunjukkan pengawalan transkripsi gen yang lebih baik termasuk gen anti-oksida dan gen berkaitan dengan penyakit Alzheimer pada tisu hippocampus, dan juga gen isyarat insulin hepatik. Tambahan pula, EBN dan sebatian aktif (laktoferin, LF dan ovotransferrin, OVF) melemahkan sitotoksiti yang disebabkan oleh H_2O_2, dan menurunkan spesies oksigen radikal (ROS) melalui peningkatan aktiviti memerangkap radikal, dengan mengubah transkripsi gen yang berkaitan dengan anti -

oksida dan apoptosis, justeru menunjukkan kecenderungan ke arah perlindungan sistem neuron.

Data mencadangkan bahawa EBN mengurangkan risiko penyakit sistem neuron dan boleh digunakan sebagai bahan nutrasutikal untuk mencegah penyakit neuron dan penyakit metabolik yang dikaitkan dengan kekurangan estrogen.

ACKNOWLEDGEMENTS

I would like to extend my deepest gratitude and appreciation to my supervisor Prof. Dr. Maznah Ismail for her endless support, generous guidance and constructive advice that contributed to the completion of this project.

My sincere gratitude also goes to my co - supervisors Prof. Dr. Rozi Mahmud and Prof. Dr. Aini Ideris, thank you for the her priceless comments and invaluable advice.

I would also like to acknowledge and thank Dr. Mustapha Umar Imam for his careful reviews and constructive criticism throughout the entire course of this research. Not forgetting all the staffs in the Laboratory of Molecularmedicine, my sincere thanks to them, especially Mrs. Norsharina Ismail, Mr. Chan Kimwei, and Mrs Norhayat Yusuf for their assistance in laboratory management. I am grateful to my labmates, especially Mr. Ooi Derjun, Mrs. Foong Lianchee, Mrs. Nur Hanisha Azmi, and Mrs. Nadarajan Sarega for their invaluable help and assistance. As well as, thank to Mr. Zhang Yida on the collaboration of EBN research.

Finally yet importantly, I would to express my heartiest appreciation and thanks to all my family members for their understanding and support throughout my studies.

I certify that a Thesis Examination Committee has met on 17 August 2015 to conduct the final examination of Hou Zhiping on her thesis entitled "Anti-Ageing Properties of Edible Bird's Nest Ascertained by *In Vitro* and *In Vivo* Studies in Animal Model" 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 Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Doctor of Philosophy.

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This is to confirm that:

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Member of Supervisory Committee: Prof. Dr. Aini Ideris

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Member of Supervisory Committee: Prof. Dr. Rozi Mahmud

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AAPH	2,2′ - azobis (2 - amidinopropane) dihydrochloride
ABTS	2,2' - azino - bis (3 - ethylbenzothiazoline - 6 - sulphonic acid)
AGE	Advanced glycation end-product
Akt	Protein kinase B
ALP	Alanine transaminase
ALT	Alkaline phosphatase
AO / PI	Acridine orange and propidium iodide
APP	Amyloid Precursor Protein
ATCC	American Type Culture Collection
CA	Cornus ammonis
CASP3	Caspase 3
CAT	Catalase
CNS	Central nervous system
DMEM / F - 12	Minimum essential Eagle's medium, Ham's nutrientmixture
DMSO	Dimethyl sulfoxide
EBN	Edible bird's nest
EGF	Epidermal growth factor
Gapdh	Glyceraldehydes - 3 - phosphate dehydrogenase
Gck	Gluckokinase
GGT	Gamma - glutamyl transferase
GLUT4	Glucose transporter type 4
HDL	High density lipoprotein
H_2O_2	Hydrogen peroxide
HOMA - IR	Homeostatic model assessment of insulin resistance
HRT	Hormone replacement therapy
IDE	Insulin - Degrading Enzyme
Ikbkb	Inhibitor of kappa light polypeptide gene enhancer in B - cells, kinase beta
Insr	Insulin receptor
Kan(s)	Kanamycin resistance
$K_2S_2O_8$	Potassium persulphate
KNJC11	Potassium inwardly rectifying channel, subfamily J, member 11
LDL	Low density lipoprotein
LF	Lactoferrin
LPk	Pyruvate kinase-liver isoform
LRP1	Low Density Lipoprotein Receptor - Related Protein1
IRS	Insulin receptor substrate
MAPK	Mitogen-activated protein kinase
MDA	3,4 - methylenedioxyamphetamine
MMP	Mitochondrial membrane potential
MTT	3 - [4,5 - dimethylthiazol - 2 - yl] - 2,5 - diphenyl-tetrazolium bromide
MWM	Morris Water Maze
$NaHCO_3$	Sodium biocarbonate
NF - κB	Nuclear factor kappa - light - chain - enhancer of activated B cells
OD	Optical density

OGTT	Oral glucose tolerance test
ORAC	Oxygen radical absorbance capacity
OVF	Ovotransferrin
OVX	Ovariectomy
PARP1	Poly (ADP - ribose) polymerase 1
PI3K	Phosphoinositide - 3 - kinase
PSEN1	Presenilin - 1
PSEN2	Presenilin - 2
p53	Cellular tumor antigen p53
MAPK	Mitogen-activated protein kinase
RA	Retinoic acid
ROS	Radical oxygen species
SIRT - 1	Situin - 1
SOD	Superoxide dismutase
TBARS	Thiobarbituric acid reactive substances

CHAPTER 1

INTRODUCTION

Biological ageing is the process of cumulative changes to molecular and cellular structures that disrupt metabolism with the passage of time, resulting in deterioration and death. Ageing related memory and cognitive decline are increasingly becoming a problem in humans especially due to improvements in healthcare delivery that have given rise to increasing longevity. Life expectancy for women is higher than for men and their menopausal transition is often accompanied with changes. Alteratives in central nervous system (CNS) are often reflected on memory and cognitive function and sensitive with body metabolic status. Over the years, the life span of Malaysian women increased to 76.8 years in 2011 (Malaysia), and the increasing longevity has meant that women live one -third of their lives beyond cessation of endogenous oestrogen production from the ovaries (Hara, et al., 2011). Before menopause, circulating oestrogen level protects women against neurodegenerative diseases, such as stroke, compared to men (Brann, et al., 2007; Mahesh, & Khan, 2007; Scott,et al., 2012 Vadlamudi, & Brann, 2012). Conversely, postmenopausal women have higher morbidity and mortality due to neurodegenerative diseases compared with age-matched men, because of reduced circulating oestrogen level (Appelros, Stegmayr, & Terént, 2009; Persky, Turtzo, & McCullough, 2010). On the other hand, the risk of metabolic diseases, like type 2 diabetes mellitus, increase significantly in women after menopause, and they are the burden of neurodegenerative diseases on the basis of literatures (de la Torre, 2004; Ulas & Cay, 2010).

Oestrogen is secreted and controlled through hypothalamus-pituitary-gonadal (HPG) axis, to regulate biological function. The decline in oestrogen level in menopause is reported to result in memory loss and metabolic perturbation soon after it starts, and sirtuin - 1 protein played important roles in hippocampus dependent memories and synaptic plasticity as reports. Eventually, low levels of oestrogen lead to other secondary metabolic abnormalities including oxidative stress, apoptosis and inflammation that together complicate the ageing-related degenerative diseases through neuropathy, dementia, Alzheimer's disease, cardiovascular disease and diabetes. Also, complications arising from oestrogen - deficit diseases are debilitating and result in a huge expenditure in health care. In addition, these degenerative diseases that are among the most common diseases affecting menopausal women, have been linked with lifestyle especially diet (WHO).

Encouragingly, hormone replacement therapy (HRT) has been shown to prevent neurodegenerative disorders as conventional usage on treating menopausal symptoms. However, the risk of life - threatenting complications it induces has limited its use. Data have reported the effects of long term HRT on the risk of breast cancer (Beral, Banks, & Reeves, 2002; Tempfer, et al., 2009)and venous thromboembolism (Jick, Derby, Myers et al., 1996 Vasilakis, & Newton, 1996). Thus, alternatives with better safety profile compared with conventional HRT have received close attention. Herbal medicine has a long history of use and is still widely practiced today, based on the theories, beliefs, and experiences indigenous to different cultures, and used in the maintenance of health as well as in the prevention, improvement or treatment of physical and mental illness (Organisation, 2012).

There is a long history of using traditional medicines in Asian countries. China, one of the early ancient civilisations, has been using edible bird's nest (EBN) since ancient dynasty. EBN is produced by swiftlets from their salivary glue, which is a cementing substance. The nests are considered to have high nutritional and medicinal values, traditionally believed to have everything from anti-ageing and anti-cancer properties to the ability to improve immunity and raise libido. Composition analysis of EBN shows the major composition is protein (62 % ~ 68 %) including glycoproteins (Hamzah, Ibrahim, Jaafar et al., 2013), followed by carbohydrate and mineral salts. Additionally, other bioactives have been reported in EBN including epidermal growth factor (EGF), testosterone (Marcone, 2005), and chondroitin glycosaminoglycans (Matsukawa, Matsumoto, Bukawa et al., 2011). Numerous *in vitro* and *in vivo* researches have shown that administration of EBN was able to boost immunity, improve anti-oxidant ability, promote neutralisation of influenza activity as well as improve osteoporosis . Sadly, however, evidence-based details of other properties of EBN are lacking. Since the practical usage of traditional medicine is not strictly enforced under scientific evidence, herbalism is just recognised as a form of alternative medicine in modern medicine. Despite EBN's long history of medicinal use, there is still a dearth of research and scientific evidence to substantiate the claims of health benefits associated with anti – ageing including its mechanistic basis.

In this study, it was aimed to explore the evidences for the use of EBN as a functional food in preventing and managing ageing-related neurodegenerative diseases in menopause, of which the risk is increased due to loss of protection from oestrogen and related hormones. The brain cells are normally sensitive to the effect of redox system because of their peculiar energetic demands (Gandhi & Abramov, 2012). In brain senescence, radical oxygen species (ROS) starts to accumulate in neurons before clinically evident signs and symptoms of the disease can be detected (Gandhi & Abramov, 2012). When ROS accumulate, oxidative damage is normally prevented by induction of protective factors, like antioxidants. On the other hand, the imbalanced redox status is involved in advanced glycation end-products (AGEs) adjustment pathway, and the depletion of cellular antioxidant mechanisms and the generation of free radicals by AGEs may play a major role in the pathogenesis of neurodegeneration (Kuhla, 2014; Prasad, et al., 2014). Furthermore, AGEs is influenced by glucose and lipid homeostasis, and may play the role in transcriptional and proteomic aspects if the insult is too overwhelming. In such cases, apoptotic mechanisms set in to remove neurons deemed irreparable (Radi,et al., 2014). Loss of neurons through these apoptotic deaths results in severe morphological and functional deficits, which manifest with progressive memory and cognitive decline. Therefore, it was hypothesised that this research will give clues on the effect of EBN in some selectedof organs and functions that are affected by low estrogenic level such as memory loss, weight increase, insulin deficiency and lipid metabolic abnormalities. Their effects on brain and liver related to anti - oxidation, apoptosis and inflammation were equally considered.

Hypotheses of the study were:

1. EBN and its bioactives (LF and OVF) protect SH-SY5Y cells against H_2O_2-induced cytotoxicity and cell oxidative stress;
2. EBN enhances spatial learning and memory in ovariectomized rats;
3. EBN preserves hippocampal SIRT - 1 activity in the menopause model, as the likely basis for enhanced spatial learning and memory;
4. EBN is neuroprotective against oestrogen deficiency - induced damage *via* increasing serum oestrogen level, and decreasing AGEs and oxidative stress;
5. EBN improves metabolic indices like glucose metabolism, lipid profile and antioxidant status in ovariectomized rats.

General objective

To study the anti - ageing effects of EBN and its mechanism through *in vitro* and *in vivo* approaches, including transcriptomic and proteomic analyses.

Specific objective

1. To examine the effects of EBN on ovariectomy - induced memory and cognitive dysfunctions, including transcriptomic and proteomic mechanisms; as well as to obtain sirtuin-1 data on hippocampus and frontal cortex parameters;
2. To determine the effects of EBN on serum AGEs and redox status, and neuro - dysfunction in ovariectomized rats, including mechanistic basis for such effects;
3. To determine the effects of EBN on weight and metabolic indices related to insulin resistance in ovariectomized rats, and mechanistic basis for such effects.
4. To characterize the bioactives (lactoferrin [LF] and ovotransferrin [OVF]) in EBN, and evaluate their anti - oxidant abilities;
5. To determine the neuroprotective potentials of EBN water extract and its constituents, LF and OVF, and related molecular mechanisms involved in H_2O_2 - induced oxidative stress and apoptosis in SH - SY5Y cells

REFERENCES

Abidin, F. Z., Hui, C. K., Luan, N. S., Ramli, E. S. M., Hun, L. T., & Ghafar, N. A. (2011). Effects of edible bird's nest (ebn) on cultured rabbit corneal keratocytes. *BMC complementary and alternative medicine, 11*(1), 94.

Adler, V., Yin, Z., Tew, K. D., & Ronai, Z. (1999). Role of redox potential and reactive oxygen species in stress signaling. *Oncogene, 18*(45), 6104-6111.

Aggarwal, B. B., Sundaram, C., Malani, N., & Ichikawa, H. (2007). Curcumin: The indian solid gold *The molecular targets and therapeutic uses of curcumin in health and disease* (pp. 1-75): Springer.

Akinloye, A. K., Oke, B. O., Akinloye, A., & Oke, B. (2010). Characterization of the uterus and mammary glands of the female african giant rats (cricetomys gambianus, waterhouse) in nigeria. *International journal of morphology, 28*(1), 93-96.

Al-Rahbi, B., Zakaria, R., Othman, Z., Hassan, A., Ismail, Z. I. M., & Muthuraju, S. (2014). Tualang honey supplement improves memory performance and hippocampal morphology in stressed ovariectomized rats. *Acta histochemica, 116*(1), 79-88.

Andersen, J. K. (2004). Oxidative stress in neurodegeneration: Cause or consequence?*Nature Reviews Neuroscience***5**, S18–S25.

Andorfer, C., Kress, Y., Espinoza, M., De Silva, R., Tucker, K. L., Barde, Y. A., Duff, K., & Davies, P. (2003). Hyperphosphorylation and aggregation of tau in mice expressing normal human tau isoforms. *Journal of neurochemistry, 86*(3), 582-590.

Appelros, P., Stegmayr, B., & Terént, A. (2009). Sex differences in stroke epidemiology a systematic review. *Stroke, 40*(4), 1082-1090.

Arkan, M. C., Hevener, A. L., Greten, F. R., Maeda, S., Li, Z.-W., Long, J. M., Wynshaw-Boris, A., Poli, G., Olefsky, J., & Karin, M. (2005). Ikk-β links inflammation to obesity-induced insulin resistance. *Nature medicine, 11*(2), 191-198.

Association, A. s. (2008). 2008 alzheimer's disease facts and figures. *Alzheimer's & dementia: the journal of the Alzheimer's Association, 4*(2), 110.

Ayres, S., Tang, M., & Subbiah, M. R. (1996). Estradiol-17β as an antioxidant: Some distinct features when compared with common fat-soluble antioxidants. *Journal of laboratory and clinical medicine, 128*(4), 367-375.

Azmi, N. H., Ismail, N., Imam, M. U., & Ismail, M. (2013). Ethyl acetate extract of germinated brown rice attenuates hydrogen peroxide-induced oxidative stress in human sh-sy5y neuroblastoma cells: Role of anti-apoptotic, pro-survival and antioxidant genes. *BMC complementary and alternative medicine, 13*(1), 177.

Baeza, I., Alvarado, C., Alvarez, P., Salazar, V., Castillo, C., Ariznavarreta, C., Fdez-Tresguerres, J., & De la Fuente, M. (2009). Improvement of leucocyte functions in ovariectomised aged rats after treatment with growth hormone, melatonin, oestrogens or phyto-oestrogens. *Journal of reproductive immunology, 80*(1), 70-79.

Baeza, I., De Castro, N., Gimenez-Llort, L., & De la Fuente, M. (2010). Ovariectomy, a model of menopause in rodents, causes a premature aging of the nervous and immune systems. *Journal of neuroimmunology, 219*(1), 90-99.

Barnes, P. M., Powell-Griner, E., McFann, K., & Nahin, R. L. (2004). *Complementary and alternative medicine use among adults: United states, 2002.* Paper presented at the Seminars in Integrative Medicine.

Barrett-Connor, E. (1998). Fortnightly review: Hormone replacement therapy. *BMJ: british medical journal, 317*(7156), 457.

Barrett-Connor, E., & Grady, D. (1998). Hormone replacement therapy, heart disease, and other considerations. *Annual review of public health, 19*(1), 55-72.

Bengmark, S. (2006). Impact of nutrition on ageing and disease. *Current opinion in clinical nutrition & metabolic care, 9*(1), 2-7.

Beral, V., Banks, E., & Reeves, G. (2002). Evidence from randomised trials on the long-term effects of hormone replacement therapy. *The lancet, 360*(9337), 942-944.

Bertram, L., & Tanzi, R. E. (2004). The current status of alzheimer's disease genetics: What do we tell the patients? *Pharmacological research, 50*(4), 385-396.

Besedovsky, H. O., & Rey, A. D. (1996). Immune-neuro-endocrine interactions: facts and hypotheses. *Endocrine reviews, 17*(1), 64-102.

Bhat, H. K., Calaf, G., Hei, T. K., Loya, T., & Vadgama, J. V. (2003). Critical role of oxidative stress in estrogen-induced carcinogenesis. *Proceedings of the national academy of sciences, 100*(7), 3913-3918.

Bhavnani, B. R. (2003). Estrogens and menopause: Pharmacology of conjugated equine estrogens and their potential role in the prevention of neurodegenerative diseases such as alzheimer's. *The Journal of steroid biochemistry and molecular biology, 85*(2), 473-482.

Biddle, F., & Belyavin, G. (1963). The haemagglutination inhibitor in edible bird-nest: its biological and physical properties. *Journal of general microbiology, 31*(1), 31-44.

Biguet, C., Wakasugi, N., Mishal, Z., Holmgren, A., Chouaib, S., Tursz, T., & Wakasugi, H. (1994). Thioredoxin increases the proliferation of human b-cell lines through a protein kinase c-dependent mechanism. *Journal of biological chemistry, 269*(46), 28865-28870.

Birge, S. J. (1997). The role of estrogen in the treatment and prevention of dementia: Introduction. *American medical journal, 103*(3a), 1s-2s.

Bin, W., YouHui, S., QingYi, L., & JianZhang, M. (2013). Breeding biology and conservation strategy of the Himalayan swiftlet (Aerodramus brevirostris innominata) in southern China. *Biodiversity science, 21*(1), 54-61.

Bodkin, N. L., Alexander, T. M., Ortmeyer, H. K., Johnson, E., & Hansen, B. C. (2003). Mortality and morbidity in laboratory-maintained rhesus monkeys and effects of long-term dietary restriction. *The journals of jerontology series A: biological sciences and medical sciences, 58*(3), B212-B219.

Brady, M. J. (2004). Irs2 takes center stage in the development of type 2 diabetes. *Journal of clinical investigation, 114*(7), 886.

Brann, D. W., Dhandapani, K., Wakade, C., Mahesh, V. B., & Khan, M. M. (2007). Neurotrophic and neuroprotective actions of estrogen: Basic mechanisms and clinical implications. *Steroids, 72*(5), 381-405.

Brayne, C., & Calloway, P. (1988). Normal ageing, impaired cognitive function, and senile dementia of the Alzheimer's type: a continuum? *The lancet, 331*(8597), 1265-1267.

Brookmeyer, R., Gray, S., & Kawas, C. (1998). Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. *American journal of public health research, 88*(9), 1337-1342.

Brune, M., Müller, M., Melino, G., Bierhaus, A., Schilling, T., & Nawroth, P. (2013). Depletion of the receptor for advanced glycation end products (rage) sensitizes towards apoptosis via p53 and p73 posttranslational regulation. *Oncogene, 32*(11), 1460-1468.

Cacho, J., Sevillano, J., de Castro, J., Herrera, E., & Ramos, M. (2008). Validation of simple indexes to assess insulin sensitivity during pregnancy in Wistar and Sprague-Dawley rats. *American journal of physiology-endocrinology and metabolism, 295*(5), E1269-E1276.

Cancer, C. G. o. H. F. i. B. (1997). Breast cancer and hormone replacement therapy: Collaborative reanalysis of data from 51 epidemiological studies of 52 705 women with breast cancer and 108 411 women without breast cancer. *The lancet, 350*(9084), 1047-1059.

Cao, G., Alessio, H. M., & Cutler, R. G. (1993). Oxygen-radical absorbance capacity assay for antioxidants. *Free radical biology and medicine, 14*(3), 303-311.

Carlson, C. J., Koterski, S., Sciotti, R. J., Poccard, G. B., & Rondinone, C. M. (2003). Enhanced basal activation of mitogen-activated protein kinases in adipocytes from type 2 diabetes potential role of p38 in the downregulation of glut4 expression. *Diabetes, 52*(3), 634-641.

Carr, A., & Frei, B. (1999). Does vitamin C act as a pro-oxidant under physiological conditions? *The FASEB journal, 13*(9), 1007-1024.

Carr, M. C. (2003). The emergence of the metabolic syndrome with menopause. *The journal of clinical endocrinology & metabolism, 88*(6), 2404-2411.

Carroll, J. C., & Rosario, E. R. (2012). The potential use of hormone-based therapeutics for the treatment of alzheimer's disease. *Current Alzheimer research, 9*(1), 18-34.

Castelo-Branco, C., Cancelo, M. J., Villero, J., Nohales, F., & Julia, M. D. (2005). Management of post-menopausal vaginal atrophy and atrophic vaginitis. *Maturitas, 52 Suppl 1*, S46-52.

Castillo, C., Ariznavarreta, M. C. C., Lahera, V., Cachofeiro, V., Gil-Loyzaga, P., & Tresguerres, J. A. (2005). Effects of ovariectomy and growth hormone administration on body composition and vascular function and structure in old female rats. *Biogerontology, 6*(1), 49-60.

Castillo, C., Salazar, V., Ariznavarreta, C., Vara, E., & Tresguerres, J. (2006). Effect of isoflavone administration on age-related hepatocyte changes in old ovariectomized femal Wistar rats. *Phytomedicine, 13*(7), 468-476.

Chan, K. W., Khong, N. M., Iqbal, S., Ch'ng, S. E., & Babji, A. S. (2012). Preparation of clove buds deodorized aqueous extract (cdae) and evaluation of its potential

to improve oxidative stability of chicken meatballs in comparison to synthetic and natural food antioxidants. *Journal of food quality, 35*(3), 190-199.

Chang, H.C., & Guarente, L. (2013). Sirt1 mediates central circadian control in the scn by a mechanism that decays with aging. *Cell, 153*(7), 1448-1460.

Christensen, H. (2001). What cognitive changes can be expected with normal ageing? *Australian and new zealand journal of psychiatry, 35*(6), 768-775.

Cheung, S., & Wu, D. Y. (Eds.). (2012). Globalization of chinese food. routledge.

Chua, K.H., Lee, T.H., Nagandran, K., Yahaya, N. H. M., Lee, C.T., Tjih, E. T. T., & Aziz, R. A. (2013). Edible bird's nest extract as a chondro-protective agent for human chondrocytes isolated from osteoarthritic knee: In vitro study. *BMC complementary and alternative medicine, 13*(1), 19.

Chua, Y. G., Chan, S. H., Bloodworth, B. C., Li, S. F. Y., & Leong, L. P. (2014). Identification of Edible Bird's Nest with Amino Acid and Monosaccharide Analysis. *Journal of agricultural and food chemistry, 63*(1), 279-289.

Chung, H. Y., Cesari, M., Anton, S., Marzetti, E., Giovannini, S., Seo, A. Y., Carter, C., Yu, B. P., & Leeuwenburgh, C. (2009). Molecular inflammation: Underpinnings of aging and age-related diseases. *Ageing research reviews, 8*(1), 18-30.

Cohen, M. M., & Shaw, M. W. (1965). Specific effects of viruses and antimetabolites on mammalian chromosomes. *In vitro, 1*(1), 50-66.

Coker, L. H., Espeland, M. A., Rapp, S. R., Legault, C., Resnick, S. M., Hogan, P., Gaussoin, S., Dailey, M., & Shumaker, S. A. (2010). Postmenopausal hormone therapy and cognitive outcomes: The women's health initiative memory study (whims). *The Journal of steroid biochemistry and molecular biology, 118*(4-5), 304-310.

Coker, L. H., Espeland, M. A., Rapp, S. R., Legault, C., Resnick, S. M., Hogan, P., Gaussoin, S., Dailey, M., & Shumaker, S. A. (2010). Postmenopausal hormone therapy and cognitive outcomes: The women's health initiative memory study (whims).*The Journal of steroid biochemistry and molecular biology, 118*(4), 304-310.

Colman, R., Lane, M., Binkley, N., Wegner, F., & Kemnitz, J. (1999). Skeletal effects of aging in male rhesus monkeys. *Bone, 24*(1), 17-23.

Cooke, B. M., & Woolley, C. S. (2005). Gonadal hormone modulation of dendrites in the mammalian cns. *Journal of neurobiology, 64*(1), 34-46. doi: 10.1002/neu.20143

Cothran, M. M., & Engberg, S. (2004). Vaginal Ring an HT Alternative. *The nurse practitioner, 29*(7), 54-55.

Csiszar, A., Pacher, P., Kaley, G., & Ungvari, Z. (2005). Role of oxidative and nitrosative stress, longevity genes and poly (adp-ribose) polymerase in cardiovascular dysfunction associated with aging. *Current vascular pharmacology, 3*(3), 285.

Cuzzocrea, S., Santagati, S., Sautebin, L., Mazzon, E., Calabrò, G., Serraino, I., Caputi, A. P., & Maggi, A. (2000). 17β-estradiol antiinflammatory activity in carrageenan-induced pleurisy. *Endocrinology, 141*(4), 1455-1463.

D'Amelio, M., Cavallucci, V., Middei, S., Marchetti, C., Pacioni, S., Ferri, A., Diamantini, A., De Zio, D., Carrara, P., & Battistini, L. (2011). Caspase-3

triggers early synaptic dysfunction in a mouse model of alzheimer's disease. *Nature neuroscience, 14*(1), 69-76.

Dartigues, J., Helmer, C., Dubois, B., Duyckaerts, C., Laurent, B., Pasquier, F., & Touchon, J. (2002). [alzheimer's disease: A public health problem: Yes, but a priority?]. *Revue neurologique, 158*(3), 311-315.

de la Torre, J. C. (2004). Is Alzheimer's disease a neurodegenerative or a vascular disorder? Data, dogma, and dialectics. *The lancet neurology, 3*(3), 184-190.

Dennerstein, L., Dudley, E. C., Hopper, J. L., Guthrie, J. R., & Burger, H. G. (2000). A prospective population-based study of menopausal symptoms. *Obstetrics & gynecology international journal, 96*(3), 351-358.

Domoney, C. (2014). Treatment of vaginal atrophy. *Womens health (Lond Engl), 10*(2), 191-200. doi: 10.2217/whe.14.9

Detrich, H. W., Westerfield, M., & Zon, L. I. (1998). Overview of the zebrafish system. *Methods in cell biology, 59*, 3-10.

Dickson, D. W. (2004). Building a more perfect beast: APP transgenic mice with neuronal loss. *The American journal of pathology, 164*(4), 1143-1146.

Dodart, J. C., Mathis, C., Bales, K., & Paul, S. (2002). Does my mouse have Alzheimer's disease? *Genes, brain and behavior, 1*(3), 142-155.

Dorsey, E., Constantinescu, R., Thompson, J., Biglan, K., Holloway, R., Kieburtz, K., Marshall, F., Ravina, B., Schifitto, G., & Siderowf, A. (2007). Projected number of people with parkinson disease in the most populous nations, 2005 through 2030. *Neurology, 68*(5), 384-386.

Fabris, N. (1990). A neuroendocrine-immune theory of aging. *International journal of neuroscience, 51*(3-4), 373-375.

Flanagan-Cato, L. M. (2000). Estrogen-induced remodeling of hypothalamic neural circuitry. *Front neuroendocrinol, 21*(4), 309-329.

Fournie, J., Hawkins, W., Krol, R., & Wolfe, M. (1996). Preparation of whole small fish for histological evaluation. *Techniques in aquatic toxicology, 1*, 577-587.

Foy, M. R., Baudry, M., Akopian, G. K., & Thompson, R. F. (2010). Regulation of hippocampal synaptic plasticity by estrogen and progesterone. *Vitamins and hormones, 82*, 219-239.

Fulco, M., Cen, Y., Zhao, P., Hoffman, E. P., McBurney, M. W., Sauve, A. A., & Sartorelli, V. (2008). Glucose restriction inhibits skeletal myoblast differentiation by activating sirt1 through ampk-mediated regulation of nampt. *Developmental cell, 14*(5), 661-673.

Gallagher, M., & Nicolle, M. M. (1993). Animal models of normal aging: relationship between cognitive decline and markers in hippocampal circuitry. *Behavioural brain research, 57*(2), 155-162.

Games, D., Adams, D., Alessandrini, R., Barbour, R., Borthelette, P., Blackwell, C., Carr, T., Clemens, J., Donaldson, T., & Gillespie, F. (1995). Alzheimer-type neuropathology in transgenic mice overexpressing v717f β-amyloid precursor protein.

Gan, L., & Mucke, L. (2008). Paths of convergence: sirtuins in aging and neurodegeneration. *Neuron, 58*(1), 10-14.

Gandhi, S., & Abramov, A. Y. (2012). Mechanism of oxidative stress in neurodegeneration. *Oxidative medicine and cellular longevity, 2012*.

Gao, J., He, J., Shi, X., Stefanovic-Racic, M., Xu, M., O'Doherty, R. M., Garcia-Ocana, A., & Xie, W. (2012). Sex-specific effect of estrogen sulfotransferase on mouse models of type 2 diabetes. *Diabetes, 61*(6), 1543-1551.

Garcia-Segura, L. M., Azcoitia, I., & DonCarlos, L. L. (2001). Neuroprotection by estradiol. *Progress in neurobiology, 63*(1), 29-60.

Garcia-Segura, L. M., Azcoitia, I., & DonCarlos, L. L. (2001). Neuroprotection by estradiol. *Progress in neurobiology, 63*(1), 29-60.

Gaspard, U. J., Gottal, J.-M., & van den Brûle, F. A. (1995). Postmenopausal changes of lipid and glucose metabolism: A review of their main aspects. *Maturitas, 21*(3), 171-178.

GE, A. B. B. H. N. (1989). Rice DW Baker EN Structure of human lactoferrin: crystallographic structure analysis and refinement at 2.8 A resolution. *Journal of molecular biology, 209*, 711.

Giansanti, F., Leboffe, L., Pitari, G., Ippoliti, R., & Antonini, G. (2012). Physiological roles of ovotransferrin. *Biochimica et Biophysica Acta (BBA)-General Subjects, 1820*(3), 218-225.

Giansanti, F., Rossi, P., Massucci, M. T., Botti, D., Antonini, G., Valenti, P., & Seganti, L. (2002). Antiviral activity of ovotransferrin discloses an evolutionary strategy for the defensive activities of lactoferrin. *Biochemistry and cell biology, 80*(1), 125-130.

Gibbs, R. B. (2010). Estrogen therapy and cognition: A review of the cholinergic hypothesis. *Endocr Rev, 31*(2), 224-253.

Glazier, M. G., & Bowman, M. A. (2001). A review of the evidence for the use of phytoestrogens as a replacement for traditional estrogen replacement therapy. *Archives of internal medicine, 161*(9), 1161-1172.

Gold, E. B., Bromberger, J., Crawford, S., Samuels, S., Greendale, G. A., Harlow, S. D., & Skurnick, J. (2001). Factors associated with age at natural menopause in a multiethnic sample of midlife women. *American journal of epidemiology, 153*(9), 865-874.

Gold, E. B., Colvin, A., Avis, N., Bromberger, J., Greendale, G. A., Powell, L, &. Matthews, K. (2006). Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: study of women's health across the nation. *American journal of public health research 96*(7), 1226-1235.

Gold, E. B., Sternfeld, B., Kelsey, J. L., Brown, C., Mouton, C., Reame, N., & Stellato, R. (2000). Relation of demographic and lifestyle factors to symptoms in a multi-racial/ethnic population of women 40-55 years of age. *American journal of epidemiology, 152*(5), 463-473.

Götz, J. (2001). Tau and transgenic animal models. *Brain research reviews, 35*(3), 266-286.

Grady, D., Rubin, S. M., Petitti, D. B., Fox, C. S., Black, D., Ettinger, B., Ernster, V. L., & Cummings, S. R. (1992). Hormone therapy to prevent disease and prolong life in postmenopausal women. *Annals of internal medicine 117*(12), 1016-1037.

Graziottin, A., & Serafini, A. (2009). Depression and the menopause: Why antidepressants are not enough? *Menopause international 15*(2), 76-81.

Greendale, G. A., Huang, M. H., Wight, R. G., Seeman, T., Luetters, C., Avis, N. E., Johnston, J., & Karlamangla, A. S. (2009). Effects of the menopause transition and hormone use on cognitive performance in midlife women. *Neurology, 72*(21), 1850-1857.

Grodstein, F., Kang, J. H., Glynn, R. J., Cook, N. R., & Gaziano, J. M. (2007). A randomized trial of beta carotene supplementation and cognitive function in men: the Physicians' Health Study II. *Archives of internal medicine, 167*(20), 2184-2190.

Grodstein, F., Stampfer, M. J., Colditz, G. A., Willett, W. C., Manson, J. E., Joffe, M., Rosner, B., Fuchs, C., Hankinson, S. E., & Hunter, D. J. (1997). Postmenopausal hormone therapy and mortality. *New england journal of medicine, 336*(25), 1769-1776.

Guglielmi, G., & Scalzo, G. (2010). Imaging tools transform diagnosis of osteoporosis. *Diagnostic imaging europe, 26*, 7-11.

Guo, C.T., Takahashi, T., Bukawa, W., Takahashi, N., Yagi, H., Kato, K., Kazuya, I.P., Miyamoto, D., Suzuki, T., & Suzuki, Y. (2006). Edible bird's nest extract inhibits influenza virus infection. *Antiviral research, 70*(3), 140-146.

Guo, L., Wu, Y., Liu, M., Wang, B., Ge, Y., & Chen, Y. (2014). Authentication of edible bird's nests by taqman-based real-time pcr. *Food Control, 44*, 220-226.

Haigis, M.C., & Guarente, L.P. (2006). Mammalian sirtuins—emerging roles in physiology, aging, and calorie restriction. *Genes & development, 20*(21), 2913-2921.

Hamzah, Z., Ibrahim, N. H., Jaafar, M. N., Lee, B.-B., Hashim, O., & Hussin, K. (2013). Nutritional properties of edible bird nest. *Journal of Asian scientific research, 3*(6), 600-607.

Hara, Y., Park, C. S., Janssen, W. G., Punsoni, M., Rapp, P. R., & Morrison, J. H. (2011). Synaptic characteristics of dentate gyrus axonal boutons and their relationships with aging, menopause, and memory in female rhesus monkeys. *The journal of neuroscience, 31*(21), 7737-7744.

Harman, D. (1960). The free radical theory of aging: the effect of age on serum mercaptan levels. *Journal of gerontology, 15*(1), 38-40.

Harman, D. (1961). Mutation, cancer, and ageing. *The Lancet, 277*(7170), 200-201.

Harman, D. (1962). Role of free radicals in mutation, cancer, aging, and the maintenance of life. *Radiation research, 16*(5), 753-763.

Harman, D. (1972). Free radical theory of aging: dietary implications. *The American journal of clinical nutrition, 25*(8), 839-843.

Harman, D. (1998). Aging: phenomena and theories. *Annals of the New York academy of sciences, 854*(1), 1-7.

Hayes, J., & Pulford, D. (1995). The glutathione S-transferase supergene family: Regulation of GST (as in National Library of Medicine web site) and the contribution of the isoenzymes to cancer chemoprotection and drug resistance. *Critical reviews in biochemistry and molecular biology, 30*, 445-600.

Hazzard, D. G. (1991). Relevance of the rodent model to human aging studies. *Neurobiol Aging, 12*(6), 645-649.

Heo, J. H., Lee, S. T., Chu, K., Oh, M., Park, H. J., Shim, J. Y., & Kim, M. (2008). An open-label trial of korean red ginseng as an adjuvant treatment for cognitive

impairment in patients with alzheimer's disease. *European journal of neurology, 15*(8), 865-868.

Hess, R., Thurston, R. C., Hays, R. D., Chang, C.-C. H., Dillon, S. N., Ness, R. B., Bryce, C. L., Kapoor, W. N., & Matthews, K. A. (2012). The impact of menopause on health-related quality of life: Results from the stride longitudinal study. *Quality of life research, 21*(3), 535-544.

Hirsch, E., Costa, C., & Ciraolo, E. (2007). Phosphoinositide 3-kinases as a common platform for multi-hormone signaling. *Journal of endocrinology, 194*(2), 243-256.

Ho, S.-C., Liu, J.-H., & Wu, R.-Y. (2003). Establishment of the mimetic aging effect in mice caused by D-galactose. *Biogerontology, 4*(1), 15-18.

Ho, Y.-S., So, K.-F., & Chang, R. C.-C. (2010). Anti-aging herbal medicine—How and why can they be used in aging-associated neurodegenerative diseases? *Ageing research reviews, 9*(3), 354-362.

Holliday, R. (2006). Aging is no longer an unsolved problem in biology. *Annals of the New Yorkacademy of sciences, 1067*(1), 1-9.

Hotamisligil, G. S. (2006). Inflammation and metabolic disorders. *Nature, 444*(7121), 860-867.

Houdret, N., Lhermitte, M., Degand, P., & Roussel, P. (1974). [purification and chemical study of a collocalia glycoprotein]. *Biochimie, 57*(5), 603-608.

Howe, C., Lee, L. T., & Rose, H. M. (1961). Collocalia mucoid: a substrate for myxovirus neuraminidase. *Archives of biochemistry and biophysics, 95*(3), 512-520.

Huang, A. J., Grady, D., Jacoby, V. L., Blackwell, T. L., Bauer, D. C., & Sawaya, G. F. (2008). Persistent hot flushes in older postmenopausal women. *Archives of internal medicine, 168*(8), 840-846.

Hyman, B. T., Van Hoesen, G. W., Damasio, A. R., & Barnes, C. L. (1984). Alzheimer's disease: cell-specific pathology isolates the hippocampal formation. *Science, 225*(4667), 1168-1170.

Ibrahim, H. R., Hoq, M. I., & Aoki, T. (2007). Ovotransferrin possesses sod-like superoxide anion scavenging activity that is promoted by copper and manganese binding. *International journal of biological macromolecules, 41*(5), 631-640.

Igarashi, M., Wakasaki, H., Takahara, N., Ishii, H., Jiang, Z.Y., Yamauchi, T., Kuboki, K., Meier, M., Rhodes, C. J., & King, G. L. (1999). Glucose or diabetes activates p38 mitogen-activated protein kinase via different pathways. *Journal of clinical investigation, 103*(2), 185.

Imam, M. U., Ishaka, A., Ooi, D.-J., Zamri, N. D. M., Sarega, N., Ismail, M., & Esa, N. M. (2014). Germinated brown rice regulates hepatic cholesterol metabolism and cardiovascular disease risk in hypercholesterolaemic rats. *Journal of functional foods, 8*, 193-203.

Inostroza, M., Cid, E., Brotons-Mas, J., Gal, B., Aivar, P., Uzcategui, Y. G., Sandi, C., & de la Prida, L. M. (2011). Hippocampal-dependent spatial memory in the water maze is preserved in an experimental model of temporal lobe epilepsy in rats. *PLoS One, 6*(7), e22372.

Ismail, N., Ismail, M., Farhana Fathy, S., Asma Musa, S. N., Umar Imam, M., Foo, J. B., & Iqbal, S. (2012). Neuroprotective effects of germinated brown rice

against hydrogen peroxide induced cell death in human sh-sy5y cells. *International journal of molecular sciences, 13*(8), 9692-9708.

Ismail, N., Ismail, M., Latiff, L. A., Mazlan, M., & Mariod, A. A. (2008). Black cumin seed (nigella sativa linn.) oil and its fractions protect against beta amyloid peptide-induced toxicity in primary cerebellar granule neurons. *Journal of food lipids, 15*(4), 519-533.

Jick, H., Derby, L. E., Myers, M. W., Vasilakis, C., & Newton, K. M. (1996). Risk of hospital admission for idiopathic venous thromboembolism among users of postmenopausal oestrogens. *The lancet, 348*(9033), 981-983.

Jacobs, D. R., Gross, M. D., & Tapsell, L. C. (2009). Food synergy: an operational concept for understanding nutrition. *The American journal of clinical nutrition, 89*(5), 1543S-1548S.

Jones, P. (2002). Risk and benefits of estrogen plus progestin in healthy postmenopausal women. *Jama, 288*, 321-323.

Jorm, A. F., & Jolley, D. (1998). The incidence of dementia A meta-analysis. *Neurology, 51*(3), 728-733.

Kaeberlein, M., Jegalian, B., & McVey, M. (2002). AGEID: a database of aging genes and interventions. *Mechanisms of ageing and development, 123*(8), 1115-1119.

Kang, N., Hails, C., & Sigurdsson, J. (1991). Nest construction and egg-laying in Edible-nest Swiftlets Aerodramus spp. and the implications for harvesting. *Ibis, 133*(2), 170-177.

Kanungo, M. S. (2005). *Genes and aging*: Cambridge University Press.

Karim, S., Adams, D. H., & Lalor, P. F. (2012). Hepatic expression and cellular distribution of the glucose transporter family. *World journal of gastroenterology: WJG, 18*(46), 6771.

Karlovich, C. A., John, R. M., Ramirez, L., Stainier, D. Y., & Myers, R. M. (1998). Characterization of the Huntington's disease (HD) gene homolog in the zebrafish Danio rerio. *Gene, 217*(1), 117-125.

Kaufman, P. L., & Bito, L. Z. (1982). The occurrence of senile cataracts, ocular hypertension and glaucoma in rhesus monkeys. *Experimental eye research, 34*(2), 287-291.

Kawas, C., Gray, S., Brookmeyer, R., Fozard, J., & Zonderman, A. (2000). Age-specific incidence rates of Alzheimer's disease The Baltimore Longitudinal Study of Aging. *Neurology, 54*(11), 2072-2077.

Keating, N. L., Cleary, P. D., Rossi, A. S., Zaslavsky, A. M., & Ayanian, J. Z. (1999). Use of hormone replacement therapy by postmenopausal women in the united states.*Annals of internal medicine, 130*(7), 545-553.

Khatami, M. (2009). Inflammation, aging, and cancer: Tumoricidal versus tumorigenesis of immunity. *Cell biochemistry and biophysics, 55*(2), 55-79.

Khudoley, V. V. (1984). Use of aquarium fish, danio rerio and poecilia reticulata, as test species for evaluation of nitrosamine carcinogenicity. *National Cancer Institute Monograph, 65*, 65-70.

Kong, Y., Keung, W., Yip, T., Ko, K., Tsao, S., & Ng, M. (1987). Evidence that epidermal growth factor is present in swiftlet's (collocalia) nest. *Comparative*

Biochemistry and Physiology Part B: Comparative biochemistry, 87(2), 221-226.

Khushairay, E. S. I., Ayub, M. K., & Babji, A. S. (2014). *Effect of enzymatic hydrolysis of pancreatin and alcalase enzyme on some properties of edible bird's nest hydrolysate*. Paper presented at the the 2014 UKM 1st postgraduate colloquium: Proceedings of the Universiti Kebangsaan Malaysia, Faculty of Science and Technology 2014 Postgraduate Colloquium.

Kim, J.-E., Chen, J., & Lou, Z. (2008). DBC1 is a negative regulator of SIRT1. *Nature, 451*(7178), 583-586.

Kim, K. C., Kang, K. A., Lim, C. M., Park, J. H., Jung, K. S., & Hyun, J. W. (2012). Water extract of edible bird's nest attenuated the oxidative stress-induced matrix metalloproteinase-1 by regulating the mitogen-activated protein kinase and activator protein-1 pathway in human keratinocytes. *Journal of the Korean society for applied biological chemistry, 55*(3), 347-354.

Kong, Y. C., Keung, W. M., Yip, T. T., Ko, K. M., Tsao, S. W., & Ng, M. H. (1987). Evidence that epidermal growth factor is present in swiftlet's (collocalia) nest. *Comparative biochemistry and physiology. B, Comparative biochemistry, 87*(2), 221-226.

Koon, L. Cranbrook, earl of. 2002. *Swiftlets of Borneo: builders of edible nests*.

Kuhla, A., Ludwig, S. C., Kuhla, B., Munch, G., & Vollmar, B. (2015). Advanced glycation end products are mitogenic signals and trigger cell cycle reentry of neurons in alzheimer's disease brain. *Neurobiol aging, 36*(2), 753-761.

Kretz, O., Fester, L., Wehrenberg, U., Zhou, L., Brauckmann, S., Zhao, S., & Frotscher, M. (2004). Hippocampal synapses depend on hippocampal estrogen synthesis. *The journal of neuroscience, 24*(26), 5913-5921.

Krikorian, R., Nash, T. A., Shidler, M. D., Shukitt-Hale, B., & Joseph, J. A. (2010). Concord grape juice supplementation improves memory function in older adults with mild cognitive impairment. *British journal of nutrition, 103*(05), 730-734.

Lau, A. S., & Melville, D. S. (1994). *International trade in Swiftlet nests with special reference to Hong Kong*: Traffic International.

Lavrovsky, Y., Chatterjee, B., Clark, R., & Roy, A. (2000). Role of redox-regulated transcription factors in inflammation, aging and age-related diseases. *Experimental gerontology, 35*(5), 521-532.

Lee, C.-E. (2011). Activation of p53 and nf-kb degradation by socs1 to promote cancer cell apoptosis and to suppress implanted tumor growth. *The Journal of immunology, 186*(Meeting Abstracts 1), 165.147.

Lee, S.-T., Chu, K., Sim, J.-Y., Heo, J.-H., & Kim, M. (2008). Panax ginseng enhances cognitive performance in Alzheimer disease. *Alzheimer disease & associated disorders, 22*(3), 222-226.

Leimer, U., Lun, K., Romig, H., Walter, J., Grünberg, J., Brand, M., & Haass, C. (1999). Zebrafish (danio rerio) presenilin promotes aberrant amyloid β-peptide production and requires a critical aspartate residue for its function in amyloidogenesis. *Biochemistry, 38*(41), 13602-13609.

Lenzen, S. (2014). A fresh view of glycolysis and glucokinase regulation: History and current status. *Journal of biological chemistry, 289*(18), 12189-12194.

Lin, J.-R., Zhou, H., Lai, X.-P., Hou, Y., Xian, X.-M., Chen, J.-N., Wang, P.-X., Zhou, L., & Dong, Y. (2009). Genetic identification of edible birds' nest based on mitochondrial DNA sequences. *Food research international, 42*(8), 1053-1061.

Lin, J., Zhou, H., & Lai, X. (2006). [application of stereoscopy on edible birds nest identification]. *Zhong yao cai Journal of Chinese medicinal materials, 29*(3), 219-221.

Liu, X., Lai, X., Zhang, S., Huang, X., Lan, Q., Li, Y., Li, B., Chen, W., Zhang, Q., & Hong, D. (2012). Proteomic profile of edible bird's nest proteins. *Journal of agricultural and food chemistry, 60*(51), 12477-12481.

Longo, V. D., & Kennedy, B. K. (2006). Sirtuins in aging and age-related disease. *Cell, 126*(2), 257-268.

Louet, J.-F., LeMay, C., & Mauvais-Jarvis, F. (2004). Antidiabetic actions of estrogen: insight from human and genetic mouse models. *Current atherosclerosis reports, 6*(3), 180-185.

Luo, Q., Cai, Y., Yan, J., Sun, M., & Corke, H. (2004). Hypoglycemic and hypolipidemic effects and antioxidant activity of fruit extracts from Lycium barbarum. *Life sciences, 76*(2), 137-149.

Ma, F., & Liu, D. (2012). Sketch of the edible bird's nest and its important bioactivities. *Food research international, 48*(2), 559-567.

MA, F., LIU, D., & DAI, M. (2012). The effects of the edible bird's nest on sexual function of male castrated rats. *African journal of pharmacy and pharmacology,*

Malaysia, D. o. s. Life expectency at birth. from http://www.statistics.gov.my/

Manson, J. E., & Martin, K. A. (2001). Postmenopausal hormone-replacement therapy. *New England journal of medicine, 345*(1), 34-40.

Marcone, M. F. (2005). Characterization of the edible bird's nest the "caviar of the east". *Food research international, 38*(10), 1125-1134.

Martindale, J. L., & Holbrook, N. J. (2002). Cellular response to oxidative stress: Signaling for suicide and survival*. *Journal of cellular physiology, 192*(1), 1-15.

Matsukawa, N., Matsumoto, M., Bukawa, W., Chiji, H., Nakayama, K., Hara, H., & Tsukahara, T. (2011). Improvement of bone strength and dermal thickness due to dietary edible bird's nest extract in ovariectomized rats. *Bioscience, biotechnology, and biochemistry, 75*(3), 590-592.

McEwen, B. (2002). Estrogen actions throughout the brain. *Recent progress in hormone research, 57*, 357-384.

McEwen, B. S. (2001). Invited review: Estrogens effects on the brain: Multiple sites and molecular mechanisms. *Journal of applied physiology, (1985), 91*(6), 2785-2801.

Miller, S., Bowman, B., & Jee, W. (1995). Available animal models of osteopenia—small and large. *Bone, 17*(4), S117-S123.

Miquel, J., Economos, A., Fleming, J., & Johnson, J. (1980). Mitochondrial role in cell aging. *Experimental gerontology, 15*(6), 575-591.

Monteiro, S. C., Matté, C., Bavaresco, C. S., Netto, C. A., & Wyse, A. T. (2005). Vitamins e and c pretreatment prevents ovariectomy-induced memory deficits in water maze. *Neurobiology of learning and memory, 84*(3), 192-199.

Moreira, P. I., Nunomura, A., Honda, K., Aliev, G., Casadenus, G., Zhu, X., Smith, M. A., & Perry, G. (2007). The key role of oxidative stress in alzheimer's disease. *Oxidative stress and neurodegenerative disorders,* 451-466.

Morens, D., Davis, J., Grandinetti, A., Ross, G., Popper, J., & White, L. (1996). Epidemiologic observations on parkinson's disease incidence and mortality in a prospective study of middle-aged men. *Neurology, 46*(4), 1044-1050.

Morrison, J. H., Brinton, R. D., Schmidt, P. J., & Gore, A. C. (2006). Estrogen, menopause, and the aging brain: how basic neuroscience can inform hormone therapy in women. *The journal of neuroscience, 26*(41), 10332-10348.

Morrison, J. H., & Hof, P. R. (1997). Life and death of neurons in the aging brain. *Science, 278*(5337), 412-419.

Moscrip, T. D., Ingram, D. K., Lane, M. A., Roth, G. S., & Weed, J. L. (2000). Locomotor activity in female rhesus monkeys assessment of age and calorie restriction effects. *The journals of gerontology series A: biological sciences and medical sciences, 55*(8), B373-B380.

Muhammad, S. I., Maznah, I., Mahmud, R. B., Saeed, M. I., Imam, M. U., & Ishaka, A. (2013). Estrogen receptor modulatory effects of germinated brown rice bioactives in the uterus of rats through the regulation of estrogen-induced genes. *Drug design, development and therapy, 7*, 1409.

Muhammad, S. I., Maznah, I., Mahmud, R. B., Saeed, M. I., Imam, M. U., & Ishaka, A. (2013). Estrogen receptor modulatory effects of germinated brown rice bioactives in the uterus of rats through the regulation of estrogen-induced genes. *Drug Des Devel Ther, 7*, 1409-1420. doi: 10.2147/dddt.s50861

Muthusami, S., Ramachandran, I., Muthusamy, B., Vasudevan, G., Prabhu, V., Subramaniam, V., Jagadeesan, A., & Narasimhan, S. (2005). Ovariectomy induces oxidative stress and impairs bone antioxidant system in adult rats. *Clinica chimica Acta, 360*(1), 81-86.

Musa, A., Lehrach, H., & Russo, V. E. (2001). Distinct expression patterns of two zebrafish homologues of the human APP gene during embryonic development. *Development genes and evolution, 211*(11), 563-567.

Nakagawa, H., Hama, Y., Sumi, T., Li, S.-C., Maskos, K., Kalayanamitra, K., Mizumoto, S., Sugahara, K., & Li, Y.-T. (2007). Occurrence of a nonsulfated chondroitin proteoglycan in the dried saliva of collocalia swiftlets (edible bird's-nest). *Glycobiology, 17*(2), 157-164.

Nand, S. L., Webster, M. A., Baber, R., & O'Connor, V. (1998). Bleeding pattern and endometrial changes during continuous combined hormone replacement therapy. *Obstetrics & Gynecology, 91*(5), 678-684.

National institutes of health state-of-the-science conference statement: Management of menopause-related symptoms. (2005). *Annals of internal medicine, 142*(12 Pt 1), 1003-1013.

Nedrow, A., Miller, J., Walker, M., Nygren, P., Huffman, L. H., & Nelson, H. D. (2006). Complementary and alternative therapies for the management of menopause-related symptoms: A systematic evidence review. *Archives of internal medicine, 166*(14), 1453-1465.

Neer, R. M., Arnaud, C. D., Zanchetta, J. R., Prince, R., Gaich, G. A., Reginster, J.-Y., Hodsman, A. B., Eriksen, E. F., Ish-Shalom, S., & Genant, H. K. (2001). Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *New England journal of medicine, 344*(19), 1434-1441.

Nelson, H. D. (2008). Menopause. *Lancet, 371*(9614), 760-770.

Nelson, H. D., Humphrey, L. L., Nygren, P., Teutsch, S. M., & Allan, J. D. (2002). Postmenopausal hormone replacement therapy: scientific review. *Jama, 288*(7), 872-881.

Netzel, M., Strass, G., Bitsch, I., Könitz, R., Christmann, M., & Bitsch, R. (2003). Effect of grape processing on selected antioxidant phenolics in red wine. *Journal of food engineering, 56*(2), 223-228.

Newbold, R. R., Padilla-Banks, E., & Jefferson, W. N. (2006). Adverse effects of the model environmental estrogen diethylstilbestrol are transmitted to subsequent generations. *Endocrinology, 147*(6), s11-s17.

Ng, M., Chan, K., & Kong, Y. (1986). Potentiation of mitogenic response by extracts of the swiftlet's (collocalia) nest. *Biochemistry international, 13*(3), 521-531.

Nielsen, H., Lolk, A., & Kragh-SØRensen, P. (1998). Age-associated memory impairment—pathological memory decline or normal aging? *Scandinavian journal of psychology, 39*(1), 33-37.

Oddo, S., Caccamo, A., Shepherd, J. D., Murphy, M. P., Golde, T. E., Kayed, R., Metherate, R., Mattson, M. P., Akbari, Y., & LaFerla, F. M. (2003). Triple-transgenic model of alzheimer's disease with plaques and tangles: Intracellular aβ and synaptic dysfunction. *Neuron, 39*(3), 409-421.

Okazaki, Y., Kono, I., Kuriki, T., Funahashi, S., Fushimi, S., Iqbal, M., Okada, S., & Toyokuni, S. (2012). Bovine lactoferrin ameliorates ferric nitrilotriacetate-induced renal oxidative damage in rats. *Journal of clinical biochemistry and nutrition, 51*(2), 84.

Organization, W. H. (2012). Traditional medicine: Definitions.

Ou, K., Seow, T. K., Liang, R. C., Lee, B. W., Goh, D. L., Chua, K. Y., & Chung, M. (2001). Identification of a serine protease inhibitor homologue in bird's nest by an integrated proteomics approach. *Electrophoresis, 22*(16), 3589-3595.

Pallas, M., Pizarro, J., Gutierrez-Cuesta, J., Crespo-Biel, N., Alvira, D., Tajes, M., Yeste-Velasco, M., Folch, J., Canudas, A., & Sureda, F. (2008). Modulation of sirt1 expression in different neurodegenerative models and human pathologies. *Neuroscience, 154*(4), 1388-1397.

Persky, R. W., Turtzo, L. C., & McCullough, L. D. (2010). Stroke in women: disparities and outcomes. *Current cardiology reports, 12*(1), 6-13.

Picard, F., Kurtev, M., Chung, N., Topark-Ngarm, A., Senawong, T., De Oliveira, R. M., Leid, M., McBurney, M. W., & Guarente, L. (2004). Sirt1 promotes fat mobilization in white adipocytes by repressing ppar-γ. *Nature, 429*(6993), 771-776.

Pitozzi, V., Jacomelli, M., Catelan, D., Servili, M., Taticchi, A., Biggeri, A., . . . Giovannelli, L. (2012). Long-term dietary extra-virgin olive oil rich in polyphenols reverses age-related dysfunctions in motor coordination and contextual memory in mice: role of oxidative stress. *Rejuvenation research, 15*(6), 601-612.

Pizarro, J. G., Verdaguer, E., Ancrenaz, V., Junyent, F., Sureda, F., Pallàs, M., Folch, J., & Camins, A. (2011). Resveratrol inhibits proliferation and promotes apoptosis of neuroblastoma cells: Role of sirtuin 1. *Neurochemical research, 36*(2), 187-194.

Polito, F., Marini, H., Bitto, A., Irrera, N., Vaccaro, M., Adamo, E. B., . . . Altavilla, D. (2012). Genistein aglycone, a soy‐derived isoflavone, improves skin changes induced by ovariectomy in rats. *British journal of pharmacology, 165*(4), 994-1005.

Powis, G., Briehl, M., & Oblong, J. (1995). Redox signalling and the control of cell growth and death. *Pharmacology & therapeutics, 68*(1), 149-173.

Prasad, C., Imrhan, V., Marotta, F., Juma, S., & Vijayagopal, P. (2014). Lifestyle and Advanced Glycation End Products (AGEs) Burden: Its Relevance to Healthy Aging. *Aging and disease, 5*(3), 212.

Proks, P., Girard, C., & Ashcroft, F. M. (2005). Functional effects of kcnj11 mutations causing neonatal diabetes: Enhanced activation by mgatp. *Human molecular genetics, 14*(18), 2717-2726.

Qi, Z., & Li, S. (1981). Determination of the chemical composition of fructus lycii. *J. Ningxia University, 1*, 67-72.

Radi, E., Formichi, P., Battisti, C., & Federico, A. (2014). Apoptosis and oxidative stress in neurodegenerative diseases. *Journal of Alzheimer's disease, 42*, S125-S152.

Rahimi, R., Nikfar, S., Larijani, B., & Abdollahi, M. (2005). A review on the role of antioxidants in the management of diabetes and its complications. *Biomedicine & Pharmacotherapy, 59*(7), 365-373.

Rainard, P. (1986). Bacteriostatic activity of bovine milk lactoferrin against mastitic bacteria. *Veterinary microbiology, 11*(4), 387-392.

Rapp, P. R., & Amaral, D. G. (1991). Recognition memory deficits in a subpopulation of aged monkeys resemble the effects of medial temporal lobe damage. *Neurobiol Aging, 12*(5), 481-486.

Rashed, A. A., & Nazaimoon, W. W. (2010). Effect of Edible Bird's Nest on Caco-2 Cell Proliferation. *Journal of food technology, 8*(3), 126-130.

Raval, A. P., Lin, H. W., Dave, K. R., DeFazio, R. A., Morte, D. D., Kim, E. J., & Perez-Pinzon, M. A. (2008). Resveratrol and ischemic preconditioning in the brain. *Current medicinal chemistry, 15*(15), 1545-1551.

Reese, C. M., Cherry, K. E., & Copeland, A. L. (2000). Knowledge of normal versus pathological memory aging in younger and older adults. *Aging, Neuropsychology, and Cognition, 7*(1), 1-8.

Reiter, R. J. (1995). Oxidative processes and antioxidative defense mechanisms in the aging brain. *The FASEB journal, 9*(7), 526-533.

Resnick, S. M., Metter, E. J., & Zonderman, A. B. (1997). Estrogen replacement therapy and longitudinal decline in visual memory A possible protective effect? *Neurology, 49*(6), 1491-1497.

Roberts, C. K., & Sindhu, K. K. (2009). Oxidative stress and metabolic syndrome. *Life sciences, 84*(21), 705-712.

Rodstrom, K., Bengtsson, C., Lissner, L., Milsom, I., Sundh, V., & Bjorkelund, C. (2002). A longitudinal study of the treatment of hot flushes: the population

study of women in Gothenburg during a quarter of a century. *Menopause, 9*(3), 156-161.

Roh, K.-B., Lee, J., Kim, Y.-S., Park, J., Kim, J.-H., Lee, J., & Park, D. (2011). Mechanisms of edible bird's nest extract-induced proliferation of human adipose-derived stem cells. *Evidence-Based complementary and alternative Medicine, 2012*.

Rossouw, J. E., Prentice, R. L., Manson, J. E., Wu, L., Barad, D., Barnabei, V. M., Ko, M., LaCroix, A. Z., Margolis, K. L., & Stefanick, M. L. (2007). Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *Jama, 297*(13), 1465-1477.

Roth, G. S., Mattison, J. A., Ottinger, M. A., Chachich, M. E., Lane, M. A., & Ingram, D. K. (2004). Aging in rhesus monkeys: Relevance to human health interventions. *Science, 305*(5689), 1423-1426.

Rousseau, E., Michel, P. P., & Hirsch, E. C. (2013). The iron-binding protein lactoferrin protects vulnerable dopamine neurons from degeneration by preserving mitochondrial calcium homeostasis. *Molecular pharmacology, 84*(6), 888-898.

Russell, M., Lange-Carter, C. A., & Johnson, G. L. (1995). Direct interaction between ras and the kinase domain of mitogen-activated protein kinase kinase kinase (mekk1). *Journal of biological chemistry, 270*(20), 11757-11760.

Saleh, N. K., & Saleh, H. A. (2010). Olive oil improved the impairment of *in vitro* insulin-stimulated glucose uptake by diaphragm in ovariectomized female Wistar rats. *Experimental gerontology, 45*(12), 964-969.

Salthouse, T. A. (2009). When does age-related cognitive decline begin? *Neurobiol Aging, 30*(4), 507-514.

Sánchez-Rodríguez, M. A., Zacarías-Flores, M., Arronte-Rosales, A., Correa-Muñoz, E., & Mendoza-Núñez, V. M. (2012). Menopause as risk factor for oxidative stress. *Menopause, 19*(3), 361-367.

Schaffer, J., & Fantl, J. A. (1996). 4 Urogenital effects of the menopause. *Baillière's clinical obstetrics and gynaecology, 10*(3), 401-417.

Scott, E., Zhang, Q.-g., Wang, R., Vadlamudi, R., & Brann, D. (2012). Estrogen neuroprotection and the critical period hypothesis. *Front neuroendocrinol, 33*(1), 85-104.

Semba, R. D., Ferrucci, L., Sun, K., Beck, J., Dalal, M., Varadhan, R., Walston, J., Guralnik, J. M., & Fried, L. P. (2009). Advanced glycation end products and their circulating receptors predict cardiovascular disease mortality in older community-dwelling women. *Aging clinical and experimental research, 21*(2), 182-190.

Semba, R. D., Najjar, S. S., Sun, K., Lakatta, E. G., & Ferrucci, L. (2009). Serum carboxymethyl–lysine, an advanced glycation end product, is associated with increased aortic pulse wave velocity in adults. *American journal of hypertension, 22*(1), 74-79.

Shieh, P.-C., Tsao, C.-W., Li, J.-S., Wu, H.-T., Wen, Y.-J., Kou, D.-H., & Cheng, J.-T. (2008). Role of pituitary adenylate cyclase-activating polypeptide (pacap) in the action of ginsenoside rh2 against beta-amyloid-induced inhibition of rat brain astrocytes. *Neuroscience letters, 434*(1), 1-5.

Simpkins, J. W., Yi, K. D., Yang, S. H., & Dykens, J. A. (2010). Mitochondrial mechanisms of estrogen neuroprotection. *Biochimica et biophysica acta, 1800*(10), 1113-1120.

Sims, R. (1961). The identification of malaysian species of swiftlets collocalia. *Ibis, 103*(2), 205-210.

Singh, R., Barden, A., Mori, T., & Beilin, L. (2001). Advanced glycation end-products: a review. *Diabetologia, 44*(2), 129-146.

Sinn, N., Milte, C. M., Street, S. J., Buckley, J. D., Coates, A. M., Petkov, J., & Howe, P. R. (2012). Effects of n-3 fatty acids, epa v. Dha, on depressive symptoms, quality of life, memory and executive function in older adults with mild cognitive impairment: A 6-month randomised controlled trial. *British Journal of Nutrition, 107*(11), 1682-1693.

Song, X., Bao, M., Li, D., & Li, Y. M. (1999). Advanced glycation in D-galactose induced mouse aging model. *Mechanisms of ageing and development, 108*(3), 239-251

Soules, M. R., Sherman, S., Parrott, E., Rebar, R., Santoro, N., Utian, W., & Woods, N. (2001). Executive summary: Stages of reproductive aging workshop (straw). *Climacteric, 4*(4), 267-272.

Sourander, L., Rajala, T., Räihä, I., Mäkinen, J., Erkkola, R., & Helenius, H. (1998). Cardiovascular and cancer morbidity and mortality and sudden cardiac death in postmenopausal women on oestrogen replacement therapy (ert). *The lancet, 352*(9145), 1965-1969.

Spangler, J. (1996). Guide to clinical preventive services. *Archives of family medicine, 5*(6), 363.

Spitsbergen, J. M., & Kent, M. L. (2003). The state of the art of the zebrafish model for toxicology and toxicologic pathology research—advantages and current limitations. *Toxicologic pathology, 31*(1 suppl), 62-87.

Stampfer, M. J., Colditz, G. A., Willett, W. C., Manson, J. E., Rosner, B., Speizer, F. E., & Hennekens, C. H. (1991). Postmenopausal estrogen therapy and cardiovascular disease: Ten-year follow-up from the nurses' health study. *New England journal of medicine, 325*(11), 756-762.

Stampfer, M. J., Willett, W. C., Colditz, G. A., Rosner, B., Speizer, F. E., & Hennekens, C. H. (1985). A prospective study of postmenopausal estrogen therapy and coronary heart disease. *New England journal of medicine, 313*(17), 1044-1049.

Stern, E. A., Bacskai, B. J., Hickey, G. A., Attenello, F. J., Lombardo, J. A., & Hyman, B. T. (2004). Cortical synaptic integration *in vivo* is disrupted by amyloid-β plaques. *The Journal of neuroscience, 24*(19), 4535-4540.

Stohs, S., & Bagchi, D. (1995). Oxidative mechanisms in the toxicity of metal ions. *Free radical biology and medicine, 18*(2), 321-336.

Strehlow, K., Rotter, S., Wassmann, S., Adam, O., Grohé, C., Laufs, K., & Nickenig, G. (2003). Modulation of antioxidant enzyme expression and function by estrogen. *Circulation research, 93*(2), 170-177.

Suematsu, N., Hosoda, M., & Fujimori, K. (2011). Protective effects of quercetin against hydrogen peroxide-induced apoptosis in human neuronal sh-sy5y cells. *Neuroscience letters, 504*(3), 223-227.

Sun, S., Liang, X., & Yang, X. (2001). FIRT method applied for rapid identification of 6 edible bird's nest. *Analytical chemistry, 29*, 552-554.

Suzuki, S., Brown, C. M., & Wise, P. M. (2009). Neuroprotective effects of estrogens following ischemic stroke. *Front Neuroendocrinol, 30*(2), 201-211.

Swiftlet habitation living area. from http://www.acetech.com.my/Svc/Bird_Nest.htm

Szmuilowicz, E. D., Stuenkel, C. A., & Seely, E. W. (2009). Influence of menopause on diabetes and diabetes risk. *Nature Reviews endocrinology, 5*(10), 553-558.

Takahashi, M., Oikawa, M., & Nagano, A. (2000). Effect of age and menopause on serum concentrations of pentosidine, an advanced glycation end product. *The Journals of gerontology series A: biological sciences and medical sciences, 55*(3), M137-M140.

Tan, S., Wood, M., & Maher, P. (1998). Oxidative stress induces a form of programmed cell death with characteristics of both apoptosis and necrosis in neuronal cells. *Journal of neurochemistry, 71*(1), 95-105.

Tang, M.-X., Jacobs, D., Stern, Y., Marder, K., Schofield, P., Gurland, B., Andrews, H., & Mayeux, R. (1996). Effect of oestrogen during menopause on risk and age at onset of alzheimer's disease. *The lancet, 348*(9025), 429-432.

Tempfer, C. B., Froese, G., Heinze, G., Bentz, E.-K., Hefler, L. A., & Huber, J. C. (2009). Side effects of phytoestrogens: A meta-analysis of randomized trials. *American medical journal, 122*(10), 939-946. e939.

Tanzi, R. E., & Bertram, L. (2001). New frontiers in Alzheimer's disease genetics. *Neuron, 32*(2), 181-184.

Tempfer, C. B., Froese, G., Heinze, G., Bentz, E.-K., Hefler, L. A., & Huber, J. C. (2009). Side effects of phytoestrogens: a meta-analysis of randomized trials. *American medical journal, 122*(10), 939-946. e939.

Teo, P., Ma, F., & Liu, D. (2013). Evaluation of Taurine by HPTLC Reveals the Mask of Adulterated Edible Bird's Nest. *Journal of chemistry, 2013*.

Torre, P., & Fowler, C. G. (2000). Age-related changes in auditory function of rhesus monkeys (macaca mulatta). *Hearing research, 142*(1), 131-140.

Tresguerres, J. A., Kireev, R., Tresguerres, A. F., Borras, C., Vara, E., & Ariznavarreta, C. (2008). Molecular mechanisms involved in the hormonal prevention of aging in the rat. *The Journal of steroid biochemistry and molecular biology, 108*(3), 318-326.

Tuna, V., ALKIȘ, I., Safiye, A. S., Imamoglu, N., Bayram, N., & ALI ISMET, T. (2010). Variations in blood lipid profile, thrombotic system, arterial elasticity and psychosexual parameters in the cases of surgical and natural menopause. *Australian and New Zealand journal of obstetrics and gynaecology, 50*(2), 194-199.

Ulas, M., & Cay, M. (2010). The effects of 17β-estradiol and vitamin E treatments on oxidative stress and antioxidant levels in brain cortex of diabetic ovariectomized rats. *Acta physiologica hungarica, 97*(2), 208-215.

Uribarri, J., Cai, W., Peppa, M., Goodman, S., Ferrucci, L., Striker, G., & Vlassara, H. (2007). Circulating glycotoxins and dietary advanced glycation endproducts: Two links to inflammatory response, oxidative stress, and aging. *The journals of gerontology series A: biological sciences and medical sciences, 62*(4), 427-433.

Van Snick, J., & Masson, P. (1976). The binding of human lactoferrin to mouse peritoneal cells. *The Journal of experimental medicine, 144*(6), 1568-1580.

Vegeto, E., Benedusi, V., & Maggi, A. (2008). Estrogen anti-inflammatory activity in brain: a therapeutic opportunity for menopause and neurodegenerative diseases. *Front neuroendocrinol, 29*(4), 507-519.

Vest, R. S., & Pike, C. J. (2013). Gender, sex steroid hormones, and Alzheimer's disease. *Hormones and behavior, 63*(2), 301-307.

Vimala, B., Hussain, H., & Nazaimoon, W. W. (2012). Effects of edible bird's nest on tumour necrosis factor-alpha secretion, nitric oxide production and cell viability of lipopolysaccharide-stimulated raw 264.7 macrophages. *Food and agricultural immunology, 23*(4), 303-314.

Wang, C. C. (1921). The composition of chinese edible birds'nests and the nature of their proteins. *Journal of biological chemistry, 49*(2), 429-439.

Waters, E. M., Mitterling, K., Spencer, J. L., Mazid, S., McEwen, B. S., & Milner, T. A. (2009). Estrogen receptor alpha and beta specific agonists regulate expression of synaptic proteins in rat hippocampus. *Brain Res, 1290*, 1-11.

Weindruch, R., & Masoro, E. J. (1991). Concerns about rodent models for aging research. *Journal of gerontology, 46*(3), B87-B88.

WHO. from http://www.who.int/nutrition/topics/ageing/en/index1.html

wikipedia. Osteoporosis. from http://en.wikipedia.org/wiki/Osteoporosis

Winston, D., & Maimes, S. (2007). Adaptogens: herbs for strength, stamina, and stress relief: *Inner Traditions/Bear & Co.*

Wolff, S. P., Jiang, Z. Y., & Hunt, J. V. (1991). Protein glycation and oxidative stress in diabetes mellitus and ageing. *Free radical biology and medicine, 10*(5), 339-352.

Woolley, C. S., & McEwen, B. S. (1992). Estradiol mediates fluctuation in hippocampal synapse density during the estrous cycle in the adult rat. *The Journal of neuroscience : the official journal of the Society for Neuroscience, 12*(7), 2549-2554.

Wu-Peng, S., Rosenbaum, M., Nicolson, M., Chua, S. C., & Leibel, R. L. (1999). Effects of exogenous gonadal steroids on leptin homeostasis in rats. *Obesity research, 7*(6), 586-592.

Wu, C.-C., Chawla, F., Games, D., Rydel, R. E., Freedman, S., Schenk, D., Young, W. G., Morrison, J. H., & Bloom, F. E. (2004). Selective vulnerability of dentate granule cells prior to amyloid deposition in pdapp mice: Digital morphometric analyses. *Proceedings of the national academy of sciences of the United States of America, 101*(18), 7141-7146.

Wu, Y., Chen, Y., Wang, B., Bai, L., Ge, Y., & Yuan, F. (2010). Application of sybrgreen pcr and 2dge methods to authenticate edible bird's nest food. *Food research international, 43*(8), 2020-2026.

Xie, H., Huff, G. R., Huff, W. E., Balog, J. M., & Rath, N. C. (2002). Effects of ovotransferrin on chicken macrophages and heterophil-granulocytes. *Developmental & Comparative immunology, 26*(9), 805-815.

Xu, F. B. (1985). *Sub-acute toxicity ofd-galactose. Proceedings of the second national conference onaging research.*, Herbin, China.

Xu, J., Zhu, J., Shi, C., Guo, K., & Yew, D. T. (2007). Effects of genistein on hippocampal neurodegeneration of ovariectomized rats. *Journal of molecular neuroscience : MN, 31*(2), 101-112.

Yaffe, K., Sawaya, G., Lieberburg, I., & Grady, D. (1998). Estrogen therapy in postmenopausal women: Effects on cognitive function and dementia. *Jama, 279*(9), 688-695.

Yagi, H., Yasukawa, N., Yu, S.-Y., Guo, C.-T., Takahashi, N., Takahashi, T., Bukawa, W., Suzuki, T., Khoo, K.-H., & Suzuki, Y. (2008). The expression of sialylated high-antennary n-glycans in edible bird's nest. *Carbohydrate research, 343*(8), 1373-1377.

Yang, M., Cheung, S.-H., Li, S. C., & Cheung, H.-Y. (2014). Establishment of a holistic and scientific protocol for the authentication and quality assurance of edible bird's nest. *Food chemistry, 151*, 271-278.

Yassa, M. A., Muftuler, L. T., & Stark, C. E. (2010). Ultrahigh-resolution microstructural diffusion tensor imaging reveals perforant path degradation in aged humans *in vivo*. *Proceedings of the national academy of sciences, 107*(28), 12687-12691.

Ye, L., Chan, M. Y., & Leung, L. K. (2009). The soy isoflavone genistein induces estrogen synthesis in an extragonadal pathway. *Molecular and cellular endocrinology, 302*(1), 73-80.

Yew, M. Y., Koh, R. Y., Chye, S. M., Othman, I., & Ng, K. Y. (2014). Edible bird's nest ameliorates oxidative stress-induced apoptosis in sh-sy5y human neuroblastoma cells. *BMC complementary and alternative medicine, 14*(1), 391.

Yida, Z., Imam, M. U., & Ismail, M. (2014). *In vitro* bioaccessibility and antioxidant properties of edible bird's nest following simulated human gastro-intestinal digestion. *BMC complementary and alternative medicine, 14*(1), 468.

Yu-Qin, Y., Liang, X., Hua, W., Hui-Xing, Z., Xin-Fang, Z., & Bu-Sen, L. (2000). Determination of edible bird's nest and its products by gas chromatography. *Journal of chromatographic science, 38*(1), 27-32.

Yu, M.-S., Lai, C. S.-W., Ho, Y.-S., Zee, S.-Y., So, K.-F., Yuen, W.-H., & Chang, R. C.-C. (2007). Characterization of the effects of anti-aging medicine fructus lycii on β-amyloid peptide neurotoxicity. *International journal of molecular medicine, 20*(2), 261-268.

Yu, M.-S., Leung, S. K.-Y., Lai, S.-W., Che, C.-M., Zee, S.-Y., So, K.-F., Yuen, W.-H., & Chang, R. C.-C. (2005). Neuroprotective effects of anti-aging oriental medicine lycium barbarum against β-amyloid peptide neurotoxicity. *Experimental gerontology, 40*(8), 716-727.

Zamri, N. D. M., Imam, M. U., Ghafar, S. A. A., & Ismail, M. (2014). Antioxidative Effects of Germinated Brown Rice-Derived Extracts on H 2 O 2-Induced Oxidative Stress in HepG2 Cells. *Evidence-based complementary and alternative medicine: eCAM, 2014*.

Zandi, P. P., Carlson, M. C., Plassman, B. L., Welsh-Bohmer, K. A., Mayer, L. S., Steffens, D. C., & Breitner, J. C. (2002). Hormone replacement therapy and incidence of alzheimer disease in older women: The cache county study. *Jama, 288*(17), 2123-2129.

Zhang, L. (1908). Ben cao feng yuan: *Wei nan yan shi.*

Zhang, S., Lai, X., Liu, X., Li, Y., Li, B., Huang, X., Zhang, Q., Chen, W., Lin, L., & Yang, G. (2013). Development of monoclonal antibodies and quantitative sandwich enzyme linked immunosorbent assay for the characteristic sialoglycoprotein of edible bird's nest. *Journal of immunoassay and immunochemistry*, *34*(1), 49-60.

Zhang, Z., Andersen, A., Smith, C., Grondin, R., Gerhardt, G., & Gash, D. (2000). Motor slowing and parkinsonian signs in aging rhesus monkeys mirror human aging. *The Journals of Gerontology Series A: Biological sciences and medical sciences*, *55*(10), B473-B480.

Zhao, H., Li, Q., Zhang, Z., Pei, X., Wang, J., & Li, Y. (2009). Long-term ginsenoside consumption prevents memory loss in aged SAMP8 mice by decreasing oxidative stress and up-regulating the plasticity-related proteins in hippocampus. *Brain research*, *1256*, 111-122.

Zucchetto, A., Serraino, D., Polesel, J., Negri, E., De Paoli, A., Dal Maso, L., Montella, M., La Vecchia, C., Franceschi, S., & Talamini, R. (2009). Hormone-related factors and gynecological conditions in relation to endometrial cancer risk. *European journal of cancer prevention*, *18*(4), 316-321.