UNIVERSITI PUTRA MALAYSIA

BIOGENIC AMINES AND UROCANIC ACID IN KEROPOK LEKOR, AND THEIR EFFECTS ON CYTOTOXICITY AND PROINFLAMMATORY MEDIATOR SECRETION OF MACROPHAGE CELL CULTURE

HUSNIZA BINTI HUSSAIN

FSTM 2018 24

BIOGENIC AMINES AND UROCANIC ACID IN *KEROPOK LEKOR*, AND THEIR EFFECTS ON CYTOTOXICITY AND PROINFLAMMATORY MEDIATOR SECRETION OF MACROPHAGE CELL CULTURE

By

HUSNIZA BINTI HUSSAIN

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

August 2017

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

BIOGENIC AMINES AND UROCANIC ACID IN *KEROPOK LEKOR*, AND THEIR EFFECTS ON CYTOTOXICITY AND PROINFLAMMATORY MEDIATOR SECRETION OF MACROPHAGE CELL CULTURE

By

HUSNIZA BINTI HUSSAIN

August 2017

Chair: Hasanah Mohd. Ghazali, PhD
Faculty: Food Science and Technology

Scombroid fish poisoning (SFP) or histamine fish poisoning (HFP) is caused by consumption of mishandled fish or fishery products containing high contents of histamine and leads to allergy-like reaction. *Keropok lekor* or Malaysian fish sausage is a widely consume fish product. In fish products, some spoilage indicators are used including the levels of biogenic amines (BAs), urocanic acid (UCA), and presence of microorganisms. This thesis work aimed to develop rapid and robust methods for quantification/screening of nine BAs, UCA isomers and amino acid decarboxylase-producing bacteria in *keropok lekor* processed at different stages. Furthermore, the cytotoxicity and induction of proinflammatory mediator secretion by individual or mixture of the investigated compounds were carried out on RAW 264.7 macrophage cell culture. The modified Ultra High Performance Liquid Chromatography enabled rapid verification measurement of BAs and UCA regardless of inclusion of internal standard. The validated Liquid Chromatography-Mass Spectrometry using high strength silica polyfluorophenyl column allowed simultaneous measurement of all investigated compounds. The Møller Decarboxylase Micro-Method for screening of BAs-producing bacteria showed cost-effectiveness with small volume of growth media used, less laborious with reduce waste disposal. The developed method for determination of simultaneous cells viability using multilabel microplate reader may serve as an alternative application of acridine orange and propidium iodide in addition to their common usage in confocal microscopy imaging. This study revealed that BAs levels did not increase following the heat treatment i.e. boiling and frying of the *keropok lekor*. Nonetheless, frying process was showed to be best eliminating the amino-acid decarboxylase-producing bacteria. Several microorganisms were identified in both the fresh and processed *keropok lekor*. These include *Proteus vulgaris*, *Proteus mirabilis*, *Kocuria rhizophila*, *Kocuria kristinae*, *Lactococcus garvieae*, *Granulicatella elegans* and *Candida parapsilosis*. The study on the effects of BAs on RAW 264.7 macrophage cell culture showed that individual tyramine, tryptamine, spermine and spermidine induced inflammation in the macrophages led to apoptosis and necrosis, but no progression of inflammation nor secretion of proinflammatory mediators were observed with the *keropok lekor* extracts and its BAs mixtures. Spermine and

spermidine were the most cytotoxic and the inhibition concentrations at 50% cell viability (IC_{50}) were 28.35 µg/ml and 56.01 µg/ml, respectively. Taken together, this thesis work develops several modified methods that are rapid and robust for quantifying and screening of BAs, UCA and microorganisms in fishery products i.e. *keropok lekor*. The study also suggests that effective heat treatment i.e. frying could improve the microbiological quality of *keropok lekor* but not the contents of BAs. In addition, different food-related BAs exhibit different cytotoxicity effects on the RAW 264.7 macrophage cell culture. Future research on *in vitro* cytotoxicity effects of BAs in fishery products or other foods using different cell lines to resemble *in vivo* study is warranted.

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

AMINA BIOGENIK DAN ASID UROCANIC DI DALAM KEROPOK LEKOR, DAN KESAN TERHADAP SITOTOKSISITI DAN PEREMBESAN MEDIATOR PRO-INFLAMASI DARI KULTUR SEL MAKROFAJ

Oleh

HUSNIZA BINTI HUSSAIN

Ogos 2017

Pengerusi: Hasanah Mohd. Ghazali, PhD
Fakulti: Sains dan Teknologi Makanan

Keracunan ikan Scombroid (SFP) atau keracunan ikan histamine (HFP) disebabkan oleh pengambilan ikan membusuk atau produk perikanan yang mengandungi kadar histamin yang tinggi dan menyebabkan tindak balas seperti alergi. Keropok lekor atau sosej ikan Malaysia adalah produk ikan yang popular. Dalam produk ikan, beberapa petunjuk tahap kerosakan digunakan termasuk tahap amina biogenik (BA), asid urocanic (UCA), dan kehadiran mikroorganisma. Tesis ini bertujuan untuk membangunkan kaedah yang cepat dan mantap untuk kuantifikasi/pemeriksaan kehadiran sembilan BA, isomer UCA dan bakteria penghasil enzim decarboxylase asid amino di dalam keropok lekor yang pada peringkat pemprosesan yang berbeza. Selain itu, kesan sitotoksisiti dan induksi rembesan mediator pro-inflamasi oleh kompaun individu atau sebatian telah dikaji pada kultur sel makrofaj RAW 264.7. *Ultra High Perfromance Liquid Chromatography* (UHPLC) yang diubah suai membolehkan kuantifikasi pantas BA dan UCA bersama/tanpa kemasukan standard dalaman (IS). *Liquid Chromatography-Mass Spectrometry (LC-MS)* yang divalidasikan menggunakan kolum silika polifluorofenil berkekuatan tinggi membenarkan pengukuran seiring semua sebatian yang dikaji. *Møller Decarboxylase Micro-Method* untuk pemeriksaan kehadiran bakteria penghasil BA memperlihatkan keberkesanan kos dengan menggunakan jumlah media pertumbuhan yang kecil, lebih ringkas dan kurang penghasilan sisa. Kaedah yang dibangunkan untuk menentukan viabiliti sel dan *non-viability* sel menggunakan pembaca mikroplat multilabel boleh berfungsi sebagai aplikasi alternatif *acridine orange* (AO) dan propidium iodida (PI) sebagai tambahan kepada aplikasi terdahulu untuk pengimejan melalui mikroskopi *confocal*. Kajian ini mennunjukkan bahawa tahap BA tidak meningkat berikutan pendidihan dan penggorengan keropok lekor. Walau bagaimanapun, proses penggorengan menunjukkan bahawa ia adalah terbaik untuk menghapuskan bakteria penghasil enzim decarboksilasi asid amino. Beberapa mikroorganisma telah dikenal pasti di dalam kedua-dua keropok lekor yang segar dan diproses. Ini termasuk *Proteus vulgaris, Proteus mirabilis, Kocuria rhizophila, Kocuria kristinae, Lactococcus garvieae, Granulicatella elegans* dan *Candida parapsilosis*. Kajian mengenai kesan BA pada kultur sel makrofaj RAW 264.7 menunjukkan bahawa tyramine, tryptamine, spermine

dan spermidine individu yang menyebabkan inflamasi pada makrofaj yang menjurus kepada apoptosis dan nekrosis, tetapi tiada perkembangan inflamasi atau rembesan mediator pro-inflamasi diperhatikan dengan ekstrak keropok lekor dan sebatian BA. Spermine dan spermidine adalah yang paling sitotoksik dan kepekatan yang menyebabkan kerencatan viabiliti sel pada kadar 50% (IC_{50}) masing-masing adalah 28.35 μg/ml dan 56.01 μg/ml. Secara keseluruhan, tesis ini menghasilkan beberapa kaedah ujikaji yang diubahsuai dan divalidasi agar lebih cepat dan mantap untuk kuantifikasi BA dan UCA dan penyaringan mikroorganisma dalam produk perikanan keropok lekor. Kajian ini juga menunjukkan bahawa aplikasi haba yang berkesan iaitu penggorengan boleh menghapuskan mikroorganisma dalam keropok lekor tetapi tidak ke atas kandungan BA. Di samping itu, BA yang berbeza memberikan kesan sitotoksisiti yang berbeza pada kultur sel makrofaj RAW 264.7. Kesan sitotoksik *in vitro* BA dalam produk perikanan atau makanan lain dengan menggunakan kultur sel yang berbeza untuk menyamai kajian *in vivo* adalah wajar dijalankan di masa hadapan.

ACKNOWLEDGEMENTS

In the name of Allah, the Beneficent, the Merciful.
Read: In the name of thy Lord who createth,
Createth man from a clot. [Surah 96 (Al-Alaq), Ayat 1-2].

First and foremost, I would like to express my utmost gratitude to Allah for bestowing numerous sustenance through camaraderie with the best acquaintances to whom I have crossed my path with, and for giving me the knowledge which I could convey to others for the benefit of mankind. May all of them be rewarded sufficiently.

With sincere heartfelt, I would like to thank my supervisors, Prof. Dr. Hasanah Mohd. Ghazali, Prof. Dr. Jamilah Bakar, Dr. Wan Nazaimoon Wan Mohamud and Dr. Mohd. Fuat Abd. Razak for their continuous guidance and teachings throughout my ten years of post-graduate study in the Universiti Putra Malaysia.

Special thanks to my companions whom with their presence has added joy to my life and makes my journey very meaningful; to Zarafina Abdul Rahman, Dr. Too ChunLai, Ms. B. Vimala d/o R.M.T. Balasubramaniam and Ms. Lee Sin who constantly being there in my rainy days, and willingly sharing knowledge and expertise in completing this dissertation; to Hafeezah for being strong through ups and downs, and continue believing in me; to Hafeezudin for standing by me and being my protector; and to IA who holds endeavours in bringing hopes to reality.

Finally, I am thankful for having supportive parents, Hjh. Siti Zauyah Osman and Hj. Hussain Zainal Abidin, whom have shown me the meaning of love and being my first two persons whom I could rely on.

I certify that a Thesis Examination Committee has met on 11 August 2017 to conduct the final examination of Husniza binti Hussain on her thesis entitled "Biogenic Amines and Urocanic Acid in *Keropok Lekor*, and their Effects on Cytoxicity and Proinflammatory Mediator Secretion of Macrophage Cell Culture" 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.

Members of the Thesis Examination Committee were as follows:

Azizah binti Abdul Hamid, PhD
Professor
Faculty of Food Science and Technology
Universiti Putra Malaysia
(Chairman)

Nazamid bin Saari, PhD
Professor
Faculty of Food Science and Technology
Universiti Putra Malaysia
(Internal Examiner)

Yaya Rukayadi, PhD
Associate Professor
Faculty of Food Science and Technology
Universiti Putra Malaysia
(Internal Examiner)

Fatih Ozogul, PhD
Professor
Cukurova University
Turkey
(External Examiner)

NOR AINI AB. SHUKOR, PhD
Professor and Deputy Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 29 January 2018

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

Hasanah Mohd. Ghazali, PhD
Professor
Faculty of Food Science and Technology
Universiti Putra Malaysia
(Chairman)

Jamilah Bakar, PhD
Professor
Faculty of Food Science and Technology
Universiti Putra Malaysia
(Member)

Wan Nazaimoon Wan Mohamud, PhD
Cardiovascular, Diabetes & Nutrition Research Centre,
Institute for Medical Research
(Member)

Mohd. Fuat Abd. Razak, PhD
Bacteriology Unit,
Infectious Disease Research Centre
Institute for Medical Research
(Member)

_____

ROBIAH BINTI YUNUS, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

Date:

Declaration by graduate student

I hereby confirm that:

- this thesis is my original work;
- quotations, illustrations and citations have been duly referenced;
- this thesis has not been submitted previously or concurrently for any other degree at any other institutions;
- intellectual property from the thesis and copyright of thesis are fully-owned by Universiti Putra Malaysia, as according to the Universiti Putra Malaysia (Research) Rules 2012;
- written permission must be obtained from supervisor and the office of Deputy Vice-Chancellor (Research and Innovation) before thesis is published (in the form of written, printed or in electronic form) including books, journals, modules, proceedings, popular writings, seminar papers, manuscripts, posters, reports, lecture notes, learning modules or any other materials as stated in the Universiti Putra Malaysia (Research) Rules 2012;
- there is no plagiarism or data falsification/fabrication in the thesis, and scholarly integrity is upheld as according to the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) and the Universiti Putra Malaysia (Research) Rules 2012. The thesis has undergone plagiarism detection software.

Signature: _____ Date: _____

Name and Matric No.: Husniza binti Hussain (GS19468)

Declaration by Members of Supervisory Committee

This is to confirm that:

- the research conducted, and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

Signature: _____
Name of Chairman of Supervisory Committee: Hasanah Mohd. Ghazali

Signature: _____
Name of Member of Supervisory Committee: Jamilah Bakar

Signature: _____
Name of Member of Supervisory Committee: Wan Nazaimoon Wan Mohamud

Signature: _____
Name of Member of Supervisory Committee: Mohd. Fuat Abd. Razak

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

AGM	Agmatine
ANOVA	Analysis of Variance
ARG	Arginine
BA	Biogenic amines
BGB	Brilliant green bile
CAD	Cadaverine
CI	Combination index
CO_2	Carbon dioxide
CYS	Cysteine
DMEM	Dulbecco's Modified Eagle Medium
DMSO	Dimethyl sulfoxide
ELISA	Enzyme-linked immunosorbent assay
ESTD	External standard
FBS	Foetal Bovine Serum
H_2O	Water
HBSS	Hank's Buffered Salt Solution
HEPES	4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid
HIM	Histamine
HIS	Histidine
HPLC	High Performance Liquid Chromatography
hr	Hour
IDL	Instrument Detection Limit
IFN-γ	Interferon-gamma
IL-12	Interleukin-12
IQL	Instrument Quantification Limit
ISTD	Internal standard
KLAB	*Keropok lekor* after boiling
KLAC	*Keropok lekor* after cooling
KLAF	*Keropok lekor* after frying
KLD	*Keropok lekor* dough
LC	Liquid chromatography
LC-MS	Liquid chromatography-mass spectrometry
L-NAME	L-Nitro-Arginine Methyl Ester
LoB	Limit of Blank
LoD	Limit of Detection
LoQ	Limit of Quantification
LSB	Lauryl sulphate broth
LYS	Lysine
MDBB	Moeller decarboxylase base broth
MDL	Method Detection Limit
MFM	Minced fish meat
min	Minute
MQL	Method Quantification Limit
MWCO	Molecular weight cut-off
NaCl	Sodium chloride
$NaHCO_3$	Sodium bicarbonate
NaOH	Sodium hydroxide

NO	Nitric oxide
ORN	Ornithine
PBS	Phosphate Buffered Saline
PBST	Phosphate Buffered Saline with Tween 20
PC	Principal component
PCA	Plate count agar
PCA*	Principal Component Analysis
PGE_2	Prostaglandin E_2
PHE	Phenylalanine
PHM	2-phenylethylamine
PLA_2	Phospholipase A_2
PUT	Putrescine
RBC	Rose-Bengal chloramphenicol
RKL	Rod-shaped *keropok lekor*
RT	Room temperature
s	Second
SKL	Sliced *keropok lekor*
SPD	Spermidine
SPM	Spermine
TNF-α	Tumor necrosis factor-alpha
TPM	Tryptamine
TRP	Tryptophan
TYM	Tyramine
TYR	Tyrosine
UCA	Urocanic acid
UHPLC	Ultra High Performance Liquid Chromatography
VRBGA	Violet red bile glucose agar

CHAPTER 1

INTRODUCTION

Eating fish regularly can be very beneficial for our health, and it can help reduce risk for some diseases, particularly those related to the heart. However, toxins in contaminated fish can cause health problems such as scombroid fish poisoning (SFP). SFP is caused by eating fish that has not been properly refrigerated or preserved and thus contains high contents of histamine. Without adequate cooling or improper preservation, some symbiotic bacteria such as *Escherichia coli*, *Morganella morganii*, *Proteus* and *Klebsiella* species can convert histidine, present in the fish tissues, to histamine. In raw fish left at room temperature, these bacteria multiply rapidly; increase the histidine-to-histamine conversion rate, raising the histamine levels and reaching toxic concentration within 12 hours. In SFP cases, histamine is thought to produce the clinical manifestations of illness, thus also termed as histamine fish poisoning (HFP).

Although SFP is caused by bacterially-generated toxins i.e. histamine in the fish, its symptoms usually resemble an allergic reaction, such as flushing of the face, headache, heart palpitations, itching, blurred vision, cramps, diarrhoea and a burning sensation or peppery taste in the mouth. Thus, SFP are often misdiagnosed as allergy reaction (Vlieg-Boerstra et *al*., 2005). SFP cases were rarely reported in Malaysia. Nonetheless, isolated cases were documented in various developed countries (Merson et *al*., 1974; Stratton et *al*., 1991).

The main biogenic amines (BAs) encountered in foods include histamine (HIM), 2-phenylethylamine (PHM), tyramine (TYM), tryptamine (TPM), putrescine (PUT), cadaverine (CAD), spermine (SPM), spermidine (SPD) and agmatine (AGM). These compounds were studied extensively in SFP-related food toxicity (Taylor, 1989; Til et *al*., 1997; Ansorena, et *al*., 2002). The four former amines have important physiological effects in human, either psychoactive which affect the nervous system or vasoactive which act on the vascular system (Lovenberg, 1973), whilst other secondary amines (i.e. agmatine, spermine and spermidine) in fish, meat and vegetable products are known to be converted to carcinogenic *N*-nitrosamines with the presence of nitrite. Consumption of foods containing high amount of these amines can be toxic (Shalaby, 1996).

In addition to the presence of histamine through consumption of mishandled fish or seafood-based products, there is another mechanism which had been suggested contributing to SFP i.e. the presence of urocanic acid (UCA). Urocanic acid is an intermediate in the catabolism of L-histidine. Urocanic acid is found predominantly in the stratum corneum of the skin and is likely that most of it is derived from filaggrin catabolism (a histidine-rich protein) (Moodycliffe et *al*.,

1992). When exposed to ultraviolet B (UVB) irradiation, *trans*-urocanic acid is converted *in vitro* and *in vivo* to the *cis* isomer. *Cis*-urocanic acid is the triggering agent in the UVB induced immunosuppression. It stimulates the release of neuropeptides which in turn cause the release of endogenous histamine and tumour necrosis factor-α (TNF-α) in mast cells. The release of this histamine also elicits allergic-like reaction.

Histamine can be formed endogenously in the human body and it is released by mast cells in an allergy reaction (Johnson & Erdös, 1973). When histamine is consumed in food due to microbial contamination, it is inactivated by amine oxidases in the gut (Halász et *al.*, 1994; Stadnik & Dolatowski, 2010). The enzyme activity can however be inhibited in individuals with susceptible genetic risk factors, gastrointestinal diseases, or consumed certain medicines and alcohol (Maintz & Novak, 2007).

Cases on HFP had been reported in various developed countries. Thus, research on biogenic amine levels on *keropok lekor*, the popular fish-based food in Malaysia needs to be undertaken. In Malaysia, the study of BAs or microorganisms in fish-based foods including the widely consumed snack named *keropok lekor* had been scarce (Hassan et *al*., 2009; Mahmud et *al*., 2009). Thus, it is crucial to determine and identify the main microorganisms that generate the BAs in the *keropok lekor* to prevent the occurrence of SFP. This study is a revisited study over the investigation done by Mahmud et *al*. (2009a & 2009b) on *keropok lekor*. Their findings showed that the biogenic amine levels were < 100 mg/kg. The observed low level may not reflect the whole *keropok lekor* industry in Malaysia. Various reports also had stated that biogenic amines were present in high level in fish-based foods (Tsai et *al.*, 2005; Saaid et *al.*, 2009; Zaman et *al.*, 2011), thus, the inconsistencies would likely be present in different manufacturing sites.

The roles of biogenic amines and urocanic acid compounds in food intolerance and toxicity is poorly understood (De Meulenaer, 2006). However, the involvement of immune response in food intolerance or food toxicity had been discussed in relation to the cytokine levels (Gallardo et *al*., 1994; Jacobsen et *al*., 2000; Chang & Adami, 2006). Our body defenses against microbial infection, injury and toxic compounds in food allergy, food intolerance and food toxicity led to inflammation (Genuis, 2010; Langerholc et *al.* 2011). Macrophages are among the first immune cells confronting absorbed food compounds. Thus, the study of the effects for BAs and urocanic acid compounds on macrophages is needed to understand their roles in initiation of inflammation due to consumption of mishandled fish.

In food industry, low-histamine technology in food processing has been introduced and practiced (Bodmer et *al*., 1999). It is timely and relevant to determine the levels of biogenic amines and urocanic acid in *keropok lekor* during its processing, after frying and those which are commercially available in markets. Taken

together, we can compare the freshness and levels of biogenic amines/urocanic acid of differently processed or commercially available *keropok lekor* in the markets based on the Biogenic Amines Index (Mietz & Karmas, 1977; Veciana-Nogues et *al*., 1997).

Different methods based on liquid chromatography have been used for the detection of biogenic amines and urocanic acid independently in food. Thus, there is a need to develop a robust liquid chromatography method for quantification of biogenic amines and urocanic acid simultaneously in a single assay as well as developing a better screening method for amino acid decarboxylase-producing bacteria in foods.

This study was done to visit another *keropok lekor* manufacturing site and to determine the microbiological quality and biogenic amine contents in the minced fish meat obtained by the manufacturer and the quality of fresh, processed and fried *keropok lekor*. This study is carried out based on the following objectives:

(i) To develop quantification/screening methods for biogenic amines, *trans*- and *cis*-urocanic acid and amino acid decarboxylase-producing bacteria in *keropok lekor*,
(ii) To determine biogenic amines and *trans*- and *cis*-urocanic acid contents in fresh, processed and fried *keropok lekor*,
(iii) To enumerate and identify the amino acid decarboxylase-producing bacteria present in *keropok lekor*,
(iv) To determine the cytotoxic and induction of pro-inflammatory mediator secretion effects of BAs, *trans*- and *cis*-UCA, and *keropok lekor* extracts on RAW 264.7 macrophage cell.

REFERENCES

Ababouch, L. & Gram, L. 5.1.2 Production of biogenic amines in Assessment and Management of Seafood Safety and Quality Fisheries and Aquaculture Department. Retrieved from http://www.fao.org/docrep/006/y4743e/y4743e0a.htm [accessed 10 May 2017].

Adams, D. O., & Hamilton, T. A. (1984). The cell biology of macrophage activation. *Annual Review of Immunology* 2(1): 283-318.

Ahmad, S., Israf, D. A., Lajis, N. H., Shaari, K., Mohamed, H., Wahab, A. A., ... & Sulaiman, M. R. (2006). Cardamonin, inhibits pro-inflammatory mediators in activated RAW 264.7 cells and whole blood. *European Journal of Pharmacology* 538(1): 188-194.

Ansorena, D., Montel, M. C., Rokka, M., Talon, R., Eerola, S., Rizzo, A., Raemaekers, M., Demeyer, D. (2002). Analysis of biogenic amines in northern and southern European sausages and role of flora in amine production. *Meat Science* 61: 141-147.

Arnold, S. H., & Brown, W. D. (1978). Histamine (?) toxicity from fish products. *Advances in Food Research* 24: 113-154.

Attaran, R. R., & Probst, F. (2002). Histamine fish poisoning: a common but frequently misdiagnosed condition. *Emergency Medicine Journal* 19(5): 474-475.

Authority, A. N. Z. F., & Australia ANZFA, A. C. T. (1998). Australia New Zealand Food Authority. Service Charter. Canberra, Australia: ANZFA.

Authority, Australia New Zealand Food. (2001). *Safe food Australia: A Guide to the Food Safety Standards*: Australia New Zealand Food Authority.

Awang, C. R. (2004). Teknologi pemprosesan keropok lekor. MARDI Kuala Terengganu Report 1-18.

Azuma, Y., & Ohura, K. (2001). Comparison of the effect of lidocaine–epinephrine and prilocaine–felypressine to alter macrophage functions. *International Immunopharmacology* 1(5): 911-923.

Azuma, Y., Shinohara, M., Wang, P-L., & Ohura, K. (2001). 15-Deoxy-Δ 12, 14-prostaglandin J 2 is a negative regulator of macrophage functions. *International Immunopharmacology* 1(12): 2101-2108.

Bakar, J., Yassoralipour, A., Bakar, F. A., & Rahman, R. A. (2010). Biogenic amine changes in barramundi (*Lates calcarifer*) slices stored at 0 C and 4 C. *Food Chemistry* 119(2): 467-470.

Bamias, G., Nyce, M. R., Sarah, A., & Cominelli, F. (2005). New concepts in the pathophysiology of inflammatory bowel disease. *Annals of Internal Medicine* 143(12): 895-904.

Bank, H. L. (1988). Rapid assessment of islet viability with acridine orange and propidium iodide. *In vitro Cellular & Developmental Biology* 24(4): 266-273.

Baranowski, J. D., Brust, P. A., & Frank, H. A. (1985). Growth of *Klebsiella pneumoniae* UH-2 and properties of its histidine decarboxylase system in resting cells. *Journal of Food Biochemistry* 9(4): 349-360.

Bardocz, S. (1995). Polyamines in food and their consequences for food quality and human health. *Trends in Food Science and Technology* 6(10): 341-346.

Bardócz, S., Duguid, T. J., Brown, D. S., Grant, G., Pusztai, A., White, A., & Ralph, A. (1995). The importance of dietary polyamines in cell regeneration and growth. *British Journal of Nutrition* 73(06): 819-828.

Bartholomew, B. A., Berry, P. R., Rodhouse, J. C., Gilbert, R. J., & Murray, C. K. (1987). Scombrotoxic fish poisoning in Britain: features of over 250 suspected incidents from 1976 to 1986. *Epidemiology and Infection* 99(03): 775-782.

Bengigirey, B., Craven, C., & An, H. (1998). Histamine formation in albacore muscle analyzed by AOAC and enzymatic methods. *Journal of Food Science* 63(2): 210-214.

Bergey's Manual of Determinative Bacteriology (7th ed.). (1964). *American Journal of Public Health and the Nations Health* 54(3): 544.

Bieganski, T., Kusche, J., Lorenz, W., Hesterberg, R., Stahlknecht, C., & Feussner, K. (1983). Distribution and properties of human intestinal diamine oxidase and its relevance for the histamine catabolism. *Biochimica et Biophysica Acta* (BBA) - General Subjects 756: 196-203.

Bjeldanes, L. F., Schutz, D. E., & Morris, M. M. (1978). On the aetiology of scombroid poisoning: cadaverine potentiation of histamine toxicity in the guinea-pig. *Food and Cosmetics Toxicology* 16(2): 157-159.

Bodmer, S., Imark, C., & Kneubühl, M. (1999). Biogenic amines in foods: histamine and food processing. *Inflammation Research* 48(6): 296-300.

Borade, P. S., Ballary, C. C., & Lee, D. K. C. (2007). A fishy cause of sudden near fatal hypotension. *Resuscitation* 72(1): 158-160.

Botham, P. A. (2004). Acute systemic toxicity - Prospects for tiered testing strategies. *Toxicology In Vitro* 18: 227-230.

Bover-Cid, S., & Holzapfel, W. H. (1999). Improved screening procedure for biogenic amine production by lactic acid bacteria. *International Journal of Food Microbiology* 53(1): 33-41.

Bover-Cid, S., Izquierdo-Pulido, M., Vidal-Carou, M. C. (2001). Effect of the interaction between a low tyramine-producing *Lactobacillus* and proteolytic *staphylococci* on biogenic amine production during ripening and storage of dry sausage. *International Journal of Food Microbiology* 65: 113-123.

Brimblecombe, R. W., Downing, D. F., Green, D. M., & Hunt, R. R. (1964). Some pharmacological effects of a series of tryptamine derivatives. *British Journal of Pharmacology and Chemotherapy* 23(1): 43-54.

Bulushi, I. M., Guizani, N., & Dykes, G. A. (2013). Effect of ambient storage on the microbial characteristics of traditional dried anchovies (*Encrasicholina punctifer*). *African Journal of Microbiology Research* 7(28): 3575-3581.

Burghardt, R. C., & Droleskey, R. (2006). Transmission electron microscopy. *Current Protocols in Microbiology:* 2B. 1.1-2B. 1.39.

Cahill, M. M. (1990). Bacterial flora of fishes: A review. *Microbial Ecology*, 19, 21-41.

Casella, I. G., Gatta, M., & Desimoni, E. (2001). Determination of histamine by high-pH anion-exchange chromatography with electrochemical detection. *Food Chemistry* 73(3): 367-372.

Chang, E. T. and Adami, H-O. (2006). "The Enigmatic Epidemiology of Nasopharyngeal Carcinoma. *Cancer Epidemiology Biomarkers & Prevention* 15(10): 1765-1777.

Chavadej, S., Brisson, N., McNeil, J. N., & De Luca, V. (1994). Redirection of tryptophan leads to production of low indole glucosinolate canola. *Proceedings of the National Academy of Sciences of the United States of America* 91: 2166-2170.

Che, W., Liu, G., Qiu, H., Zhang, H., Ran, Y., Zeng, X., Shu, Y. (2010). Comparison of immunotoxic effects induced by the extracts from methanol and gasoline engine exhausts *in vitro*. *Toxicology In Vitro* 24(4): 1119-1125.

Chen, K. C., Culbertson, N. J., Knapp, J. S., Kenny, G. E., & Holmes, K. K. (1982). Rapid method for simultaneous detection of the arginine dihydrolase system and amino acid decarboxylases in microorganisms. *Journal of Clinical Microbiology* 16(5): 909-919.

Chen, K. T., & Malison, M. D. (1987). Outbreak of scombroid fish poisoning, Taiwan. *American Journal of Public Health* 77(10): 1335-1336.

Cheng, Y. H., Ding, S. T., Chang, M. H. (2006). Effect of fumonisins on macrophage immune functions and gene expression of cytokines in broilers. *Archives of Animal Nutrition* 60(4): 267-276.

Chou, T. C. (2010). Drug combination studies and their synergy quantification using the Chou-Talalay method. *Cancer Research* 70(2): 440-446.

Chow, Y-L., Lee, K-H., Vidyadaran, S., Lajis, N. H., Akhtar, M. N., Israf, D. A., & Syahida, A. (2012). Cardamonin from Alpinia rafflesiana inhibits inflammatory responses in IFN-γ/LPS-stimulated BV2 microglia via NF-κB signalling pathway. *International Immunopharmacology* 12(4): 657-665.

Clifford, M. N., & Walker, R. (1992). The aetiology of scombrotoxicosis. *International Journal of Food Science & Technology* 27(6): 721-724.

Clifford, M. N., Walker, R., Wright, J. (1989). Studies with volunteers on the role of histamine in suspected scombrotoxicosis. *Journal of the Science of Food and Agriculture* 47: 365-375.

CLSI (2012). Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline—Second Edition. CLSI document EP17-A2.

Cobo, M., & Silva, M. (1999). Continuous solid-phase extraction and dansylation of low-molecular-mass amines coupled on-line with liquid chromatography and peroxyoxalate chemiluminescence-based detection. *Journal of Chromatography A* 848(1): 105-115.

Coombes, J. L., & Powrie, F. (2008). Dendritic cells in intestinal immune regulation. *Nature Reviews Immunology* 8(6): 435-446.

Cumming, G., Fidler, F., & Vaux, D. L. (2007). Error bars in experimental biology. *The Journal of Cell Biology* 177(1): 7-11.

Darzynkiewicz, Z., Bruno, S., Del Bino, G., Gorczyca, W., Hotz, M. A., Lassota, P., & Traganos, F. (1992). Features of apoptotic cells measured by flow cytometry. *Cytometry* 13: 795-808.

Davies, K. (2006). Interleukins, http://people.wscu.edu/wonge/bio537/Interleukins _kristin .pdf [Accessed 2007 November 9].

De las Rivas, B., Marcobal, Á., & Muñoz, R. (2005). Improved multiplex-PCR method for the simultaneous detection of food bacteria producing biogenic amines. *FEMS Microbiology Letters* 244(2): 367-372.

Delgado, M., & Ganea, D. (2008). Anti-inflammatory neuropeptides: a new class of endogenous immunoregulatory agents. *Brain, Behavior, and Immunity* 22(8): 1146-1151.

De Meulenaer, B. (2006). Chemical hazards. *Safety in the Agri-food Chain*. Wageningen Academic Publishers, The Netherlands: 145-208.

de Villiers, André, Lestremau, François, Szucs, Roman, Gélébart, Sylvie, David, Frank, & Sandra, Pat. (2006). Evaluation of ultra performance liquid chromatography: Part I. Possibilities and limitations. *Journal of Chromatography A* 1127(1): 60-69.

Demoncheaux, J. P., Michel, R., Mazenot, C., Duflos, G., Iacini, C., Delaval, F., & Renard, J. C. (2012). A large outbreak of scombroid fish poisoning associated with eating yellowfin tuna (*Thunnus albacares*) at a military mass catering in Dakar, Senegal. *Epidemiology and Infection* 140(06): 1008-1012.

Del Pozo, V., de Andres, B., Gallardo, S., Cardaba, B., de Arruda-Chaves, E., Cortegano, M. I., Jurado, A., Palomino, P., Oliva, H., Aguilera, B., Posada, M., Lahoz, C. (1997). Cytokine mRNA expression in lung tissue from toxic oil syndrome patients: a TH2 immunological mechanism. *Toxicology* 118(1): 61-70.

den Brinker, C., Rayner, C., Kerr, M. (2002). Investigation of biogenic amines in fermented fish and fish products. 1st edition Public Health Division, Victorian Government Department of Human Services.

Dhesi, I., Marsh, M. N., Kelly, C., & Crowe, P. (1984). Morphometric analysis of small intestinal mucosa. *Virchows Archiv A* 403(2): 173-180.

Dickinson, G. (1982). Scombroid fish poisoning syndrome. *Annals of Emergency Medicine* 11(9): 487-489.

DOF. (2011). Fish Crackers. Official Website of Department of Fisheries Malaysia. Retrieved from http://www.dof.gov.my/index.php/pages/view/143 [accessed 10 May 2017].

Durlu-Özkaya, F., Ayhan, K., & Vural, N. (2001). Biogenic amines produced by Enterobacteriaceae isolated from meat products. *Meat Science* 58: 163-166.

Eigenmann, P. A., & Frossard, C. P. (2003). The T Lymphocyte in food allergy disorders. *Current Opinion in Allergy and Clinical Immunology* 3(3):199-203.

Elmore, S. (2007). Apoptosis: a review of programmed cell death. *Toxicologic Pathology* 35(4): 495-516.

European Federation of Asthma and Allergy Associations & Pharmacia & Upjohn (1997). *Adverse Reactions to Food*, http://www.efanet.org/ activities/documents /AdverseReactionstoFood.pdf [Accessed 2007 October 29].

Evaluation of Detection Capability for Clinical Lab Measurement: EP17-A2 - CLSI Shop. Retrieved from http://shop.clsi.org/site/Sample _pdf/EP17A2_sample.pdf [accessed 10 May 2017].

Ezzat, M. A., Zare, D., Karim, R., & Ghazali, H. M. (2015). Trans-and cis-urocanic acid, biogenic amine and amino acid contents in *ikan pekasam* (fermented fish) produced from Javanese carp (*Puntius gonionotus*) and black tilapia (*Oreochromis mossambicus*). *Food chemistry* 172: 893-899.

Feldman, K. A., Werner, S. B., Cronan, S., Hernandez, M., Horvath, A. R., Lea, C. S., & Vugia, D. J. (2005). A large outbreak of scombroid fish poisoning associated with eating escolar fish (*Lepidocybium flavobrunneum*). *Epidemiology and Infection* 133(01): 29-33.

Feng, X., Chen, S., Xu, Y., Du, W., Luo, Q., & Liu, B. F. (2008). Separation and determination of biogenic amines in fish using MEKC with novel multiphoton excitation fluorescence detection. *Journal of Separation Science* 31(5): 824-828.

Fish and Fishery Products Hazards and Controls Guidance – FDA. Retrieved from https://www.fda.gov/downloads/food/guidanceregulation/ucm251970 .pdf [accessed 10 May 2017].

Fonzi, W. A. (1989). Regulation of *Saccharomyces cerevisiae* ornithine decarboxylase expression in response to polyamine. *Journal of Biological Chemistry* 264: 18110-18118.

Frank, H. A., Baranowski, J. D., Chongsiriwatana, M., Brust, P. A., & Premaratne, R. J. (1985). Identification and decarboxylase activities of bacteria isolated from decomposed mahimahi (*Coryphaena hippurus*) after incubation at 0 and 32 C. *International Journal of Food Microbiology* 2(6): 331-340.

Fujiwara, N., & Kobayashi, K. (2005). Macrophages in inflammation. *Current Drug Targets-Inflammation & Allergy* 4(3): 281-286.

Gallardo, S., del Pozo, V., Cardaba, B., de Andres, B., Martin-Orozco, E., Fernandez, J. C., & Lahoz, C. (1994). Immunological basis of toxic oil syndrome (TOS). *Toxicology* 93(2-3): 289-299.

Galluzzi, L., Maiuri, M. C., Vitale, I., Zischka, H., Castedo, M., Zitvogel, L., & Kroemer, G. (2007). Cell death modalities: classification and pathophysiological implications. *Cell Death and Differentiation* 14(7): 1237-1242.

Gastrointestinal tract – Wikipedia. Retrieved from https://en.wikipedia .org/wiki/ Gastrointestinal_tract [accessed 30 March 2016].

Genuis, S. J. (2010). Sensitivity-related illness: the escalating pandemic of allergy, food intolerance and chemical sensitivity. *Science of the Total Environment* 408(24): 6047-6061.

Gessner, B. D., Hokama, Y. & Isto, S. (1996). Scombrotoxicosis-like illness following the ingestion of smoked salmon that demonstrated low histamine levels and high toxicity on mouse bioassay. *Clinical Infectious Diseases:* 1316-1318.

Ghazanfari, T., Yaraee, R., Farahnejad, Z., Rahmati, B., & Hakimzadeh, H. (2010). Macrophages activation and nitric oxide alterations in mice treated with *Pleurotus florida*. *Immunopharmacology and Immunotoxicology* 32(1): 47-50.

Gram, L., & Huss, H. H. (1996). Microbiological spoilage of fish and fish products. *International Journal of Food Microbiology* 33: 121-137.

Grana, E., & Lilla, L. (1959). The Inhibition of Amine Oxidase and the Central Stimulating Action of the Stereoisomeric Amphetamines and 1-Phenylethylamines. *British Journal of Pharmacology and Chemotherapy* 14(4): 501-504.

Grant, Florida Sea. (2011). Fish and fishery products hazards and controls guidance. *Center for Food Safety and Applied Nutrition* 240: 402-2300.

Halasz, A., Barath, A., Simon-Sarkadi, L., Holzapfel, W. (1994). Biogenic amines and their production by microorganisms in food. *Trends in Food Science and Technology* 5: 42-49.

Hart, P. H., Grimbaldeston, M. A., Swift, G. J., Hosszu, E. K., & Finlay-Jones, J. J. (1999). A Critical Role for Dermal Mast Cells in *Cis*-Urocanic Acid-induced Systemic Suppression of Contact Hypersensitivity Responses in Mice. *Photochemistry and Photobiology* 70(5): 807-812.

Hassan, Z., Bakar, J., Ali, R., & Rusul, G. (2009). Microbiological quality of *keropok lekor* during processing. *International Food Research Journal* 16(2): 215-223.

Heby, O., Oredsson, S. M., Olsson, I., & Marton, L. J. (1982). A Role for The Polyamines in Mouse Embryonal Carcinoma (F9 and PCC3) Cell-Differentiation but not in Human Premyelocytic Leukemia (HL-60) Cell-Differentiation. *Advances in Polyamine Research* 4: 727-742.

Helander, H. F., & Fändriks, L. (2014). Surface area of the digestive tract–revisited. *Scandinavian Journal of Gastroenterology* 49(6): 681-689.

Henry, C. M., Hollville, E. & Martin, S. J. (2013). Measuring apoptosis by microscopy and flow cytometry. *Methods* 61(2): 90-97.

Hensel, G., Männel, D. N., Pfizenmaier, K., & Krönke, M. (1987). Autocrine stimulation of TNF-alpha mRNA expression in HL-60 cells. *Lymphokine Research* 6(2): 119-125.

Hernandez-Jover, T., Izquierdo-Pulido, M., Veciana-Nogues, M. T., Marine-Font, A., Vidal-Carou, M. C. (1997). Biogenic amine and polyamine contents in meat and meat products. *Journal of Agriculture and Food Chemistry* 45: 2098-2102.

Hewett, J. A., & Roth, R. A. (1993). Hepatic and extrahepatic pathobiology of bacterial lipopolysaccharides. *Pharmacological Reviews* 45(4): 382-411.

Histamine in Seafood. Method 977.13. Retrieved from http://www.aoac.org/ aoac_prod_imis /AOAC_Docs/OMA/977_13aoacmethod.pdf [accessed 10 May 2017].

Hsu, H. H., Chuang, T. C., Lin, H. C., Huang, Y. R., Lin, C. M., Kung, H. F., & Tsai, Y. H. (2009). Histamine content and histamine-forming bacteria in dried milkfish (*Chanos chanos*) products. *Food Chemistry* 114(3): 933-938.

Hughes, J. M., & Merson, M. H. (1976). Fish and shellfish poisoning. New England Journal of Medicine 295(20): 1117-1120.

Hungerford, J. M. (2010). Scombroid poisoning: A review. *Toxicon* 56: 231-243.

Huss, H. H., Ababouch, L., Gram, L. (2004). Assessment and management of seafood safety and quality. *FAO Fisheries Technical Paper 444*. Food and Agriculture Organization of the United Nations.

Huss, H. H. (1997). Control of indigenous pathogenic bacteria in seafood. *Food Control* 8: 91-98.

Hwang, D-F., Chang, S-H., Shiua, C-Y., & Chai, T-J. (1997). High-performance liquid chromatographic determination of biogenic amines in fish implicated in food poisoning. *Journal of Chromatography B: Biomedical Sciences and Applications* 693(1): 23-30.

ICMSF. (1986). Sampling for microbiological analysis: *Principles and Specific Applications*. Blackwell Scientific Publication 2: 127-278.

Ishiyama, M., Tominaga, H., Shiga, M., Sasamoto, K., Ohkura, Y., & Ueno, K. (1996). A combined assay of cell vability and in vitro cytotoxicity with a highly water-soluble tetrazolium salt, neutral red and crystal violet. *Biological and Pharmaceutical Bulletin* 19(11): 1518-1520.

Jacobsen, M. B., Aukrust, P., Kittang, E., Muller, F., Ueland, T., Bratlie, J., Bjerkeli, V., Vatn, M. H. (2000). Relation between food provocation and systematic immune activation in patients with food intolerance. *The Lancet* 356: 400-401.

Ji, Y., Sakata, Y. & Tso, P. (2011). Nutrient-induced inflammation in the intestine. *Current Opinion in Clinical Nutrition and Metabolic Care* 14(4): 315.

Johannsson, S. G. O., Hourihane, J. O. B., Bousquet, J., Bruijnzeel-Koomen, C., Dreborg, S., Haahtela, T., Kowalski, M. L., Mygind, N., Ring, J., van Cauwenberge, P., van Hage-Hamsten, M., Wuthrich, B. (2001). A revised nomenclature for allergy: An EAACI position statement from the EAACI nomenclature task force. *Allergy* 56: 813-824.

Johnson, A. R. and Erdös, E. G. (1973). Release of histamine from mast cells by vasoactive peptides. *Experimental Biology and Medicine* 142(4): 1252-1256.

Jovanovic, D. V., Di Battista, J. A., Martel-Pelletier, J., Jolicoeur, F. C., He, Y., Zhang, M., ... & Pelletier, J. P. (1998). IL-17 stimulates the production and expression of proinflammatory cytokines, IL-β and TNF-α, by human macrophages. *The Journal of Immunology* 160(7): 3513-3521.

Karin, M., Lawrence, T., & Nizet, V. (2006). Innate immunity gone awry: linking microbial infections to chronic inflammation and cancer. *Cell* 124(4): 823-835.

Karovičová, J., Gabriel, G-M., Greifova-Jolana (2006). Effects of NaCl concentration and initial pH value on biogenic amine formation dynamics by *Enterobacter* spp. bacteria in model conditions. *Journal of Food and Nutrition Research* 45(1): 21-29.

Karovičová, J., & Kohajdová, Z. (2005). Biogenic amines in food. *Chemical Papers* 59: 70-79.

Kaslow (2006). Immune restoration, http://www.drkaslow.com/ html/immune _restoration.html [Accessed 2007 October 18].

Kawabata, T., & Suzuki, S. (1959). Studies on the food poisoning associated with putrefaction of marine products-VIII. *Nippon Suisan Gakkaishi* 25(6), 473-480.

Kawano, T., & Asakawa, M. (1964). Distribution of amino acid decarboxylases in various microorganisms. *Yakugaku zasshi: Journal of the Pharmaceutical Society of Japan* 84: 884.

Kerr, G. W., & Parke, T. R. (1998). Scombroid poisoning--a pseudoallergic syndrome. *Journal of the Royal Society of Medicine* 91(2): 83.

Kim, J. D., & Lall, S. P. (2000). Amino acid composition of whole body tissue of Atlantic halibut (*Hippoglossus hippoglossus*), yellowtail flounder (*Pleuronectes ferruginea*) and Japanese flounder (*Paralichthys olivaceus*). *Aquaculture* 187(3): 367-373.

Koo, H. L., Jiang, Z-D., Brown, E., Garcia, C., Qi, H., & DuPont, H. L. (2008). Coliform Contamination of Vegetables Obtained from Popular Restaurants in Guadalajara, Mexico, and Houston, Texas. *Clinical Infectious Diseases* 47(2): 218-221.

Kovacic, P., & Somanathan, R. (2014). Inflammation and Anti-Inflammatory Agents–Reactive Oxygen Species and Toxicity Systems Biology of Free Radicals and Antioxidants (pp. 3197-3216): Springer.

Kraneveld, A. D., Sagar, S., Garssen, J., & Folkerts, G. (2012). The two faces of mast cells in food allergy and allergic asthma: The possible concept of Yin Yang. *Biochimica et Biophysica Acta* - Molecular Basis of Disease 1822: 93-99.

Kung, H. F., Lee, Y. H., Teng, D. F., Hsieh, P. C., Wei, C. I., & Tsai, Y. H. (2006). Histamine formation by histamine-forming bacteria and yeast in mustard pickle products in Taiwan. *Food Chemistry* 99: 579-585.

Kupcsik, L. (2011). Estimation of cell number based on metabolic activity: the MTT reduction assay. *Mammalian Cell Viability: Methods and Protocols*: 13-19.

Ladero, V., Calles-Enríquez, M., Fernández, M., & A. Alvarez, M. (2010). Toxicological effects of dietary biogenic amines. *Current Nutrition & Food Science* 6(2): 145-156.

Lange, J., Thomas, K., Wittmann, C. (2002). Comparison of a capillary electrophoresis method with high-performance liquid chromatography for the determination of biogenic amines in various food samples. *Journal of Chromatography B* 779: 229-239.

Lange, J., & Wittmann, C. (2002). Enzyme sensor array for the determination of biogenic amines in food samples. *Analytical and Bioanalytical Chemistry* 372: 276-283.

Langerholc, T., Maragkoudakis, P. A., Wollgast, J., Gradisnik, L., & Cencic, A. (2011). Novel and established intestinal cell line models–An indispensable tool in food science and nutrition. *Trends in Food Science & Technology* 22: S11-S20.

Latapi G., & Barrett, D. M. (2006). Influence of pre-drying treatments on quality and safety of sun-dried tomatoes. Part II. Effects of storage on nutritional and sensory quality of sun-dried tomatoes pretreated with sulfur, sodium metbisulfite, or salt. *Journal of Food Scienc*, 71: S32-S37.

Lawson, A., & Quinn, A. G. (1967). Studies on amino acid decarboxylases in *Escherichia coli*. *Biochemical Journal* 105(2): 483-490.

Lehane, L., & Olley, J. (2000). Histamine fish poisoning revisited. *International Journal of Food Microbiology* 58: 1-37.

Lehman, D. C. (2007). Biochemical Identification of Gram-Negative Bacteria. *Textbook of Diagnostic Microbiology* 3: 226-232.

Leist, M., Single, B., Castoldi, A. F., Kühnle, S. & Nicotera, P. (1997). Intracellular adenosine triphosphate (ATP) concentration: a switch in the decision between apoptosis and necrosis. *The Journal of Experimental Medicine* 185(8): 1481-1486.

Lejbkowicz, F., & Kassis, I. (2002). *Granulicatella* and *Abiotrophia* species: cause or consequence? *Clinical Microbiology Newsletter* 24(16): 125-127.

Leuschner, R. G., Heidel, M., Hammes, W. P. (1998). Histamine and tyramine degradation by food fermenting microorganisms. *International Journal of Food Microbiology* 39: 1-10.

Lovenberg, W. (1973). Some Vaso-and Psychoactive Substances in Food: Amines, Stimulants, Depressants, and Hallucinogens. *Toxicants Occurring Naturally in Foods*, Washington, D. C.: National Academy of Sciences: 170.

Luster, A. D. (1998). Chemokines—chemotactic cytokines that mediate inflammation. *New England Journal of Medicine* 338(7): 436-445.

Maccani, J. E. (1979). Aerobically incubated medium for decarboxylase testing of *Enterobacteriaceae* by replica-plating methods. *Journal of Clinical Microbiology* 10(6): 940-942.

Mah, J. H., & Hwang, H. J. (2009). Inhibition of biogenic amine formation in a salted and fermented anchovy by *Staphylococcus xylosus* as a protective culture. *Food Control* 20(9): 796-801.

Mahmud, A. R., Hassan, Z., Bakar, J. & Rusul, R. A. G. (2009). Microbiological quality of keropok lekor during processing. *International Food Research Journal* 16: 215-223.

Mahmud, A. R., Hassan, Z., Bakar, J. & Rusul, R. A. G. & Ismail-Fitry, M. R. (2009). Histamine and Histamine-Forming Bacteria in Keropok lekor (Malaysian Fish Sausage) during Processing. *Food Science and Technology Research* 15: 395-402.

Maijala, R. L., Eerola, S. H., Aho, M. A., & Hirn, J. A. (1993). The effect of GDL-induced pH decreases on the formation of biogenic amines in meat. *Journal of Food Protection* 56(2): 125-129.

Maintz, L., & Novak, N. (2007). Histamine and histamine intolerance. *The American Journal of Clinical Nutrition* 85(5): 1185-1196.

Manafi, M. (2003). Chapter 12 Media for detection and enumeration of 'total' *Enterobacteriaceae*, coliforms and *Escherichia coli* from water and foods. *Progress in Industrial Microbiology* 37: 167-193.

Mao, H. M., Chen, B. G., Qian, X. M., & Liu, Z. (2009). Simultaneous determination of twelve biogenic amines in serum by high performance liquid chromatography. *Microchemical Journal* 91(2): 176-180.

Marcobal, A., Martin-Alvarez, P. J., Moreno-Arribas, M. V., Munoz, R. (2006). A multifactorial design for studying factors influencing growth and tyramine production of the lactic acid bacteria Lactobacillus brevis CECT4669 and *Enterococcus faecium* BIFI-58. *Research in Microbiology* 157: 417-424.

Marino, M., Maifreni, M., Moret, S., Rondinini, G. (2000). The capacity of *Enterobacteriacceae* species to produce biogenic amines in cheese. *Letters in Applied Microbiology* 31: 169-173.

Marklinder, I., Lonner, C. (1992). Fermentation properties of intestinal strains of *Lactobacillus*, of a sour dough and a yoghurt starter culture in an oat-based nutritive solution. *Food Microbiology* 9: 197-205.

Marsh, M. N. (1980). Studies of intestinal lymphoid tissue. III. Quantitative analyses of epithelial lymphocytes in the small intestine of human control subjects and of patients with celiac sprue. *Gastroenterology* 79(3): 481-492.

Marsh, M. N., Mathan, M., & Mathan, V. I. (1983). Studies of intestinal lymphoid tissue. VII. The secondary nature of lymphoid cell "activation" in the jejunal lesion of tropical sprue. *The American Journal of Pathology* 112(3): 302.

Martuscelli, M., Gardini, F., Torriani, S., Mastrocola, D., Serio, A., Chaves-Lopez, C., Schirone, M., Suzzi, G. (2005). Production of biogenic amines during the ripening of Pecorino Abruzzese cheese. *International Dairy Journal* 15: 571-578.

Mathlouthi, M. (2001). Water content, water activity, water structure and the stability of foodstuffs. *Food Control* 12: 409-417.

Mazzeo, M. F., Sorrentino, A., Gaita, M., Cacace, G., Di Stasio, M., Facchiano, A., Siciliano, R. A. (2006). Matrix-assisted laser desorption ionization-time of flight mass spectrometry for the discrimination of food-borne microorganisms. *Applied Environmental Microbiology* 72(2): 1180-1189.

Merson, M. H., Baine, W. B., Gangarosa, E. J., & Swanson, R. C. (1974). Scombroid fish poisoning: outbreak traced to commercially canned tuna fish. *JAMA* 228(10): 1268-1269.

Mietz, J. L., & Karmas, E. (1977). Chemical quality index of canned tuna as determined by high-pressure liquid chromatography. *Journal of Food Science* 42(1): 155-158.

Møller, V. (1954). Distribution of amino acid decarboxylases in *Enterobacteriaceae. APMIS* 35(3): 259-277.

Møller, V. (1955). Simplified tests for some amino acid decarboxylases and for the arginine dihydrolase system. *APMIS* 36(2): 158-172.

Moodycliffe, A., Kimber, I., & Norval, M. (1992). The effect of ultraviolet B irradiation and urocanic acid isomers on dendritic cell migration. *Immunology* 77(3): 394.

Murakami, A., Takahashi, D., Koshimizu, K., & Ohigashi, H. (2003). Synergistic suppression of superoxide and nitric oxide generation from inflammatory cells by combined food factors. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis* 523: 151-161.

National Sea Grant College Fisheries Extension Enhancement grant program (2004). http://www.iceyourfish.seagrant.org/haccp.html [Accessed 2007 November 9].

Norval, M., Gibbs, N. K., & Gilmour, J. (1995). The Role of Urocanic Acid In Uv-Induced Immunosuppression: Recent Advances (1992–1994). *Photochemistry and Photobiology* 62(2): 209-217.

Maintz L, Novak N (2007). Histamine and histamine intolerance. *American Journal of Clinical Nutrition* 85: 1185-1196.

O'Flaherty, J. T., Rossi, A. G., Redman, J. F., & Jacobson, D. P. (1991). Tumor necrosis factor-alpha regulates expression of receptors for formyl-methionyl-leucyl-phenylalanine, leukotriene B4, and platelet-activating factor. Dissociation from priming in human polymorphonuclear neutrophils. *The Journal of Immunology* 147(11): 3842-3847.

Ohnuma S., Higa M., Hamanaka S., Matsushima K., Yamamuro W. (2001). An outbreak of allergy-like food poisoning. *Internal Medicine* 40(8): 833-835.

Önal, A. (2007). A review: Current analytical methods for the determination of biogenic amines in foods. *Food Chemistry* 103(4): 1475-1486.

Opie, E. L. (1962). On the relation of necrosis and inflammation to denaturation of proteins. *The Journal of Experimental Medicine* 115(3): 597-608.

Orrell, T. M., Collette, B. B., & Johnson, G. D. (2006). Molecular data support separate scombroid and xiphioid clades. *Bulletin of Marine Science* 79(3): 505-519.

Pang, L., & Hoult, J. R. S. (1997). Repression of inducible nitric oxide synthase and cyclooxygenase-2 by prostaglandin E2 and other cyclic AMP stimulants in J774 macrophages. *Biochemical Pharmacology* 53(4): 493-500.

Pinho, O., Pintado, A. I., Gomes, A. M., Pintado, M. M. E., Malcata, F. X., & Ferreira, I. M. (2004). Interrelationships among microbiological, physicochemical, and biochemical properties of Terrincho cheese, with emphasis on biogenic amines. *Journal of Food Protection*® 67(12): 2779-2785.

Proestos, C., Loukatos, P., & Komaitis, M. (2008). Determination of biogenic amines in wines by HPLC with precolumn dansylation and fluorimetric detection. *Food Chemistry* 106(3): 1218-1224.

Raschke, W. C., Baird, S., Ralph, P., & Nakoinz, I. (1978). Functional macrophage cell lines transformed by Abelson leukemia virus. *Cell* 15(1): 261-267.

Reagan-Shaw, S., Nihal, M. & Ahmad, N. (2008). Dose translation from animal to human studies revisited. *The FASEB Journal* 22(3): 659-661.

Rodriguez, M. B. R., da Silva Carneiro, C., da Silva Feijó, M. B., Júnior, C. A. C. & Mano, S. B. (2014). Bioactive amines: aspects of quality and safety in food. *Food and Nutrition Sciences* 5(02): 138.

Rogers, P. and Staruszkiewicz, W. (2000). Histamine test kit comparison. *Journal of Aquatic Food Product Technology* 9(2): 5-17.

Ross, J. A., Auger, M. J., Burke, B., & Lewis, C. E. (2002). The biology of the macrophage. *The Macrophage* 2: 16-23.

Saaid, M., Saad, B., Hashim, N.H., Ali, A. S. M. & Saleh, M. I. (2009). Determination of biogenic amines in selected Malaysian food. *Food Chemistry* 113(4): 1356-1362.

Sagratini, G., Fernández-Franzón, M., De Berardinis, F., Font, G., Vittori, S., & Mañes, J. (2012). Simultaneous determination of eight underivatised biogenic amines in fish by solid phase extraction and liquid chromatography–tandem mass spectrometry. *Food Chemistry* 132(1): 537-543.

Sampson, H. A. (1999). Food allergy. Part 1: immunopathogenesis and clinical disorders. *Journal of Allergy and Clinical Immunology* 103(5): 717-728.

Sato, K., Ozaki, K., Oh, I., Meguro, A., Hatanaka, K., Nagai, T. & Ozawa, K. (2007). Nitric oxide plays a critical role in suppression of T-cell proliferation by mesenchymal stem cells. *Blood* 109(1): 228-234.

Sattler, J., & Lorenz, W. (1990). Intestinal diamine oxidases and enteral-induced histaminosis: studies on three prognostic variables in an epidemiological model. In Amine Oxidases and Their Impact on Neurobiology (pp. 291-314). Springer, Vienna.

Seckinger, P., Isaaz, S. & Dayer, J. M. (1988). A human inhibitor of tumor necrosis factor alpha. *Journal of Experimental Medicine* 167(4): 1511-1516.

Seibold, F. (2005). Food-induced immune responses as origin of bowel disease? *Digestion* 71(4): 251-260.

Self, R. L., & Wu, W-H. (2012). Determination of eight biogenic amines in selected seafood products by MSPD extraction followed by UHPLC-Orbitrap MS. *Journal of Food Composition and Analysis* 27(2): 169-173.

Self, R. L., Wu, W-H, & Marks, H. S. (2011). Simultaneous quantification of eight biogenic amine compounds in tuna by matrix solid-phase dispersion followed by HPLC–orbitrap mass spectrometry. *Journal of Agricultural and Food Chemistry* 59(11): 5906-5913.

Shalaby, A. R. (1996). Significance of biogenic amines to food safety and human health. *Food Research International* 29: 675-690.

Silla Santos, M. H. (1996). Biogenic amines: Their importance in foods. *International Journal of Food Microbiology* 29: 213-231.

Simidu, W., & Hibiki, S. (1955). Studies on putrefaction of aquatic products. XXIII. On the critical concentration of poisoning for histamine. *Bulletin of the Japanese Society for the Science of Fish* 21: 365-367.

Smolinska, S., Jutel, M., Crameri, R., & O'mahony, L. (2014). Histamine and gut mucosal immune regulation. *Allergy* 69(3): 273-281.

Soler, A. A., Salas, J. & Chaparro, M. (1995). Miniaturized analytical method for the detection of amine production by microorganisms. *Journal of Rapid Methods & Automation in Microbiology* 3(4): 267-273.

Stadnik, J. and Dolatowski, Z. J. (2010). Biogenic amines in meat and fermented meat products. *Acta Scientiarum Polonorum Technologia Alimentaria* 9(3): 251-263.

Stell, I. M. (1997). Trouble with tuna: two cases of scombrotoxin poisoning. *Journal of Accident & Emergency Medicine* 14(2): 110-111.

Stratton, J. E., Hutkins, R. W., & Taylor, S. L. (1991). Biogenic Amines in Cheese and other Fermented Foods: A Review. *Journal of Food Protection* 54(6): 460-470.

Sugarman, B. J., Aggarwal, B. B., Hass, P. E., Figari, I. S., Palladino, M. A., & Shepard, H. M. (1985). Recombinant human tumor necrosis factor-alpha: effects on proliferation of normal and transformed cells *in vitro*. *Science* 230(4728): 943-945.

Swinehart, D. F. (1962). The Beer-Lambert law. *Journal of Chemical Education* 39(7): 333.

Taylor, R. C., Cullen, S. P., & Martin, S. J. (2008). Apoptosis: controlled demolition at the cellular level. *Nature Reviews Molecular Cell Biology* 9(3): 231-241.

Taylor, S. L, & Lieber, E. R. (1979). *In vitro* inhibition of rat intestinal histamine-metabolizing enzymes. *Food and Cosmetics Toxicology* 17(3): 237-240.

Taylor, S. L., Stratton, J. E., & Nordlee, J. A. (1989). Histamine poisoning (scombroid fish poisoning): an allergy-like intoxication. *Journal of Toxicology: Clinical Toxicology* 27(4-5): 225-240.

Ten Brink, B., Damink, C., Joosten, H. M. L. J., & In't Veld, J. H. J. Huis. (1990). Occurrence and formation of biologically active amines in foods. *International Journal of Food Microbiology* 11(1): 73-84.

Thornley, M. J. (1960). The differentiation of Pseudomonas from other Gram-negative bacteria on the basis of arginine metabolism. *Journal of Applied Microbiology* 23(1): 37-52.

Til, H. P., Falke, H. E., Prinsen, M. K., & Willems, M. I. (1997). Acute and subacute toxicity of tyramine, spermidine, spermine, putrescine and cadaverine in rats. *Food and Chemical Toxicology* 35(3): 337-348.

Tkachenko, A., Nesterova, L. & Pshenichnov, M. (2001). The role of the natural polyamine putrescine in defense against oxidative stress in *Escherichia coli*. *Archives of Microbiology* 176(1-2): 155-157.

Todar, K. Immune Defense against Bacterial Pathogens: Adaptive or Acquired Immunity Todar's Online Textbook of Bacteriology. Retrieved from http://textbookofbacteriology.net/adaptive_2.html [accessed 10 May 2017].

Tsai, Y. H., Lin, C. Y., Chang, S. C., Chen, H. C., Kung, H. F., Wei, C. I., & Hwang, D. F. (2005). Occurrence of histamine and histamine-forming bacteria in salted mackerel in Taiwan. *Food Microbiology* 22(5): 461-467.

Tsuda, K., Nagano, H., Ando, A., Shima, J., & Ogawa, J. (2015). Isolation and characterization of psychrotolerant endospore-forming *Sporosarcina* species associated with minced fish meat (surimi). *International Journal of Food Microbiology* 199: 15-22.

Tung, Y-T., Chua, M-T, Wang, S-Y, & Chang, S-T. (2008). Anti-inflammation activities of essential oil and its constituents from indigenous cinnamon (*Cinnamomum osmophloeum*) twigs. *Bioresource Technology* 99(9): 3908-3913.

United States Food and Drug Administration (2001). Processing parameters needed to control pathogens in cold smoked fish, http://vm.cfsan.fda.gov/~comm/ift2amin.html [Accessed 2006 October 8].

VanDenBerg, C. M., Blob, L. F., Kemper, E. M., & Azzaro, A. J. (2003). Tyramine pharmacokinetics and reduced bioavailability with food. *The Journal of Clinical Pharmacology* 43(6): 604-609.

van den Broek, M. J. M., Mossel, D. A. A., & Mol, H. (1984). Microbiological quality of retail fresh fish fillets in The Netherlands. *International Journal of Food Microbiology* 1: 53-61.

Veciana-Nogues, M. T., Mariné-Font, A., & Vidal-Carou, M. C. (1997). Biogenic amines as hygienic quality indicators of tuna. Relationships with microbial counts, ATP-related compounds, volatile amines, and organoleptic changes. *Journal of Agricultural and Food Chemistry* 45(6): 2036-2041.

Vendrell, D., Balcázar, J. L., Ruiz-Zarzuela, I., De Blas, I., Gironés, O., & Múzquiz, J. L. (2006). *Lactococcus garvieae* in fish: a review. *Comparative Immunology, Microbiology and Infectious Diseases* 29(4): 177-198.

Vlieg-Boerstra B.J., van der Heide S., Oude Elberink J. N. G., Kluin-Nelemans J. C., Dubois A. E. J. (2005). Mastocytosis and adverse reactions to biogenic amines and histamine-releasing foods: what is the evidence? *The Journal of Medicine* 63(7): 244-249.

Walsh, M. C., Bourcier, T., Takahashi, K., Shi, L., Busche, M. N., Rother, R. P., ... & Stahl, G. L. (2005). Mannose-binding lectin is a regulator of inflammation that accompanies myocardial ischemia and reperfusion injury. *The Journal of Immunology* 175(1): 541-546.

Watson, W. H., Yanming, Z., & Chawla, R. K. (1999). S-Adenosylmethionine attenuates the lipopolysaccharide-induced expression of the gene for tumour necrosis factor α. *Biochemical Journal* 342(1): 21-25.

Wille, J. J., Kydonieus, A. F., & Murphy, G. F. (1999). *cis*-Urocanic Acid Induces Mast Cell Degranulation and Release of Preformed TNF--α: A Possible Mechanism Linking UVB and cis-Urocanic Acid to Immunosuppression of Contact Hypersensitivity. *Skin Pharmacology and Physiology* 12(1-2): 18-27.

Wilson, B. J., Musto, R. J., & Ghali, W. A. (2012). A case of histamine fish poisoning in a young atopic woman. *Journal of General Internal Medicine* 27(7): 878-881.

Wu, L., Ashraf, M. H. N., Facci, M., Wang, R., Paterson, P. G., Ferrie, A., & Juurlink, B. H. (2004). Dietary approach to attenuate oxidative stress, hypertension, and inflammation in the cardiovascular system. *Proceedings of the National Academy of Sciences of the United States of America* 101(18): 7094-7099.

Yassoralipour, A., Bakar, J., Rahman, R. A. & Bakar, F. A. (2012). Biogenic amines formation in barramundi (*Lates calcarifer*) fillets at 8 C kept in modified atmosphere packaging with varied CO 2 concentration. *LWT-Food Science and Technology* 48(1): 142-146.

Zaman, M. Z., Abu Bakar, F., Jinap, S., & Bakar, J. (2011). Novel starter cultures to inhibit biogenic amines accumulation during fish sauce fermentation. *International Journal of Food Microbiology* 145(1): 84-91.

Zamzami, N., Susin, S. A., Marchetti, P., Hirsch, T., Gómez-Monterrey, I., Castedo, M. & Kroemer, G. (1996). Mitochondrial control of nuclear apoptosis. *The Journal of Experimental Medicine* 183(4): 1533-1544.

Zare, D., Muhammad, K., Bejo, M. H. & Ghazali, H. M. (2013). Changes in urocanic acid, histamine, putrescine and cadaverine levels in Indian mackerel (*Rastrelliger kanagurta*) during storage at different temperatures. *Food Chemistry* 139(1): 320-325.

Zare, D., Muhammad, K., Bejo, M. H., & Ghazali, H. M. (2015). Determination of trans-and cis-Urocanic Acid in Relation to Histamine, Putrescine, and Cadaverine Contents in Tuna (*Auxis thazard*) at Different Storage Temperatures. *Journal of Food Science* 80(2): T479-T483.

Zhang, X., & Morrison, D. C. (1993). Lipopolysaccharide-induced selective priming effects on tumor necrosis factor alpha and nitric oxide production in mouse peritoneal macrophages. *Journal of Experimental Medicine* 177(2): 511-516.