THERAPEUTIC AND PROPHYLACTIC POTENTIAL OF ORGANIC FERMENTED SOYBEAN EXTRACT AGAINST PLUMBUM-INDUCED ZEBRAFISH VIA NMR METABOLOMICS APPROACH

By

CHONG SIOK GEOK

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

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DEDICATION

This thesis is dedicated to my beloved parents, family and friend

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

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Chair : Professor ChM Intan Safinar Ismail, PhD
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Soybeans (*Glycine max*) are rich in proteins and isoflavones, with fermentation enhancing their nutritional value but differences between the chemical profiles of organic and non-organic soybeans are unclear. In this study, the chemical profiles of non-organic and organic soybeans and their metabolite changes of the latter after fermentation with *Rhizopus oligosporus* were investigated using NMR metabolomic approach. A clear separation was only observed between non-organic G and organic Z, which were then selected for further investigation in the fermentation of soybeans (GF and ZF). Even though there were some intensity differences of selected metabolites namely sucrose and citrate, but overall, these most distinctive unfermented soybeans, organic (Z) and non-organic (G), showed negligible differentiation. Although the chemical compositions between non-organic and organic soybeans exhibited no noticeable differences, the fermentation process undeniably heightened the nutritional value of soybeans. Fermentation enhanced the nutritional value of soybeans, transforming higher sugar content into higher amino acids and organic acids content.

The study also explored the potential of fermented soybean extracts (FSE) as an alternative to chelation therapy for mitigating lead (Pb) toxicity as chelation therapy is associated with various side effects and is less effective for patients with low Pb toxicity. Therefore, FSE was evaluated for its therapeutic and prophylactic effect against Pb-induced inflammation in the zebrafish model using NMR metabolomic approach. Preliminary studies were done on various Pb and FSE concentrations with additional support from behavioural assessment (open field test) and transmission electron microscope (TEM). The behaviour of zebrafish altered after Pb inducement and the differential metabolites were increased and decreased in low (5 mg/L) and high (10 mg/ L)

Pb concentrations, respectively. Whereas for FSE, the 50 mg/L group significantly alter the four metabolites of sn-glycerol-3-phosphocholine, glucose, isoleucine and glutamine and did not exhibit any necrosis-like cell death in TEM results as the 300 mg/L did. The 50 mg/L dosage of FSE exhibited particularly promising results, demonstrating a small ameliorative effect against Pb-induced inflammation. These results suggested that FSE potentially retrieves the effect of Pb toxicity. Therapeutic measures are essential once damage occurs, however, prophylactic approaches would be better in preventing damage from occurring in the first place and help avoid the potentially serious and long-term health consequences.

The potential prophylactic effect of FSE against Pb-induced inflammation on zebrafish was studied using different groups, including a control group without any pre-treatment of FSE and without Pb-induction (N), a placebo group without any pre-treatment of FSE before Pb-induction (N+Pb), and pre-treated groups that were pre-treated with FSE before Pb-induction (FSE+Pb). Mortality was observed in the N+Pb group shortly after 24-h Pb induction at 95dpf, but not in the FSE+Pb group.

The N+Pb group showed increased lactate and decreased glutamate and isoleucine levels, indicative of Pb-induced inflammation. At 95dpf, Pb induction triggered the synthesis of glutathione, and its level increased in the N+Pb group but decreased in the FSE+Pb group. At 120dpf, after 24 days in Pb-free conditions, inflammation persists due to the residual Pb, and the level of glutathione depleted in the N+Pb group but elevated in the FSE+Pb group. Although both N+Pb and FSE+Pb underwent Pb induction at the same time, but difference in glutathione levels suggests that FSE possesses a prophylactic effect that lessens the inflammatory effect of Pb toxicity. In short, this research analysed the chemical profiles of organic and non-organic soybeans and the effects of fermentation and found that fermentation enhances their nutritional value. Fermented soybean extracts showed potential in alleviating lead (Pb) toxicity in a zebrafish model. Prophylactic approaches, like using fermented soybean extracts, demonstrated better results in preventing inflammation due to Pb toxicity compared to therapeutic interventions.

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

POTENSI TERAPEUTIK DAN PROFILAKTIK ESTRAK TAPAI KACANG SOYA ORGANIK TERHADAP PLUMBUM-TERARUH ZEBRAFISH MELALUI PENDEKATAN NMR METABOLOMIK

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Kacang soya (*Glycine max*) kaya dengan protein dan isoflavon, dengan penapaian meningkatkan nilai pemakanannya tetapi perbezaan antara profil kimia kacang soya organik dan bukan organik tidak jelas. Dalam kajian ini, profil kimia kacang soya bukan organik dan organik dan perubahan metabolitnya selepas penapaian dengan *Rhizopus oligosporus* telah disiasat menggunakan pendekatan metabolomik NMR. Pemisahan yang jelas hanya diperhatikan antara G bukan organik dan Z organik, yang kemudiannya dipilih untuk penyiasatan lanjut dalam penapaian kacang soya (GF dan ZF). Walaupun terdapat beberapa perbezaan keamatan metabolit terpilih iaitu sukrosa dan sitrat, tetapi secara keseluruhannya, kacang soya tidak ditapai yang paling tersendiri, organik (Z) dan bukan organik (G), menunjukkan pembezaan yang boleh diabaikan. Walaupun komposisi kimia antara kacang soya bukan organik dan organik tidak menunjukkan perbezaan yang ketara, proses penapaian tidak dapat dinafikan meningkatkan nilai pemakanan kacang soya. Penapaian meningkatkan nilai pemakanan kacang soya, mengubah kandungan gula yang lebih tinggi kepada kandungan asid amino dan asid organik yang lebih tinggi.

Kajian ini juga meneroka potensi ekstrak kacang soya yang ditapai (FSE) sebagai alternatif kepada terapi khelasi untuk mengurangkan ketoksikan plumbum (Pb) kerana terapi khelasi dikaitkan dengan pelbagai kesan sampingan dan kurang berkesan untuk pesakit yang mempunyai ketoksikan Pb rendah. Oleh itu, FSE dinilai untuk kesan terapeutik dan profilaksisnya terhadap keradangan yang disebabkan oleh Pb dalam model ikan zebra menggunakan pendekatan metabolomik NMR. Kajian awal telah dilakukan ke atas pelbagai kepekatan Pb dan FSE dengan sokongan tambahan daripada penilaian tingkah laku (open field test) dan mikroskop elektron penghantaran (TEM). Tingkah laku zebrafish berubah dengan ketara selepas induksi Pb dan

metabolit berbeza meningkat dalam kepekatan Pb rendah (5 mg/L) dan menurun dalam kepekatan Pb tinggi (10 mg/L). Kumpulan FSE 50 mg/L mengubah empat metabolit sn-gliserol-3-fosfokolina, glukosa, isoleusin dan glutamin dan tidak menunjukkan sebarang kematian sel seperti nekrosis dalam keputusan TEM seperti mana yang ditunjukkan oleh 300 mg/L. Dos 50 mg/L FSE menunjukkan sedikit kesan pemulihan terhadap keradangan daripada Pb. Keputusan ini mencadangkan FSE berpotensi pulih ketoksikan Pb. Pendekatan terapeutik adalah penting sebaik sahaja kerosakan berlaku, bagaimanapun, pendekatan profilaksis adalah lebih baik dalam mencegah kerosakan awal dan elak akibat kesihatan yang berpotensi serius dan berjangka panjang.

Potensi profilaksis FSE terhadap keradangan daripada Pb telah dikaji menggunakan kumpulan yang berbeza, termasuk kumpulan kawalan tanpa sebarang pra-rawatan FSE dan induksi Pb (N), kumpulan plasebo tanpa sebarang pra-rawatan FSE sebelum induksi Pb (N+Pb), dan kumpulan pra-rawatan yang telah dirawat dengan FSE sebelum induksi Pb (FSE+Pb). Kematian diperhatikan dalam kumpulan N+Pb selepas induksi Pb selama 24-jam pada 95dpf, tetapi bukan dalam kumpulan FSE+Pb (kecuali kumpulan FSE200+Pb). Kumpulan N+Pb menunjukkan peningkatan laktat dan penurunan paras glutamat dan isoleucine, menunjukkan keradangan yang disebabkan oleh Pb. Pada 95dpf, induksi Pb mencetuskan sintesis glutation, dan tahapnya meningkat dalam kumpulan N+Pb tetapi menurun dalam kumpulan FSE+Pb. Pada 120dpf, selepas 24 hari dalam keadaan bebas Pb, keradangan berterusan disebabkan oleh baki Pb, dan tahap glutation berkurangan dalam kumpulan N+Pb tetapi meningkat dalam kumpulan FSE+Pb. Walaupun kedua-dua N+Pb dan FSE+Pb menjalani induksi Pb pada masa yang sama, tetapi perbezaan dalam tahap glutation menunjukkan bahawa FSE mempunyai kesan profilaksis yang mengurangkan kesan keradangan ketoksikan Pb. Penyelidikan ini menganalisis profil kimia kacang soya organik dan bukan organik serta kesan penapaian dan mendapati bahawa penapaian meningkatkan nilai pemakanannya. Ekstrak kacang soya yang ditapai menunjukkan potensi dalam mengurangkan ketoksikan plumbum (Pb) dalam model zebrafish. Pendekatan profilaksis, seperti menggunakan ekstrak kacang soya yang ditapai, menunjukkan hasil yang lebih baik dalam mencegah keradangan akibat ketoksikan Pb berbanding dengan campur tangan terapeutik.

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LIST OF ABBREVIATIONS

δ	Delta for chemical shift in ppm
1D	One-dimensional
^{1}H	Proton
2D	Two-dimensional
^{13}C	Carbon-13
[M+H]+	Protonated parent ion
ALAD	Aminolevulinic acid dehydratase
ANOVA	Analysis of variance
ATCC	American type culture collection
BBB	Blood-brain barrier
BLL	Blood lead levels
BMRB	Biological magnetic resonance data bank
CoA	Coenzyme A
COSY	Correlation spectroscopy
CPMG	Carr-Purcell-Meiboom-Gill
d	Doublet
dd	Doublet of doublets
DMSA	Dimercaptosuccinic acid
DOSY	Diffusion-ordered spectroscopy
dpf	Days post-fertilization
EDTA	Ethylenediaminetetraacetic acid
ESI	Electrospray ionization
FBMN	Feature-based molecular networking
FT-IR	Fourier transform infrared

GABA	Gamma-aminobutyric acid
GC	Gas Chromatography
GNPS	Global Natural Products Social
HCA	Hierarchical cluster analysis
HMBC	Heteronuclear multiple bond correlation
HMDB	Human metabolome database
HSQC	Heteronuclear single-quantum coherence
IACUC	Institutional Animal Care and Use Committee
J-Res	*J*-resolved spectroscopy
KEGG	Kyoto Encyclopedia of Genes and Genome
LAB	Lactic acid bacteria
LC50	Lethal concentration at 50 percent
LCMS	Liquid chromatography-mass spectrometry
m	Multiplet
m/z	Mass-to-charge ratio
MetPA	Metabolic pathways analysis
MHz	Megahertz
MS	Mass spectrometry
MVDA	Multivariate data analysis
NMR	Nuclear magnetic resonance
OECD	Organisation for Economic Co-operation and Development
OFT	Open field test
OPLS	Orthogonal partial least square
OPLS-DA	Orthogonal partial least square-discriminant analysis
PC	Principal components

PCA	Principal component analysis
PLS	Partial least square
PLS-DA	Partial least square- discriminant analysis
q	quartet
ROS	Reactive oxygen species
s	Singlet
SEM	Standard error of the mean
SIMCA	Soft independent modeling of class analogy
t	Triplet
TCA cycle	Tricarboxylic acid cycle
TEM	Transmission electron microscope
TSP	3-trimethylsilanepropionic acid sodium salt
UHPLC-MS/MS	Ultra-high performance liquid chromatography with tandem mass spectrometry
UVDA	Univariate data analyses
VIP	Variable importance of projection

CHAPTER 1

INTRODUCTION

1.1 Research background

Lead or plumbum (Pb) is a non-essential heavy metal that cannot degrade in the environment and remain in the soil for a very long time. Pb is banned since the 1970s and the trends in work-related lead exposure have significantly improved since 1994 (NIOSH, 2023). However, workers in specific industries, such as manufacturing, still face potential lead exposure risks (CDC, 2023; NIOSH, 2023; Jarvis and Fawell, 2021). Malay Mail (2019) reported that Kampung Jenjarom in Kuala Langat, Selangor, Malaysia was polluted with lead due to the illegal dumping of the heavy metal in rivers nearby and the Pb level detected in the worker's and resident's hair samples were beyond the minimum safety level of 10 mg/L. Exposure to Pb affects multiple body systems, regardless of its exposure level, route, or period (Jhamtani et al. 2017). The major organs affected by Pb include the brain, kidneys, intestine and liver (Tchounwou et al., 2012). Pb poisoning is generally treated with chelators such as ethylenediaminetetraacetic acid (EDTA) and dimercaptosuccinic acid (DMSA), yet they bind to and eliminate the metals from the body regardless of whether those metals are essential (calcium, zinc or iron) or non-essential (Pb, cadmium or mercury). Thus, chelators are less effective for patients with low blood lead levels (BLL) and can cause a range of negative side effects (Naranjo et al., 2020). Hence, alternative strategies such as dietary or food intervention have become more desirable as it is widely available with the least side effects. Few studies suggested that plant extracts or compound supplementation are able to reduce the susceptibility to the toxic effect of Pb (Abdou & Hassan, 2014; Ros & Mwanri, 2003). A soybean diet is also reported to effectively reduce the toxicity effect of Pb, by preventing oxidative stress, bone loss and testis damage induced by Pb (Moustafa et al., 2008; Li et al., 2020b).

Soybean (*Glycine max* [L.] Merr.) that are rich in proteins can be consumed in various forms, either in their original or in fermented forms and both forms offer good health benefits to humans. However, the fermented form is suggested to be better in terms of nutritional value, as the fermentation process is able to help in releasing bioactive peptides, increase the antioxidant activities, and reduce the anti-nutritional components of soybean thus having better digestibility and bioavailability than its original form (Hong et al., 2004; Nkhata et al., 2018; Nout & Kiers, 2005; Ahmad et al. 2015). Hamad et al. (2014) reported that a greater reduction of inflammation was observed in rats fed with a fermented soybean diet than in those with an unfermented soybean diet. Malaysia does not cultivate its own soybean and depends on imported soybeans (Khazanah Research Institute, 2019). Many believe that eating organic foods or products is better for health as they have higher nutrients

compared to non-organic ones. The elements and phytochemicals of organic soybean are suggested to be higher than those of non-organic soybean (Bøhn et al., 2014). However, Bernacchia et al., (2016) reviewed that only a small difference in nutrients was observed between organic and non-organic food products.

Zebrafish (*Danio rerio*) have rapidly become a well-known model organism in toxicology research. This small aquatic vertebrate is commonly worked in heavy metals screening, where we can directly assess the toxicity effect based on their mortality, morphology, behavioural phenotype, and brain physiology (Kim et al. 2020; Chen et al. 2012; Li et al. 2019). The absorption, distribution and metabolism of the zebrafish can be accessed via the metabolomics approach to identify the metabolic pathway and correlate with their behaviours (Hill et al. 2005; Gupta et al. 2014; Lin et al. 2014; Cassar et al., 2020; Souza et al. 2017; Wang et al. 2012). Metabolomics qualitatively and quantitatively measures all the metabolic responses of an organism toward any external stimulant or internal changes (Wang et al., 2010). This emerging 'omics' approach can be used as a disease diagnostic tool to evaluate the effect of diseases and therapeutic protocol where the biomarker may be discovered (Shi et al., 2016; Nicholson et al., 1999).

1.2 Problem statement

Malaysia does not produce its own soybeans, all the soybeans in the market are imported regardless of whether they are grown conventionally or organic. However, organic products always sold at a higher price are always claimed to be better, in terms of nutritional value than the non-organic products. However, the differences between organic and non-organic soybean in terms of their chemical profile remain to be further elucidated. The easiest and safest way to increase the nutritional value of the original food is through fermentation. Fermented soy products are reported to provide more health benefits to the body than unfermented soy products. Tempeh is a widely consumed fermented soybean product in Malaysia, is produced by inoculating soybeans with *Rhizopus oligosporus* and controlled incubation, leading to enzymatic hydrolysis of nutrients and diverse metabolite release. However, the metabolite changes of soybean during fermentation with *R. oligosporus* remains to be explicated. Thus, NMR metabolomics was employed to investigate the chemical differences between organic and non-organic soybeans that are available in Malaysia and assesses the impact of fermentation on the nutritional value of soybean. Lead intoxication even in small amounts will cause adverse effects on human health. Chelators are generally used to treat Pb toxicity, however, it is less effective for low BLL patients and will cause various negative side effects. The exploration of non-toxic prophylactic or therapeutic alternatives, such as food intervention might potentially be useful to protect the body system before the harm of Pb is done, or to alleviate the Pb toxicity effect. A soy diet has been demonstrated to mitigate the toxicity effect in rats or flies induced by cadmium (Cd) or Pb, respectively (Ferramola et al., 2012; Li et al., 2020). However, the protective potentials of soybeans especially in the

fermented form, on in vivo model such as zebrafish under Pb exposure remain to be deciphered. To comprehensively explore the protective potential of soybeans, particularly in fermented forms, against lead toxicity in zebrafish under lead exposure, NMR metabolomics is employed to identify specific biomarkers associated with related biological mechanisms.

1.3 Objectives

This study targeted to evaluate the prophylactic potential of organic fermented soybean extract (FSE) against Pb-induced toxicity and identify their possible mechanism and biomarkers in the zebrafish model. The targets were accomplished along with the following objectives:

1. To establish the metabolic fingerprint of organic and non-organic soybeans marketed in Malaysia and their fermentation by *Rhizopus oligosporus*.
2. To determine the suitable Pb concentration and exposure period via acute toxicity.
3. To evaluate the exposure effect of organic fermented soybean extract (FSE) in various concentrations on zebrafish.
4. To identify the possible biomarker(s) in therapeutic and protective effect of fermented soybean extracts under acute lead-induced toxicity in zebrafish.

1.4 Outline of the thesis

This thesis is presented in seven chapters. In Chapter 1 covers the general research background and intentions of the study on the toxicity of Pb, the use of zebrafish and metabolomics approaches in toxicity study, the adverse effect of chelation therapy and the benefits of soybeans. Chapter 2 provides a comprehensive literature review that related to the current study. Chapters 3-6 are the research chapters with the listed objectives accordingly. Chapter 3 is on the investigation of the chemical profiles on non-organic and organic soybeans and their metabolite changes after fermentation with *Rhizopus oligosporus* observed via a nuclear magnetic resonance (NMR)-based metabolomics approach along with liquid chromatography with tandem mass spectrometry (LC-MS/MS) analysis. Chapter 4 shares the determination of the suitable Pb concentration and exposure period via acute toxicity as a preliminary investigation before the actual therapeutic and prophylactic studies in the following chapters. Chapter 5 discusses the therapeutic effect of FSE against Pb-induced toxicity using the zebrafish model and the suitable exposure concentrations of FSE were evaluated. Chapter 6 explains the prophylactic effect of fermented soybean extracts against Pb-induced toxicity using the zebrafish model by evaluating their metabolic changes and potential biomarkers. Chapter 7 concludes all the research chapters with some of their limitations faced throughout the study and suggested several future applications and recommendations.

REFERENCES

Abadin, H., Ashizawa, A., Stevens, Y.-W., Llados, F., Diamond, G., Sage, G., Citra, M., Quinones, A., Bosch, S. J., & Swarts, S. (2020). *Toxicological Profile for Lead.* The United States Public Health Service, Agency for Toxic Substances and Disease Registry.

Abbaspour, N., Hurrell, R., & Kelishadi, R. (2014). Review on iron and its importance for human health. *Journal of Research in Medical Sciences*,*19*(2).

Abdou, H. M., & Hassan, M. A. (2014). Protective Role of Omega-3 Polyunsaturated Fatty Acid against Lead Acetate-Induced Toxicity in Liver and Kidney of Female Rats. *BioMed research international*, *2014*, 435857.

Abdulwaliyu, I., Arekemase, S. O., Adudu, J. A., Batari, M. L., Egbule, M. N., & Okoduwa, S. I. R. (2019). Investigation of the medicinal significance of phytic acid as an indispensable anti-nutrient in diseases. *Clinical Nutrition Experimental*, *28*.

Adav, S. S., & Wang, Y. (2021). Metabolomics signatures of aging: Recent advances. *Aging and Disease*, *12*(2).

Aderemi, A. V., Ayeleso, A. O., Oyedapo, O. O., & Mukwevho, E. (2021). Metabolomics: A scoping review of its role as a tool for disease biomarker discovery in selected non-communicable diseases. *Metabolites*, *11*(7).

Ahmad Azam, A., Ismail, I. S., Shaikh, M. F., Abas, F., & Shaari, K. (2021). Multi-Platform Metabolomics Analyses Revealed the Complexity of Serum Metabolites in LPS-Induced Neuroinflammed Rats Treated with Clinacanthus nutans Aqueous Extract. *Frontiers in Pharmacology*, *12*.

Ahmad, A., Ramasamy, K., Jaafar, S. M., Majeed, A. B. A. & Mani, V. (2014). Total isoflavones from soybean and tempeh reversed scopolamine-induced amnesia, improved cholinergic activities and reduced neuroinflammation in brain. *Food and Chemical Toxicology*, *65*, 120–128.

Ahmad, A., Ramasamy, K., Majeed, A. B. A., & Mani, V. (2015). Enhancement of β-secretase inhibition and antioxidant activities of tempeh, a fermented soybean cake through enrichment of bioactive aglycones*. Pharmaceutical Biology, 53*(5), 758–766.

Ahnan-Winarno, A. D., Cordeiro, L., Winarno, F. G., Gibbons, J., & Xiao, H. (2021). Tempeh: A semicentennial review on its health benefits, fermentation, safety, processing, sustainability, and affordability*. Comprehensive Reviews in Food Science and Food Safety, 20*(2), 1717-1767.

Ahnan-Winarno, A. D., Cordeiro, L., Winarno, F. G., Gibbons, J., & Xiao, H. (2021). Tempeh: A semicentennial review on its health benefits, fermentation, safety, processing, sustainability, and affordability.

Comprehensive Reviews in Food Science and Food Safety, *20*(2).

Aiello, F., Gerretzen, J., Simons, M. G., Davies, A. N., & Dani, P. (2021). A multivariate approach to investigate the NMR CPMG pulse sequence for analysing low MW species in polymers. *Magnetic Resonance in Chemistry*, *59*(2).

Aiello, F., Gerretzen, J., Simons, M. G., Davies, A. N., & Dani, P. (2021). A multivariate approach to investigate the NMR CPMG pulse sequence for analysing low MW species in polymers. *Magnetic Resonance in Chemistry*, *59*(2).

Akhtar, M. T., Samar, M., Shami, A. A., Mumtaz, M. W., Mukhtar, H., Tahir, A., Shahzad-Ul-hussan, S., Chaudhary, S. U., & Kaka, U. (2021). H-NMR-based metabolomics: An integrated approach for the detection of the adulteration in chicken, chevon, beef and donkey meat. *Molecules*, *26*(15).

Almghawesh, E., Slik, S., & Okkou, H. (2022). Processing of Functional Yoghurt-Like Product from Soymilk Supplemented by Probiotics. *International Journal of Food Science*.

Alonso-Moreno, P., Rodriguez, I., & Izquierdo-Garcia, J. L. (2023). Benchtop NMR-Based Metabolomics: First Steps for Biomedical Application. *Metabolites*, *13*(5).

Amadi, C. N., Offor, S. J., Frazzoli, C., & Orisakwe, O. E. (2019). Natural antidotes and management of metal toxicity. *Environmental Science and Pollution Research*, *26*(18).

Amara, A., Frainay, C., Jourdan, F., Naake, T., Neumann, S., Novoa-del-Toro, E. M., Salek, R. M., Salzer, L., Scharfenberg, S., & Witting, M. (2022). Networks and Graphs Discovery in Metabolomics Data Analysis and Interpretation. *Frontiers in Molecular Biosciences*, *9*.

Aranda-Rivera, A. K., Cruz-Gregorio, A., Arancibia-Hernández, Y. L., Hernández-Cruz, E. Y., & Pedraza-Chaverri, J. (2022). RONS and Oxidative Stress: An Overview of Basic Concepts. *Oxygen*, *2*(4).

Arun, K. B., Madhavan, A., Sindhu, R., Emmanual, S., Binod, P., Pugazhendhi, A., Sirohi, R., Reshmy, R., Awasthi, M. K., Gnansounou, E., & Pandey, A. (2021). Probiotics and gut microbiome − Prospects and challenges in remediating heavy metal toxicity. *Journal of Hazardous Materials*, *420*.

Assi, M. A., Hezmee, M. N. M., Haron, A. W., Sabri, M. Y. M., & Rajion, M. A. (2016). The detrimental effects of lead on human and animal health. *Veterinary World, 9*(6), 660–671.

ATSDR, Agency for Toxic Substances and Disease Registry. (2020). *Toxicological Profile for Lead*. https://www.atsdr.cdc.gov/toxprofiles/tp13.pdf

Azam, A. A., Ismail, I. S., Kumari, Y., Shaikh, M. F., Abas, F., & Shaari, K. (2020). The anti-neuroinflammatory effects of *Clinacanthus nutans* leaf extract on metabolism elucidated through ^{1}H NMR in correlation with cytokines microarray. *PLoS ONE, 15*(9).

Balisteiro, D. M., Rombaldi, C. V. & Genovese, M. I. (2013). Protein, isoflavones, trypsin inhibitory and in vitro antioxidant capacities: Comparison among conventionally and organically grown soybeans. *Food Research International*, *51*(1): 8–14.

Banwo, K., Alonge, Z., & Sanni, A. I. (2021). Binding Capacities and Antioxidant Activities of *Lactobacillus plantarum* and *Pichia kudriavzevii* Against Cadmium and Lead Toxicities. *Biological Trace Element Research*, *199*(2).

Barbazuk, W. B., Korf, I., Kadavi, C., Heyen, J., Tate, S., Wun, E., Bedell, J. A., McPherson, J. D., & Johnson, S. L. (2000). The syntenic relationship of the zebrafish and human genomes. *Genome Research*, *10*(9), 1351–1358.

Bayan, L., Koulivand, P. H., & Gorji, A. (2014). Garlic: a review of potential therapeutic effects. *Avicenna Journal of Phytomedicine*, *4*(1).

Bechara EJ, Medeiros MH, Monteiro HP, Hermes-Lima M, Pereira B, & Demasi M. (1993). A Free Radical Hypothesis of Lead Poisoning and Inborn Porphyrias Associated with 5-Aminolevulinic Acid Overload. *Quim Nova*, *16*(4), 385–392.

Belo, M. A. A., Oliveira, M. F., Oliveira, S. L., Aracati, M. F., Rodrigues, L. F., Costa, C. C., Conde, G., Gomes, J. M. M., Prata, M. N. L., Barra, A., Valverde, T. M., de Melo, D. C., Eto, S. F., Fernandes, D. C., Romero, M. G. M. C., Corrêa Júnior, J. D., Silva, J. O., Barros, A. L. B., Perez, A. C., & Charlie-Silva, I. (2021). Zebrafish as a model to study inflammation: A tool for drug discovery. *Biomedicine and Pharmacotherapy*, *144*.

Berlin, C. M., Gorman, R. L., May, D. G., Notterman, D. A., Weismann, D. N., Wilson, G. S., Wilson, J. T., Bennett, D. R., Mulinare, J., Kaufman, P., Licata, S. A., Tomich, P., Troendle, G., Yaffe, S. J., Cote, C. J., & Banner, W. (1995). Treatment guidelines for lead exposure in children. *Pediatrics*, *96*(1).

Bernacchia, R., Preti, R. & Vinci, G. (2016). Organic and conventional foods: Differences in nutrients. *Italian Journal of Food Science*, *28*, 565–578.

Berntssen, M. H. G., Aatland, A., & Handy, R. D. (2003). Chronic dietary mercury exposure causes oxidative stress, brain lesions, and altered behaviour in Atlantic salmon (*Salmo salar*) parr. *Aquatic Toxicology, 65*(1), 55-72.

Berry, J. P., Roy, U., Jaja-Chimedza, A., Sanchez, K., Matysik, J., & Alia, A. (2016). High-Resolution Magic Angle Spinning Nuclear Magnetic Resonance of Intact Zebrafish Embryos Detects Metabolic Changes

Following Exposure to Teratogenic Polymethoxyalkenes from Algae. *Zebrafish, 13*(5), 456-465.

Bhutia, S. K., Panda, P. K., Sinha, N., Praharaj, P. P., Bhol, C. S., Panigrahi, D. P., Mahapatra, K. K., Saha, S., Patra, S., Mishra, S. R., Behera, B. P., Patil, S., & Maiti, T. K. (2019). Plant lectins in cancer therapeutics: Targeting apoptosis and autophagy-dependent cell death. *Pharmacological Research*, *144*.

Bisanz, J. E., Enos, M. K., Mwanga, J. R., Changalucha, J., Burton, J. P., Gloor, G. B., & Reid, G. (2014). Randomized Open-Label pilot study of the influence of probiotics and the gut microbiome on toxic metal levels in Tanzanian pregnant women and school children. *MBio*, *5*(5).

Blaise, B. J., Correia, G. D. S., Haggart, G. A., Surowiec, I., Sands, C., Lewis, M. R., Pearce, J. T. M., Trygg, J., Nicholson, J. K., Holmes, E., & Ebbels, T. M. D. (2021). Statistical analysis in metabolic phenotyping. *Nature Protocols*, 16(9).

Bøhn, T., Cuhra, M., Traavik, T., Sanden, M., Fagan, J. and Primicerio, R. (2014). Compositional differences in soybeans on the market: Glyphosate accumulates in Roundup Ready GM soybeans. *Food Chemistry*, *153*, 207–215.

Bøhn, T., Cuhra, M., Traavik, T., Sanden, M., Fagan, J., & Primicerio, R. (2014). Compositional differences in soybeans on the market: Glyphosate accumulates in Roundup Ready GM soybeans. *Food Chemistry*, *153*.

Bos, T. S., Knol, W. C., Molenaar, S. R. A., Niezen, L. E., Schoenmakers, P. J., Somsen, G. W., & Pirok, B. W. J. (2020). Recent applications of chemometrics in one- and two-dimensional chromatography. In *Journal of Separation Science* (Vol. 43, Issues 9–10). https://doi.org/10.1002/jssc.202000011

Bovolini, A., Garcia, J., Andrade, M. A., & Duarte, J. A. (2021). Metabolic Syndrome Pathophysiology and Predisposing Factors. *International Journal of Sports Medicine*, *42*(3).

Bowley, G., Kugler, E., Wilkinson, R., Lawrie, A., van Eeden, F., Chico, T. J. A., Evans, P. C., Noël, E. S., & Serbanovic-Canic, J. (2022). Zebrafish as a tractable model of human cardiovascular disease. *British Journal of Pharmacology*, *179*(5).

Breza-Boruta, B., Ligocka, A., & Bauza-Kaszewska, J. (2022). Natural Bioactive Compounds in Organic and Conventional Fermented Food. *Molecules*, *27*(13).

Bro, R., & Smilde, A. K. (2014). Principal component analysis. *Analytical Methods*, *6*(9), 2812–2831.

Bundy, J. G., Davey, M. P., & Viant, M. R. (2009). Environmental metabolomics: A critical review and future perspectives. *Metabolomics*,

5(1).

Byanju, B., Rahman, M. M., Hojilla-Evangelista, M. P., & Lamsal, B. P. (2020). Effect of high-power sonication pretreatment on extraction and some physicochemical properties of proteins from chickpea, kidney bean, and soybean. *International Journal of Biological Macromolecules*, *145*.

Caballero, M. V., & Candiracci, M. (2018). Zebrafish as screening model for detecting toxicity and drugs efficacy. *Journal of Unexplored Medical Data*, *3*(2).

Cachat, J., Stewart, A., Grossman, L., Gaikwad, S., Kadri, F., Chung, K. M., Wu, N., Wong, K., Roy, S., Suciu, C., Goodspeed, J., Elegante, M., Bartels, B., Elkhayat, S., Tien, D., Tan, J., Denmark, A., Gilder, T., Kyzar, E., Dileo, J., Frank, K., Chang, K., Utterback, E., Hart, P., & Kalueff, A. V. (2010). Measuring behavioural and endocrine responses to novelty stress in adult zebrafish*. Nature Protocols, 5*(11), 1786–1799.

Calabrese, E. J. (2008). U-Shaped Dose Response in Behavioural Pharmacology: Historical Foundations*. Critical Reviews in Toxicology, 38*(7), 591–598.

Calabrese, E. J., & Baldwin, L. A. (2001). U-shaped dose-responses in biology, toxicology, and public health*. Annual Review of Public Health, 22*, 15-33.

Calvano, C. D., Cataldi, T. R. I., Kögel, J. F., Monopoli, A., Palmisano, F. & Sundermeyer, J. (2017). Structural Characterization of Neutral Saccharides by Negative Ion MALDI Mass Spectrometry Using a Superbasic Proton Sponge as Deprotonating Matrix. *Journal of the American Society for Mass Spectrometry*, 28(8), 1666–1675.

Cao, Z. H., Green-Johnson, J. M., Buckley, N. D. & Lin, Q. Y. (2019). Bioactivity of soy-based fermented foods: A review. *Biotechnology Advances*, 37(1), 223–238.

Cao, Z. H., Green-Johnson, J. M., Buckley, N. D., & Lin, Q. Y. (2019). Bioactivity of soy-based fermented foods: A review. *Biotechnology Advances*, *37*(1), 223–238.

Carnovali, M., Valli, R., Banfi, G., Porta, G., & Mariotti, M. (2021). Soybean meal-dependent intestinal inflammation induces different patterns of bone-loss in adult zebrafish scale. *Biomedicines*, *9*(4).

Cassar, S., Adatto, I., Freeman, J. L., Gamse, J. T., Iturria, I., Lawrence, C., Muriana, A., Peterson, R. T., Van Cruchten, S., & Zon, L. I. (2020). Use of Zebrafish in Drug Discovery Toxicology. *Chemical Research in Toxicology*, *33*(1).

Catalán, N., Villasante, A., Wacyk, J., Ramírez, C., & Romero, J. (2018). Fermented Soybean Meal Increases Lactic Acid Bacteria in Gut Microbiota of Atlantic Salmon (*Salmo salar*). *Probiotics and Antimicrobial Proteins*, *10*(3).

CDC, Centers for Disease Control and Prevention. (2023). *National Notifiable Diseases Surveillance System (NNDSS), Lead, elevated blood lead level.* https://ndc.services.cdc.gov/case-definitions/lead-in-blood/

Chahardehi, A. M., Arsad, H., & Lim, V. (2020). Zebrafish as a Successful Animal Model for Screening Toxicity of Medicinal Plants. *Plants*, *9*(10), 1345.

Chai, C., Ju, H. K., Kim, S. C., Park, J. H., Lim, J., Kwon, S. W., & Lee, J. (2012). Determination of bioactive compounds in fermented soybean products using GC/MS and further investigation of correlation of their bioactivities. *Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences*, *880*(1), 42–49.

Chan, E. W. C., Wong, S. K., Kezuka, M., Oshiro, N., & Chan, H. T. (2021). Natto and miso: An overview on their preparation, bioactive components and health-promoting effects. *Food Research*, *5*(3).

Chan, Y. C., Lee, I. Te, Wang, M. F., Yeh, W. C., & Liang, B. C. (2018). Tempeh attenuates cognitive deficit, antioxidant imbalance, and amyloid β of senescence-accelerated mice by modulating Nrf2 expression via MAPK pathway. *Journal of Functional Foods*, *50*.

Chang, C. T., Hsu, C. K., Chou, S. T., Chen, Y. C., Huang, F. S., & Chung, Y. C. (2009). Effect of fermentation time on the antioxidant activities of tempeh prepared from fermented soybean using *Rhizopus oligosporus. International Journal of Food Science and Technology, 44*(4), 799–806.

Chang, J. H., Kim, M. S., Kim, T. W., & Lee, S. S. (2008). Effects of soybean supplementation on blood glucose, plasma lipid levels, and erythrocyte antioxidant enzyme activity in type 2 diabetes mellitus patients. *Nutrition Research and Practice*, *2*(3).

Chang, Y., & Choue, R. (2013). Plasma pharmacokinetics and urinary excretion of isoflavones after ingestion of soy products with different aglycone/glucoside ratios in South Korean women. *Nutrition Research and Practice*, *7*(5), 393–399.

Chen, H. C., Hsu, P. W., Tzaan, W. C., & Lee, A. W. (2013). Effects of the combined administration of vitamins C and E on the oxidative stress status and programmed cell death pathways after experimental spinal cord injury*. Spinal Cord, 52*(1), 24–28.

Chen, J., Chen, Y., Liu, W., Bai, C., Liu, X., Liu, K., Li, R., Zhu, J., & Huang, C. (2012). Neurotoxicology and Teratology Developmental lead acetate exposure induces embryonic toxicity and memory deficit in adult zebrafish*. Neurotoxicology and Teratology, 34*(6), 581–586.

Chen, L., Zhong, F., & Zhu, J. (2020). Bridging targeted and untargeted mass spectrometry-based metabolomics via hybrid approaches. *Metabolites*, *10*(9), 1–19.

Cheng, D., Shami, G. J., Morsch, M., Chung, R. S., & Braet, F. (2016). Ultrastructural Mapping of the Zebrafish Gastrointestinal System as a Basis for Experimental Drug Studies. *BioMed Research International, 2016*.

Chibowska, K., Baranowska-Bosiacka, I., Falkowska, A., Gutowska, I., Goschorska, M., & Chlubek, D. (2016). Effect of lead (Pb) on inflammatory processes in the brain. In *International Journal of Molecular Sciences*, *12*(12).

Chong, J., & Xia, J. (2020). Using MetaboAnalyst 4.0 for Metabolomics Data Analysis, Interpretation, and Integration with Other Omics Data. *Methods in Molecular Biology*, *2104*.

Collins, S. L., Koo, I., Peters, J. M., Smith, P. B., & Patterson, A. D. (2021). Current Challenges and Recent Developments in Mass Spectrometry-Based Metabolomics. *Annual Review of Analytical Chemistry*, *5*.

Crenn, P., Messing, B., & Cynober, L. (2008). Citrulline as a biomarker of intestinal failure due to enterocyte mass reduction. *Clinical Nutrition, 27*(3), 328–339.

Crook, A. A., & Powers, R. (2020). Quantitative NMR-Based Biomedical Metabolomics: Current Status and Applications. *Molecules*, *25*(21).

da Silva, A. F., Galon, L., Aspiazu, I., Alves, E., Concenco, G., Ramos Junior, E. U. & Ribeiro Roch, P. R. (2013). Weed Management in the Soybean Crop. In El-Shemy (Ed.), *Soybean - Pest Resistance*. London: IntechOpen.

Dalman, M. R., Deeter, A., Nimishakavi, G., & Duan, Z. H. (2012). Fold change and p-value cutoffs significantly alter microarray interpretations. *BMC Bioinformatics, 13*(S11), 1–4.

Danzi, F., Pacchiana, R., Mafficini, A., Scupoli, M. T., Scarpa, A., Donadelli, M., & Fiore, A. (2023). To metabolomics and beyond: a technological portfolio to investigate cancer metabolism. *Signal Transduction and Targeted Therapy*, *8*(1).

Das, D., Sarkar, S., Borsingh Wann, S., Kalita, J., & Manna, P. (2022). Current perspectives on the anti-inflammatory potential of fermented soy foods. *Food Research International*, *152*, 110922.

de Sotto, R., Medriano, C., Cho, Y., Seok, K.-S., Park, Y., & Kim, S. (2016). Significance of metabolite extraction method for evaluating sulfamethazine toxicity in adult zebrafish using metabolomics. *Ecotoxicology and Environmental Safety, 127*, 127–134.

Debik, J., Sangermani, M., Wang, F., Madssen, T. S., & Giskeødegård, G. F. (2022). Multivariate analysis of NMR-based metabolomic data. *NMR in Biomedicine*, *35*(2).

DePasquale, C., Franklin, K., Jia, Z., Jhaveri, K., & Buderman, F. E. (2022). The effects of exploratory behavior on physical activity in a common animal model of human disease, zebrafish (Danio rerio). *Frontiers in Behavioral Neuroscience*, *16*.

Dias, A. L. B., de Aguiar, A. C., & Rostagno, M. A. (2021). Extraction of natural products using supercritical fluids and pressurized liquids assisted by ultrasound: Current status and trends. In *Ultrasonics sonochemistry*, *74*.

Diederen, T., Delabrière, A., Othman, A., Reid, M. E., & Zamboni, N. (2021). Metabolomics. *Metabolic Engineering: Concepts and Applications*, *13*, 259–299.

Diez-Simon, C., Eichelsheim, C., Mumm, R., & Hall, R. D. (2020). Chemical and Sensory Characteristics of Soy Sauce:A Review. *Journal of Agricultural and Food Chemistry*, *68*(42), 11612.

Divate, N. R., Ardanareswari, K., Yu, Y. P., Chen, Y. C., Liao, J. W., & Chung, Y. C. (2023). Effects of Soybean and Tempeh Water Extracts on Regulation of Intestinal Flora and Prevention of Colon Precancerous Lesions in Rats. *Processes*, *11*(1).

Dix, D. J., Houck, K. A., Martin, M. T., Richard, A. M., Setzer, R. W., & Kavlock, R. J. (2007). The ToxCast Program for Prioritizing Toxicity Testing of Environmental Chemicals. *Toxicological Sciences*, *95*(1), 5–12.

Dixit, A. ., Antony, J. I. ., Sharma, N. K., & Tiwari, R. K. (2011). Soybean constituents and their functional benefits. *Research Signpost*, *661*(2).

Do Prado, F. G., Miyaoka, M. F., Pereira, G. V. de M., Pagnoncelli, M. G. B., Prado, M. R. M., Bonatto, S. J. R., Spier, M. R., & Soccol, C. R. (2021). Fungal-mediated biotransformation of soybean supplemented with different cereal grains into a functional compound with antioxidant, anti-inflammatory and antitumoral activities. *Biointerface Research in Applied Chemistry*, *11*(1).

do Prado, F. G., Pagnoncelli, M. G. B., de Melo Pereira, G. V., Karp, S. G., & Soccol, C. R. (2022). Fermented Soy Products and Their Potential Health Benefits: A Review. *Microorganisms*, *10*(8).

Doke, S. K., & Dhawale, S. C. (2015). Alternatives to animal testing: A review. *Saudi Pharmaceutical Journal*, *23*(3).

Donkor, O. N., & Shah, N. P. (2008). Production of β-glucosidase and hydrolysis of isoflavone phytoestrogens by *Lactobacillus acidophilus*, *Bifidobacterium lactis*, and *Lactobacillus casei* in soymilk. *Journal of Food Science*, *73*(1).

Dunn, W. B., Bailey, N. J. C., & Johnson, H. E. (2005). Measuring the metabolome: Current analytical technologies. In *Analyst*, *130*(5).

Echevarria, D. J., Buske, C., Toms, C. N., & Jouandot, D. J. (2011). A novel test battery to assess drug-induced changes in zebrafish social behaviour. *Neuromethods, 51*.

El-Serafy, R. S., El-Sheshtawy, A. N. A., Abd El-Razek, U. A., Abd El-Hakim, A. F., Hasham, M. M. A., Sami, R., Khojah, E., & Al-Mushhin, A. A. M. (2021). Growth, yield, quality, and phytochemical behavior of three cultivars of quinoa in response to moringa and azolla extracts under organic farming conditions. *Agronomy*, *11*(11).

Emwas, A. H., Roy, R., McKay, R. T., Tenori, L., Saccenti, E., Nagana Gowda, G. A., Raftery, D., Alahmari, F., Jaremko, L., Jaremko, M., & Wishart, D. S. (2019). Nmr spectroscopy for metabolomics research. *Metabolites*, *9*(7).

Emwas, A.-H., Roy, R., McKay, R. T., Tenori, L., Saccenti, E., Gowda, G. A. N., Raftery, D., Alahmari, F., Jaremko, L., Jaremko, M., & Wishart, D. S. (2019). NMR Spectroscopy for Metabolomics Research. *Metabolites*, *9*(7), 123.

Ercal, N., Gurer-Orhan, H., & Aykin-Burns, N. (2001). Toxic metals and oxidative stress part I: mechanisms involved in metal-induced oxidative damage. *Current Topics in Medicinal Chemistry*, *1*(6).

Eriksson, L, Byrne, T., Johansson, E., Trygg, J., & Vikström, C. (2013). Multi- and Megavariate Data Analysis Basic Principles and Applications. *Technometrics*.

Eriksson, L., Johansson, E., & Trygg, J. (2021). An Introduction to Some Basic Chemometric Tools. In *Chemometrics and Cheminformatics in Aquatic Toxicology*.

Eriksson, L., Trygg, J. & Wold, S. (2014). A chemometrics toolbox based on projections and latent variables. *Journal of Chemometrics*, 28(5), 332–346.

Fahey, J. W., & Kensler, T. W. (2021). Phytochemicals: Do they belong on our plate for sustaining healthspan? *Food Frontiers*, *2*(3).

Farooq, S. U., Kishor, K., & Sharma, A. (2023). Metabolomics: a radical approach to molecular study. *Journal of Livestock Science*, *14*(1).

Ferramola, M. L., Pérez Díaz, M. F. F., Honoré, S. M., Sánchez, S. S., Antón, R. I., Anzulovich, A. C., & Giménez, M. S. (2012). Cadmium-induced oxidative stress and histological damage in the myocardium. Effects of a soy-based diet. *Toxicology and Applied Pharmacology, 265*(3), 380–389.

Finkeldey, L., Schmitz, E., & Ellinger, S. (2021). Effect of the intake of isoflavones on risk factors of breast cancer—a systematic review of randomized controlled intervention studies. *Nutrients*, *5*(3).

Flora, G., Gupta, D., & Tiwari, A. (2012). Toxicity of lead: A review with recent updates. *Interdisciplinary Toxicology, 5*(2), 47–58.

Fraga-Corral, M., Carpena, M., Garcia-Oliveira, P., Pereira, A. G., Prieto, M. A., & Simal-Gandara, J. (2022). Analytical Metabolomics and Applications in Health, Environmental and Food Science. *Critical Reviews in Analytical Chemistry*, *52*(4).

Froger, N., Moutsimilli, L., Cadetti, L., Jammoul, F., Wang, Q. P., Fan, Y., Gaucher, D., Rosolen, S. G., Neveux, N., Cynober, L., Sahel, J. A., & Picaud, S. (2014). Taurine: The comeback of a neutraceutical in the prevention of retinal degenerations. *Progress in Retinal and Eye Research, 41*, 44–63.

Fu, J., Gong, Z., & Kelly, B. C. (2019). Metabolomic profiling of zebrafish (Danio rerio) embryos exposed to the antibacterial agent triclosan. *Environmental Toxicology and Chemistry*, *38*(1).

Gao, B., Chi, L., Mahbub, R., Bian, X., Tu, P., Ru, H., & Lu, K. (2017). Multi-Omics Reveals that Lead Exposure Disturbs Gut Microbiome Development, Key Metabolites, and Metabolic Pathways. *Chemical Research in Toxicology*, *30*(4).

Garreta-Lara, E., Gómez-Canela, C., Campos, B., Barata, C., Tauler, R., & Lacorte, S. (2021). Combined targeted/untargeted analytical and chemometric approaches in the characterization of Daphnia magna metabolomic changes under bisphenol A exposure. *Microchemical Journal*, *165*.

Gąstoł, M. & Domagala-Świątkiewicz, I. (2013). Comparing nutritional content of fruits, vegetables and juices from organic and conventional crops. *CABI Reviews*, 8(60), 1-10.

Gazwi, H. S. S., Yassien, E. E., & Hassan, H. M. (2020). Mitigation of lead neurotoxicity by the ethanolic extract of Laurus leaf in rats. *Ecotoxicology and Environmental Safety*, *192*.

Georgetti, S. R., Casagrande, R., Moura-de-Carvalho Vicentini, F. T., Verri, W. A., & Fonseca, M. J. V. (2006). Evaluation of the antioxidant activity of soybean extract by different in vitro methods and investigation of this activity after its incorporation in topical formulations. *European Journal of Pharmaceutics and Biopharmaceutics*, *64*(1).

Gerlai, R., Lahav, M., Guo, S., & Rosenthal, A. (2000). Drinks like a fish: Zebrafish (*Danio rerio*) as a behaviour genetic model to study alcohol effects. Pharmacology Biochemistry and Behaviour, *67*(4).

Gerlai, Robert. (2011). Zebrafish, a Potential Novel Research Tool for the Analysis and Modeling of Anxiety. *Different Views of Anxiety Disorders*.

Ghaddar, B., & Diotel, N. (2022). Zebrafish: A New Promise to Study the Impact of Metabolic Disorders on the Brain. *International Journal of*

Molecular Sciences, *23*(10).

Godwin, J., Sawyer, S., Perrin, F., Oxendine, S. E., & Kezios, Z. D. (2012). Adapting the Open Field Test to Assess Anxiety-Related Behaviour in Zebrafish. In: A. Kalueff & J. Cachat (Ed.), *Zebrafish Neurobehavioural Protocols*. (pp. 181-189). Humana Press.

Gómez-Zorita, S., González-Arceo, M., Fernández-Quintela, A., Eseberri, I., Trepiana, J., & Portillo, M. P. (2020). Scientific evidence supporting the beneficial effects of isoflavones on human health. *Nutrients*, *12*(12).

González-Peña, D., Angulo, J., Vallejo, S., Colina-Coca, C., De Ancos, B., Sánchez-Ferrer, C. F., Peiró, C., & Sánchez-Moreno, C. (2014). High-cholesterol diet enriched with onion affects endothelium-dependent relaxation and NADPH oxidase activity in mesenteric microvessels from Wistar rats. *Nutrition and Metabolism*, *11*(1).

Gopikrishna, T., Suresh Kumar, H. K., Perumal, K., & Elangovan, E. (2021). Impact of Bacillus in fermented soybean foods on human health. *Annals of Microbiology*, *71*(1).

Gowda, G. A. N., & Raftery, D. (2021). *NMR-Based Metabolomics*, 19–37.

Greaves, K. A., Wilson, M. D., Rudel, L. L., Williams, J. K., & Wagner, J. D. (2000). Consumption of soy protein reduces cholesterol absorption compared to casein protein alone or supplemented with an isoflavone extract or conjugated equine estrogen in ovariectomized cynomolgus monkeys. *Journal of Nutrition*, *130*(4).

Greco, S., Pellegrino, P., Zannotti, A., Carpini, G. D., Ciavattini, A., Reis, F. M., & Ciarmela, P. (2021). Phytoprogestins: Unexplored food compounds with potential preventive and therapeutic effects in female diseases. *Nutrients*, *13*(12).

Gu, C., Yang, Q., Li, S., Zhao, L., Lyu, B., Wang, Y., & Yu, H. (2023). Effects of Soybean Trypsin Inhibitor on Pancreatic Oxidative Damage of Mice at Different Growth Periods. *Foods*, *12*(8).

Gupta, P., Khobragade, S., Rajaram, S., & Shingatgeri, V. (2014). Assessment of locomotion behaviour in adult Zebrafish after acute exposure to different pharmacological reference compounds. *Drug Development and Therapeutics, 5*(2), 127–133.

Hamad, A., Mani, V., Ramasamy, K., Lim, S. M., & Majeed, A. B. A. (2016). Memory enhancement in rats by soybean and tempeh extracts is associated with improved cholinergic and reduced neuroinflammatory activities (Peningkatan daya ingatan dalam tikus oleh ekstrak soya dan tempeh dikaitkan dengan peningkatan aktiviti kolinergik. *Sains Malaysiana*, *45*(9), 1299–1310.

Han, Q., Zhang, W., Guo, J., Zhu, Q., Chen, H., Xia, Y., & Zhu, G. (2021). Mitochondrion: A sensitive target for Pb exposure. In *Journal of*

Toxicological Sciences, 46(8).

Handoyo, T., & Morita, N. (2006). Structural and Functional Properties of Fermented Soybean (Tempeh) by Using *Rhizopus oligosporus*. *International Journal of Food Properties*, *9*, 347–355.

Handoyo, T., & Morita, N. (2006). Structural and functional properties of fermented soybean (Tempeh) by using rhizopus oligosporus. *International Journal of Food Properties*, *9*(2).

He, Z., Liu, Z., & Gong, L. (2021). Biomarker identification and pathway analysis of rheumatoid arthritis based on metabolomics in combination with ingenuity pathway analysis. *Proteomics*, *21*(11–12).

Hedrera, M. I., Galdames, J. A., Jimenez-Reyes, M. F., Reyes, A. E., Avendaño-Herrera, R., Romero, J., & Feijóo, C. G. (2013). Soybean Meal Induces Intestinal Inflammation in Zebrafish Larvae. *PLoS ONE*, *8*(7).

Hill, A. J., Teraoka, H., Heideman, W., & Peterson, R. E. (2005). Zebrafish as a Model Vertebrate for Investigating Chemical Toxicity*. Toxicological Sciences, 86*(1), 6–19.

Hong, K.-J., Lee, C.-H. & Kim, S. W. (2004). *Aspergillus oryzae* GB-107 fermentation improves nutritional quality of food soybeans and feed soybean meals. *Journal of Medicinal Food*, 7(4): 430–435.

Hsiao, Y. H., Ho, C. T., & Pan, M. H. (2020). Bioavailability and health benefits of major isoflavone aglycones and their metabolites. *Journal of Functional Foods*, *74*.

Hu, C., Wong, W. T., Wu, R., & Lai, W. F. (2020). Biochemistry and use of soybean isoflavones in functional food development. *Critical Reviews in Food Science and Nutrition*, *60*(12).

Huang, C., & Freter, C. (2015). Lipid Metabolism, Apoptosis and Cancer Therapy*. International Journal of Molecular Sciences, 16*(1), 924.

Hultberg, B., Andersson, A., & Isaksson, A. (2001). Interaction of metals and thiols in cell damage and glutathione distribution: potentiation of mercury toxicity by dithiothreitol. *Toxicology*, *156*(2-3), 93–100.

Hutson, S. M., Lieth, E., & Lanoue, K. F. (2001). Function of leucine in excitatory neurotransmitter metabolism in the central nervous system. *Journal of Nutrition*, *131*(3).

Hwang, J. H., Wu, S. J., Wu, P. L., Shih, Y. Y., & Chan, Y. C. (2019). Neuroprotective effect of tempeh against lipopolysaccharide-induced damage in BV-2 microglial cells. *Nutritional Neuroscience*, *22*(12).

Hwang, J. H., Wu, S. J., Wu, P. L., Shih, Y. Y., & Chan, Y. C. (2019). Neuroprotective effect of tempeh against lipopolysaccharide-induced damage in BV-2 microglial cells. *Nutritional Neuroscience*, *22*(12).

Ishaque, A., & Al-Rubeai, M. (2002). Role of vitamins in determining apoptosis and extent of suppression by bcl-2 during hybridoma cell culture. *Apoptosis, 7*(3), 231–239.

Jangid, A. P., John, P. J., Yadav, D., Mishra, S., & Sharma, P. (2012). Impact of Chronic Lead Exposure on Selected Biological Markers. *Indian Journal of Clinical Biochemistry*, *27*(1), 83.

Jarvis, P., & Fawell, J. (2021). Lead in drinking water – An ongoing public health concern?. *Current Opinion in Environmental Science & Health, 20*, 100239.

Jayachandran, M., & Xu, B. (2019). An insight into the health benefits of fermented soy products. *Food Chemistry*, *271*.

Jayachandran, M., & Xu, B. (2019). An insight into the health benefits of fermented soy products. *Food Chemistry*, *271*.

Jeevanandam, M., Young, D. H., Ramias, L., & Schiller, W. R. (1990). Effect of major trauma on plasma free amino acid concentrations in geriatric patients. *The American Journal of Clinical Nutrition, 51*(6),1040–1045.

Jeong, D. Y., Ryu, M. S., Yang, H. J., & Park, S. (2021). γ-PGA-Rich Chungkookjang, short-term fermented soybeans: Prevents memory impairment by modulating brain insulin sensitivity, neuro-inflammation, and the gut–microbiome–brain axis. *Foods*, *10*(2).

Jervis, J., Kastl, C., Hildreth, S. B., Biyashev, R., Grabau, E. A., Saghai-Maroof, M. A. & Helm, R. F. (2015). Metabolite Profiling of Soybean Seed Extracts from Near-Isogenic Low and Normal Phytate Lines Using Orthogonal Separation Strategies. *Journal of Agricultural and Food Chemistry*, 63(44), 9879–9887.

Jhamtani, R. C., Shukla, S., Dahiya, M. S., & Agarwal, R. (2017). Evaluation of Acute Effects of Lead at Sub-Lethal Concentrations in Zebrafish. *Research Journal of Environmental Toxicology, 11*(3).

Jhamtani, R. C., Shukla, S., Dahiya, M. S., & Agarwal, R. (2017). Evaluation of Acute Effects of Lead at Sub-Lethal Concentrations in Zebrafish. *Research Journal of Environmental Toxicology*, *11*(3).

Jong, C. J., Azuma, J., & Schaffer, S. (2012). Mechanism underlying the antioxidant activity of taurine: Prevention of mitochondrial oxidant production. *Amino Acids, 42*(6).

Kallweit, A. R., Baird, C. H., Stutzman, D. K., & Wischmeyer, P. E. (2012). Glutamine Prevents Apoptosis in Intestinal Epithelial Cells and Induces Differential Protective Pathways in Heat and Oxidant Injury Models. *Journal of Parenteral and Enteral Nutrition, 36*(5), 551–555.

Kaplan, O., Koçak, E., & Çelebier, M. (2020). Comparison of Different Sample Preparation Techniques for Untargeted Metabolomics Utilizing Q-TOF

LC/MS and MetaboAnalyst 4.0. *Current Metabolomics and Systems Biology*, *8*(1).

Kataba, A., Botha, T. L., Nakayama, S. M. M., Yohannes, Y. B., Ikenaka, Y., Wepener, V., & Ishizuka, M. (2022). Environmentally relevant lead (Pb) water concentration induce toxicity in zebrafish (Danio rerio) larvae. *Comparative Biochemistry and Physiology Part - C: Toxicology and Pharmacology*, *252*.

Kaushik, S. J., & Hemre, G. I. (2008). Plant proteins as alternative sources for fish feed and farmed fish quality*. Improving Farmed Fish Quality and Safety*, 300-327.

Kehoe, R. A. (1987). Studies of lead administration and elimination in adult volunteers under natural and experimentally induced conditions over extended periods of time. *Food and Chemical Toxicology*, *25*(6).

Kelainy, E. G., Ibrahim Laila, I. M., & Ibrahim, S. R. (2019). The effect of ferulic acid against lead-induced oxidative stress and DNA damage in kidney and testes of rats. *Environmental Science and Pollution Research*, *26*(31).

Kermen, F., Kermen, F., Kermen, F., Kermen, F., Darnet, L., Darnet, L., Wiest, C., Wiest, C., Palumbo, F., Bechert, J., Bechert, J., Uslu, O., Uslu, O., Yaksi, E., Yaksi, E., & Yaksi, E. (2020). Stimulus-specific behavioral responses of zebrafish to a large range of odors exhibit individual variability. *BMC Biology*, *18*(1).

Khabib, M. N. H., Sivasanku, Y., Lee, H. B., Kumar, S., & Kue, C. S. (2022). Alternative animal models in predictive toxicology. *Toxicology*, *5*(3).

Khazanah Research Institute. (2019). *Soy: The King of Beans*. Kuala Lumpur: Khazanah Research Institute.

Khodarahmi, M., Jafarabadi, M. A., Moludi, J., & Abbasalizad Farhangi, M. (2019). A systematic review and meta-analysis of the effects of soy on serum hs-CRP. *Clinical nutrition*, *38*(3), 996–1011.

Khosravi, A., & Razavi, S. H. (2021). Therapeutic effects of polyphenols in fermented soybean and black soybean products. *Journal of Functional Foods*, *81*.

Khosravi, A., & Razavi, S. H. (2021). Therapeutic effects of polyphenols in fermented soybean and black soybean products. *Journal of Functional Foods*, *81*.

Kiehn, O., & Dougherty, K. (2016). Locomotion: circuits and physiology. In D. W. Pfaff (Ed.), *Neuroscience in the 21st Century*. New York, NY: Springer,.

Kim, H. J., Mahboob, S., Viayaraghavan, P., Abdullah Al-Ghanim, K., Al-Misned, F., Ock Kim, Y., & Ahmed, Z. (2020). Determination of toxic

effects of lead acetate on different sizes of zebrafish (*Danio rerio*) in soft and hard water. *Journal of King Saud University - Science, 32*(2), 1390–1394.

Kim, H. K., Choi, Y. H. & Verpoorte, R. (2010). NMR-based metabolomic analysis of plants. *Nature Protocols*, *5*(3), 536–549.

Kim, I. S., Kim, C. H., & Yang, W. S. (2021). Physiologically active molecules and functional properties of soybeans in human health—a current perspective. In *International Journal of Molecular Sciences* (Vol. 22, Issue 8).

Kim, J. J., Kim, Y. S., & Kumar, V. (2019). Heavy metal toxicity: An update of chelating therapeutic strategies. *Journal of Trace Elements in Medicine and Biology*, *54*.

Kim, S., Yoon, D., Lee, M., Yoon, C., & Kim, S. (2016). Metabolic responses in zebrafish (*Danio rerio*) exposed to zinc and cadmium by nuclear magnetic resonance -based metabolomics. *Chemistry and Ecology, 32*(2), 136–148.

Kiran, Bharti, R., & Sharma, R. (2021). Effect of heavy metals: An overview. *Materials Today: Proceedings*, *51*.

Kitamura, M. (2013). The unfolded protein response triggered by environmental factors. In *Seminars in Immunopathology*, 35(3).

Kitawaki, R., Nishimura, Y., Takagi, N., Iwasaki, M., Tsuzuki, K., & Fukuda, M. (2009). Effects of lactobacillus fermented soymilk and soy yogurt on hepatic lipid accumulation in rats fed a cholesterol-free diet. *Bioscience, Biotechnology and Biochemistry*, *73*(7).

Kjeldahl, K., & Bro, R. (2010). Some common misunderstandings in chemometrics. *Journal of Chemometrics*, *24*(7–8).

Ko, J. W., Chung, Y. S., Kwak, C. S., & Kwon, Y. H. (2019). Doenjang, a Korean traditional fermented soybean paste, ameliorates neuroinflammation and neurodegeneration in mice fed a high-fat diet. *Nutrients*, *11*(8).

Ko, J. W., Chung, Y. S., Kwak, C. S., & Kwon, Y. H. (2019). Doenjang, a Korean traditional fermented soybean paste, ameliorates neuroinflammation and neurodegeneration in mice fed a high-fat diet. *Nutrients*, *11*(8).

Kraeuter, A. K., Guest, P. C., & Sarnyai, Z. (2019). The Open Field Test for Measuring Locomotor Activity and Anxiety-Like Behaviour. *Methods in Molecular Biology*,*1916*.

Krogdahl, Å., Chikwati, E. M., Krasnov, A., Dhanasiri, A., Berge, G. M., Aru, V., Khakimov, B., Engelsen, S. B., Vinje, H., & Kortner, T. M. (2023). Dietary Fish Meal Level and a Package of Choline, β -Glucan, and Nucleotides Modulate Gut Function, Microbiota, and Health in Atlantic Salmon (Salmo

salar, L.). *Aquaculture Nutrition*, *2023*.

Kumar, N., Krishnani, K. K., Brahmane, M. P., Gupta, S. K., Kumar, P., & Singh, N. P. (2018). Temperature induces lead toxicity in Pangasius hypophthalmus: an acute test, antioxidative status and cellular metabolic stress. *International Journal of Environmental Science and Technology*, *15*(1).

Kutscha, R. & Pflügl, S. (2020). Microbial Upgrading of Acetate into Value-Added Products—Examining Microbial Diversity, Bioenergetic Constraints and Metabolic Engineering Approaches. *International Journal of Molecular Sciences*, *21*(22), 8777.

Lasley, S. M., & Gilbert, M. E. (2002). Rat hippocampal glutamate and GABA release exhibit biphasic effects as a function of chronic lead exposure level. *Toxicological Sciences*, *66*(1).

Lee, A. Y., Symes, S. J. K., & Troisi, J. (2022). Experimental design in metabolomics. In *Metabolomics Perspectives: From Theory to Practical Application*.

Lee, H. P., Lee, J., Gourley, L., Duffy, S. W., Day, N. E., & Estève, J. (1991). Dietary effects on breast-cancer risk in Singapore. *The Lancet*, *337*(8751).

Lee, J. O., Park, M. H., Choi, Y. H., Ha, Y. L. & Ryu, C. H. (2007). New fermentation technique for complete digestion of soybean protein. *Journal of Microbiology and Biotechnology*, *17*(11), 1904-7.

Lee, J., & Freeman, J. L. (2014). Zebrafish as a model for investigating developmental lead (Pb) neurotoxicity as a risk factor in adult neurodegenerative disease: A mini-review. *NeuroToxicology*, *43*, 57–64.

Lemmer, I. L., Willemsen, N., Hilal, N., & Bartelt, A. (2021). A guide to understanding endoplasmic reticulum stress in metabolic disorders. *Molecular Metabolism*, *47*.

Letertre, M. P. M., Dervilly, G., & Giraudeau, P. (2021). Combined Nuclear Magnetic Resonance Spectroscopy and Mass Spectrometry Approaches for Metabolomics. *Analytical Chemistry*, *93*(1).

Li, F., Liu, Z. H., Tian, X., Liu, T., Wang, H. L., & Xiao, G. (2020a). Black soybean seed coat extract protects *Drosophila melanogaster* against Pb toxicity by promoting iron absorption*. Journal of Functional Foods, 75*, 104201.

Li, S., Ding, G., Song, F., Sang, C., Wang, A., & Chen, N. (2020b). Comparison of dehulled, fermented and enzyme-treated soybean meal in diets for largemouth bass, *Micropterus salmoides*: Effects on growth performance, feed utilization, immune response and intestinal morphology. *Animal Feed Science and Technology*, *267*(May), 114548.

Li, X., Liu, X., Li, T., Li, X., Feng, D., Kuang, X., Xu, J., Zhao, X., Sun, M.,

Chen, D., Zhang, Z., & Feng, X. (2017). SiO2 nanoparticles cause depression and anxiety-like behaviour in adult zebrafish. *RSC Advances*, *7*(5).

Li, X., Xin, Y., Mo, Y., Marozik, P., He, T., & Guo, H. (2022). The Bioavailability and Biological Activities of Phytosterols as Modulators of Cholesterol Metabolism. *Molecules*, *27*(2).

Li, X., Yang, Y., Zhang, B. Lin, X., Fu, X., An, Y., Zou, Y., Wang, J. X., Wang, Z., & Yu, T. (2022). Lactate metabolism in human health and disease. *Signal transduction and targeted therapy*, *7*(1), 305.

Li, X., Zhang, B., Li, N., Ji, X., Liu, K., & Jin, M. (2019). Zebrafish neurobehavioural phenomics applied as the behavioural warning methods for fingerprinting endocrine disrupting effect by lead exposure at environmentally relevant level*. Chemosphere, 231*, 315-325.

Lidsky, T. I., & Schneider, J. S. (2003). Lead neurotoxicity in children: Basic mechanisms and clinical correlates. *Brain*, *126*(1).

Liebelt, E. L., & Shannon, M. W. (1994). Oral chelators for childhood lead poisoning. *Pediatric annals*, *23*(11).

Liener, I. E. (1994). Implications Of Antinutritional Components In Soybean Foods. *Critical Reviews in Food Science and Nutrition*, *34*(1).

Lin, T., Yu, S., Chen, Y., & Chen, W. (2014). Integrated biomarker responses in zebrafish exposed to sulfonamides*. Environmental Toxicology and Pharmacology, 38*(2), 444–452.

Litwack, G. (2018). Insulin and Sugars. *Human Biochemistry*, 131–160.

Liu, W., Feng, H., Zheng, S., Xu, S., Massey, I. Y., Zhang, C., Wang, X., & Yang, F. (2021). Pb Toxicity on Gut Physiology and Microbiota. *Frontiers in Physiology*, *12*.

Lo, D., Romulo, A., Lin, J. Y., Wang, Y. T., Wijaya, C. H., & Wu, M. C. (2022). Effect of different fermentation conditions on antioxidant capacity and isoflavones content of soy tempeh. *AIMS Agriculture and Food*, *7*(3).

Lucas-torres, C., Bernard, T., Huber, G., Berthault, P., Nishiyama, Y., Kandiyal, P. S., Elena-herrmann, B., Molin, L., Solari, F., Bouzier-sore, A. K., & Wong, A. (2020). General guidelines for sample preparation strategies in HR-μMAS NMR-based metabolomics of microscopic specimens. *Metabolites*, *10*(2).

Maisl, C., Doppler, M., Seidl, B., Bueschl, C., & Schuhmacher, R. (2023). Untargeted Plant Metabolomics: Evaluation of Lyophilization as a Sample Preparation Technique. *Metabolites*, *13*(6).

Mak, C. W., Ching-Fong Yeung, K., & Chan, K. M. (2019). Acute toxic effects of polyethylene microplastic on adult zebrafish. *Ecotoxicology and*

Environmental Safety, *182*, 109442.

Mak, C. W., Ching-Fong Yeung, K., & Chan, K. M. (2019). Acute toxic effects of polyethylene microplastic on adult zebrafish. *Ecotoxicology and Environmental Safety*, *182*, 109442.

Malay Mail. (2019, April 19). Report: Over 6,000 Kampung Jenjarom folk at risk of lead poisoning. *Malay Mail*.

Manosalva, C., Quiroga, J., Hidalgo, A. I., Alarcón, P., Anseoleaga, N., Hidalgo, M. A., & Burgos, R. A. (2022). Role of Lactate in Inflammatory Processes: Friend or Foe. *Frontiers in Immunology*, *12*.

Marini, H., Polito, F., Adamo, E. B., Bitto, A., Squadrito, F. & Benvenga, S. (2012). Update on genistein and thyroid: An overall message of safety. *Frontiers in Endocrinology*, *3*(94).

Martin Molinero, G. D., Boldrini, G. G., Pérez Chaca, M. V., Moyano, M. F., Armonelli Fiedler, S., Giménez, M. S., Gómez, N. N., López, P. H. H., & Álvarez, S. M. (2022). A soybean based-diet prevents Cadmium access to rat cerebellum, maintaining trace elements homeostasis and avoiding morphological alterations. *BioMetals*.

Messina, M., Duncan, A., Messina, V., Lynch, H., Kiel, J., & Erdman, J. W. (2022). The health effects of soy: A reference guide for health professionals. *Frontiers in Nutrition*, *9*.

Messina, M., Shearer, G., & Petersen, K. (2021). Soybean oil lowers circulating cholesterol levels and coronary heart disease risk, and has no effect on markers of inflammation and oxidation. *Nutrition*, *89*.

Moco, S. (2022). Studying Metabolism by NMR-Based Metabolomics. In *Frontiers Molecular Biosciences*, *9*.

Mok, W. K., Tan, Y. X., Lee, J., Kim, J. & Chen, W. N. (2019). A metabolomic approach to understand the solid-state fermentation of okara using *Bacillus subtilis* WX-17 for enhanced nutritional profile. *AMB Express*, *9*(1), 60.

Mosana, M., Ayeleso, A., Nyakudya, T., Erlwanger, K., & Mukwevho, E. (2020). Potential Protective Effects of Neonatal Supplementation with Oleanolic Acid on Peroxisome Proliferator-Activated Receptor Gamma (PPARγ)-Ligand Dependent Regulation of Glucose Homeostasis in High Fructose-Fed Rats. *Natural Product Communications*, *15*(3).

Moustafa, A. H. A., Mohamed, T. M., Ali, E. M. M., & Ahmed, A. A. (2008). Effect of soybean on bone and gonad hormones in lead intoxicated rats. *Journal of Biological Research*, *9*.

Mumtaz, S., Ali, S., Khan, R., Shakir, H. A., Tahir, H. M., Mumtaz, S., & Andleeb, S. (2020). Therapeutic role of garlic and vitamins C and E against toxicity induced by lead on various organs. *Environmental*

Science and Pollution Research, *27*(9).

Mun, E. G., Park, J. E., & Cha, Y. S. (2019). Effects of doenjang, a traditional Korean soybean paste, with high-salt diet on blood pressure in Sprague–Dawley rats. *Nutrients*, *11*(11).

Nachvak, S. M., Moradi, S., Anjom-shoae, J., Rahmani, J., Nasiri, M., Maleki, V., & Sadeghi, O. (2019). Soy, Soy Isoflavones, and Protein Intake in Relation to Mortality from All Causes, Cancers, and Cardiovascular Diseases: A Systematic Review and Dose–Response Meta-Analysis of Prospective Cohort Studies. *Journal of the Academy of Nutrition and Dietetics*, *119*(9).

Nakata, R., Yoshinaga, N., Teraishi, M., Okumoto, Y., Huffaker, A., Schmelz, E. A. & Mori, N. (2018). A fragmentation study of isoflavones by IT-TOF-MS using biosynthesized isotopes. *Bioscience, Biotechnology and Biochemistry*, *82*(8), 1309–1315.

Nalbantoglu, S. (2019). Metabolomics: Basic Principles and Strategies. In *Molecular Medicine*. IntechOpen.

Naranjo, V. I., Hendricks, M., & Jones, K. S. (2020). Lead Toxicity in Children: An Unremitting Public Health Problem. *Pediatric Neurology*, *113*.

Nascimento, F. P., Macedo-Júnior, S. J., Lapa-Costa, F. R., Cezar-dos-Santos, F., & Santos, A. R. S. (2021). Inosine as a Tool to Understand and Treat Central Nervous System Disorders: A Neglected Actor? *Frontiers in Neuroscience*, *15*.

Nguyen, M., Stewart, A. M., & Kalueff, A. V. (2014). Aquatic blues: Modeling depression and antidepressant action in zebrafish. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *55*.

Ni, H., Peng, L., Gao, X., Ji, H., Ma, J., Li, Y., & Jiang, S. (2019). Effects of maduramicin on adult zebrafish (*Danio rerio*): Acute toxicity, tissue damage and oxidative stress*. Ecotoxicology and Environmental Safety, 168*, 249–259.

Nicholson, J. K., Lindon, J. C., & Holmes, E. (1999). "Metabonomics": Understanding the metabolic responses of living systems to pathophysiological stimuli via multivariate statistical analysis of biological NMR spectroscopic data. *Xenobiotica*, *29*(11).

Nile, S. H., Nile, A., Oh, J. W., & Kai, G. (2020). Soybean processing waste: Potential antioxidant, cytotoxic and enzyme inhibitory activities. *Food Bioscience*, *38*.

NIOSH, National Institute for Occupational Safety and Health. (n.d.). *Lead*. https://www.cdc.gov/niosh/topics/lead/trends.html#print

Niu, C., Dong, M., & Niu, Y. (2023). Lead toxicity and potential therapeutic effect of plant-derived polyphenols. *Phytomedicine*, *114*.

Nkhata, S. G., Ayua, E., Kamau, E. H. & Shingiro, J. B. (2018). Fermentation and germination improve nutritional value of cereals and legumes through activation of endogenous enzymes. *Food Science & Nutrition*, *6*(8), 2446.

Nout, M. J. R. & Kiers, J. L. (2005). Tempe fermentation, innovation and functionality: Update into the third millenium. *Journal of Applied Microbiology*, *98*(4), 789–805.

OECD. (2019). *Test No. 203: Fish, Acute Toxicity Test, OECD Guidelines for the Testing of Chemicals*. Paris: OECD Publishing.

Oh, M. K., Rohlin, L., Kao, K. C. & Liao, J. C. (2002). Global expression profiling of acetate-grown *Escherichia coli*. *Journal of Biological Chemistry*, *277*, 13175–13183.

Olesti, E., González-Ruiz, V., Wilks, M. F., Boccard, J., & Rudaz, S. (2021). Approaches in metabolomics for regulatory toxicology applications. *Analyst*, *146*(6).

Oliveira, M. D. S, Feddern, V., Kupski, L., Cipolatti, E. P., Badiale-Furlong, E. & de Souza-Soares, L. A. (2011). Changes in lipid, fatty acids and phospholipids composition of whole rice bran after solid-state fungal fermentation. *Bioresour Technol*, *102*(17), 8335-8338.

Oyeyemi, W. A., Daramola, O. O. O., Akinola, A. O., Idris, A. O., & Aikpitanyi, I. (2020). Hepatic and reproductive toxicity of sub-chronic exposure to dichlorvos and lead acetate on male Wistar rats. *Asian Pacific Journal of Reproduction*, *9*(6).

Papaioannou, N., Distel, E., de Oliveira, E., Gabriel, C., Frydas, I. S., Anesti, O., Attignon, E. A., Odena, A., Díaz, R., Aggerbeck, M., Horvat, M., Barouki, R., Karakitsios, S., & Sarigiannis, D. A. (2021). Multi-omics analysis reveals that co-exposure to phthalates and metals disturbs urea cycle and choline metabolism. *Environmental Research*, *192*.

Papes, F., Surpili, M. J., Langone, F., Trigo, J. R. & Arruda, P. (2001). The essential amino acid lysine acts as precursor of glutamate in the mammalian central nervous system. *FEBS Letters*, *488*(1–2), 34–38.

Perez De Souza, L., Alseekh, S., Brotman, Y., & Fernie, A. R. (2020). Network-based strategies in metabolomics data analysis and interpretation: from molecular networking to biological interpretation. In *Expert Review of Proteomics*, *17*(4).

Pinu, F. R., Beale, D. J., Paten, A. M., Kouremenos, K., Swarup, S., Schirra, H. J., & Wishart, D. (2019). Systems biology and multi-omics integration: Viewpoints from the metabolomics research community. *Metabolites*, *9*(4).

Pires, V. C., Gollücke, A. P. B., Ribeiro, D. A., Lungato, L., D'Almeida, V., & Aguiar, O. (2013). Grape juice concentrate protects reproductive parameters of male rats against cadmium-induced damage: A chronic

assay. *British Journal of Nutrition*, *110*(11).

Poli, V., Madduru, R., Aparna, Y., Kandukuri, V., & Motireddy, S. R. (2022). Amelioration of Cadmium-Induced Oxidative Damage in Wistar Rats by Vitamin C, Zinc and N-Acetylcysteine. *Medical Sciences (Basel, Switzerland)*, *10*(1).

Popova, A., & Mihaylova, D. (2019). Antinutrients in Plant-based Foods: A Review. *The Open Biotechnology Journal*, *13*(1).

Qin, P., Wang, T., & Luo, Y. (2022). A review on plant-based proteins from soybean: Health benefits and soy product development. *Journal of Agriculture and Food Research*, *7*.

Qiu, S., Cai, Y., Yao, H., Lin, C., Xie, Y., Tang, S., & Zhang, A. (2023). Small molecule metabolites: discovery of biomarkers and therapeutic targets. In *Signal Transduction and Targeted Therapy*, *8*(1).

Rahman, N. S. N. A., Hamid, N. W. A., & Nadarajah, K. (2021). Effects of abiotic stress on soil microbiome. *International Journal of Molecular Sciences*, *22*(16).

Ramos, B., El Mouedden, M., Claro, E., & Jackowski, S. (2002). Inhibition of CTP: phosphocholine cytidylyltransferase by C2-ceramide and its relationship to apoptosis*. Molecular Pharmacology, 62*(5), 1068–1075.

Reddy, G. R., Basha, M. R., Devi, C. B., Suresh, A., Baker, J. L., Shafeek, A., Heinz, J., & Chetty, C. S. (2003). Lead induced effects on acetylcholinesterase activity in cerebellum and hippocampus of developing rat*. International Journal of Developmental Neuroscience, 21*(6), 347–352.

Reddy, S. Y., Pullakhandam, R., & Kumar, B. D. (2010). Thiamine reduces tissue lead levels in rats: Mechanism of interaction. *BioMetals*, *23*(2).

Reddy, Y. A., Chalamaiah, M., Ramesh, B., Balaji, G., & Indira, P. (2014). Ameliorating activity of ginger (*Zingiber officinale*) extract against lead induced renal toxicity in male rats. *Journal of Food Science and Technology*, *51*(5).

Reddy, Y. S., Kiranmayi, V. S., Bitla, A. R., Krishna, G. S., Srinivasa Rao, P. V. L. N., & Sivakumar, V. (2015). Nitric oxide status in patients with chronic kidney disease*. Indian Journal of Nephrology, 25*(5), 287.

Reimand, J., Isserlin, R., Voisin, V., Kucera, M., Tannus-Lopes, C., Rostamianfar, A., Wadi, L., Meyer, M., Wong, J., Xu, C., Merico, D., & Bader, G. D. (2019). Pathway enrichment analysis and visualization of omics data using g:Profiler, GSEA, Cytoscape and EnrichmentMap. *Nature Protocols*, *14*(2).

Resmim, C. M., Borba, J. V., Pretzel, C. W., Santos, L. W., Rubin, M. A., & Rosemberg, D. B. (2023). Assessing the exploratory profile of two

zebrafish populations: Influence of anxiety-like phenotypes and independent trials on homebase-related parameters and exploration. *Behavioural Processes*, *210*.

Richetti, S. K., Rosemberg, D. B., Ventura-Lima, J., Monserrat, J. M., Bogo, M. R., & Bonan, C. D. (2011). Acetylcholinesterase activity and antioxidant capacity of zebrafish brain is altered by heavy metal exposure. *NeuroToxicology*, *32*(1), 116–122.

Rosa, J. G. S., Lima, C., & Lopes-Ferreira, M. (2022). Zebrafish Larvae Behavior Models as a Tool for Drug Screenings and Pre-Clinical Trials: A Review. *International Journal of Molecular Sciences*, *23*(12).

Rosenberg, A. G., & Haynes, J. H. (2019). Management of Ingested Lead Pellets with Elevated Blood Lead Levels in a Pediatric Patient. *Journal of Pediatric Gastroenterology and Nutrition*, *69*(6).

Rost-Roszkowska, M. M., Vilimova, J., & Chajec, Ł. (2010). Fine structure of the midgut epithelium of *nicoletia phytophila* gervais, 1844 (Zygentoma: Nicoletiidae: Nicoletiinae) with special emphasis on its degeneration. *Folia Biologica, 58*(3-4), 217–227.

Roy, N. M., Dewolf, S., Schutt, A., Wright, A., & Steele, L. (2014). Neurotoxicology and Teratology Neural alterations from lead exposure in zebrafish. *Neurotoxicology and Teratology*, *46*, 40–48.

Sachett, A., Benvenutti, R., Reis, C. G., Gallas-Lopes, M., Bastos, L. M., Aguiar, G. P. S., Herrmann, A. P., Oliveira, J. V., Siebel, A. M., & Piato, A. (2022). Micronized Curcumin Causes Hyperlocomotion in Zebrafish Larvae. *Neurochemical Research*, *47*(8), 2307–2316.

Sadeghi, A., Bideskan, A. E., Alipour, F., Fazel, A., & Haghir, H. (2013). The effect of ascorbic acid and garlic administration on lead-induced neural damage in rat offspring's hippocampus. *Iranian Journal of Basic Medical Sciences*, *16*(2).

Sadka, A., Shlizerman, L., Kamara, I. & Blumwald, E. (2019). Primary Metabolism in Citrus Fruit as Affected by Its Unique Structure. *Frontiers in Plant Science*, *10*, 1–14.

Sakaguchi, Y., Kaimori, J. Y., & Isaka, Y. (2023). Plant-Dominant Low Protein Diet: A Potential Alternative Dietary Practice for Patients with Chronic Kidney Disease. *Nutrients*, *15*(4).

Salem, M. A., De Souza, L. P., Serag, A., Fernie, A. R., Farag, M. A., Ezzat, S. M., & Alseekh, S. (2020). Metabolomics in the context of plant natural products research: From sample preparation to metabolite analysis. In *Metabolites*, *10*(1).

Samtiya, M., Aluko, R. E., & Dhewa, T. (2020). Plant food anti-nutritional factors and their reduction strategies: an overview. In *Food Production, Processing and Nutrition*, *2*(1).

Schaffer, S., Takahashi, K., & Azuma, J. (2000). Role of osmoregulation in the actions of taurine. *Amino Acids, 19*(3-4), 527-546.

Schroder, L. P., Tilleman, J. A., & Desimone, E. M. (2015). Lead toxicity and chelation therapy. *U.S. Pharmacist*, *40*(5), 40–44.

Shahrajabian, M. H., Sun, W., & Cheng, Q. (2019). Clinical aspects and health benefits of ginger (Zingiber officinale) in both traditional Chinese medicine and modern industry. In *Acta Agriculturae Scandinavica Section B: Soil and Plant Science*, *69*(6).

Shao, Y., Yan, G., Xuan, Y., Peng, H., Huang, Q. J., Wu, R., & Xu, H. (2015). Chronic social isolation decreases glutamate and glutamine levels and induces oxidative stress in the rat hippocampus. *Behavioural Brain Research*, *282*.

Sharifi-Rad, M., Anil Kumar, N. V., Zucca, P., Varoni, E. M., Dini, L., Panzarini, E., Rajkovic, J., Tsouh Fokou, P. V., Azzini, E., Peluso, I., Prakash Mishra, A., Nigam, M., El Rayess, Y., Beyrouthy, M. El, Polito, L., Iriti, M., Martins, N., Martorell, M., Docea, A. O., … Sharifi-Rad, J. (2020). Lifestyle, Oxidative Stress, and Antioxidants: Back and Forth in the Pathophysiology of Chronic Diseases. In *Frontiers in Physiology*, *11*.

Shen, J., Petersen, K. F., Behar, K. L., Brown, P., Nixon, T. W., Mason, G. F., Petroff, O. A. C., Shulman, G. I., Shulman, R. G., & Rothman, D. L. (1999). Determination of the rate of the glutamate/glutamine cycle in the human brain by in vivo 13C NMR. *Proceedings of the National Academy of Sciences of the United States of America*, *96*(14).

Shi, J., Cao, B., Wang, X. W., Aa, J. Y., Duan, J. A., Zhu, X. X., Wang, G. J., & Liu, C. X. (2016). Metabolomics and its application to the evaluation of the efficacy and toxicity of traditional Chinese herb medicines. *Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences*, *1026*.

Shin, H. K., & Linkswiler, H. M. (1974). Tryptophan and methionine metabolism of adult females as affected by vitamin B-6 deficiency. *Journal of Nutrition, 104*(10), 1348-1455.

Silva, R. A., Pereira, T. C. S., Souza, A. R., & Ribeiro, P. R. (2020). 1H NMR-based metabolite profiling for biomarker identification. In *Clinica Chimica Acta*, *502*.

Sireeni, J., Bakker, N., Jaikumar, G., Obdam, D., Slabbekoorn, H., Tudorache, C., & Schaaf, M. (2020). Profound effects of glucocorticoid resistance on anxiety-related behavior in zebrafish adults but not in larvae. *General and Comparative Endocrinology*, *292*.

Smith, P. G., Morrow, R. H., & Ross, D. A. (Eds.). (2015). *Field Trials of Health Interventions: A Toolbox*. (3rd ed.). Oxford, 2015; online edn, Oxford Academic.

Smith-Spangler, C., Brandeau, M. L., Hunter, G. E., Bavinger, J. C., Pearson, M., Eschbach, P.J. Sundaram, V., Liu, H., Schirmer, P., Stave, C., Olkin, I., & Bravata, D. M. (2012). Are organic foods safer or healthier than conventional alternatives?: a systematic review. *Annals of Internal Medicine*, *157*(5), 348-66.

Soliman, G. A. (2019). Dietary fiber, atherosclerosis, and cardiovascular disease. *Nutrients*, *11*(5).

Song, D. H., Chun, B. H., Lee, S., Son, S. Y., Reddy, C. K., Mun, H. I., Jeon, C. O., & Lee, C. H. (2021). Comprehensive metabolite profiling and microbial communities of doenjang (Fermented soy paste) and ganjang (fermented soy sauce): A comparative study. *Foods*, *10*(3).

Song, J., Liu, C., Li, D. & Gu, Z. (2013). Evaluation of sugar, free amino acid, and organic acid compositions of different varieties of vegetable soybean (*Glycine max* [L.] Merr). *Industrial Crops and Products*, *50*, 743–749.

Song, J., Wu, G., Li, T., Liu, C. & Li, D. (2020). Changes in the sugars, amino acids and organic acids of postharvest spermine treated immature vegetable soybean (*Glycine max* L. Merr.) as determined by ^{1}H NMR spectroscopy. *Food Production, Processing and Nutrition*, *2*(7).

Souza, J. P., Baretta, J. F., Santos, F., Paino, I. M. M., & Zucolotto, V. (2017). Toxicological effects of graphene oxide on adult zebrafish (*Danio rerio*). *Aquatic Toxicology, 186*, 11–18.

Speciale, I., Notaro, A., Garcia-Vello, P., Di Lorenzo, F., Armiento, S., Molinaro, A., Marchetti, R., Silipo, A., & De Castro, C. (2022). Liquid-state NMR spectroscopy for complex carbohydrate structural analysis: A hitchhiker's guide. *Carbohydrate Polymers*, *277*.

Stephanie, T. S., Kartawidjajaputra, F., Silo, W., Yogiara, Y., & Suwanto, A. (2019). Tempeh consumption enhanced beneficial bacteria in the human gut. *Food Research, 3*(1), 57–63.

Stewart, A. M., Braubach, O., Spitsbergen, J., Gerlai, R., & Kalueff, A. V. (2014). Zebrafish models for translational neuroscience research: from tank to bedside. *Trends Neurosci*, *37*(5), 264–278.

Stewart, A., Cachat, J. M., Wong, K., Wu, N., Grossman, L., Suciu, C., Goodspeed, J., Elegante, M. F., Bartels, B. K., Elkhayat, S. I., Tien, D. H., Gaikwad, S., Kadri, F., Chung, K. M., Tan, J., Denmark, A., Gilder, T., Dileo, J., Chang, K., Frank, K., Utterback, E., Viviano, P., & Kalueff, A. V. (2011). Phenotyping of zebrafish homebase behaviours in novelty-based tests. In A. Kalueff & J. Cachat (Eds.), *Zebrafish Neurobehavioural Protocols* (pp. 143-155). Humana Press.

Sui, X., Zhang, T., & Jiang, L. (2021). Soy Protein: Molecular Structure Revisited and Recent Advances in Processing Technologies. *Annual Review of Food Science and Technology*, *12*.

Sulinskiene, J., Baranauskiene, D., Naginiene, R., & Ivanov, L. (2015). Protective effect of zinc ions against lead and nickel induced inhibition of δ-aminolevulinic acid dehydratase activity in mice liver. *Trace Elements and Electrolytes*, *32*(2).

Surai, P. F., Earle-payne, K., & Kidd, M. T. (2021). Taurine as a Natural Antioxidant: From Direct Antioxidant Effects to Protective Action in Various Toxicological Models. *Antioxidants, 10*(12), 1876.

Surya, R., Romulo, A., & Suryani, Y. (2021). Tempeh extract reduces cellular ROS levels and upregulates the expression of antioxidant enzymes. *Food Research*, *5*(3).

Surya, R., Romulo, A., & Suryani, Y. (2021). Tempeh extract reduces cellular ROS levels and upregulates the expression of antioxidant enzymes. *Food Research*, *5*(3).

Surya, Reggie, & Romulo, A. (2020). Steaming Process Does Not Affect the Antioxidant Activities of Tempeh Ethanol Extract. *Journal of Physics: Conference Series*, *1655*(1).

Tahavorgar, A., Vafa, M., Shidfar, F., Gohari, M., & Heydari, I. (2014). Whey protein preloads are more beneficial than soy protein preloads in regulating appetite, calorie intake, anthropometry, and body composition of overweight and obese men. *Nutrition Research*, *34*(10).

Takahashi, Y., Sasanuma, T. & Abe, T. (2013). Accumulation of gamma-aminobutyrate (GABA) caused by heat-drying and expression of related genes in immature vegetable soybean (edamame). *Breeding Science*, *63*(2), 205–210.

Tamam, B., Puryana, I. G. B. P., Suratiah, & Sutiari, N. K. (2023). Nutritional aspects and amino acid profiles of tempe from local, imported, and black soybean relating to the functional properties. *IOP Conference Series: Earth and Environmental Science*, *1177*(1).

Tchounwou, P. B., Yedjou, C. G., Patlolla, A. K., & Sutton, D. J. (2012). Heavy Metals Toxicity and the Environment. In A. Luch (Ed.), *Molecular, Clinical and Environmental Toxicology*. (pp. 133-164). Basel: Springer.

Teixeira, C. P., Florencio-Silva, R., Sasso, G. R. S., Carbonel, A. A. F., Simões, R. S., & Simões, M. J. (2019). Soy isoflavones protect against oxidative stress and diminish apoptosis in ovary of middle-aged female rats. *Gynecological Endocrinology*, *35*(7).

Teskey, G., Abrahem, R., Cao, R., Gyurjian, K., Islamoglu, H., Lucero, M., Martinez, A., Paredes, E., Salaiz, O., Robinson, B., & Venketaraman, V. (2018). Glutathione as a Marker for Human Disease. *Advances in Clinical Chemistry*, *87*.

Thi, N. H. B., Thi, N. A. N., Audira, G., Siregar, P., Liang, S. T., Huang, J. C., & Hsiao, C. Der. (2020). Chronic exposure to low concentration lead

chloride-induced anxiety and loss of aggression and memory in zebrafish. *International Journal of Molecular Sciences*, *21*(5).

Thurmond, J. B., Lasley, S. M., Kramarcy, N. R., & Brown, J. W. (1979). Differential tolerance to dietary amino acid-induced changes in aggressive behaviour and locomotor activity in mice. *Psychopharmacology*, *66*(3).

Tian, F., Zhai, Q., Zhao, J., Liu, X., Wang, G., Zhang, H., Zhang, H., & Chen, W. (2012). Lactobacillus plantarum CCFM8661 alleviates lead toxicity in mice. *Biological Trace Element Research*, *150*(1–3).

Tito, A., Carola, A., Bimonte, M., Barbulova, A., Arciello, S., De Laurentiis, F., Monoli, I., Hill, J., Gibertoni, S., Colucci, G., & Apone, F. (2011). A tomato stem cell extract, containing antioxidant compounds and metal chelating factors, protects skin cells from heavy metal-induced damages. *International Journal of Cosmetic Science*, *33*(6).

Todorov, H., Searle-White, E., & Gerber, S. (2020). Applying univariate vs. multivariate statistics to investigate therapeutic efficacy in (pre)clinical trials: A Monte Carlo simulation study on the example of a controlled preclinical neurotrauma trial. *PLoS ONE*, *15*(3).

Tohidpour, A., Morgun, A. V., Boitsova, E. B., Malinovskaya, N. A., Martynova, G. P., Khilazheva, E. D., Kopylevich, N. V., Gertsog, G. E., & Salmina, A. B. (2017). Neuroinflammation and Infection: Molecular Mechanisms Associated with Dysfunction of Neurovascular Unit. *Frontiers in Cellular and Infection Microbiology*, *7*(JUN), 276.

Tounta, V., Liu, Y., Cheyne, A., & Larrouy-Maumus, G. (2021). Metabolomics in infectious diseases and drug discovery. In *Molecular Omics*, *17*(3).

Troisi, J., Troisi, G., Scala, G., & Richards, S. M. (2022). Data analysis in metabolomics: from information to knowledge. *Metabolomics Perspectives: From Theory to Practical Application*.

Valentino, G., Graziani, V., D'Abrosca, B., Pacifico, S., Fiorentino, A., & Scognamiglio, M. (2020). NMR-based plant metabolomics in nutraceutical research: An overview. *Molecules*, *25*(6).

van de Poll, M. C. G., Ligthart-melis, G. C., Boelens, P. G., Deutz, N. E. P., Van Leeuwen, P. A. M., & Dejong, C. H. C. (2007). Intestinal and hepatic metabolism of glutamine and citrulline in humans. *The Journal of Physiology, 581*(Pt 2), 819-827.

Vandenberg, L. N., Colborn, T., Hayes, T. B., Heindel, J. J., Jacobs, D. R., Lee, D. H., Shioda, T., Soto, A. M., vom Saal, F. S., Welshons, W. V., Zoeller, R. T., & Myers, J. P. (2012). Hormones and endocrine-disrupting chemicals: Low-dose effects and nonmonotonic dose responses. *Endocrine Reviews, 33*(3), 378-455.

Velayati, A. A., Farnia, P., Ibrahim, T. A., Haroun, R. Z., Kuan, H. O., Ghanavi, J., Farnia, P., Kabarei, A. N., Tabarsi, P., Omar, A. R., Varahram, M., &

Masjedi, M. R. (2009). Differences in cell wall thickness between resistant and nonresistant strains of Mycobacterium tuberculosis: using transmission electron microscopy. *Chemotherapy, 55*(5), 303–307.

Vignoli, A., Ghini, V., Meoni, G., Licari, C., Takis, P. G., Tenori, L., Turano, P., & Luchinat, C. (2019). High-Throughput Metabolomics by 1D NMR. In *Angewandte Chemie - International Edition*, *58*(4).

Vijayakumar, V., & M, H. (2021). *Nutraceutical Legumes: A Brief Review on the Nutritional and Medicinal Values of Legumes*.

Virgolini, M. B., & Aschner, M. (2021). Molecular mechanisms of lead neurotoxicity. *Advances in Neurotoxicology*, *5*.

Vollmann, J., Wagentristl, H. & Hartl, W. (2010). The effects of simulated weed pressure on early maturity soybeans. *European Journal of Agronomy*, *32*(4), 243–248.

Vong, W. C., Hua, X. Y. & Liu, S. Q. (2018). Solid-state fermentation with *Rhizopus oligosporus* and *Yarrowia lipolytica* improved nutritional and flavour properties of okara. *LWT - Food Science and Technology*, *90*, 316-322.

Wang, J. H., Byun, J. & Pennathur, S. (2010). Analytical Approaches to Metabolomics and Applications to Systems Biology. *Semin Nephrol*, *30*(5), 500–511.

Wang, X., Wang, H., Zhang, A., Lu, X., Sun, H., Dong, H., & Wang, P. (2012). Metabolomics study on the toxicity of aconite root and its processed products using ultraperformance liquid-chromatography/electrospray-ionization synaptic high-definition mass spectrometry coupled with pattern recognition approach and ingenuity pathways analysis. *Journal of Proteome Research, 11*(2), 1284–1301.

Wang, Y., Zhu, W., Wang, D., Teng, M., Yan, J., Miao, J., & Zhou, Z. (2017). ^{1}H NMR-based metabolomics analysis of adult zebrafish (*Danio rerio*) after exposure to diniconazole as well as its bioaccumulation behaviour. *Chemosphere, 168*, 1571–1577.

Wang, Z., Zhao, H., Xu, Y., Zhao, J., Song, Z., Bi, Y., Li, Y., Lan, X., Pan, C., Foulkes, N. S., & Zhang, S. (2022). Early-life lead exposure induces long-term toxicity in the central nervous system: From zebrafish larvae to juveniles and adults. *Science of the Total Environment*, *804*.

Wang, Z., Zhao, H., Xu, Y., Zhao, J., Song, Z., Bi, Y., Li, Y., Lan, X., Pan, C., Foulkes, N. S., & Zhang, S. (2022). Early-life lead exposure induces long-term toxicity in the central nervous system: From zebrafish larvae to juveniles and adults. *Science of the Total Environment*, *804*.

Wani, A. L., Ara, A., & Usmani, J. A. (2015). Lead toxicity: a review. *Interdisciplinary Toxicology, 8*(2), 55-64.

Wanichthanarak, K., Fan, S., Grapov, D., Barupal, D. K., & Fiehn, O. (2017). Metabox: A toolbox for metabolomic data analysis, interpretation and integrative exploration. *PLoS ONE*, *12*(1).

Weber, D. N., Dingel, W. M., Panos, J. J., & Steinpreis, R. E. (1997). Alterations in neurobehavioural responses in fishes exposed to lead and lead-chelating agents. *American Zoologist, 37*(4), 354-362.

Westerfield, M. (2000). *The Zebrafish Book*, *A guide for the laboratory use of zebrafish (Danio rerio)*. Oregon: University of Oregon Press.

Wijesinghe, J., Botheju, S. M., Nallaperuma, B., & Kanuwana, N. (2023). Organic farming: The influence on soil health. In *One Health: Human, Animal, and Environment Triad*.

Wilhelmi, P., Giri, V., Zickgraf, F. M., Haake, V., Henkes, S., Driemert, P., Michaelis, P., Busch, W., Scholz, S., Flick, B., Barenys, M., Birk, B., Kamp, H., Landsiedel, R., & Funk-Weyer, D. (2023). A metabolomics approach to reveal the mechanism of developmental toxicity in zebrafish embryos exposed to 6-propyl-2-thiouracil. *Chemico-Biological Interactions*, *382*.

William J. Langston, & Maria J. Bebianno. (1998). Metal Metabolism in Aquatic Environments. In *Metal Metabolism in Aquatic Environments*.

Wiprich, M. T., Zanandrea, R., Altenhofen, S., & Bonan, C. D. (2020). Influence of 3-nitropropionic acid on physiological and behavioral responses in zebrafish larvae and adults. *Comparative Biochemistry and Physiology Part - C: Toxicology and Pharmacology*, *234*.

Wishart, D. S., Cheng, L. L., Copié, V., Edison, A. S., Eghbalnia, H. R., Hoch, J. C., Gouveia, G. J., Pathmasiri, W., Powers, R., Schock, T. B., Sumner, L. W., & Uchimiya, M. (2022). NMR and Metabolomics—A Roadmap for the Future. *Metabolites*, *12*(8).

Witkowska, D., Słowik, J., & Chilicka, K. (2021). Review heavy metals and human health: Possible exposure pathways and the competition for protein binding sites. *Molecules*, *26*(19).

Woo, D.-C., Kim, G.-Y., Kim, H.-J., Bang, E., Rhim, H.-S., Kim, S.-Y., Lee, D.-W., Choi, C.-B., Seoung, Y.-H., & Choe, B.-Y. (2013). Metabolic Alterations of the Zebrafish Brain after Acute Alcohol Treatment by ^{1}H Nuclear Magnetic Resonance Spectroscopy. *Journal of Spectroscopy, 2013*.

Worley, B., & Powers, R. (2013). Multivariate Analysis in Metabolomics. *Current Metabolomics*, *1*(1), 92–107.

Xia, J., Sinelnikov, I. V., Han, B., & Wishart, D. S. (2015). MetaboAnalyst 3.0-making metabolomics more meaningful. *Nucleic Acids Research, 43*(W1), W251-257.

Xia, Jizhou, Lu, L., Jin, C., Wang, S., Zhou, J., Ni, Y., Fu, Z., & Jin, Y. (2018). Effects of short term lead exposure on gut microbiota and hepatic metabolism in adult zebrafish. *Comparative Biochemistry and Physiology Part - C: Toxicology and Pharmacology*, *209*.

Yalavarth, P., Prabhakar, O., & Arun, K. (2020). Role of dietary proteins in cardiovascular diseases. *Journal of Advanced Scientific Research*, *11*(2).

Yang, M. J., Xu, D., Yang, D. X., Li, L., Peng, X., Chen, X., Gui, Z., & Li, H. (2020). Malate enhances survival of zebrafish against *Vibrio alginolyticus* infection in the same manner as taurine. *Virulence, 11*(1), 349-364.

Yang, W. J., Wang, Y. W., Zhou, Q. F., & Tang, H. R. (2008). Analysis of human urine metabolites using SPE and NMR spectroscopy. *Science in China, Series B: Chemistry*, *51*(3).

Ye, T., Zheng, C., Zhang, S., Gowda, G. A. N., Vitek, O., & Raftery, D. (2012). "add to Subtract": A simple method to remove complex background signals from the 1H nuclear magnetic resonance spectra of mixtures. *Analytical Chemistry*, *84*(2).

Ye, Z., Wang, S., Zhang, C., & Zhao, Y. (2020). Coordinated Modulation of Energy Metabolism and Inflammation by Branched-Chain Amino Acids and Fatty Acids. *Frontiers in Endocrinology*, *11*(September), 5–9.

Yuseran, H., Hartoyo, E., Nurseta, T., & Kalim, H. (2021). Genistein inhibits the proliferation of human choriocarcinoma cells via the downregulation of estrogen receptor-α phosphorylation at serine 118. *Clinical Nutrition*.

Yusof, H. M., Ali, N. M., Yeap, S. K., Ho, W. Y., Beh, B. K., Koh, S. P., Long, K., Abdul Aziz, S., & Alitheen, N. B. (2013). Hepatoprotective effect of fermented soybean (nutrient enriched soybean tempeh) against alcohol-induced liver damage in mice. *Evidence-Based Complementary and Alternative Medicine*, *2013*.

Yusof, H. M., Ali, N. M., Yeap, S. K., Ho, W. Y., Beh, B. K., Koh, S. P., Long, K., & Alitheen, N. B. (2019). Anti-inflammatory, analgesic and acute toxicity effects of fermented soybean. *BMC Complementary and Alternative Medicine*, *19*(1), 1–7.

Zabegalov, K. N., Kolesnikova, T. O., Khatsko, S. L., Volgin, A. D., Yakovlev, O. A., Amstislavskaya, T. G., Friend, A. J., Bao, W., Alekseeva, P. A., Lakstygal, A. M., Meshalkina, D. A., Demin, K. A., de Abreu, M. S., Rosemberg, D. B., & Kalueff, A. V. (2019). Understanding zebrafish aggressive behaviour. *Behavioural Processes*, *158*.

Zaric, B. L., Radovanovic, J. N., Gluvic, Z., Stewart, A. J., Essack, M., Motwalli, O., Gojobori, T., & Isenovic, E. R. (2020). Atherosclerosis Linked to Aberrant Amino Acid Metabolism and Immunosuppressive Amino Acid Catabolizing Enzymes. *Frontiers in Immunology, 11*.

Zeeshan, H. M. A., Lee, G. H., Kim, H. R., & Chae, H. J. (2016). Endoplasmic

reticulum stress and associated ROS. *International Journal of Molecular Sciences*,*17*(3).

Zeisel, S. H. (2004). Antioxidants Suppress Apoptosis*. The Journal of Nutrition, 134*(11), 3179S-3180S.

Zhai, Q., Wang, G., Zhao, J., Liu, X., Tian, F., Zhang, H., & Chen, W. (2013). Protective effects of *lactobacillus plantarum* ccfm8610 against acute cadmium toxicity in mice. *Applied and Environmental Microbiology*, *79*(5).

Zhang, S., Yang, W., Chen, H., Liu, B., Lin, B. & Tao, Y. (2019). Metabolic engineering for efficient supply of acetyl-CoA from different carbon sources in *Escherichia coli*. *Microbial Cell Factories*, *18*, 130.

Zhang, W., Tan, B., Deng, J., Dong, X., Yang, Q., Chi, S., Liu, H., Zhang, S., Xie, S., & Zhang, H. (2021). Effects of high level of fermented soybean meal substitution for fish meal on the growth, enzyme activity, intestinal structure protein and immune-related gene expression and intestinal flora in juvenile pearl gentian grouper*. Aquaculture Nutrition, 27*(5), 1433–1447.

Zhang, Y., Jiang, Y., Wang, Z., Wang, J., Zhu, M., & Yang, H. (2022). Effects of Dietary Resveratrol, Bile Acids, Allicin, Betaine, and Inositol on Recovering the Lipid Metabolism Disorder in the Liver of Rare Minnow Gobiocypris rarus Caused by Bisphenol A. *Aquaculture Nutrition*, 2022.

Zhang, Y., Wei, R., Azi, F., Jiao, L., Wang, H., He, T., Liu, X., Wang, R., & Lu, B. (2022). Solid-state fermentation with Rhizopus oligosporus RT-3 enhanced the nutritional properties of soybeans. *Frontiers in Nutrition*, *9*.

Zhao, P. H., Hou, Y. C., Wang, Z., Liao, A. M., Pan, L., Zhang, J., Dong, Y. Q., Hu, Z. Y., Huang, J. H., & Ou, X. Q. (2023). Effect of fermentation on structural properties and antioxidant activity of wheat gluten by Bacillus subtilis. *Frontiers in Nutrition*, *10*.

Zhao, X., Rajashekar, C. B., Carey, E. E. & Wang, W. (2006). Does Organic Production Enhance Phytochemical Content of Fruit and Vegetables? Current Knowledge and Prospects for Research. *HortTechnology*, *16*(3), 449-456.

Zheng, X., Lee, S. K., & Chun, O. K. (2016). Soy Isoflavones and Osteoporotic Bone Loss: A Review with an Emphasis on Modulation of Bone Remodeling. In *Journal of Medicinal Food*, *19*(1).

Zhou, Y., Zhu, Y., & Wong, W. K. (2023). Statistical tests for homogeneity of variance for clinical trials and recommendations. In *Contemporary Clinical Trials Communications*, *33*.

Zuberi, Z., Eeza, M. N. H., Matysik, J., Berry, J. P., & Alia, A. (2019). NMR-based metabolic profiles of intact zebrafish embryos exposed to aflatoxin b1 recapitulates hepatotoxicity and supports possible neurotoxicity. *Toxins*, *11*(5).

Zwolak, I. (2021). Epigallocatechin gallate for management of heavy metal-induced oxidative stress: Mechanisms of action, efficacy, and concerns. In *International Journal of Molecular Sciences*, *22*.