IN VITRO ANTI-ALLERGIC ACTIVITY OF ALPHA-CYCLODEXTRIN MORINGIN COMPLEX IN RAT BASOPHILIC LEUKEMIA (RBL-2H3) CELL LINE

By

ALNAKEEB EBTISAM YOUSEF A

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

May 2023

IB 2023 3

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

IN VITRO ANTI-ALLERGIC ACTIVITY OF ALPHA-CYCLODEXTRIN MORINGIN COMPLEX IN RAT BASOPHILIC LEUKEMIA (RBL-2H3) CELL LINE

By

EBTISAM YOUSEF A ALNAKEEB

May 2023

Chairman : Ahmad Faizal bin Abdull Razis, PhD
Institute : Bioscience

Allergic disease has become a more prominent public health problem. According to the World Health Organization (WHO), the disease affects 30–40% of the world's population. The most common diseases associated with allergies are asthma, atopic dermatitis, allergic rhinitis, and pollen diseases. In Malaysia, the prevalence rate of allergic rhinitis (AR) was estimated at 7.1%, higher than other Southeast Asian countries. Therefore, the strategies of using phyto-therapeutic agents as alternative sources for anti-allergic therapy have become necessary. *Moringa oleifera* Lam is a tropical plant widely used in traditional medicines and possesses antioxidant, antimicrobial, and anti-inflammation properties. Its beneficial effects are believed due to the presence of isothiocyanate (ITC), which is known as moringin (MG). The plant also has been traditionally used to alleviate allergic conditions; however, the bioactive compound in the form of alpha-cyclodextrin moringin (α-CD/MG) complex and its anti-allergic effects remain unexplored. Thus, the purpose of the present study was to investigate the anti-allergic effects of a new formulation of *M. oleifera*-derived 4-(α-L-rhamnopyranosyloxy) benzyl isothiocyanate as a complex with alpha-cyclodextrin α-CD/MG on rat basophilic leukaemia (RBL-2H3) cell line. NMR showed protons H7, H8, and H9 of moringin (benzyl moiety) with alpha-cyclodextrins proton H3 was involved in the complex formation. The cell proliferation was examined by 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H tetrazolium, inner salt (MTS) assay reagent to determine the concentration of α-CD/MG with high cell viability. Chemical shifts of H7, H8, and H9 protons were observed due to interactions between alpha-cyclodextrin and moringin molecules. Low concentrations of α-CD/MG (5, 2.5, 1.25μM) showed no toxicity against RBL-2H3 at 24, 48, and 72 hours, while a higher concentration (10μM) showed significant toxicity. For *in vitro* model of immunoglobulin E (IgE)-mediated mast cell degranulation, monoclonal anti-dinitrophenyl (DNP) IgE-sensitised RBL-2H3 cells were pre-treated with α-CD/MG before being challenged with dinitrophenyl-bovine serum albumin (DNP-BSA) to induce degranulation. The anti-allergic activity of the complex and ketotifen fumarate as a positive control was evaluated for the early and late phases of allergic reactions. The

early phase was determined based on the inhibition of beta-hexosaminidase (β-hexosaminidase) and histamine release; while the late phase was based on the inhibition of interleukin (IL-4), tumour necrosis factor (TNF-α), and prostaglandin D_2 (PGD_2) release. Interestingly, the results showed that α-CD/MG significantly inhibited mast cell degranulation by inhibiting β-hexosaminidase and histamine release for early phases at concentrations of 5, 2.5 μM and 5, 2.5, 1.25 and, 0.625 μM respectively with $p<0.005$. Similarly, 5, 2.5, 1.25 and, 0.625 μM of α-CD/MG significantly inhibited TNF-α and PGD_2 ($P<0.001$) during late phases. On the other hand, IL-4 was significantly inhibited at the concentration of 5, 2.5 and 0.625 μM ($p< 0.001$) compared with the negative control. Therefore, the study suggested that α-CD/MG potentially has an anti-allergic activity by inhibiting both early and late phases of allergic reactions.

Key words: Anti-allergic; alpha-cyclodextrin moringin; RBL-2H3; histamine; PGD_2; *β*-hexosaminidase; TNF-α; IL-4.

SDG: GOAL 4: Quality Education, GOAL 3: Good Health and Well-Being.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

AKTIVITI ANTI-ALERGIK *IN VITRO* BAGI KOMPLEKS MORINGIN ALFA-SIKLODEKTRIN DALAM SEL LEUKEMIA BASOFILIK TIKUS (RBL-2H3)

Oleh

EBTISAM YOUSEF A ALNAKEEB

Mei 2023

Pengerusi : Ahmad Faizal bin Abdull Razis, PhD
Institut : Biosains

Penyakit alahan telah menjadi masalah kesihatan awam yang lebih ketara. Menurut Pertubuhan Kesihatan Sedunia (WHO), penyakit ini menjejaskan 30–40% penduduk dunia. Penyakit yang berkaitan dengan alahan ialah asma, dermatitis atopik, rinitis alergi dan penyakit debunga. Di Malaysia, kadar prevalens rinitis alergi (AR) dianggarkan pada 7.1 %, lebih tinggi daripada negara Asia Tenggara yang lain. Oleh itu, strategi menggunakan agen fitoterapeutik sebagai sumber alternatif bagi terapi anti-alergik telah menjadi keperluan. *Moringa oleifera* Lam adalah tumbuhan tropika yang digunakan secara meluas dalam perubatan tradisional dan memiliki sifat antioksidan, antimikrobial, dan anti-inflamasi. Kesannya yang bermanfaat dipercayai disebabkan oleh kehadiran isotiosianat (ITC), yang dikenali sebagai moringin (MG). Tumbuhan tersebut juga telah digunakan secara tradisional bagi melegakan keadaan alahan; walau bagaimanapun, sebatian bioaktif dalam bentuk kompleks moringin alfa-siklodektrin (α-CD/MG) dan kesan anti-alahannya masih belum diselidiki. Oleh itu, tujuan kajian ini adalah untuk menyiasat kesan anti-alahan formulasi baru *M. oleifera* yang berasal dari 4-(α-L-rhamnopyranosyloxy) benzyl isothiocyanate sebagai kompleks dengan alfa-siklodektrin (α-CD/MG) dalam sel leukemia basofilik tikus (RBL-2H3). NMR menunjukkan proton H7, H8, dan H9 moringin (benzil moiety) dengan alfa-siklodektrin proton H3 terlibat dalam pembentukan kompleks tersebut. Proliferasi sel telah diperiksa melalui reagen asai MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium garam sebatian (MTS) untuk menentukan kepekatan α-CD/MG dengan viabiliti sel yang tinggi. Perubahan kimia telah dilihat pada proton H7, H8, dan H9 oleh sebab interaksi antara alfa-siklodektrin dan molekul moringin. Kepekatan α-CD/MG (5, 2.5, 1.25μM) yang rendah menunjukkan tiada ketoksikan terhadap RBL-2H3 dalam masa 24, 48, dan 72 jam, manakala kepekatan yang lebih tinggi (10μM) menunjukkan ketoksikan yang ketara. Untuk model *in vitro* imunoglobulin E (IgE)- pengantara degranulasi sel, RBL-2H3 sel sensitif-anti-dinitrofenil monoklonal (DNP)-IgE telah dirawat terlebih dahulu dengan α-CD/MG sebelum dicabar dengan albumin serum dinitrofenil-bovine untuk mengaruh degranulasi. Aktiviti anti-alergik kompleks tersebut dan fumarat ketotifen sebagai kawalan positif telah dinilai bagi fasa reaksi alergik awal dan lewat. Fasa awal ditentukan berdasarkan perencatan beta-heksosaminidas (β-

hexosaminidase) dan pelepasan histamina; manakala fasa lewat berdasarkan perencatan interleukin (IL-4), alfa-faktor nekrosis tumor (TNF-α), dan pelepasan prostaglandin D_2 (PGD_2). Yang menariknya, keputusan menunjukkan bahawa α-CD/MG secara signifikan merencat degranulasi sel mast melalui perencatan beta-heksosaminidas dan pelepasan histamina pada fasa awal pada kepekatan (5, 2.5μM) dan (5, 2.5, 1.25 dan 0.625 μM) pada $p<0.005$. Begitu juga, 5, 2.5, 1.25 dan, 0.625μM bagi α-CD/MG secara ketara merencat TNF-α dan PGD_2 ($p<0.001$) pada fasa lewat. Manakala IL-4 secara ketara direncat pada kepekatan (5, 2.5 dan 0.625 μM) ($p< 0.001$) berbanding dengan kawalan negatif. Oleh itu, kajian ini mengesyorkan α-CD/MG berpotensi mempunyai aktiviti anti-alergik dengan merencat reaksi alergik bagi kedua-dua fasa awal dan lewat.

Kata kunci: Anti-alergik; moringin alfa-siklodektrin; RBL-2H3; histamina; PGD_2; *β*-hexosaminidase; TNF-α; IL-4.

SDG: MATLAMAT 4: Pendidikan Berkualiti, MATLAMAT 3: Kesihatan dan Kesejahteraan Yang Baik.

ACKNOWLEDGEMENTS

First, my praises and thanks to Almighty Allah, the most merciful and the highest, for His showers of blessings throughout my research to its successful completion.

I would like to extend my deepest and sincerest gratitude to my mentor, supervisor, and advisor, Associate Professor Dr Ahmad Faizal Bin Abdull Razis, for his generous guidance, tolerance, patience, interest, and support throughout my research.

My thanks and gratitude to my co-supervisor, Associate Professor Dr Tham Chau Ling as well as Universiti Putra Malaysia and its Institute of Bioscience.

I am extremely grateful to my father and mother, who have been supportive, prayerful, and optimistic about my success. I am also very thankful to my uncle, husband, sons, brothers, and sisters. I would like to extend my gratitude to my lab mates for their moral support throughout my entire stay in the lab

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

Ahmad Faizal bin Abdull Razis, PhD
Associate Professor
Faculty of Food Science and Technology
Universiti Putra Malaysia
(Chairman)

Tham Chau Ling, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

ZALILAH MOHD SHARIFF, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 08 August 2024

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

AD	Allergic diseases
AIT	Allergen-specific immunotherapy
AKT	Protein kinase B
AP-1	Activator protein-1
AR	Allergy rhinitis
ARE	Antioxidant response element
ATRs	Allergic transfusion reactions
BAL fluid	Bronchoalveolar lavage (BAL) fluid
C/EBP	CCAAT/enhancer binding proteins
COX2	Cyclooxygenase-2
CREB	cAMP-response element binding protein
D_2O	Deuterium oxide
DMSO	Dimethyl sulfoxide
DNP IgE	Monoclonal anti-dinitrophenyl (DNP) IgE antibody produced in mouse
DNP-BSA	Dinitrophenyl-bovine serum albumin
ERK½	Extracellular signal-regulated protein kinase ½
FA	Food allergy
FBS	Foetal bovine serum
FcRI	High-affinity IgE receptor (FcRI)
FcεRI	Fc receptor for IgE
GINA	Global Initiative for Asthma
GSH	Glutathione
HMC-1	Human mast cell-1

HO-1	Heme oxygenase-1
IAV	Influenza A virus
IFN-g	Interferon-g (IFN-g)
IFN-Ɣ	Interferon gamma
IgE	Immunoglobulin E
IkB	Inhibitor nuclear factor Kappa B
IL-12a	Interleukin-12a
IL-17A and IL-17 receptor A	Interleukin-17A (IL-17A) and IL-17 receptor A (IL-17RA)
IL-1β	Interleukin-1β
IL-4, 6, 8, 12, 13, 17, 22, 23, and 27	Interleukin-4, 6, 8, 12, 13, 17, 22, 23 and 27
ITC	Isothiocyanate
JAK2	Janus kinase
JNK	c-jun NH2-terminal kinases
KEAP1	Kelch-like ECH-associated protein 1
LPS	Lipopolysaccharide
MAPK	Mitogen-activated protein kinases (MAPK)
MEM	Minimum essential media with Earle's salts and L-glutamine and sodium pyruvate
MHC II	Histocompatibility complex (MHC II)
MTS	(3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H tetrazolium, inner salt) assay
NADPH	Nicotinamide adenine di nucleotide phosphate
NF-κB	Nuclear factor of Kappa- light- chain- enhancer of activated B cells
NO	Nitric oxide

NQO-1	Quinone oxidoreductase 1
Nrf2	Nuclear factor (erythroid-derived 2)-l
OVA	Egg ovalbumin
P65	Phosphorylation 65
PBS	Phosphate buffer saline
PGE_2	Prostaglandin E_2
PMACI	Phorbol 12-myristate 13-acetate and the calcium ionophore A23187
RBL-2H3	Rat basophilic leukaemia
ROS	Reactive oxygen species
RT-PCR	Real time-polymerase chain reaction
SCID	Severe combined immunodeficiency disease
STAT3	Signal transducer and activator of transcription 3
TCR_S	T cell receptors
Th1 and Th2	T helper type 1 and T helper type 2
TLR4	Toll-like receptor 4
TNF-α	Tumour necrosis factor-alpha
TSLP	Thymic stromal lymphopoietin
TSP	Trimethylsilylpropanoic acid
WAO	World Allergy Organization

CHAPTER 1

INTRODUCTION

1.1 Background of the Study

Allergic diseases (AD) is an inappropriate hypersensitive reaction to antigen(s). Over the past few years, the number of AD in the public has increased. According to World Health Organization (WHO), AD affects 30 to 40% of the global population which, in turn, significantly affects global health and medical services as well as the economy of some nations (Biagioni et al., 2020). The prevalence of AD has increased globally due to factors such as indoor and outdoor allergens, air pollution, and changing environmental conditions. Allergies affect individuals of all ages and can lead to health issues, particularly in children (Mwakalukwa et al., 2019). AD such as bronchial asthma and allergy disorders are life-threatening. Approximately 420, 000 people died of asthma every year, meaning that a little over 1000 people died of asthma every day. As such, in 2019, the activities of the World Allergy Organization (WAO) and Global Initiative for Asthma (GINA) focused on life-threatening pathological illnesses (Hossny et al., 2019)(Gumeniuk et al., 2020).

Allergies result from abnormal immune responses to specific substances like foods, pollen, and animal dander. Types of AD have different induction mechanisms and symptoms. Type I AD, caused by mast cells and basophils, is the most common (Lei et al., 2021). There is a rising prevalence of type I hypersensitivity-related conditions like food allergies, allergic rhinitis, and asthma. These conditions are characterized by symptoms such as sneezing, tissue swelling, and erythema. Mast cells, found in various tissues, are involved in allergic reactions. Mast cells play a crucial role in type I AD by releasing histamine and other mediators. They degranulated in response to different stimuli (Subramanian et al., 2019). In type I AD, allergens bind to IgE on mast cells, triggering degranulation and the release of inflammatory substances (Xiaolei et al., 2018). Allergic reactions can be categorized into early and late-phase reactions, involving the release of histamine, granule proteins, leukotrienes, prostaglandins, and cytokines from activated mast cells (Tan et al., 2017).

The current clinical guidelines suggest a comprehensive treatment approach that includes patient education, allergen avoidance, pharmacotherapy, and allergy immunotherapy. Despite the availability of safe and affordable drugs for treating allergic symptoms, a considerable number of patients express dissatisfaction with the level of symptom relief achieved (Larsen et al., 2016). Molecular and clinical studies guide the management of allergic inflammation, with anti-allergic medications developed to inhibit inflammation. Treatment should be tailored to the specific type of allergic inflammation. Certain natural food components, like flavonoids and polyphenols, which have anti-inflammatory or antioxidant properties, have been found to decrease allergy symptoms (Han et al., 2017). Phytochemicals like sulforaphane (SFN) derived from cruciferous vegetables are used to alleviate symptoms of allergic dermatitis (AD) (Jeon et al., 2020). SFN inhibits caspase-1 activation, mitogen-activated protein kinases (MAPK), and nuclear factor of Kappa-

light-chain-enhancer of activated B cells (NF-κB) signalling pathways, reducing inflammatory cytokines. SFN also decreases the expression of interleukin-1β (IL-1β), cyclooxygenase-2 (COX-2), tumour necrosis factor-alpha (TNF-α), and inducible nitric oxide synthase (iNOS) in macrophages (N. R. Han et al., 2018; Yehuda et al., 2012) Phenethyl isothiocyanate (PEITC) and 6-(methylsulfinyl) hexyl isothiocyanate (6-MSITC) were studied for their impact on mast cells. PEITC reduced IL-13 and TNF-α levels while increasing thymic stromal lymphopoietin (TSLP). 6-MSITC decreased COX-2, cytokine production, and inhibited iNOS, key mediators of inflammation. These findings highlight the potential of phytochemicals in managing inflammatory responses in mast cells and AD (Uto et al., 2012). The anti-allergy effect of alpha-cyclodextrin moringin (α-CD/MG) relies on its suppression of mast cell degranulation. Therefore, this present study assesses the anti-allergy activity of α-CD/MG on rat basophilic leukaemia cells (RBL-2H3) stimulated by dinitrophenyl-IgE/bovine serum albumin (DNP-IgE/BSA).

1.2 Problem Statement

Allergy reactions are becoming more common over time. The responses can be as minor as a rash or as serious as anaphylactic shock, which can be fatal. Following allergen contact, mast cells degranulated, producing mediators that cause allergic symptoms. *Moringa oleifera* Lam is a tropical plant widely used in traditional medicines and possesses antioxidant, antimicrobial, and anti-inflammation properties (Abd Rani et al., 2019). Its beneficial effects are believed due to the presence of isothiocyanate (ITC), which is known as moringin (MG). The plant also has been traditionally used to alleviate allergic conditions; however, the bioactive compound in the form of alpha-cyclodextrin moringin (α-CD/MG) complex and its anti-allergic effects remain unexplored.

1.3 Significance of the Study

This present study is significant due to the following reasons:

a. Apart from the known effects of α-CD/MG, this study describes its effect on the suppression of the early- and late-phases of allergies.

b. Although α-CD/MG from *M. oleifera* seed is rich in glucosinolate and ITC, its *in vitro* anti-allergy activity has not been examined.

c. This present study thoroughly examines the therapeutic impact of α-CD/MG on common health issues, especially its *in vitro* anti-allergy activity via the modulation of histamine, β-hexosaminidase, IL-4, TNF-α, and prostaglandin D_2 (PGD_2).

1.4 Research Hypothesis

1.4.1 Null hypothesis (Ho)

Alpha-cyclodextrin moringin (α-CD/MG) isolated from *M. oleifera* does not show anti-allergy activity in *in vitro* model of allergic disease.

1.4.2 Alternate Hypothesis (H_A)

Alpha-cyclodextrin moringin (α-CD/MG) isolated from *M. oleifera* has anti-allergy activity in *in vitro* model of allergic disease.

1.5 Research Objectives

1.5.1 General Objective

To evaluate the *in vitro* anti-allergic activity of α-CD/MG and mechanism through which it elicits the anti-allergic effect on RBL-2H3.

1.5.2 Specific Objectives

a. To elucidate the characterization of α-CD/MG by using NMR

b. To determine the cytotoxicity effect of α-CD/MG on the RBL-2H3 cell line.

c. To evaluate the anti-allergic effect of α-CD/MG on RBL-2H3 for early and late phases of the allergic reactions.

REFERENCES

Abd Rani, N. Z., Kumolosasi, E., Jasamai, M., Jamal, J. A., Lam, K. W., & Husain, K. (2019). In vitro anti-allergic activity of Moringa oleifera Lam. extracts and their isolated compounds. *BMC Complementary and Alternative Medicine*, *19*(1), 1–16. https://doi.org/10.1186/s12906-019-2776-1

Ahmed, K. S., Jahan, I. A., Jahan, F., & Hossain, H. (2021). Antioxidant activities and simultaneous HPLC-DAD profiling of polyphenolic compounds from moringa oleifera lam. Leaves grown in Bangladesh. *Food Research*, *5*(1), 401–408. https://doi.org/10.26656/fr.2017.5(1).410

Al-Harbi, N. O., Nadeem, A., Ahmad, S. F., AlThagfan, S. S., Alqinyah, M., Alqahtani, F., Ibrahim, K. E., & Al-Harbi, M. M. (2019). Sulforaphane treatment reverses corticosteroid resistance in a mixed granulocytic mouse model of asthma by upregulation of antioxidants and attenuation of Th17 immune responses in the airways. *European Journal of Pharmacology*, *855*(April), 276–284. https://doi.org/10.1016/j.ejphar.2019.05.026

Alphonsine, R.-T., Moumouni, K., Nabere, O., Marius, L., & Innocent, P. G. (2019). A comparative study of phytochemical profile and antioxidant activity of Sahelian plants used in the treatment of infectious diseases in northern part of Burkina Faso: Acacia seyal Delile and Acacia tortilis (Forssk.) Hayne subsp. raddiana (Savi). *Journal of Pharmacognosy and Phytotherapy*, *11*(3), 74–79. https://doi.org/10.5897/jpp2019.0555

Amore, E., Manca, M. L., Ferraro, M., Valenti, D., La Parola, V., Di Vincenzo, S., Gjomarkaj, M., Giammona, G., Bondì, M. L., & Pace, E. (2019). Salmeterol Xinafoate (SX) loaded into mucoadhesive solid lipid microparticles for COPD treatment. *International Journal of Pharmaceutics*, *562*(March), 351–358. https://doi.org/10.1016/j.ijpharm.2019.03.059

Anderson, H. M., Lemanske, R. F., Evans, M. D., Gangnon, R. E., Pappas, T., Grindle, K., Bochkov, Y. A., Gern, J. E., & Jackson, D. J. (2017). Assessment of wheezing frequency and viral etiology on childhood and adolescent asthma risk. *Journal of Allergy and Clinical Immunology*, *139*(2), 692–694. https://doi.org/10.1016/j.jaci.2016.07.031

Anderson, S. D. (2018). Repurposing drugs as inhaled therapies in asthma. *Advanced Drug Delivery Reviews*, *133*, 19–33. https://doi.org/10.1016/j.addr.2018.06.006

Ayed, K., Hadi Khalifa, I. L., Mokaddem, S., & Ben Khamsa Jameleddine, S. (2020). Paradoxical bronchoconstriction caused by β2-adrenoceptor agonists. *Drug Target Insights*, *14*(1), 12–15. https://doi.org/10.33393/dti.2020.2188

Azeem, M., Kader, H., Kerstan, A., Hetta, H. F., Serfling, E., Goebeler, M., & Muhammad, K. (2020). Intricate relationship between adaptive and innate immune system in allergic contact dermatitis. *Yale Journal of Biology and Medicine*, *93*(5), 699–709.

Baldo, B. A., & Pham, N. H. (2013). Drug allergy: Clinical aspects, diagnosis, mechanisms, structure-activity relationships. *Drug Allergy: Clinical Aspects, Diagnosis, Mechanisms, Structure-Activity Relationships*, *9781461472*, 1–447. https://doi.org/10.1007/978-1-4614-7261-2

Bao, Y., Xiao, J., Weng, Z., Lu, X., Shen, X., & Wang, F. (2020). A phenolic glycoside from Moringa oleifera Lam. improves the carbohydrate and lipid metabolisms through AMPK in db/db mice. *Food Chemistry*, *311*(December 2019), 125948. https://doi.org/10.1016/j.foodchem.2019.125948

Basu, S., & Banik, B. K. (2018). Hypersensitivity : An Overview. *Immunol Curr Res*, *2*(1), 2–3.

Berni Canani, R., Di Costanzo, M., Bedogni, G., Amoroso, A., Cosenza, L., Di Scala, C., Granata, V., & Nocerino, R. (2017). Extensively hydrolyzed casein formula containing Lactobacillus rhamnosus GG reduces the occurrence of other allergic manifestations in children with cow's milk allergy: 3-year randomized controlled trial. *Journal of Allergy and Clinical Immunology*, *139*(6), 1906-1913.e4. https://doi.org/10.1016/j.jaci.2016.10.050

Biagioni, B., Annesi-Maesano, I., D'Amato, G., & Cecchi, L. (2020). The rising of allergic respiratory diseases in a changing world: from climate change to migration. *Expert Review of Respiratory Medicine*, *0*(0). https://doi.org/10.1080/17476348.2020.1794829

Boo, Y. C. (2020). Natural Nrf2 modulators for skin protection. *Antioxidants*, *9*(9), 1–31. https://doi.org/10.3390/antiox9090812

Boyanapalli, S. S. S., Paredes-Gonzalez, X., Fuentes, F., Zhang, C., Guo, Y., Pung, D., Saw, C. L. L., & Kong, A. N. T. (2014). Nrf2 knockout attenuates the anti-inflammatory effects of phenethyl isothiocyanate and curcumin. *Chemical Research in Toxicology*, *27*(12), 2036–2043. https://doi.org/10.1021/tx500234h

Cardozo, L. F. M. F., Alvarenga, L. A., Ribeiro, M., Dai, L., Shiels, P. G., Stenvinkel, P., Lindholm, B., & Mafra, D. (2020). Cruciferous vegetables: rationale for exploring potential salutary effects of sulforaphane-rich foods in patients with chronic kidney disease. *Nutrition Reviews*, *00*(0), 1–21. https://doi.org/10.1093/nutrit/nuaa129

Cassia, L., Ulmus, L., Lee, E. K., Song, J., Seo, Y., Koh, E. M., & Kim, S. (n.d.). *molecules Inhibitory E ff ects of AF-343 , a Mixture of Responses in RBL-2H3 Cells*. 1–12.

Cedrowski, J., Dąbrowa, K., Przybylski, P., Krogul-Sobczak, A., & Litwinienko, G. (2021). Antioxidant activity of two edible isothiocyanates: sulforaphane and erucin is due to their thermal decomposition to sulfenic acids and methylsulfinyl radicals. *Food Chemistry*, *353*, 129213. https://doi.org/10.1016/j.foodchem.2021.129213

Chang, C., Leung, P. S. C., Todi, S., & Zadoorian, L. (2019). Definition of Allergens: Inhalants, Food, and Insects Allergens. In *Allergy and Asthma*. https://doi.org/10.1007/978-3-319-58726-4_3-1

Chen, G. L., Xu, Y. B., Wu, J. L., Li, N., & Guo, M. Q. (2020). Hypoglycemic and hypolipidemic effects of Moringa oleifera leaves and their functional chemical constituents. *Food Chemistry*, *333*(June). https://doi.org/10.1016/j.foodchem.2020.127478

Cherrez Ojeda, I., Vanegas, E., Felix, M., Mata, V., Cherrez, S., Simancas-Racines, D., Greiding, L., Cano, J., Cherrez, A., & Calderon, J. C. (2018). Etiology of chronic urticaria: The Ecuadorian experience. *World Allergy Organization Journal*, *11*(1), 1–8. https://doi.org/10.1186/s40413-017-0181-0

Cheung, K. L., Khor, T. O., & Kong, A. N. (2009). Synergistic effect of combination of phenethyl isothiocyanate and sulforaphane or curcumin and sulforaphane in the inhibition of inflammation. *Pharmaceutical Research*, *26*(1), 224–231. https://doi.org/10.1007/s11095-008-9734-9

Chhikara, N., Kaur, A., Mann, S., Garg, M. K., Sofi, S. A., & Panghal, A. (2021). Bioactive compounds, associated health benefits and safety considerations of Moringa oleifera L.: an updated review. *Nutrition and Food Science*, *51*(2), 255–277. https://doi.org/10.1108/NFS-03-2020-0087

Cho, H. J., Lee, K. W., & Yoon Park, J. H. (2013). Erucin exerts anti-inflammatory properties in murine macrophages and mouse skin: Possible mediation through the inhibition of NFκB signaling. *International Journal of Molecular Sciences*, *14*(10), 20564–20577. https://doi.org/10.3390/ijms141020564

Chodur, G. M., Olson, M. E., Wade, K. L., Stephenson, K. K., Nouman, W., Garima, & Fahey, J. W. (2018). Wild and domesticated Moringa oleifera differ in taste, glucosinolate composition, and antioxidant potential, but not myrosinase activity or protein content. *Scientific Reports*, *8*(1), 1–10. https://doi.org/10.1038/s41598-018-26059-3

Choi, Y. J., Lee, W. S., Lee, E. G., Sung, M. S., & Yoo, W. H. (2014). Sulforaphane Inhibits IL-1β-Induced Proliferation of Rheumatoid Arthritis Synovial Fibroblasts and the Production of MMPs, COX-2, and PGE2. *Inflammation*, *37*(5), 1496–1503. https://doi.org/10.1007/s10753-014-9875-4

Chung, H. Y., Hsieh, C. J., Tseng, C. C., & Yiin, L. M. (2016). Association between the first occurrence of allergic rhinitis in preschool children and air pollution in taiwan. *International Journal of Environmental Research and Public Health*, *13*(3), 6–12. https://doi.org/10.3390/ijerph13030268

Church, M. K., & Labeaga, L. (2017). Bilastine: a new H1-antihistamine with an optimal profile for updosing in urticaria. *Journal of the European Academy of Dermatology and Venereology*, *31*(9), 1447–1452. https://doi.org/10.1111/jdv.14305

de Figueiredo, S., Binda, N., Nogueira-Machado, J., Vieira-Filho, S., & Caligiorne, R. (2015). The Antioxidant Properties of Organosulfur Compounds (Sulforaphane). *Recent Patents on Endocrine, Metabolic & Immune Drug Discovery*, *9*(1), 24–39. https://doi.org/10.2174/1872214809666150505164138

Dey, M., Ribnicky, D., Kurmukov, A. G., & Raskin, I. (2006). In vitro and in vivo anti-inflammatory activity of a seed preparation containing phenethylisothiocyanate. *Journal of Pharmacology and Experimental Therapeutics*, *317*(1), 326–333. https://doi.org/10.1124/jpet.105.096511

Ding, Z., Li, X., Lu, Y., Rong, G., Yang, R., Zhang, R., Wang, G., Wei, X., Ye, Y., Qian, Z., Liu, H., Zhu, D., Zhou, R., Zhu, K., Ni, R., Xia, K., Luo, N., & Pei, C. (2016). A randomized, controlled multicentric study of inhaled budesonide and intravenous methylprednisolone in the treatment on acute exacerbation of chronic obstructive pulmonary disease. *Respiratory Medicine*, *121*, 39–47. https://doi.org/10.1016/j.rmed.2016.10.013

Eckl-Dorna, J., Villazala-Merino, S., Linhart, B., Karaulov, A. V., Zhernov, Y., Khaitov, M., Niederberger-Leppin, V., & Valenta, R. (2019). Allergen-specific antibodies regulate secondary allergen-specific immune responses. *Frontiers in Immunology*, *10*(JAN), 1–15. https://doi.org/10.3389/fimmu.2018.03131

Eisa, N. H., Khodir, A. E., El-Sherbiny, M., Elsherbiny, N. M., & Said, E. (2021). Phenethyl isothiocyanate attenuates diabetic nephropathy via modulation of glycative/oxidative/inflammatory signaling in diabetic rats. *Biomedicine and Pharmacotherapy*, *142*(April), 111666. https://doi.org/10.1016/j.biopha.2021.111666

El-Sharnoby, M. M., Ali, A. A.-E., Omar, H. H., Eldin Habib, M., & Hasanin Salama, H. (2017). Study of the role of allergy diagnosed by immunoglobulin E in the etiology of pediatric otitis media with effusion. *Menoufia Medical Journal*, *30*(1), 151. https://doi.org/10.4103/mmj.mmj_245_16

Fard, M., Arulselvan, P., Karthivashan, G., Adam, S., & Fakurazi, S. (2015). Bioactive extract from moringa oleifera inhibits the pro-inflammatory mediators in lipopolysaccharide stimulated macrophages. *Pharmacognosy Magazine*, *11*(44), 556. https://doi.org/10.4103/0973-1296.172961

Feltis, B. N., Elbaz, A., Wright, P. F. A., Mackay, G. A., Turney, T. W., & Lopata, A. L. (2015). Characterizing the inhibitory action of zinc oxide nanoparticles on allergic-type mast cell activation. *Molecular Immunology*, *66*(2), 139–146. https://doi.org/10.1016/j.molimm.2015.02.021

Fernandes, Â., Bancessi, A., Pinela, J., Dias, M. I., Liberal, Â., Calhelha, R. C., Ćirić, A., Soković, M., Catarino, L., Ferreira, I. C. F. R., & Barros, L. (2021). Nutritional and phytochemical profiles and biological activities of Moringa oleifera Lam. edible parts from Guinea-Bissau (West Africa). *Food Chemistry*, *341*(August 2020), 128229. https://doi.org/10.1016/j.foodchem.2020.128229

Flora, S. J. S., & Pachauri, V. (2011). Moringa (Moringa oleifera) Seed Extract and the Prevention of Oxidative Stress. In *Nuts and Seeds in Health and Disease Prevention*. Elsevier Inc. https://doi.org/10.1016/B978-0-12-375688-6.10092-1

Franklin, P. H., Liu, N. C., & Ladlow, J. F. (2021). Nebulization of epinephrine to reduce the severity of brachycephalic obstructive airway syndrome in dogs. *Veterinary Surgery*, *50*(1), 62–70. https://doi.org/10.1111/vsu.13523

Fritz, I., Wagner, P., Broberg, P., Einefors, R., & Olsson, H. (2020). Desloratadine and loratadine stand out among common H1-antihistamines for association with improved breast cancer survival. *Acta Oncologica*, *59*(9), 1103–1109. https://doi.org/10.1080/0284186X.2020.1769185

Fu, S., Ni, S., Wang, D., Fu, M., & Hong, T. (2019). Berberine suppresses mast cell-mediated allergic responses via regulating FcεRI-mediated and MAPK signaling. *International Immunopharmacology*, *71*(October 2018), 1–6. https://doi.org/10.1016/j.intimp.2019.02.041

Fu, S., Ni, S., Wang, D., & Hong, T. (2018). Coptisine suppresses mast cell degranulation and ovalbumin-induced allergic rhinitis. *Molecules*, *23*(11). https://doi.org/10.3390/molecules23113039

Gao, W., Zan, Y., Wang, Z. J. J., Hu, X. Y., & Huang, F. (2016). Quercetin ameliorates paclitaxel-induced neuropathic pain by stabilizing mast cells, and subsequently blocking PKCϵ-dependent activation of TRPV1. *Acta Pharmacologica Sinica*, *37*(9), 1166–1177. https://doi.org/10.1038/aps.2016.58

Geisel, J., Brück, J., Glocova, I., Dengler, K., Sinnberg, T., Rothfuss, O., Walter, M., Schulze-Osthoff, K., Röcken, M., & Ghoreschi, K. (2014). Sulforaphane Protects from T Cell–Mediated Autoimmune Disease by Inhibition of IL-23 and IL-12 in Dendritic Cells. *The Journal of Immunology*, *192*(8), 3530–3539. https://doi.org/10.4049/jimmunol.1300556

Giacoppo, S., Iori, R., Rollin, P., Bramanti, P., & Mazzon, E. (2017). Moringa isothiocyanate complexed with α-cyclodextrin: A new perspective in neuroblastoma treatment. *BMC Complementary and Alternative Medicine*, *17*(1), 1–10. https://doi.org/10.1186/s12906-017-1876-z

Giacoppo, S., Rajan, T. S., Iori, R., Rollin, P., Bramanti, P., & Mazzon, E. (2017). The α-cyclodextrin complex of the Moringa isothiocyanate suppresses lipopolysaccharide-induced inflammation in RAW 264.7 macrophage cells through Akt and p38 inhibition. *Inflammation Research*, *66*(6), 487–503. https://doi.org/10.1007/s00011-017-1033-7

González-Deolano, D., & Álvarez-Twose, I. (2018). Mast cells as key players in allergy and inflammation. *Journal of Investigational Allergology and Clinical Immunology*, *28*(6), 365–378. https://doi.org/10.18176/jiaci.0327

Gumeniuk, G. L., Zaikov, S. V., & Opimakh, S. G. (2020). World Asthma Day and World Allergy Week 2020: the Challenge To Save Lives. *Asthma and Allergy*, *2*, 27–34. https://doi.org/10.31655/2307-3373-2020-2-27-34

Gupta, S. K., Kumar, B., Srinivasan, B. P., Nag, T. C., Srivastava, S., Saxena, R., & Aggarwal, A. (2013). Retinoprotective effects of Moringa oleifera via antioxidant, anti-inflammatory, and anti-angiogenic mechanisms in streptozotocin-induced diabetic rats. *Journal of Ocular Pharmacology and Therapeutics*, *29*(4), 419–426. https://doi.org/10.1089/jop.2012.0089

Han, N. R., Moon, P. D., Ryu, K. J., Kim, H. M., & Jeong, H. J. (2018). Phenethyl isothiocyanate decreases thymic stromal lymphopoietin-induced inflammatory reactions in mast cells. *Journal of Food Biochemistry*, *42*(1), 1–7. https://doi.org/10.1111/jfbc.12449

Han, S., Sun, L., He, F., & Che, H. (2017). Anti-Allergic activity of glycyrrhizic acid on IgE-mediated allergic reaction by regulation of allergy-related immune cells. *Scientific Reports*, *7*(1), 1–9. https://doi.org/10.1038/s41598-017-07833-1

Haodang, L., Lianmei, Q., Ranhui, L., Liesong, C., Jun, H., Yihua, Z., Cuiming, Z., Yimou, W., & Xiaoxing, Y. (2019). HO-1 mediates the anti-inflammatory actions of Sulforaphane in monocytes stimulated with a mycoplasmal lipopeptide. *Chemico-Biological Interactions*, *306*(March), 10–18. https://doi.org/10.1016/j.cbi.2019.04.007

Hiemori-Kondo, M., Morikawa, E., Fujikura, M., Nagayasu, A., & Maekawa, Y. (2021). Inhibitory effects of cyanidin-3-O-glucoside in black soybean hull extract on RBL-2H3 cells degranulation and passive cutaneous anaphylaxis reaction in mice. *International Immunopharmacology*, *94*(February), 107394. https://doi.org/10.1016/j.intimp.2021.107394

Ho, J. N., Kang, E. R., Yoon, H. G., Jeon, H., Jun, W., Watson, R. R., & Lee, J. (2011). Inhibition of premature death by isothiocyanates through immune restoration in LP-BM5 leukemia retrovirus-infected C57BL/6 Mice. *Bioscience, Biotechnology and Biochemistry*, *75*(7), 1234–1239. https://doi.org/10.1271/bbb.100840

Hossny, E., Ebisawa, M., El-Gamal, Y., Arasi, S., Dahdah, L., El-Owaidy, R., Galvan, C. A., Lee, B. W., Levin, M., Martinez, S., Pawankar, R., Tang, M. L. K., Tham, E. H., & Fiocchi, A. (2019). Challenges of managing food allergy in the developing world. *World Allergy Organization Journal*, *12*(11), 100089. https://doi.org/10.1016/j.waojou.2019.100089

Hu, Y., Xu, Z., Jiang, F., Li, S., Liu, S., Wu, M., Yan, C., Tan, J., Yu, G., Hu, Y., Yin, Y., & Tong, S. (2020). Relative impact of meteorological factors and air pollutants on childhood allergic diseases in Shanghai, China. *Science of the Total Environment*, *706*. https://doi.org/10.1016/j.scitotenv.2019.135975

Huang, C. Z., Jiang, Z. H., Wang, J., Luo, Y., & Peng, H. (2019). Antihistamine effects and safety of fexofenadine: A systematic review and Meta-analysis of randomized

controlled trials. *BMC Pharmacology and Toxicology*, *20*(1), 1–18. https://doi.org/10.1186/s40360-019-0363-1

Huang, P. Y., Huang, Y. H., Guo, M. M. H., Chang, L. S., & Kuo, H. C. (2021). Kawasaki Disease and Allergic Diseases. *Frontiers in Pediatrics*, *8*(January), 1–8. https://doi.org/10.3389/fped.2020.614386

Jaafaru, M. S., Nordin, N., Shaari, K., Rosli, R., & Abdull Razis, A. F. (2018). Isothiocyanate from Moringa oleifera seeds mitigates hydrogen peroxide-induced cytotoxicity and preserved morphological features of human neuronal cells. *PLoS ONE*, *13*(5), 1–17. https://doi.org/10.1371/journal.pone.0196403

Janson, C. (2020). Treatment with inhaled corticosteroids in chronic obstructive pulmonary disease. *Journal of Thoracic Disease*, *12*(4), 1561–1569. https://doi.org/10.21037/jtd.2020.02.51

Jarosz, M., Syed, S., Błachut, M., & Badura Brzoza, K. (2020). Emotional distress and quality of life in allergic diseases. *Wiadomosci Lekarskie (Warsaw, Poland : 1960)*, *73*(2), 370–373. https://doi.org/10.36740/wlek202002131

Jeon, M., Lee, J., Lee, H. K., Cho, S. J., Lim, J. H., Choi, Y., Pak, S., & Jeong, H. J. (2020). Sulforaphane mitigates mast cell-mediated allergic inflammatory reactions in in silico simulation and in vitro models. *Immunopharmacology and Immunotoxicology*, *42*(2), 74–83. https://doi.org/10.1080/08923973.2020.1724141

Jo, W. R., & Park, H. J. (2017). Antiallergic effect of fisetin on IgE-mediated mast cell activation in vitro and on passive cutaneous anaphylaxis (PCA). *Journal of Nutritional Biochemistry*, *48*, 103–111. https://doi.org/10.1016/j.jnutbio.2017.06.010

Kee, J. Y., & Hong, S. H. (2019). Ginsenoside Rg3 suppresses mast cell–mediated allergic inflammation via mitogen-activated protein kinase signaling pathway. *Journal of Ginseng Research*, *43*(2), 282–290. https://doi.org/10.1016/j.jgr.2018.02.008

Kim, M., Kim, S. Y., Randy, A., Lim, S. J., Dorjsembe, B., & Nho, C. W. (2016). Inhibitory effect of the Larix sibirica and its various flavonoids on the IgE-stimulated mast cell activation and anaphylaxis. *Journal of Functional Foods*, *27*, 631–644. https://doi.org/10.1016/j.jff.2016.10.009

Kong, Z. L., Sudirman, S., Lin, H. J., & Chen, W. N. (2020). In vitro anti-inflammatory effects of curcumin on mast cell-mediated allergic responses via inhibiting FcεRI protein expression and protein kinase C delta translocation. *Cytotechnology*, *72*(1), 81–95. https://doi.org/10.1007/s10616-019-00359-6

Larsen, J. N., Broge, L., & Jacobi, H. (2016). Allergy immunotherapy: The future of allergy treatment. *Drug Discovery Today*, *21*(1), 26–37. https://doi.org/10.1016/j.drudis.2015.07.010

Lee, Y. M., Kim, J., & Kim, J. (2011). *1, * 1, * 1. 14*(4), 377–385.

Lei, W., Liu, C., Pan, L., Peng, C., Wang, J., & Zhou, H. (2021). Screening of probiotic Lactobacilli with potential anti-allergic activity based on hyaluronidase inhibition and degranulation of RBL-2H3 cells in vitro. *Lwt*, *140*(1), 110707. https://doi.org/10.1016/j.lwt.2020.110707

Leone, A., Bertoli, S., Di Lello, S., Bassoli, A., Ravasenghi, S., Borgonovo, G., Forlani, F., & Battezzati, A. (2018). Effect of moringa oleifera leaf powder on postprandial blood glucose response: In vivo study on saharawi people living in refugee camps. *Nutrients*, *10*(10), 1–14. https://doi.org/10.3390/nu10101494

Li, Q., Zhan, S., Liu, Q., Su, H., Dai, X., Wang, H., Beng, H., & Tan, W. (2018). Preparation of a Sustained-Release Nebulized Aerosol of R-terbutaline Hydrochloride Liposome and Evaluation of Its Anti-asthmatic Effects via Pulmonary Delivery in Guinea Pigs. *AAPS PharmSciTech*, *19*(1), 232–241. https://doi.org/10.1208/s12249-017-0816-z

Lin, P., Cao, M., Xia, F., Liao, H., Sun, H., Wang, Q., Lee, J., Zhou, Y., Guan, Y., Zhang, C., Xu, Z., Li, F., Wei, J. F., & Ling, D. (2021). A Phosphatase-Mimetic Nano-Stabilizer of Mast Cells for Long-Term Prevention of Allergic Disease. *Advanced Science*, *8*(8), 1–7. https://doi.org/10.1002/advs.202004115

Lohning, A., Kidachi, Y., Kamiie, K., Sasaki, K., Ryoyama, K., & Yamaguchi, H. (2021). 6-(methylsulfinyl)hexyl isothiocyanate (6-MITC) from Wasabia japonica alleviates inflammatory bowel disease (IBD) by potential inhibition of glycogen synthase kinase 3 beta (GSK-3β). *European Journal of Medicinal Chemistry*, *216*, 113250. https://doi.org/10.1016/j.ejmech.2021.113250

Lopez-Rodriguez, N. A., Gaytán-Martínez, M., de la Luz Reyes-Vega, M., & Loarca-Piña, G. (2020). Glucosinolates and Isothiocyanates from Moringa oleifera: Chemical and Biological Approaches. *Plant Foods for Human Nutrition*, *75*(4), 447–457. https://doi.org/10.1007/s11130-020-00851-x

Lorz, L. R., Kim, D., Kim, M. Y., & Cho, J. Y. (2020). Panax ginseng–derived fraction BIOGF1K reduces atopic dermatitis responses via suppression of mitogen-activated protein kinase signaling pathway. *Journal of Ginseng Research*, *44*(3), 453–460. https://doi.org/10.1016/j.jgr.2019.02.003

Luetragoon, T., Sranujit, R. P., Noysang, C., Thongsri, Y., Potup, P., Somboonjun, J., Maichandi, N., Suphrom, N., Sangouam, S., & Usuwanthim, K. (2021). Evaluation of anti-inflammatory effect of moringa oleifera lam. And cyanthillium cinereum (less) h. rob. lozenges in volunteer smokers. *Plants*, *10*(7). https://doi.org/10.3390/plants10071336

Lv, C., Zhang, Y., Zou, L., Sun, J., Song, X., Mao, J., & Wu, Y. (2021). Simultaneous Hydrolysis and Extraction Increased Erucin Yield from Broccoli Seeds. *ACS Omega*, *6*(9), 6385–6392. https://doi.org/10.1021/acsomega.0c06319

Ma, N., Tang, Q., Wu, W. T., Huang, X. A., Xu, Q., Rong, G. L., Chen, S., & Song, J. P. (2018). Three constituents of moringa oleifera seeds regulate expression of Th17-relevant cytokines and ameliorate tpa-induced psoriasis-like skin lesions in mice. *Molecules*, *23*(12), 7–9. https://doi.org/10.3390/molecules23123256

MacDonald, L. D., MacKay, A., Kaliaperumal, V., Weir, G., Penwell, A., Rajagopalan, R., Langley, J. M., Halperin, S., Mansour, M., & Stanford, M. M. (2018). Type III hypersensitivity reactions to a B cell epitope antigen are abrogated using a depot forming vaccine platform. *Human Vaccines and Immunotherapeutics*, *14*(1), 59–66. https://doi.org/10.1080/21645515.2017.1375637

Mahajan, S. G., Mali, R. G., & Mehta, A. A. (2007). Effect of Moringa oleifera Lam. seed extract on toluene diisocyanate-induced immune-mediated inflammatory responses in rats. *Journal of Immunotoxicology*, *4*(2), 85–96. https://doi.org/10.1080/15476910701337472

Martelli, A., Piragine, E., Gorica, E., Citi, V., Testai, L., Pagnotta, E., Lazzeri, L., Pecchioni, N., Ciccone, V., Montanaro, R., Mannelli, L. D. C., Ghelardini, C., Brancaleone, V., Morbidelli, L., & Calderone, V. (2021). The h2 s-donor erucin exhibits protective effects against vascular inflammation in human endothelial and smooth muscle cells. *Antioxidants*, *10*(6), 1–16. https://doi.org/10.3390/antiox10060961

Mathiron, D., Iori, R., Pilard, S., Rajan, T. S., Landy, D., Mazzon, E., Rollin, P., & Djedaïni-Pilard, F. (2018). A combined approach of NMR and mass spectrometry techniques applied to the α-cyclodextrin/moringin complex for a novel bioactive formulation. *Molecules*, *23*(7). https://doi.org/10.3390/molecules23071714

Matsui, T., Ito, C., Masubuchi, S., & Itoigawa, M. (2015). Licarin A is a candidate compound for the treatment of immediate hypersensitivity via inhibition of rat mast cell line RBL-2H3 cells. *Journal of Pharmacy and Pharmacology*, *67*(12), 1723–1732. https://doi.org/10.1111/jphp.12475

Melli, L. C. F. L., do Carmo-Rodrigues, M. S., Araújo-Filho, H. B., Solé, D., & de Morais, M. B. (2016). Intestinal microbiota and allergic diseases: A systematic review. *Allergologia et Immunopathologia*, *44*(2), 177–188. https://doi.org/10.1016/j.aller.2015.01.013

Min, S. Y., Park, C. H., Yu, H. W., & Park, Y. J. (2021). Anti-inflammatory and anti-allergic effects of saponarin and its impact on signaling pathways of raw 264.7, rbl-2h3 and hacat cells. *International Journal of Molecular Sciences*, *22*(16). https://doi.org/10.3390/ijms22168431

Molen, T. Van Der, Foster, J. M., Caeser, M., Müller, T., & Postma, D. S. (2010). Difference between patient-reported side effects of ciclesonide versus fluticasone propionate. *Respiratory Medicine*, *104*(12), 1825–1833. https://doi.org/10.1016/j.rmed.2010.05.021

Moon, P. D., & Kim, H. M. (2012). Anti-inflammatory effect of phenethyl isothiocyanate, an active ingredient of Raphanus sativus Linne. *Food Chemistry*, *131*(4), 1332–1339. https://doi.org/10.1016/j.foodchem.2011.09.127

Mwakalukwa, R., Ashour, A., Amen, Y., Niwa, Y., Tamrakar, S., Miyamoto, T., & Shimizu, K. (2019). Anti-allergic activity of polyphenolic compounds isolated from olive mill wastes. *Journal of Functional Foods*, *58*(January), 207–217. https://doi.org/10.1016/j.jff.2019.04.058

Myers, A., & Godden, C. (2010). Peripheral oedema as a side-effect of fluticasone. *BMJ Case Reports*, *2010*, 2009–2010. https://doi.org/10.1136/bcr.09.2009.2264

Nouman, W., Anwar, F., Gull, T., Newton, A., Rosa, E., & Domínguez-Perles, R. (2016). Profiling of polyphenolics, nutrients and antioxidant potential of germplasm's leaves from seven cultivars of Moringa oleifera Lam. *Industrial Crops and Products*, *83*, 166–176. https://doi.org/10.1016/j.indcrop.2015.12.032

Novack, G. D. (2019). Treatment Duration and Side Effect Profile of Long-term Use of Intravitreal Preservative-free Triamcinolone Acetonide in Uveitis. *American Journal of Ophthalmology*, *202*, 151. https://doi.org/10.1016/j.ajo.2018.11.025

Okamoto, T., Akita, N., Nagai, M., Hayashi, T., & Suzuki, K. (2014). 6-Methylsulfinylhexyl isothiocyanate modulates endothelial cell function and suppresses leukocyte adhesion. *Journal of Natural Medicines*, *68*(1), 144–153. https://doi.org/10.1007/s11418-013-0784-x

Okechukwu, V. U., Eze, S. O., Omokpariola, D. O., & Okereke, J. C. (2021). Evaluation of phytochemical constituents of Methanol extract of Moringa oleifera Lam. whole leaf by Gas Chromatography-Mass Spectrometry and Fourier transform infrared spectroscopy analysis. *World News of Natural Sciences*, *37*(April), 18–30.

Oldoni, T. L. C., Merlin, N., Bicas, T. C., Prasniewski, A., Carpes, S. T., Ascari, J., de Alencar, S. M., Massarioli, A. P., Bagatini, M. D., Morales, R., & Thomé, G. (2021). Antihyperglycemic activity of crude extract and isolation of phenolic compounds with antioxidant activity from Moringa oleifera Lam. leaves grown in Southern Brazil. *Food Research International*, *141*(June 2020). https://doi.org/10.1016/j.foodres.2020.110082

Owens, F. S., Dada, O., Cyrus, J. W., Adedoyin, O. O., & Adunlin, G. (2020). The effects of Moringa oleifera on blood glucose levels: A scoping review of the literature. *Complementary Therapies in Medicine*, *50*(February). https://doi.org/10.1016/j.ctim.2020.102362

Oyoshi, M., & Chinthrajah, R. S. (2020). Editorial: Insights Into the Etiology, Prevention, and Treatment of Food Allergy. *Frontiers in Immunology*, *11*(August), 10–12. https://doi.org/10.3389/fimmu.2020.01937

Oyoshi, M. K., Oettgen, H. C., Chatila, T. A., Geha, R. S., & Bryce, P. J. (2014). Food allergy: Insights into etiology, prevention, and treatment provided by murine

models. *Journal of Allergy and Clinical Immunology*, *133*(2), 309–317. https://doi.org/10.1016/j.jaci.2013.12.1045

Parisi, G. F., Leonardi, S., Ciprandi, G., Corsico, A., Licari, A., Miraglia Del Giudice, M., Peroni, D., Salpietro, C., & Marseglia, G. L. (2020). Cetirizine use in childhood: An update of a friendly 30-year drug. *Clinical and Molecular Allergy*, *18*(1), 1–6. https://doi.org/10.1186/s12948-020-00118-5

Pekar, J., Ret, D., & Untersmayr, E. (2018). Stability of allergens. *Molecular Immunology*, *100*(March), 14–20. https://doi.org/10.1016/j.molimm.2018.03.017

Polito, V., Barbacki, A., & Isabwe, G. (2020). Type i allergic reaction to rituximab upon first lifetime exposure: A case report. *Allergy, Asthma and Clinical Immunology*, *16*(1), 1–3. https://doi.org/10.1186/s13223-020-00448-8

Quesada, J. M. (2022). Special Issue: Alternaria alternata: Should We Still Consider This Fungus as a Minor Brother in the Etiology of Respiratory Allergy? *Journal of Fungi*, *8*(8), 10–12. https://doi.org/10.3390/jof8080796

Rajan, T. S., Giacoppo, S., Iori, R., De Nicola, G. R., Grassi, G., Pollastro, F., Bramanti, P., & Mazzon, E. (2016). Anti-inflammatory and antioxidant effects of a combination of cannabidiol and moringin in LPS-stimulated macrophages. *Fitoterapia*, *112*, 104–115. https://doi.org/10.1016/j.fitote.2016.05.008

Recio, R., Elhalem, E., Benito, J. M., Fernández, I., & Khiar, N. (2018). NMR study on the stabilization and chiral discrimination of sulforaphane enantiomers and analogues by cyclodextrins. *Carbohydrate Polymers*, *187*(December 2017), 118–125. https://doi.org/10.1016/j.carbpol.2017.12.022

Riedl, M. A., Saxon, A., & Diaz-Sanchez, D. (2009). Oral sulforaphane increases Phase II antioxidant enzymes in the human upper airway. *Clinical Immunology*, *130*(3), 244–251. https://doi.org/10.1016/j.clim.2008.10.007

Rodriguez Amado, J. R., Prada, A. L., Duarte, J. L., Keita, H., da Silva, H. R., Ferreira, A. M., Sosa, E. H., & Carvalho, J. C. T. (2017). Development, stability and in vitro delivery profile of new loratadine-loaded nanoparticles. *Saudi Pharmaceutical Journal*, *25*(8), 1158–1168. https://doi.org/10.1016/j.jsps.2017.07.008

Ross, G. M. S., Bremer, M. G. E. G., & Nielen, M. W. F. (2018). Consumer-friendly food allergen detection: moving towards smartphone-based immunoassays. *Analytical and Bioanalytical Chemistry*, *410*(22), 5353–5371. https://doi.org/10.1007/s00216-018-0989-7

Ruhee, R. T., & Suzuki, K. (2020). The integrative role of sulforaphane in preventing inflammation, oxidative stress and fatigue: A review of a potential protective phytochemical. *Antioxidants*, *9*(6), 1–13. https://doi.org/10.3390/antiox9060521

Sakurai, H., Morishima, Y., Ishii, Y., Yoshida, K., Nakajima, M., Tsunoda, Y., Hayashi, S. Y., Kiwamoto, T., Matsuno, Y., Kawaguchi, M., Yamamoto, M., & Hizawa,

N. (2018). Sulforaphane ameliorates steroid insensitivity through an Nrf2-dependent pathway in cigarette smoke-exposed asthmatic mice. *Free Radical Biology and Medicine*, *129*, 473–485. https://doi.org/10.1016/j.freeradbiomed.2018.10.400

Saleem, A., Saleem, M., & Akhtar, M. F. (2020). Antioxidant, anti-inflammatory and antiarthritic potential of Moringa oleifera Lam: An ethnomedicinal plant of Moringaceae family. *South African Journal of Botany*, *128*, 246–256. https://doi.org/10.1016/j.sajb.2019.11.023

Schleimer, R. P., & Berdnikovs, S. (2017). Etiology of epithelial barrier dysfunction in patients with type 2 inflammatory diseases. *Journal of Allergy and Clinical Immunology*, *139*(6), 1752–1761. https://doi.org/10.1016/j.jaci.2017.04.010

Shao, Y. Y., Zhou, Y. M., Hu, M., Li, J. Z., Chen, C. J., Wang, Y. J., Shi, X. Y., Wang, W. J., Zhang, T. T., & Battino, M. (2017). The anti-allergic rhinitis effect of traditional Chinese medicine of Shenqi by regulating mast cell degranulation and Th1/Th2 cytokine balance. *Molecules*, *22*(3), 1–11. https://doi.org/10.3390/molecules22030504

Shin, D., Park, S. H., Choi, Y. J., Kim, Y. H., Antika, L. D., Habibah, N. U., Kang, M. K., & Kang, Y. H. (2015). Dietary compound kaempferol inhibits airway thickening induced by allergic reaction in a bovine serum albumin-induced model of asthma. *International Journal of Molecular Sciences*, *16*(12), 29980–29995. https://doi.org/10.3390/ijms161226218

Shirley, D., McHale, C., & Gomez, G. (2016). Resveratrol preferentially inhibits IgE-dependent PGD2 biosynthesis but enhances TNF production from human skin mast cells. *Biochimica et Biophysica Acta - General Subjects*, *1860*(4), 678–685. https://doi.org/10.1016/j.bbagen.2016.01.006

Shousha, W. G., Aboulthana, W. M., Salama, A. H., Saleh, M. H., & Essawy, E. A. (2019). Evaluation of the biological activity of Moringa oleifera leaves extract after incorporating silver nanoparticles, in vitro study. *Bulletin of the National Research Centre*, *43*(1). https://doi.org/10.1186/s42269-019-0221-8

Singh, A. K., Rana, H. K., Tshabalala, T., Kumar, R., Gupta, A., Ndhlala, A. R., & Pandey, A. K. (2020). Phytochemical, nutraceutical and pharmacological attributes of a functional crop Moringa oleifera Lam: An overview. *South African Journal of Botany*, *129*, 209–220. https://doi.org/10.1016/j.sajb.2019.06.017

Solé, D., Spindola, M. A. C., Aun, M. V., Araújo Azi, L. M. T. de, Bernd, L. A. G., Garcia, D. B., Capelo, A. V., Cumino, D. de O., Lacerda, A. E., Lima, L. C., Morato, E. F., Nunes, R. R., Rubini, N. de P. M., Silva, J. da, Tardelli, M. A., Watanabe, A. S., Curi, E. F., & Sano, F. (2020). Update on perioperative hypersensitivity reactions: joint document from the Brazilian Society of Anesthesiology (SBA) and Brazilian Association of Allergy and Immunology (ASBAI) - Part II: etiology and diagnosis. *Brazilian Journal of Anesthesiology (English Edition)*, *70*(6), 642–661. https://doi.org/10.1016/j.bjane.2020.10.005

Subramanian, V. S., Priya, V. V., & Gayathri, R. (2019). Antiallergic activity of alpha-lipoic acid. *Drug Intervention Today*, *11*(6), 1499–1501. https://web.a.ebscohost.com/abstract?direct=true&profile=ehost&scope=site&authtype=crawler&jrnl=09757619&AN=139165776&h=JClYA%2FzDn%2FNntKujwEOnHQfarIGHnjp6f8i%2FIy7XsjcEn0Eh9c%2FSqbGbDD8%2BJH1bMhf1FdRqZ55cCg%2Bd4rDseA%3D%3D&crl=c&resultNs=AdminWebAuth&re

Sun, Y. H., Ge, L. T., Jiang, J. X., Shen, H. J., Jia, Y. L., Dong, X. W., Sun, Y., & Xie, Q. M. (2015). Formoterol synergy with des-ciclesonide inhibits IL-4 expression in IgE/antigen-induced mast cells byinhibitingJNKactivation. *European Journal of Pharmacology*, *761*, 161–167. https://doi.org/10.1016/j.ejphar.2015.05.008

Tan, J. W., Israf, D. A., Harith, H. H., Md Hashim, N. F., Ng, C. H., Shaari, K., & Tham, C. L. (2017). Anti-allergic activity of 2,4,6-trihydroxy-3-geranylacetophenone (tHGA) via attenuation of IgE-mediated mast cell activation and inhibition of passive systemic anaphylaxis. *Toxicology and Applied Pharmacology*, *319*, 47–58. https://doi.org/10.1016/j.taap.2017.02.002

ThankGod Eze, C., Michelangeli, F., & Otitoloju, A. A. (2019). In vitro cyto-toxic assessment of heavy metals and their binary mixtures on mast cell-like, rat basophilic leukemia (RBL-2H3) cells. *Chemosphere*, *223*, 686–693. https://doi.org/10.1016/j.chemosphere.2019.02.035

Tran, H. T. T., Stetter, R., Herz, C., Spöttel, J., Krell, M., Hanschen, F. S., Schreiner, M., Rohn, S., Behrens, M., & Lamy, E. (2021). Allyl Isothiocyanate: A TAS2R38 Receptor-Dependent Immune Modulator at the Interface Between Personalized Medicine and Nutrition. *Frontiers in Immunology*, *12*(April), 1–13. https://doi.org/10.3389/fimmu.2021.669005

Ufelle, S. A., Onyekwelu, K. C., Achukwu, P. U., & Ezeh, C. O. (2018). Haematological effects of leaf extract of moringa oleifera lam in normal and myelo-suppressed Wistar rats. *African Journal of Biomedical Research*, *21*(1), 87–90.

Uto, T., Hou, D. X., Morinaga, O., & Shoyama, Y. (2012). Molecular mechanisms underlying anti-inflammatory actions of 6-(methylsulfinyl)hexyl isothiocyanate derived from wasabi (wasabia japonica). *Advances in Pharmacological Sciences*, *2012*(Figure 1). https://doi.org/10.1155/2012/614046

Viel, S., Pescarmona, R., Belot, A., Nosbaum, A., Lombard, C., Walzer, T., & Bérard, F. (2018). A case of type 2 hypersensitivity to rasburicase diagnosed with a Natural Killer cell activation assay. *Frontiers in Immunology*, *9*(JAN), 9–12. https://doi.org/10.3389/fimmu.2018.00110

Washio, K., Masaki, T., Fujii, S., Hatakeyama, M., Oda, Y., Fukunaga, A., & Natsuaki, M. (2018). Anaphylaxis caused by a centipede bite: A “true” type-I allergic reaction. *Allergology International*, *67*(3), 419–420. https://doi.org/10.1016/j.alit.2018.01.005

Woo, K. J., & Kwon, T. K. (2007). Sulforaphane suppresses lipopolysaccharide-induced cyclooxygenase-2 (COX-2) expression through the modulation of multiple

targets in COX-2 gene promoter. *International Immunopharmacology*, *7*(13), 1776–1783. https://doi.org/10.1016/j.intimp.2007.09.018

Wu, C. Y., Huang, H. Y., Pan, W. C., Liao, S. L., Hua, M. C., Tsai, M. H., Lai, S. H., Yeh, K. W., Chen, L. C., Huang, J. L., & Yao, T. C. (2021). Allergic diseases attributable to atopy in a population sample of Asian children. *Scientific Reports*, *11*(1), 1–8. https://doi.org/10.1038/s41598-021-95579-2

Wu, W., Peng, G., Yang, F., Zhang, Y., Mu, Z., & Han, X. (2019). Sulforaphane has a therapeutic effect in an atopic dermatitis murine model and activates the Nrf2/HO-1 axis. *Molecular Medicine Reports*, *20*(2), 1761–1771. https://doi.org/10.3892/mmr.2019.10405

Xiao, X., Wang, J., Meng, C., Liang, W., Wang, T., Zhou, B., Wang, Y., Luo, X., Gao, L., & Zhang, L. (2020). Moringa oleifera Lam and its Therapeutic Effects in Immune Disorders. *Frontiers in Pharmacology*, *11*(December), 1–9. https://doi.org/10.3389/fphar.2020.566783

Xiaolei, S., Bo, W., Lu, Z., Ying, W., Jie, Y., Xuwen, L., & Yongri, J. (2018). Anti-allergic activity of 3, 5, 6, 7, 8, 3′, 4′-heptamethoxyflavone extracted from Citri Reticulatae Pericarpium. *Spectroscopy Letters*, *51*(5), 236–243. https://doi.org/10.1080/00387010.2018.1455707

Yamada-Kato, T., Nagai, M., Ohnishi, M., & Yoshida, K. (2012). Inhibitory effects of wasabi isothiocyanates on chemical mediator release in RBL-2H3 rat basophilic leukemia cells. *Journal of Nutritional Science and Vitaminology*, *58*(4), 303–307. https://doi.org/10.3177/jnsv.58.303

Yehuda, H., Soroka, Y., Zlotkin-Frušić, M., Gilhar, A., Milner, Y., & Tamir, S. (2012). Isothiocyanates inhibit psoriasis-related proinflammatory factors in human skin. *Inflammation Research*, *61*(7), 735–742. https://doi.org/10.1007/s00011-012-0465-3

Yoo, J. M., Yang, J. H., Yang, H. J., Cho, W. K., & Ma, J. Y. (2016). Inhibitory effect of fermented Arctium lappa fruit extract on the IgE-mediated allergic response in RBL-2H3 cells. *International Journal of Molecular Medicine*, *37*(2), 501–508. https://doi.org/10.3892/ijmm.2015.2447

Zarif, A. (2020). Advances in food allergy treatment. *Yale Journal of Biology and Medicine*, *93*(5), 749–758.

Zhang, J., Liu, X., Wang, Z., Zhang, H., Gao, J., Wu, Y., Meng, X., Zhong, Y., & Chen, H. (2022). Potential Allergenicity Response to Moringa oleifera Leaf Proteins in BALB/c Mice. *Nutrients*, *14*(21), 1–16. https://doi.org/10.3390/nu14214700