



International Journal of Life Science Research Archive

ISSN: 0799-6640 (Online)

Journal homepage: <https://sciresjournals.com/ijlsra/>

(REVIEW ARTICLE)



***BORAGO OFFICINALIS* AND ASTHMA: CURRENT EVIDENCE AND THERAPEUTIC POTENTIAL**

Shahad Imad Hameed ^{1,*}, Rayaheen Mohammed Tamkeen ² and Marwan Noori Mohammed ³

¹ Department of Biology, College of Science, University of Baghdad, Baghdad, Iraq.

² College of Science, University of Baghdad, Baghdad, Iraq.

³ Mustansiriyah university, College of basic education, Department of science, Baghdad, Iraq.

* Corresponding Author; Email: Shahad.emad@sc.uobaghdad.edu.iq

ORCID Details

Shahad Imad Hameed: <https://orcid.org/0000-0001-8154-6440>

Rayaheen Mohammed Tamkeen: <https://orcid.org/0009-0001-2880-6626>

Marwan Noori Mohammed: <https://orcid.org/0009-0008-5929-9664>

International Journal of Life Science Research Archive, 2026, 11(01), 077–083

Publication history: Received on 12 August 2026; revised on 20 September 2026; accepted on 22 September 2026

Article DOI: <https://doi.org/10.53771/ijlsra.2026.11.1.0072>

Copyright © 2026 Author(s) retain the copyright of this article. This article is published under the terms of the Creative Commons Attribution License 4.0

ABSTRACT

Borage (*Borago officinalis* L.) is noted for its bioactive compounds, particularly gamma-linolenic acid (GLA), which may play a role in respiratory inflammatory processes. This study reviews its chemical makeup, anti-inflammatory and anti-asthmatic effects, and clinical data regarding asthma. Borage may influence leukotriene production and lipid mediator metabolism, potentially alleviating respiratory symptoms. However, clinical evidence is limited, and variability in plant materials and study designs complicates comparisons. Safety concerns, particularly regarding pyrrolizidine alkaloids, are significant. *B. officinalis* shows promise for asthma research, necessitating rigorous clinical studies and safety assessments to better understand its therapeutic potential.

Keywords: Asthma, *Borago Officinalis*, Gamma-Linolenic Acid (GLA), Medicinal Plants, Pyrrolizidine Alkaloids (PA).

1 INTRODUCTION

The plant *Borago officinalis* L. (family: Boraginaceae) has significant nutritional and therapeutic benefits. The facility exhibited both pharmaceutical and industrial applications [1, 2]. Borage or starflower are common names for it [3, 4]. Borage originates in the Mediterranean and has spread to North Africa, Europe, Asia, and South America. It was first grown for food and medicinal purpose[5]. Borage could flourish in a variety of environments and soil types. It germinates from November to January and is collected throughout the flowering phase prior to [6]. It grows to a height range of 70 to 100 cm [7]. According to Basar *et al.* [8] and Montaner *et al.* [9], the parts are pink to blue and infrequently white, and they emit a strong fresh cucumber-like scent.

The plant is used to gather oil and seeds; the rest is frequently disposed of as debris and then sold as herbal tea. The plant can be utilized for many reasons because it has a variety of active elements [10]. The leaves and petals can be used

as a source of affordable, healthful products [11] and are typically consumed as food [12]. Because The plant seed, which is used as a nutritional supplement to treat a variety of illnesses, has the highest content of GLA [13].

Furthermore, the Borage seed oil (BSO) has demonstrated efficacy in treating a number of conditions, including Rheumatism [14], breathing problems [15], allergic Skin irritation, symptoms associated with Menopause phase, and neuropathy diabetic [16]. Previous research on BSO showed improvements in bone health, anti-inflammatory effects, and lipid metabolism control [17, 18]; Other research revealed dermatitis, eczema, and skin hydrating [19]. Interestingly, the high GLA concentration (15–22%) of BSO is responsible for its therapeutic properties [20].

One of these disease is Asthma. The most common lung condition in the world, asthma is complicated and multifaceted. A multidisciplinary approach to asthma diagnosis and treatment is made possible by improved subtype classification made possible by advances in our understanding of its pathophysiology. Age-related differences in the differential diagnosis of asthma can range from a foreign body inhaled by a small child to a pulmonary embolism or heart failure in an elderly person [21]. In 2023, asthma killed 442,000 people and impacted an estimated 363 million people [22].

This review's goal is draw attention to *B. officinalis* L.'s possible contribution to lowering asthma-related attacks.

2 CHEMICAL CONSTITUENTS OF *B. OFFICINALIS* L. RELATED WITH ASTHMA

The metabolites reported included resins, tannins, ascorbic acid, niacin, beta-carotene, riboflavin, silicic acid, thiamin, choline arabinose, polyphenolics, and unsaturated pyrrolizidine alkaloids (PA) [7, 23, 24].

Examining the fresh leaves and flowering upper parts of borage showed significant amounts of palmitic acid found in the leaves and α -linoleic acid in the fixed oil fractions of the flowers.

Arachidonic acid was absent from the leaves, although carotenoids, flavonoids, ascorbic acid, essential oils, and chlorophyll a and b were found. According to Borowy *et al.* [25], other lipids were found to include oleic, stearic, elaidic, linolelaidic, linoleic, lauric, and myristic acids.

Fatty acids, such as γ -linolenic acid (GLA), essential oils, phenolic acids (such as rosmarinic acid), flavonoids, anthocyanins, tannins, and saponins are the primary types of useful compounds linked to Boraginaceae species. Allantoin and naphthoquinone pigments, such as shikonin, are extremely specialized. The buildup of silica (silicon dioxide) in trichomes is another characteristic that sets them apart. Mucilages are produced by certain taxa [26].

3 TRADITIONAL USE OF *B. OFFICINALIS* L.

Folk medicine uses both the above-ground portions of borage and the oil from seeds [13]. Infusions of the plant are used to treat rheumatism, bronchitis, Skin irritations and cold symptoms, and UTIs [27]. Borage extracts have historically been used to treat cardiovascular, pulmonary, and overactive gastrointestinal conditions [2].

Since ancient times, Ancient Iranian medicine has used Borage's above ground portions as a tranquilizer and to treat pneumonia, sore throats, coughs, inflammation, and edema [13]. According to Navaey *et al.* [28], borage leaves have demulcent, diuretic, expectorant, and emollient properties. In traditional medicine, borage blossoms are used as sedatives [29] and bronchodilators [13].

4 ANTI-INFLAMMATORY & ANTI-ASTHMATIC MECHANISM

Asthma is a complicated illness that causes inflammation and smooth muscle spasm, which restrict and block the airway. It has been shown that the pathophysiology of asthma is significantly influenced by the metabolism of arachidonic acid (AA) via the 5-lipoxygenase route to generate leukotrienes. In particular, the cysteinyl leukotrienes LTC₄, LTD₄, and LTE₄ cause the smooth muscles of the bronchi to contract, Mucus formation in the respiratory tract and blood vessel dilation by acting at GPCRs CysLT₁R and CysLT₂R [30, 31].

Furthermore, LTB₄ acts at a particular GPCR, BLT₁, and is a strong Granulocyte chemical attraction agent, effector T cells, and monocytes [32]. Together, leukotrienes have many pro-inflammatory characteristics, and leukotriene-altering medications have shown promise in the treatment of allergic rhinitis [33] and asthma [34].

It has been shown that adding supplementing diets with marine and plant oils based on fatty acids can lessen the rigorousness of a number of offensive conditions, such as asthma. The ability of n-6 and n-3 polyunsaturated fatty acids to change AA metabolized to generate eicosanoids has been identified as one of the main mechanisms underlying their effectiveness [35].

The 18-carbon polyunsaturated fatty acid (PUFA) gamma-linolenic acid (GLA; 18:3, n-6) found in borage seed oils is elongated to dihomo-gammalinolenic acid (DGLA) by the majority of tissues and inflammatory cells. Membrane phospholipids then incorporate freshly produced DGLA. Similar to EPA, DGLA can rival AA in the production of eicosanoids. Additionally, cyclooxygenase enzymes convert DGLA to prostaglandin (PG)H₁, which is subsequently transformed into PGE₁ [36-38].

In a way that is compatible with a decrease in inflammation, Borage essential oil dietary additives modifies 20–22C PUFA levels and decreases leukotriene formation [39].

Because of its high quantities of gamma-linolenic acid (GLA) and other useful fatty acids, *B. officinalis* L., a member of the Boraginaceae family of plants, has demonstrated potential as an anti-asthmatic agent. *B. officinalis* extract was found to dramatically lessen the intensity of airway hyperresponsiveness, wheezing, coughing, dyspnea, and sleep disturbances associated with asthma in clinical studies. It also decreased the usage of relievers, asthma exacerbations, and emergencies. Additionally, either administered alone or in combination with echium seed oil, *B. officinalis* oil can lower amounts of polyunsaturated fatty acids with 20–22 carbons (PUFAs) and leukotriene synthesis, indicating actions on the airways that reduce inflammation.

According to the research, *B. officinalis* may be a useful supplement for managing asthma [40].

In the study of [41], which involved 38 individuals with an average age of 46.8±15.3 years and an average asthma duration of 71±103 months, the group treated with borage demonstrated an improvement in the clinical findings of asthma; however, the physiological parameters, such as FENO, oxygen saturation, and sputum analysis, including neutrophil and eosinophil, remained unchanged.

5 SAFETY AND LIMITATION

Despite being frequently consumed as a vegetable or herb, borage, or *B. officinalis*, also produces lethal pyrrolizidine alkaloids (PA). Borage leaves were among the foods for which the European Union (EU) set the highest PA quantity restrictions in 2020 [42].

About 3% of blooming plants from various plant families produce pyrrolizidine alkaloids (PA), which are naturally occurring plant poisons [43]. Furthermore to plants that produce PA itself and are consumed as diet (like borage) or medicinal plants (like comfrey or coltsfoot), PA can be discovered as pollutants in a range of foods, including honey, spices and herbs, tea and herbal remedies, and nutritional supplements [44-47]. additionally, if the feed is contaminated, PA can be passed on to products derived from animals [48, 49].

After metabolic activation, 1,2-unsaturated PA can be genotoxic and hepatotoxic[50]. The molecular structure of 1,2-unsaturated PA determines its hazardous potential. The most powerful poisons are generally thought to be cyclic diesters, open-chain diesters, and monoesters [51].

In an effort to lower consumer consumption of hazardous PA, the EU set highest possible values for certain PA in a range of foods in 2020.

According to [52], For fresh as well as frozen leaves, the maximum PA content in borage is 750 µg/kg; for dried leaves, it is 1000 µg/kg.

The complex nature of dietary matrices, the prevalence of distinct The structural similarities between PA, and the absence of guidelines for standard criteria make PA analysis difficult [53].

Apart from PA assessment in feed and food products, attempts have been undertaken to examine PA adducts discovered in animal and human bio fluids or liver tissue following PA consumption [54-56].

For example, no detectable PA was found when [57] examined the above parts of a borage plant. On the other hand, the total PA content of young borage leaves was 253 µg/kg, according to [58], every product that contained borage contained PA, according to their analysis of new and frozen herbal harvests from the German shop.

The EFSA recommended deeper analyzing data collection and evaluation of PA not covered by present laws due to the paucity of information on the prevalence of PA in foods [44].

Depending on whether unsaturated double bonding is present at sites C-1 and C-2 of the necine structure, PAs are categorized as either unsaturated or saturated. Platynecine (PLA) and other saturated PAs and necine base are

recognized to be safe. The three kinds of unsaturated PAs are retronecine, heliotridine, and otonecine. Retrierversine and senecionine are PAs of the RET type, whereas clivorine and senkirkine are OTO-type PAs. Heliotrine & lasiocarpine are examples of HEL-type PAs.

It is also possible to make N-oxides by oxidizing nitrogen atoms on the necine moiety, which in many plants interact with PAs [59]. Nevertheless, otonecine-type PAs cannot generate a matching PA N-oxide because of the methylation of nitrogen in the necine base core structure. While 1,2-unsaturated PAs are extremely dangerous because of their hepatotoxic, carcinogenic, and genotoxic characteristics, saturated PAs often show little to no toxicity [44].

PAs are transferred to the liver after absorption in the small intestine. There, cytochrome P450 enzymes (CYP450) break them down into bioactive major metabolites known as dehydropyridine alkaloids (DHPAs). They are then broken down to create derivatives of dihydropyran (DHPs). DHPAs and DHPs can rapidly interact with macromolecules in cells, such as pyrrole–DNA adducts, pyrrole–protein adducts, protein–DNA cross-links, and protein–protein cross-links, due to their strong electrophilicity [60].

However, nonspecific esterase enzymes have the ability to hydrolyze PAs into necine and necic acid. The urinary tract can remove these non-toxic necines and necic acids by binding to regular polar molecules [61].

The relative lack of direct research examining the impact of borage on asthma and the small number of clinical trials are major limitations of this study; also, it is challenging to compare the studies due to differences in extract type, dosage, and preparation techniques. Furthermore, the results cannot always be applied to all plant preparations because some data is based on GLA or borage oil rather than the entire plant.

6 CONCLUSION

Borage shows promising potential for asthma management, particularly due to its content of bioactive compounds—such as gamma-linolenic acid (GLA)—that may possess anti-inflammatory properties.

The plant may affect inflammatory processes linked to asthma, including as the metabolism of lipid mediators and leukotrienes, according to available experimental and clinical data, with signs of relief in certain respiratory symptoms.

Nevertheless, there is still a lack of data, particularly when it comes to standardized herbal preparations and large-scale clinical trials. Additionally, while evaluating the plant's safety, the presence of pyrrolizidine alkaloids is an important consideration. Therefore, even though *B. officinalis* is a promising botanical option for asthma research, more carefully planned clinical trials, standardization of extracts and dosages, and thorough safety evaluations are necessary before its therapeutic efficacy in asthma patients can be determined.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of conflict of interest

There is no conflict of interest among the authors.

REFERENCES

- [1] Komaki A, Rasouli B, Shahidi S. Anxiolytic effect of *Borago officinalis* (Boraginaceae) extract in male rats. 2015.
- [2] Gilani AH, Bashir S, Khan A-u. Pharmacological basis for the use of *Borago officinalis* in gastrointestinal, respiratory and cardiovascular disorders. *Journal of Ethnopharmacology*. 2007;114(3):393-9.
- [3] Gupta M, Singh S. *Borago officinalis* Linn. an important medicinal plant of Mediterranean region: a review. *International Journal of Pharmaceutical Sciences Review and Research*. 2010;5(1):27-34.
- [4] Kaskoos RA, Ali M, Naquvi KJ. Phytochemical investigation of the leaves of *Borago officinalis* L. 2012.
- [5] Farhadi R, Balashahri MS, Tilebeni HG, Sadeghi M. Pharmacology of Borage (*Borago officinalis* L.) medicinal plant. 2012.
- [6] Mhamdi B, Wannes WA, Sriti J, Jellali I, Ksouri R, Marzouk B. Effect of harvesting time on phenolic compounds and antiradical scavenging activity of *Borago officinalis* seed extracts. *Industrial Crops and Products*. 2010;31(1):e1-e4.
- [7] Gudej J, Tomczyk M. Chromatographic analysis of polyphenolic compounds from the herbs of *Borago officinalis* (L.). 1996.

- [8] Basar SN, Rani S, Farah SA, Zaman R. Review on Borage officinalis: a wonder herb. *Int J Biol Pharm Res*. 2013;4:582-7.
- [9] Montaner C, Floris E, Alvarez J. Geitonogamy: a mechanism responsible for high selfing rates in borage (*Borago officinalis* L.). *Theoretical and Applied Genetics*. 2001;102(2):375-8.
- [10] Segovia F, Lupo B, Peiró S, Gordon MH, Almajano MP. Extraction of antioxidants from borage (*Borago officinalis* L.) leaves—Optimization by response surface method and application in oil-in-water emulsions. *Antioxidants*. 2014;3(2):339-57.
- [11] Ciriano M, Garcia-Herreros C, Larequi E, Valencia I, Ansorena D, Astiasaran I. Use of natural antioxidants from lyophilized water extracts of *Borago officinalis* in dry fermented sausages enriched in ω -3 PUFA. *Meat Science*. 2009;83(2):271-7.
- [12] Husti A, Cantor M, Buta E, Horț D. Current trends of using ornamental plants in culinary arts. *ProEnvironment Promediu*. 2013;6(13).
- [13] Asadi-Samani M, Bahmani M, Rafieian-Kopaei M. The chemical composition, botanical characteristic and biological activities of *Borago officinalis*: a review. *Asian Pacific journal of tropical medicine*. 2014;7:S22-S8.
- [14] Cameron M, Gagnier JJ, Chrubasik S. Herbal therapy for treating rheumatoid arthritis. *Cochrane Database of Systematic Reviews*. 2011(2).
- [15] Hamilton LA, Trobaugh KA. Acute respiratory distress syndrome: use of specialized nutrients in pediatric patients and infants. *Nutrition in Clinical Practice*. 2011;26(1):26-30.
- [16] Al-Khamees WaA, Schwartz MD, Alrashdi S, Algren AD, Morgan BW. Status epilepticus associated with borage oil ingestion. *Journal of Medical Toxicology*. 2011;7(2):154-7.
- [17] Wauquier F, Barquissau V, Léotoing L, Davicco M-J, Lebecque P, Mercier S, et al. Borage and fish oils lifelong supplementation decreases inflammation and improves bone health in a murine model of senile osteoporosis. *Bone*. 2012;50(2):553-61.
- [18] Guo Y, Cai X, Zhao X, Shi R. Effect of five kinds of vegetable seed oil on serum lipid and lipid peroxidation in rats. *Wei Sheng yan jiu= Journal of Hygiene Research*. 2001;30(1):50-1.
- [19] Brosche T, Platt D. Effect of borage oil consumption on fatty acid metabolism, transepidermal water loss and skin parameters in elderly people. *Archives of gerontology and geriatrics*. 2000;30(2):139-50.
- [20] Del Rio M, Fernández-Martínez J, De Haro A. Wild and cultivated *Borago officinalis* L.: sources of gamma-linolenic acid. *Grasas y aceites (Sevilla)*. 1993;44(2):125-6.
- [21] Venkatesan P. 2023 GINA report for asthma. *The Lancet Respiratory Medicine*. 2023;11(7):589.
- [22] Yuan L, Tao J, Wang J, She W, Zou Y, Li R, et al. Global, regional, national burden of asthma from 1990 to 2021, with projections of incidence to 2050: a systematic analysis of the global burden of disease study 2021. *EClinicalMedicine*. 2025;80.
- [23] Bandonien D, Murkovic M. The detection of radical scavenging compounds in crude extract of borage (*Borago officinalis* L.) by using an on-line HPLC-DPPH method. *Journal of Biochemical and Biophysical Methods*. 2002;53(1-3):45-9.
- [24] Singh M. In vitro antioxidant activity and HPTLC analysis of *Borago officinalis* Linn. *Indian Journal of Pharmaceutical Education and Research*. 2014.
- [25] Borowy A, Chwil M, Kapłan M. Biologically active compounds and antioxidant activity of borage (*Borago officinalis* L.) flowers and leaves. *Acta Scientiarum Polonorum Hortorum Cultus*. 2017;16(5):169-80.
- [26] Chrzanowska E, Denisow B, Ekiert H, Pietrzyk Ł. Metabolites obtained from Boraginaceae plants as potential cosmetic ingredients—a review. *Molecules*. 2024;29(21):5088.
- [27] Tasset-Cuevas I, Fernández-Bedmar Z, Lozano-Baena MD, Campos-Sánchez J, de Haro-Bailón A, Muñoz-Serrano A, et al. Protective effect of borage seed oil and gamma linolenic acid on DNA: in vivo and in vitro studies. *PLoS One*. 2013;8(2):e56986.
- [28] Navaey HN, Hzari MY, Seraji RAN, Eslami H. Germination reduce in Borage (*Borago officinalis* L.) seed under seed deteriorating conditions. *Inter J Farming and Allied Sci*. 2014;3:358-61.
- [29] Shahraki MR, Ahmadimoghadm M, Shahraki AR. The antinociceptive effects of hydroalcoholic extract of *Borago officinalis* flower in male rats using formalin test. *Basic and clinical neuroscience*. 2015;6(4):285.
- [30] Heise CE, O'Dowd BF, Figueroa DJ, Sawyer N, Nguyen T, Im D-S, et al. Characterization of the human cysteinyl leukotriene 2 receptor. *Journal of Biological Chemistry*. 2000;275(39):30531-6.

- [31] Lynch KR, O'Neill GP, Liu Q, Im D-S, Sawyer N, Metters KM, et al. Characterization of the human cysteinyl leukotriene CysLT1 receptor. *Nature*. 1999;399(6738):789-93.
- [32] Henz B, Jablonska S, Van De Kerkhof P, Stingl G, Blaszczyk M, Vandervalk P, et al. Double-blind, multicentre analysis of the efficacy of borage oil in patients with atopic eczema. *British journal of dermatology*. 1999;140(4):685-8.
- [33] Philip G, Malmstrom K, Hampel Jr F, Weinstein S, LaForce C, Ratner P, et al. Montelukast for treating seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled trial performed in the spring. *Clinical & Experimental Allergy*. 2002;32(7):1020-8.
- [34] Malmstrom K, Rodriguez-Gomez G, Guerra J, Villaran C, Piñeiro A, Wei LX, et al. Oral montelukast, inhaled beclomethasone, and placebo for chronic asthma: a randomized, controlled trial. *Annals of internal medicine*. 1999;130(6):487-95.
- [35] Lee TH, Hoover RL, Williams JD, Sperling RI, Ravalese III J, Spur BW, et al. Effect of dietary enrichment with eicosapentaenoic and docosahexaenoic acids on in vitro neutrophil and monocyte leukotriene generation and neutrophil function. *New England Journal of Medicine*. 1985;312(19):1217-24.
- [36] Arisaka M, Arisaka O, Yamashiro Y. Fatty acid and prostaglandin metabolism in children with diabetes mellitus. II.—the effect of evening primrose oil supplementation on serum fatty acid and plasma prostaglandin levels. *Prostaglandins, leukotrienes and essential fatty acids*. 1991;43(3):197-201.
- [37] Kapoor R, Huang Y-S. Gamma linolenic acid: an antiinflammatory omega-6 fatty acid. *Current pharmaceutical biotechnology*. 2006;7(6):531-4.
- [38] Takai S, Jin D, Kawashima H, Kimura M, Shiraishi-Tateishi A, Tanaka T, et al. Anti-atherosclerotic effects of dihomog- γ -linolenic acid in ApoE-deficient mice. *Journal of atherosclerosis and thrombosis*. 2009;16(4):480-9.
- [39] Arm JP, Boyce JA, Wang L, Chhay H, Zahid M, Patil V, et al. Impact of botanical oils on polyunsaturated fatty acid metabolism and leukotriene generation in mild asthmatics. *Lipids in health and disease*. 2013;12(1):141.
- [40] Baniamerian R, Tahermohammadi H, Daneshfard B, Agin K, Sadr S, Kaveh S, et al. Herbal treatment of COPD and asthma according to Persian medicine: A review of current evidence. *Tanaffos*. 2023;22(2):187.
- [41] Mirsadraee M, Moghaddam SK, Saeedi P, Ghaffari S. Effect of *Borago officinalis* extract on moderate persistent asthma: A phase two randomized, double blind, placebo-controlled clinical trial. *Tanaffos*. 2016;15(3):168.
- [42] Sattler M, Huch M, Bunzel D, Soukup ST, Kulling SE. Pyrrolizidine alkaloid contents and profiles in *Borago officinalis* leaves, flowers and microgreens: Implications for safety. *Food Control*. 2025;168:110930.
- [43] Smith L, Culvenor C. Plant sources of hepatotoxic pyrrolizidine alkaloids. *Journal of Natural Products*. 1981;44(2):129-52.
- [44] Chain EPoCitF, Knutsen HK, Alexander J, Barregård L, Bignami M, Brüschweiler B, et al. Risks for human health related to the presence of pyrrolizidine alkaloids in honey, tea, herbal infusions and food supplements. *EFSA Journal*. 2017;15(7):e04908.
- [45] Kopp T, Abdel-Tawab M, Mizaikoff B. Extracting and analyzing pyrrolizidine alkaloids in medicinal plants: A review. *Toxins*. 2020;12(5):320.
- [46] Rizzo S, Celano R, Piccinelli AL, Russo M, Rastrelli L. Target screening method for the quantitative determination of 118 pyrrolizidine alkaloids in food supplements, herbal infusions, honey and teas by liquid chromatography coupled to quadrupole orbitrap mass spectrometry. *Food chemistry*. 2023;423:136306.
- [47] Zhu L, Wang Z, Wong L, He Y, Zhao Z, Ye Y, et al. Contamination of hepatotoxic pyrrolizidine alkaloids in retail honey in China. *Food Control*. 2018;85:484-94.
- [48] Ma C, Liu Y, Zhu L, Ji H, Song X, Guo H, et al. Determination and regulation of hepatotoxic pyrrolizidine alkaloids in food: A critical review of recent research. *Food and Chemical Toxicology*. 2018;119:50-60.
- [49] Mulder PP, López P, Castelari M, Bodi D, Ronczka S, Preiss-Weigert A, et al. Occurrence of pyrrolizidine alkaloids in animal-and plant-derived food: results of a survey across Europe. *Food Additives & Contaminants: Part A*. 2018;35(1):118-33.
- [50] He Y, Zhu L, Ma J, Lin G. Metabolism-mediated cytotoxicity and genotoxicity of pyrrolizidine alkaloids. *Archives of toxicology*. 2021;95(6):1917-42.
- [51] Merz K-H, Schrenk D. Interim relative potency factors for the toxicological risk assessment of pyrrolizidine alkaloids in food and herbal medicines. *Toxicology letters*. 2016;263:44-57.

- [52] Regulation C. Commission Regulation (EU) 2023/915 of 25 April 2023 on maximum levels for certain contaminants in food and repealing Regulation (EC) No 1881/2006. J Eur Union. 2023;119:103-57.
- [53] Casado N, Morante-Zarero S, Sierra I. The concerning food safety issue of pyrrolizidine alkaloids: An overview. Trends in Food Science & Technology. 2022;120:123-39.
- [54] Fu PP, Xia Q, He X, Barel S, Edery N, Beland FA, et al. Detection of pyrrolizidine alkaloid DNA adducts in livers of cattle poisoned with *Heliotropium europaeum*. Chemical research in toxicology. 2017;30(3):851-8.
- [55] To YC, Pan Y, Yan X, He Y, Lin G. The toxicokinetic and metabolism of structurally diverse pyrrolizidine alkaloids in rats. Journal of Ethnopharmacology. 2024;321:117390.
- [56] Zhu L, Zhang C, Zhang W, Xia Q, Ma J, He X, et al. Developing urinary pyrrole–amino acid adducts as non-invasive biomarkers for identifying pyrrolizidine alkaloids-induced liver injury in human. Archives of Toxicology. 2021;95(10):3191-204.
- [57] Colegate SM, Upton R, Gardner DR, Panter KE, Betz JM. Potentially toxic pyrrolizidine alkaloids in *Eupatorium perfoliatum* and three related species. Implications for herbal use as boneset. Phytochemical Analysis. 2018;29(6):613-26.
- [58] Cramer L, Schiebel H-M, Ernst L, Beuerle T. Pyrrolizidine alkaloids in the food chain: development, validation, and application of a new HPLC-ESI-MS/MS sum parameter method. Journal of agricultural and food chemistry. 2013;61(47):11382-91.
- [59] Fu PP, Xia Q, Lin G, Chou MW. Pyrrolizidine alkaloids—genotoxicity, metabolism enzymes, metabolic activation, and mechanisms. Drug metabolism reviews. 2004;36(1):1-55.
- [60] Schrenk D, Gao L, Lin G, Mahony C, Mulder PP, Peijnenburg A, et al. Pyrrolizidine alkaloids in food and phytomedicine: Occurrence, exposure, toxicity, mechanisms, and risk assessment-A review. Food and Chemical Toxicology. 2020;136:111107.
- [61] Allemang A, Mahony C, Lester C, Pfuhler S. Relative potency of fifteen pyrrolizidine alkaloids to induce DNA damage as measured by micronucleus induction in HepaRG human liver cells. Food and chemical toxicology. 2018;121:72-81.