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수종 곤충류 한약재 및 함유 아미노산의 알레르기 질환 치료의 유용성 연구

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The potential usefulness of several medicinal insects and their major amino acids in allergic disorders

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ABSTRACT

Objectives : Edible insects are the widely distributed group of animals and contain high quality proteins, fatty acids and minerals. In particular, insects are a possible interesting source of essential amino acids. Insects as traditional medicines have much potential as pharmaceuticals in modern medicines including treating infections, cancer, dissolving phlegm, relieving spasms, and inflammatory diseases. The aim of this study is to investigate the immunomodulatory effect of several kinds of insects and major amino acids.

Methods : In our review we try to show the potential usefulness of insects and amino acids in searching for new therapeutic solutions for immunologic diseases. We summarized the knowledge about properties, usefulness of insect and amino acids in drug design. We hypothesized that insects and amino acids, their major ingredients, regulates airway inflammation and immunologic diseases and can be developed as therapeutic drugs for the treatment of immunologic diseases.

Results : Several insects including *Bombyx mori, Cryptotympana pustulata*, *Holotrichia diomphalia, Locusta migratoria,* etc. and amino acids such as glutamine, glutamic acid, methionine and glycine may have potential protective effects against asthma and airway neutrophilia. Glutamic acid, cystine, methionine and glycine which contribute to glutathione metabolism, which are important anti-oxidant amino acids that may affect susceptibility to asthma.

Conclusions : Our results provide evidence about the potential usefulness of several insects and their amino acids in allergic disorders. These findings suggest that several insects and amino acids have important roles in the way they affect the immune system and allergic responses.

Key words : Insect, amino acids, allergic diseases

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Ⅰ. Introduction

Traditional insect medicine is an old ancient medicinal concept that is still used in South Korea, China and other countries. The discovery of biologically useful substances contained in these traditional insects makes a potentially important medicinal application[1]. Insects are widely used as traditional medicines in the drug materials in South Korea and East Asia[2]. In Korean food code, there are six edible insects, including grasshoppers[3].

Nutritionally, insects contain quality amino acids and other essential nutrients, and are regarded an important component of the diet in different parts of the world. It also has a suitable ratio of amino acids and unsaturated fatty acids to meet the demands of human nutrition[4]. Insects have the potential to serve as sustainable, healthy alternatives to these because of their nutritional contents. Insects may have health benefits due to their high levels of essential amino acids, vitamin B_{12}, iron, zinc, fiber, omega-3 and omega-6 fatty acids, and antioxidants[5]. The bioactive amino acids or peptides from insects have beneficial effects on human health, such as antimicrobial, antioxidant and antidiabetic properties, and can also be used as functional food ingredients[6]. In addition to being used as food, insects are also used in pharmaceuticals to treat human diseases[7].

Our study aimed to describe the amino acids composition, therapeutic potential of several edible insects by reviewing recent researches on these insects and promoting the better development and utilization of edible insects and their amino acids.

Ⅱ. Materials and methods

1. Methodology

We searched Pubmed, MEDLINE, EMBASE and ScienceDirect for english-language sources using the following keywords: insects, allergic disorder, asthma, inflammation and amino acids. Preferences were given to the sources published until May 30, 2024. This search was performed by containing the following search terms : “insect”, “asthma”, “allergic disorder”, “amino acid”. We reviewed and analyzed the retrieved papers written by experts in asthma, and edible insects. We discuss potential usefulness of medicinal insects and their major amino acids in allergic disorders such as asthma. Our opinions expressed in this paper are also based on the references.

Ⅲ. Results

1. Nutritional value and amino acids of several insects

Although insects are small, they are protein-rich. There is a mean protein concentration of ~55% on a dry matter basis, and this protein concentration varies from ~20 to 80%[8]. In terms of protein content, both adult forms of the larval forms of the species *Bombyx mori* L. (23.1 g/100 g) and, the *Tenebrio molitor* species (24.13 g/100 g) and, *Tenebrio molitor* L. (25.0 g/100 g), and *Gonimbrasia belina* L. (35.2 g/100 g) contained the highest protein content[9]. Recent studies reported that protein content to 82% for migratory locust and yellow mealworm[10-12]. Whole migratory locust is considerable rich in alanine, glutamine/glutamic acid and leucine, but lacks in methionine, histidine and cysteine[11].

Martin et al. reported that the high protein contents were found in *Schistocerca gregaria* (76%), *Gryllodes sigillatus* (70%), *Alphitobius diaperinus* (67%), *Sphenarium purpurascens* (65%), *Acheta domesticus* (63%), *Locusta migratoria* (59%), *Gryllus bimaculatus* (58%), *Bombyx mori* (51%), *Gryllus assimilis* (51%), greatly exceeding that of the other insect species. Besides these species, other insect species were generally characterized by relative low protein levels (42%, 39%, 38%, 34%, and 28% in *Zophobas morio, Galleria mellonella, Macrotermes subhyalinus, Rhynchophorus ferrugineus*, and *Rhynchophorus palmarum*, respectively)[13]. Moreover, the nutritional value of proteins is evaluated by their essential amino acids content. These medicinal insects are sources of beneficial animal protein containing all essential amino acids in their composition. They can be used to enrich amino acids, including essential amino acids such as glutamine, glutamic acid, histidine, leucine, lysine, threonine, and tryptophan, with complete proteins[9]. In general, proteins are made up of over 20 amino acids, but eight of them cannot be synthesized in the body and need to be taken in from outside for nutritional requirements. All of the essential amino acids can be found in edible insect proteins. Zhou et al. reported that the high amino acids composition was found in *Bombyx mori, Cryptotympana pustulata, Holotrichia diomphalia, Locusta migratoria, Antheraea pernyi, Gryllodes sigillatus, Schistocerca gregaria, Hermetia illucens, Chilecomadia moorei, Gryllus*

bimaculatus, Tenebrio molitor, *Galleria mellonella, Periplaneta americana* etc.[14-18]. The amino acid content of several edible insects is isoleucine, leucine, lysine, methionine, cysteine, phenylalanine, tyrosine, threonine, tryptophan, valine, arginine, histidine, alanine, aspartic acid, glutamic acid, glycine, proline, serine. Glutamic acid, glycine, aspartic acid, valine, phenylalanine, proline, and alanine are the most abundant of these amino acids. Definitely, medicinal insects contain a high proportion of essential amino acids as well as a wide range of amino acids.

Ⅳ. Discussion

1. Potential usefulness of amino acids and several insects in allergic disorders

As shown table1, amino acids contribute to various immunological activities relevant to asthma pathogenesis. Glutamine, glutamic acid, Methionine and glycine may have potential protective effects[19]. Glutamic acid, cystine, methionine and glycine which contribute to glutathione metabolism[20], which are important anti-oxidant amino acids that may affect susceptibility to asthma[21]. Arginine has been shown to be elevated in asthma, and L-arginine supplementation inhibited increased airway smooth muscle relaxation and the airway hyperresponsiveness (AHR) to methacholine in guinea pig tracheal preparations[22, 23]. In addition, reduced L-arginine levels may contribute to the airway inflammation and airway hyperresponsiveness, which may involve decreased production of bronchodilating nitric oxide (NO)[24]. The intranasal administration of Poly-γ-glutamic acid to ovalbumin (OVA)-challenged mice reduced the allergic inflammation and airway hyperresponsiveness such as T helper 2 (Th2) cytokine production, goblet cell hyperplasia, eosinophilia, and leucocyte influx[25]. L-theanine (N-ethyl-L-glutamine), a unique non-protein amino acid, alleviates airway inflammation in asthma, which may occurs via the oxidative stress-responsive the nuclear factor kappa B (NF-kB) pathway[26].

Seo et al. reported that in the asthma and normal control groups, glutamine was most abundant, followed by alanine and valine. Amino acids including alanine among 27 amino acids were increased in asthma group except for four amino acids of glutamic acid, glutamine, lysine, and pyroglutamic acid[27]. Tryptophan metabolic pathway play a pivotal actor in the regulation of type 2 immunity in allergic diseases[28]. Glutamine exhibits a useful effect on murine asthma, and effectively inhibited the key features of Th2-dominant asthma, such as airway type 2 cytokine production, airway eosinophilia, the recruitment of neutrophils into the airway, and mucus formation, as well as airway hyperresponsiveness[29]. In addition, glutamine also suppressed airway neutrophilia via inhibiting p38 mitogen-activated protein kinase (MAPK) in asthmatic model mice[30]. The administration of L-glutamine suppressed allergic airway inflammation via the rapid upregulation of MAPK phosphatase (MKP)-1 by deactivating c-Jun amino-terminal kinase (JNK) and p38 MAPKs[31]. Glycine significantly suppressed allergy development by a reduction in anaphylaxis, acute allergic skin response, serum levels of whey specific immunoglobulin E (IgE), and serum monocyte chemoattractant protein-1 (MCP-1)[32].

Protein quality of edible insects is generally excellent and these insects appeared to be an excellent source of essential amino acids which provide 46 ~ 96% of edible insect protein composition[33]. In many cases, when compared with meat and plant protein, edible insects have high quality proteins in terms of essential amino acid composition, their nutritional value, total protein content, and protein efficiency[34]. In addition, the average essential amino acids content of aquatic insects is about 51%, and the most abundant essential amino acid is leucine. The small amounts of amino acids were methionine, cysteine and trptophan. The content of glutamine is the highest among all the amino acids in aquatic and terrestrial insects. The average essential amino acid content of terrestrial insects is about 49%, and the most abundant essential amino acid is leucine. The small amounts of amino acids were threonine and tryptophan[35]. Kim et al.[36], showed that *Cryptotympana pustulata* has the potential for the treatment of asthma via the inhibition of the GATA binding protein 3 (GATA-3)/Th2 and Interleukin (IL)-17/retinoid-related orphan receptor gamma t (RORγt) signaling pathways. Hong et al.[37], reported that anti-asthmatic effects of *Holotrichia diomphalia* larvae may occur through the suppression of Th2 cytokines and by inhibition of the GATA-3 transcription pathway.

Bombyx batryticatus (dried larva of *Bombyx mori* L.) is one of the most important and frequently used traditional insect medicines, which has been used to treat cough, asthma, convulsions, headaches, skin prurigo, tonsillitis, scrofula, and other diseases[14]. In recent, it is reported that silkworm (*Bombyx mori*) larval powder downregulated the expression of inflammatory cytokines and proteins while ameliorating the clinical features of atopic dermatitis[38].

Table 1. Major amino acids in medicinal insects and their biological activities in the development of immunological diseases such as asthma

Amino acids	Molecular formula	Pharmacological activities & Key findings	References
Alanine	$C_3H_7N1O_2$	MPS (MARCKS Phosphorylation Site) peptide caused a decrease in p-MARCKS (Myristoylated Alanine-Rich C Kinase Substrate), nitrotyrosine and the expression of oxidative stress enzymes, NADPH oxidase dual oxidase 1 and inducible NOS, in lung tissues.	39)
		MPS peptides inhibited C5a production and attenuated IL-17A and KC production in the airway more effectively, thus suppressing asthma symptoms.	
		Increased Escherichia spp. accompanied by increased β-alanine and 4-hydroxybutyrate appeared to reduce butyrate production. Low fecal butyrate was significantly associated with increased total serum and mite allergen-specific IgE levels in children with asthma ($P < 0.05$).	40)
Arginine	$C_6H_{14}N_4O_2$	A positive correlation between urea-1-carboxylate and AHR was observed in arginine and proline metabolism pathway.	41)
		Low arginine bioavailability plays a pivotal role in the pathogenesis of acute asthma	42)
		L-arginine is the precursor for nitric oxide (NO), polyamines, proline, glutamate, creatine, and agmatine	
		Arginase decreases bioavailability of L-arginine for nitric oxide synthase (NOS), thereby limiting NO production	43)
		Arginase may also contribute to the uncoupling of NOS and the formation of the proinflammatory oxidant peroxynitrite in the airways	
		Ex vivo studies using animal models of allergic asthma have indicated that attenuated L-arginine bioavailability to NOS causes deficiency of bronchodilating NO and increased production of procontractile peroxynitrite, which importantly contribute to allergen-induced airway hyperresponsiveness after the early and late asthmatic reaction	44)
		Reduced L-arginine levels may contribute to the airway inflammation associated with the development of airway hyperresponsiveness, which similarly may involve decreased NO synthesis and increased peroxynitrite formation.	
		Alterations in the L-arginine metabolism resulting in reduced availability of the substrate L-arginine for NO synthases contribute to the reduced NO formation and airway dysfunction in asthma.	45)
Cysteine	$C_3H_7N_1O_2S_1$	There are convincing data in favor of N-acetyl-cysteine supplementation for the patient with COPD at doses ranging between 400 and 1200 mg daily	46)
		Cysteine oxidation was present in children with difficult-to-treat asthma and accompanied by increased reactive oxygen species generation and increased CCL3 and CXCL1 mRNA expression.	47)
		Cysteine oxidations contribute to chronic inflammation and asthma, as well as insights into potential cysteine thiol-based therapeutic strategies.	48)
Glutamic Acid	$C_5H_9N_1O_4$	γ-PGA (Poly-γ-Glutamic Acid) activates DCs to favour Th1 cell induction through a TLR-4-dependent pathway and alleviates pathologic symptoms in a Th2-biased asthmatic model.	25)
		There is no evidence to support the avoidance of MSG in adults with chronic asthma	49)
Glutamine	$C_5H_{10}N_2O_3$	Glutamine suppressed airway neutrophilia by inhibiting cPLA2 (Cytosolic PhosphoLipase A2) phosphorylation, at least in part through deactivation of p38 MAPK in the asthmatic lungs	50)
		We found a significant association ($p = 0.009$) between the glutamine 27 beta2-adrenoceptor polymorphism and elevated levels of IgE.	51)

Amino acids	Molecular formula	Pharmacological activities & Key findings	References
Glycine	$C_2H_5N_1O_2$	Glycine protects against asthma, since glycine is required for the formation of glutathione, a molecule that regulates intracellular oxidation status and may be important in the pathophysiology of asthma.	19)
		In a rat model, a glycine-supplemented diet reduced oxidative stress and augmented anti-oxidant enzyme activities, while it also downregulated the expression of nuclear factor-kB and inducible nitric oxide synthetase, both of which are increased in the inflammation associated with asthma.	
		Guinea pig airway ring relaxation of ACh-induced contractions by isoproterenol was significantly left-shifted in the presence of glycine.	52)
		Glycine treatment during tachykinin- and acetylcholine-induced contractions significantly decreased the maintenance of muscle force compared to control.	
		The homozygous glycine-16 (Arg-->Gly) variant of the beta 2-adrenoceptor is known to predispose to agonist-induced down-regulation and desensitization, and may play a role in the pathogenesis of asthma severity.	53)
Histidine	$C_6H_9N_3O_2$	Urinary l-histidine levels were significantly higher in patients with ACO (Asthma-COPD Overlap) than in those with asthma or chronic obstructive pulmonary disease (COPD).	54)
		In asthma, if these peptides are broken down more rapidly by enzymes from inflammatory cells, this might contribute to exaggerated bronchial responsiveness.	55)
Leucine	$C_6H_{13}N_1O_2$	Sputum leucine-rich alpha-2 glycoprotein (LRG) concentrations were significantly higher in patients with asthma than in healthy volunteers ($p = 0.00686$).	56)
		Consistent with patients' data, bronchoalveolar lavage fluid (BALF) LRG levels in asthma model mice were significantly higher than in control mice ($p = 0.00013$).	
Lysine	$C_6H_{14}N_2O_2$	Asthma involves a variety of proteome dynamics and is controlled by protein lysine acetylation through the core motif -KAXXK-.	57)
Methionine	$C_5H_{11}N_1O_2S_1$	Palmitic acid and methionine were the main metabolites for discrimination between asthma and the control followed by pipecolic, lactic, α-ketoglutaric, and linoleic acids for high classification accuracy as potential biomarkers.	27)
Tryptophan	$C_{11}H_{12}N_2O_2$	Production of tryptophan metabolites was partly responsible for the allergen-specific immunotherapy-induced increase in Tregs, decrease in airway inflammation, and decrease in inflammatory cytokines.	58)
		An enhanced formation of NO · has been reported in patients with asthma and allergic rhinitis.	59)
		Tryptophan, kynurenine, and neopterin levels were significantly higher in asthmatic children than in healthy controls	60)
Tyrosine	$C_9H_{11}N_1O_3$	Various receptor and nonreceptor tyrosine kinase pathways contribute to aspects of airway inflammation, airway hyperresponsiveness, and remodeling of asthma.	61)

Although the reports on the food safety of insects indicate that edible insects are safe for food or medicinal source. Some report showed that incidences of allergic reactions after consuming cicadas, silkworm pupae, and crickets have been reported in China[62].

After the ingestion of edible insects, allergic reactions can be possible in sensitive individuals. The scientific communities must investigate together to promote the use of insects. More additional studies based on subjects with a confirmed insect allergy are necessary to identify major and minor allergens to suppress allergic reactions.

Ⅴ. Conclusions

In conclusion, these results provide evidence about the potential usefulness of amino acids from medicinal insects in allergic disorders. Overall, several insects

and their major amino acids have various roles in the way they affect the immune system and allergic responses and no single dietary amino acid is suitable for treating allergic disorders.

It is necessary to conduct more large scale studies with relevant animal models to arrive at meaningful recommendations for various amino acids interventions for clinical usefulness. Further scientific research will be accomplished. This issue is, and will be subject of work of many researchers from different areas.

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