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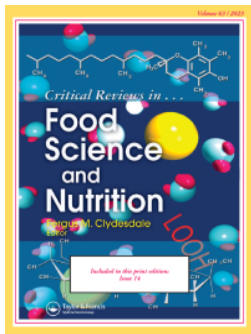


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REVIEW



Allergenicity, assembly and applications of ovalbumin in egg white: a review

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ABSTRACT

Ovalbumin (OVA), the most abundant protein in egg whites, has been widely used in various industries. Currently, the structure of OVA has been clearly established, and the extraction of high-purified OVA has become feasible. However, the allergenicity of OVA is still a serious problem because it can cause severe allergic reactions and may even be life-threatening. The structure and allergenicity of the OVA can be altered by many processing methods. In this article, a detailed description on the structure and a comprehensive overview on the extraction protocols and the allergenicity of OVA was documented. Additionally, the information on assembly and potential applications of OVA was summarized and discussed in detail. Physical treatment, chemical modification, and microbial processing can be applied to alter the IgE-binding capacity of OVA by changing its structure and linear/sequential epitopes. Furthermore, research indicated that OVA could assemble with itself or other biomolecules into various forms (particles, fibers, gels, and nanosheets), which expanded its application in the food field. OVA also shows excellent application prospects, including food preservation, functional food ingredients and nutrient delivery. Therefore, OVA demonstrates significant investigation value as a food grade ingredient.

KEYWORDS

Allergenicity; assembly; extraction; ovalbumin; potential applications; structure

Introduction

Ovalbumin (OVA), the main protein fraction of poultry eggs, is the first protein separated into monomers in egg white (Zhu et al. 2018). OVA has attracted increasing interest for its good functions, including gelling, foaming and emulsifying properties. Moreover, some studies indicated that OVA and its hydrolysates had many biological activities such as anti-bacterial, antioxidant, and anti-inflammatory. In recent years, the isolation and purification of high purity OVA from egg white proteins is no longer a great challenge due to the continuous endeavors of scientific researchers. This will provide support for further investigation and application of OVA.

OVA, an essential component in immunology and nutrition, is often used as a standard protein in dietary allergy trials (Zhang et al. 2022). Some children who consume foods containing OVA have developed hives and rashes, which are typical of allergies (Vapor, Mendonca, and Tomaz 2022). In fact, the most effective way to control OVA allergy is to avoid eating all food products that contain OVA. However, complete abstinence is unrealistic with the increasing use of OVA in food industry. Thus, a growing number of researchers have investigated the effect of different processing methods on the OVA-induced allergic reactions. The appropriate processing methods can significantly reduce the allergenicity of OVA. Currently, the commonly used processing methods include physical treatment (heat, pressure,

light, and mechanical activities), chemical modification, and biological treatment (Chizoba Ekezie, Cheng, and Sun 2018; Costa et al. 2022). OVA conformational changes induced by different processing methods can directly affect its allergenicity. Moreover, the change of OVA structure is also affected by numerous environmental factors, including ionic strength, pH value, and temperature (Xu et al. 2020). Therefore, the influence of different treatment technologies on OVA allergenicity was introduced in this review.

Generally, the assembly of OVA is achieved by covalent or non-covalent bonding driven aggregation of protein particles or fragments. Compared to natural OVA, assembly of OVA exhibited various shapes, and functional properties (Tufail et al. 2018; Huyst et al. 2022; Visentini, Perez, and Santiago 2019). Furthermore, the structural and functional characteristics of OVA can be altered by assembly with polysaccharides, proteins and phenolic compounds (Jin et al. 2022; Qian et al. 2022). In contrast to simple protein aggregation, the assembly of ovalbumin can form ordered new structures, which further enlarge the range of applications in delivery systems such as emulsion, gel, and nanoparticles.

Recently, Chen et al. reviewed the impact of the non-thermal processing on the functional properties and allergenicity of OVA (Chen et al. 2023). However, thermal treatment remains a simple and effective method to reduce protein allergenicity, and thus this review provides a

comprehensive summary on the control of OVA allergens *via* various processing methods such as physical treatment, chemical modification, and microbial processing. Additionally, the assembly of OVA and its potential applications have never been summarized. Therefore, this article gives a detailed introduction and up-to-date overview on the assembly of OVA. Also, a comprehensive review of the various applications of OVA in the food field is also presented. Finally, this article provides some helpful research directions for the utilization of OVA. In-depth understanding of the structure, extraction, allergenicity, assembly, and application of OVA is critical to developing high-value products.

Structure and extraction of OVA

Structure of OVA

OVA is a typical monomer globular phosphoglycoprotein with 3 nm diameter. The protein is composed of 385 amino acids with a molar mass of 45 kDa and isoelectric point of 4.5 (Zeng et al. 2022). OVA contains 3.5% of the glycosyl group, which is about 55% of the total egg white protein (Hu et al. 2022). The size of the OVA gene is about 7.6 kb, including eight exons and seven introns. Moreover, OVA has five different IgE-binding epitopes, four of which are exposed on the protein surface. Approximately half of this protein molecule is composed of hydrophobic amino acids, of which 1/3 are charged (Jin et al. 2021). In addition, the OVA sequence consists of four sulfhydryl groups and a disulfide bond between Cys73-Cys120 (Hu et al. 2022). It is the only protein in the egg white that the sulfhydryl group is buried in the hydrophobic core (Gharbi and Labbafi 2018). Previous studies found that OVA had an N-terminal amino acid of acetylated glycine and a C-terminal amino acid of proline, and one carbohydrate group covalently was linked to the amide nitrogen of Asn-292 (Jin et al. 2022). The three forms of OVA are A1-, A2- and A3-OVA with

2, 1, and 0 phosphate groups, respectively (Jin et al. 2021). OVA is usually presented in a dephosphorylated form. The serine residues at position 68 and/or 344 of the protein molecules have different dephosphorylated groups and potential cellulose phosphate. Moreover, OVA has been used as a model protein for scientific research due to its structural and functional properties. The structure of OVA could be altered by food processing (thermal treatment, ultrasonic treatment, high pressure, and pulsed electric field), affecting its functional properties and physicochemical properties (Zhu et al. 2018). During long-term storage of non-fertilized eggs and incubation of fertilized embryonic eggs, OVA could be converted to a heat-stable S-OVA (Liao et al. 2018; Yamasaki, Takahashi, and Hirose 2003).

For secondary structure, OVA contains 33% α -helix, 5% β -sheet, 12% β -turns, and 13% random coils. Numerous studies reported that the secondary structure of OVA could be altered by thermal and non-thermal techniques, thereby improving the functional properties and allergenicity of OVA (Chizoba Ekezie, Cheng, and Sun 2018). Moreover, the secondary structure change of OVA is closely related to pH. Alkali- or acid-induced OVA structural changes increased intermolecular or intramolecular chromophore interactions, but did not affect the polarity changes of the chromophore environment (Jin et al. 2021). The secondary structure of OVA is highly conserved at pH 3–11. OVA could form highly aggregated spheres with strong structural integrity at pH 3, while its structure became unfolded and flexible at pH 11 (Xu et al. 2020). For the crystal structure of OVA, the α -helix protrudes serves as the reactive center loop and the β -sheet was parallel to the long axis of the molecule. Furthermore, X-ray crystallography revealed that the size of the OVA monomer is $2.9 \times 3.5 \times 7.2$ nm ellipsoidal (Yamasaki, Takahashi, and Hirose 2003). The crystal structures of OVA and S-OVA are shown in Figure 1A and B, respectively. PDB ID of OVA and S-OVA are 1OVA and 1UHG, respectively (Visit website: <http://www.rcsb.org>).

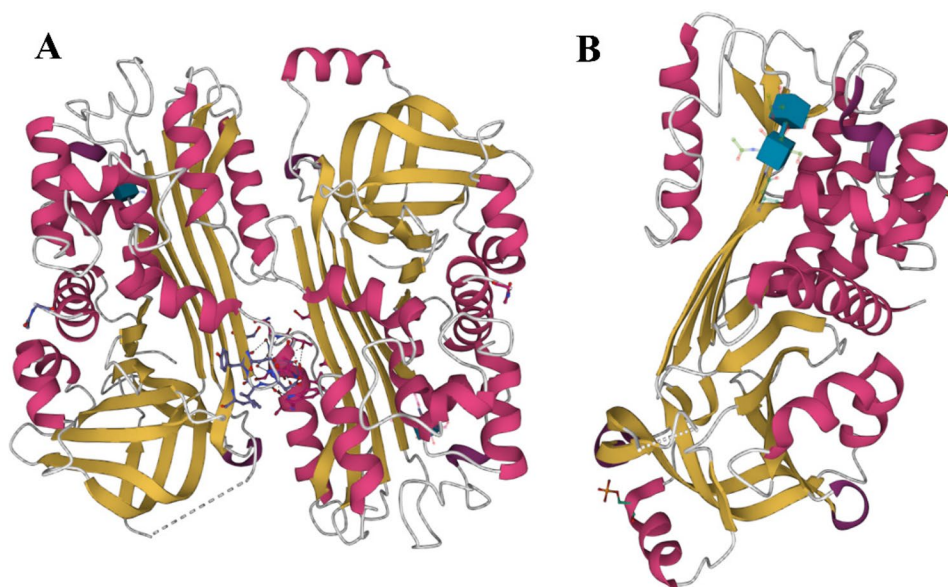


Figure 1. The crystal structure of OVA (A) and S-OVA (B).

Table 1. Extraction of OVA using different methods.

Extraction methods	Purity (%)	Recovery (%)	References
Poly(ethylene glycol) (PEG)–poly(acrylic acid) aqueous two-phase systems	–	87.4	Saravanan et al. (2008)
Two-stage ultrafiltration	98.7	–	Datta et al. (2009)
Ion-exchange chromatography	91.2	71.0	Omana, Wang, and Wu (2010)
Q Sepharose fast flow anion exchange chromatography	70	54	Tankrathok et al. (2009)
Polyethylene glycol precipitation and anion-exchange chromatography	96.4	88.6	Geng et al. (2012)
High-level ethanol (61% final concentration) or an acidic salt combination (2.5% ammonium sulfate and 2.5% citric acid)	>96	>98	Abeyrathne et al. (2014)
Reverse micellar extraction	>90	50	Ding, Cai, and Guo (2015)
Keggin-type cobalt mono-substituted silicotungstic acid doped with aniline	92	84.4	Zhang et al. (2015)
Aqueous biphasic systems composed of polyethylene glycols of different molecular weights and buffered aqueous solutions of potassium citrate/citric acid	98.9	65	Pereira et al. (2016)
Polyethylene glycol precipitation and isoelectric precipitation	95.1	46.4	Geng et al. (2019)
Tungstotellurate (VI)-coated magnetic nanoparticles	91.6	98.1	Che et al. (2019)
Aqueous two-phase flotation (composed of polyethylene glycols (PEG 1000) and $(\text{NH}_4)_2\text{SO}_4$)	92.98	82.15	Jiang et al. (2019)
Successive extraction/precipitation	>95.9	>77	Ji et al. (2020)
Ionic-liquid-based aqueous biphasic systems	100	–	Belchior et al. (2020)
Modifying polyamide hollow fiber membranes using immobilized metal affinity chromatography technique	95.2	46.4	Ozbek et al. (2022)

Note: – Indicated no data.

Extraction and purification of OVA

OVA has promising applications in the food industry, nutraceuticals, cosmeceuticals, and pharmaceuticals owing to its excellent physicochemical properties and multifunctional nature (Ji et al. 2020). Previous studies demonstrated that OVA and its hydrolysates had many biological functions, such as antioxidant, anti-hypertensive, and anti-inflammatory activity (Bueno-Gavila et al. 2021; Khueychai et al. 2018; Kim et al. 2020). Thus, the isolation and purification of OVA from egg white by various techniques appeared valuable (Table 1).

Many methods could be applied to separate high-abundance OVA from egg white protein. The common technologies for the isolation and purification of OVA are mainly divided into two categories. One regards methods that can be developed for industrial scale, including ultrafiltration, organic solvent precipitation, salting-out, isoelectric point precipitation, ion-exchange chromatography, and polyethylene glycol precipitation (Geng et al. 2012; Geng et al. 2019; Pereira et al. 2016). The other category is the lab-scale methods, including gel permeation, electrophoresis, reverse micelles, affinity chromatography, exclusion chromatography, and extraction techniques (liquid–liquid extraction, solid phase extraction, and reverse micelle extraction) (Che et al. 2019; Ding, Cai, and Guo 2015; Jiang et al. 2019). Datta et al. used a two-step ultrafiltration technique to isolate OVA with a high purity of 98.7% (Datta et al. 2009). Moreover, Omana et al. obtained OVA with high protein purity and recovery from the supernatants of the ovomucin-removed egg whites by ion-exchange chromatography (Omana, Wang, and Wu 2010). Previous studies had used two or more chromatographic methods to obtain OVA, but protein separation efficiency was limited (Tankrathok et al. 2009). Subsequently, Abeyrathne et al. proposed an efficient and cost-effective separation protocol for OVA, which not only ensured high protein purity but also further improved the yield (Abeyrathne et al. 2014). Ji et al. further optimized the separation and purification technique of OVA and also used MALDI-TOF-MS to identify the protein (Ji et al. 2020). They established an efficient and economical extraction method for the major proteins from egg white with high purity and yield.

Recently, several novel extraction materials have been increasingly used to isolate and purify proteins. Saravanan et al. investigated the separation effect of OVA in poly(ethylene glycol) (PEG)-poly(acrylic acid) aqueous biphasic systems, attaining a protein yield of 87.4% (Saravanan et al. 2008). Zhang et al. synthesized a composite of mono-substituted silicotungstic acid doped aniline with porous structure as a solid phase extractant (Zhang et al. 2015). It showed significant selective adsorption of OVA in complex biological sample matrices with maximum adsorption efficiency and recovery of 92% and 84.4%, respectively. Moreover, OVA extraction with reverse micelles has attracted much attention since some new Gemini surfactants are promising candidates for OVA extraction (Ding, Cai, and Guo 2015). A novel ionic-liquid aqueous biphasic system composed of tetraalkylammonium-based ionic liquids and potassium phosphate solution showed high extraction and recovery of OVA (Belchior et al. 2020). Ozbek et al. modified polyamide hollow fiber membranes by immobilized metal affinity chromatography for the purification of OVA (Ozbek et al. 2022).

Effects of processing methods on the allergenicity

The allergenicity of OVA is weaker than that of ovomucoid in egg white protein, but the allergenicity of OVA cannot be ignored (Vapor, Mendonca, and Tomaz 2022). OVA-induced allergic reactions are usually accompanied by elevated IgE levels, reduced T-cell levels and Th1/Th2 response imbalance (Figure 2A) (Sun et al. 2022). Recently, some researchers investigated the effects of different treatments on the allergenicity of OVA (Figure 2B and Table 2) (Zhu et al. 2018).

Physical treatment

Thermal treatment

Heating of allergenic proteins can reduce or increase allergenicity by promoting structural changes and conformational epitope destruction. Many research focused on minimizing the allergenicity of proteins by thermal

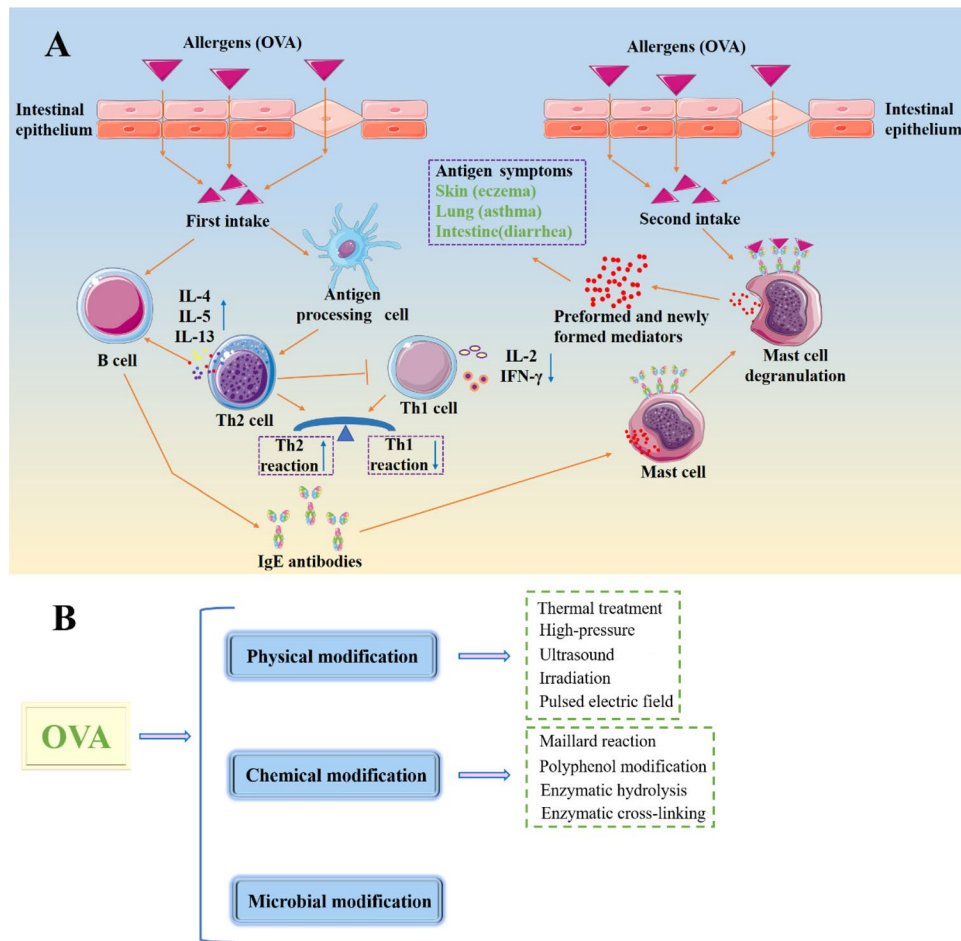


Figure 2. The mechanism of IgE-mediated allergic reaction (A) and the different processing methods for allergen OVA (B).

treatment. Watanabe et al. used heat-induced (at 100 °C for 5 min) OVA to feed mice and their results showed reduced T-cell responses and IgE binding levels (Table 2) (Watanabe et al. 2014). Moreover, the heat-treated OVA could improve allergic responses in mice by producing more type 1 CD4⁺ T cytokines and reducing histamine concentrations (Rupa, Schnarr, and Mine 2015). Heating of OVA above 80 °C (alkaline conditions) led to a significant reduction in the content of sensitizing components, suggesting that temperature and pH strongly influenced the protein structure and allergenicity (Stănciuc et al. 2016). The allergenicity of OVA samples prepared at high temperatures (>130 °C) could also be reduced.

Moreover, heat-induced OVA aggregation caused partial concealment of IgE allergen epitopes, reducing the allergic response to OVA. Claude et al. investigated the changes in allergenicity during the thermal aggregation of OVA. Their results showed that OVA aggregates formed under repulsive electrostatic conditions showed low allergenicity potential (Claude et al. 2017). Furthermore, allergen aggregation decreases absorption and transport of the epithelial layer, thus reducing its allergenicity. Notably, altering protein digestibility by heat treatment could also affect allergenicity. The heat-aggregated OVA increased its digestibility, induced basophil degranulation, and weakened IgE binding (Claude et al. 2019). Digestion products of OVA significantly reduced

allergic diarrhea and other allergenic symptoms in mice after gavage of heat-treated OVA. On the other hand, heat-treated egg digestibility increased IgG2a levels and decreased mast cell protease-1 activity in mice, indicating reduced allergenicity (Gharbi and Labbafi 2018). Therefore, thermal treatment of OVA might be an effective way to improve the efficiency of allergen-specific immunotherapy.

High-pressure processing

High pressure, also known as high hydrostatic pressure, is an effective processing technology for protein allergenicity. High-pressure technologies ranging from 100 to 800 MPa could improve protein functional properties. It has been reported that the conformational change of protein induced by high-pressure treatment was responsible for its regulation of digestibility and hypersensitivity (Zhu et al. 2018). Smith et al. found that high-pressure treatment could cause significant structural changes in ovalbumin, but its allergenicity had not been studied (Smith et al. 2000). Moreover, the researchers demonstrated rapid hydrolysis of OVA at high pressure (400 MPa) and reduced IgE binding ability of the hydrolysates (Table 2) (Lopez-Exposito et al. 2008). The binding specificity of OVA hydrolysates to IgG/IgE was not wholly lost. High-pressure treatment enhanced the digestion of the cross-linked products of transglutaminase

Table 2. Effect of different processing methods on the allergenicity of OVA.

	Processing methods	Detection methods	Impact on IgE-binding capacity	References
Physical treatment	Thermal treatment	Mice model, ELISA, RBL mediator release assay	Decrease	Claude et al. (2017)
		ELISA, RBL mediator release assay Mice model, ELISA	Decrease	Claude et al. (2019)
		ELISA	Inconclusive	Rupa, Schnarr, and Mine (2015)
		Mice model	Decrease	Stănciuc et al. (2016)
	High-pressure	ELISA	Decrease	Watanabe et al. (2014)
		Mice model, ELISA	Decrease	Lopez-Exposito et al. (2007)
	Ultrasound	ELISA	No effect	Ma, Lozano-Ojalvo, et al. (2015)
		ELISA	Increase	Yang et al. (2017)
	Irradiation	ELISA	Decrease	Yang, Tu, Wang, Zhang, and Song (2018)
		ELISA	Decrease	Yang et al. (2021)
		ELISA	Increase	Bian et al. (2022)
		ELISA	Decrease	Kim et al. (2002)
		Mice model	Decrease	Seo et al. (2007)
	Pulsed electric field	Mice model	Decrease	Yang et al. (2016)
		ELISA, RBL mediator release assay	Decrease	Li, Zhang, et al. (2022)
Physical treatment	Pulsed electric field	ELISA	Increase (low electric field intensity or short time), Decrease (high electric field intensity or long time)	Yang, Tu, Wang, Zhang, Gao, et al. (2018)
		ELISA	Decrease	Yang et al. (2022)
Chemical modification	Maillard reaction	ELISA	Decrease	Jiménez-Saiz et al. (2011)
		ELISA	Decrease	Liao et al. (2018)
		ELISA	Decrease	Yang et al. (2020)
		ELISA	Decrease	Wang, Zhong, and Wang (2022)
		ELISA	Decrease	Ma, Gao, et al. (2015)
	Polyphenol modification	Mice model, ELISA	Decrease	Medeiros et al. (2008)
		Mice model, ELISA	Decrease	Wang et al. (2013)
		Mice model, ELISA	Decrease	Zhang et al. (2019)
		Mice model, Western blot, ELISA	Inconclusive	Herath et al. (2021)
		Mice model, ELISA	Decrease	Li, Zou, and Liu (2022)
	Enzymatic hydrolysis	Western blot, ELISA, Basophil activation test	Decrease	Ognjenovic et al. (2014)
		Western blot, ELISA	Decrease	Lu et al. (2018)
		Mice model, ELISA	Decrease	Zhang, Xiao, and Huang (2020)
		Western blot, ELISA	Decrease	Benedé et al. (2014)
		ELISA	Decrease	Hwang et al. (2016)
	Enzymatic cross-linking	Mice model, ELISA	Decrease	Park et al. (2017)
		Mice model, ELISA	No effect	Ma, Lozano-Ojalvo, et al. (2015)
		ELISA	Decrease	Liu et al. (2018)
		ELISA	Decrease	Li et al. (2021)
		ELISA	Decrease	Kim, Choi, and Ji (2008)
Microbial processing	Microbiological processing	Mice model, ELISA	Decrease	Sunada, Nakamura, and Kamei (2007)
		Mice model	Decrease	Castro et al. (2012)
		Mice model, ELISA	Decrease	Liu et al. (2014)
		Mice model	Decrease	Song et al. (2020)
		Mice model	Decrease	Song et al. (2020)

Abbreviations: ELISA: Enzyme-linked immunosorbent assay; RBL: Rat basophilic leukemia.

and OVA but did not limit its allergenicity (Ma, Lozano-Ojalvo, et al. 2015). Interestingly, the allergenicity of egg white hydrolysates could be reduced by optimizing the pressure range, the type of enzyme and hydrolysis time (Hoppe et al. 2013).

Ultrasound

The ultrasound frequency can be divided into high frequency ultrasound (100kHz–1MHz) and low frequency ultrasound (20–100kHz). Ultrasound induces a cycle of expansion and compression, forming cavitation bubbles. The rupture of these bubbles generates high temperatures and high pressures around them that can be raised to 4726.85 °C and 10–100 MPa, respectively (Zhu et al. 2018). Previous studies have reported that the natural conformation and

functional properties of proteins were altered by ultrasound (Yu et al. 2019). Researchers evaluated the structural and IgG/IgE binding capacity of OVA by high-intensity ultrasound. However, they found that high-intensity ultrasound treatment (200–600 W) enhanced the IgG/IgE binding ability of OVA, especially the most potent binding ability (Zeng et al., 2022) at 600 W (Yang et al. 2017). Interestingly, high-intensity ultrasound combined with other techniques could dramatically decrease the IgE binding capacity of OVA. For example, the synergistic treatment of OVA with ultrasound (0–600 W) and glycation dramatically reduced the binding ability of IgG/IgE (Yang Tu, Wang, Zhang, and Song 2018). It has been found that ultrasound pretreatment combined with glycation resulted in reduced IgG/IgE binding capacity of OVA after digestion *via* simulated gastric and intestinal digestion (Table 2) (Yang et al. 2021).

Irradiation

Irradiation is the transfer of energy from β -rays, γ -rays and X-rays to the irradiated material. The application dose of irradiation in food processing is usually between 1 and 50 kGy, divided into medium dose (1–10 kGy) and high dose (10–50 kGy) (Chizoba Ekezie, Cheng, and Sun 2018). Proteins undergo cross-linking, folding, breaking and new groups during irradiation, causing changes in protein conformation and linear epitopes (Bian et al. 2022). Thus, irradiation might be a potential processing technique to reduce the allergenicity of proteins. KIM et al. showed that a combination of γ -rays irradiation and heat treatment could effectively reduce IgE binding ability caused by OVA (Kim et al. 2002). Electron beam and γ -rays contributed to a diminished binding ability of OVA to IgG/IgE, depending on the conformational variation of the OVA epitope and the irradiation dose. Seo et al. found that OVA treated with irradiation (50 and 100 kGy) significantly reduced T-helper type 2 (Th2) lymphocytes cytokines (IL-4 and IL-5) and IgE binding ability in mice (Seo et al. 2007). The IgE generated by Th2 lymphocytes was closely related to the occurrence of allergic diseases. Irradiation doses of 10 and 20 kGy also reduced the allergenicity of OVA, which offered the prospect of the production of hypoallergenic baked goods. A significant decrease in OVA-specific IgE was observed when gamma-irradiated OVA was fed to mice, indicating that irradiation-treated OVA increases oral tolerance to antigens (Yang et al. 2016). However, ^{60}Co γ -ray irradiation (0–100 kGy) enhanced the allergenicity of OVA in a dose-dependent manner, which might be due to the fact that the allergic epitopes of OVA are more exposed (Bian et al. 2022).

Pulsed electric field

Pulsed electric field (PEF) has been considered an effective non-thermal food processing technology, which uses an external electric field (20–80 kV) to eliminate microorganisms on the food surface while avoiding the loss of nutrients (Yang et al. 2022). PEF treatment can affect protein allergenicity, which is attributed to changes in the structural characteristics of the allergen. It has been reported that the structure of OVA was altered by PEF treatment, thereby weakening the allergenic-antibody interaction (Chizoba Ekezie, Cheng, and Sun 2018). Yang et al. found that the binding ability of OVA to IgG/IgE was significantly reduced at high electric field strength and prolonged exposure, which could be explained by the loss of OVA α -helix structure and the reduction of sulfhydryl content (Yang, Tu, Wang, Zhang, Gao, et al. 2018). Moreover, the allergenicity of OVA was significantly decreased when the electric field intensity and treatment time of PEF were 35 kV/cm and 180 μs , respectively. Li et al. also found that PEF could inhibit allergy by changing the spatial conformation of OVA (Li, Zhang, et al. 2022). This was because PEF treatment caused alterations in hydrogen bond and hydrophobic interactions in OVA, which resulted in the covering of the binding site of the allergic epitope. In another study, PEF treatment synergistic phosphorylation was found to significantly reduce

the IgG/IgE binding capacity of OVA, which also provided a new option for lowering OVA allergenicity (Yang et al. 2022).

Chemical modification

Maillard reaction

Maillard reaction (MR) is a non-enzymatic reaction of proteins or amino acids with reducing sugars during thermal processing, which has been widely used to improve food appearance, flavor, and texture (Vapor, Mendonca, and Tomaz 2022). The initial reaction of protein glycation forms Schiff bases, which are then converted into stable Amadori products. Advanced glycation end products can be developed later in the MR, which is a common way to stabilize proteins in the food industry (Table 2) (Li et al. 2020). The MR reduced IgE binding ability of OVA but increased the combination to ovomucoid in human serum experiments (Jiménez-Saiz et al. 2011). This might be due to the fact that permanent changes in protein structure cause the impact of MR on the immunogenicity and allergenicity of proteins. Liao et al. reported that preheating synergistic glycation treatment triggered a decrease in the binding of IgG/IgE by changing the structure of OVA, indicating that this method could effectively reduce the allergenicity of OVA (Liao et al. 2018). It has been reported that the glycation reaction of OVA with D-glucose and its isomers could also effectively diminish the IgG/IgE binding of OVA (Yang et al. 2020). The configuration of the hydroxyl groups at the C-3, C-4 and C-5 positions in sugars could notably affect the MR because they led to varying degrees of reduction in OVA allergenicity. Moreover, the suppression of allergic reactions in mice by different glycosylated OVA-monosaccharides, particularly OVA-mannose exhibited the least allergic symptom.

Additionally, the MR of various α -dicarbonyl compounds with OVA could markedly reduce the IgE binding level of OVA, and the degree of which was related to the content of total advanced glycation end products and N- ϵ -carboxymethyl lysine. The MR of disaccharides of different configurations with OVA could observably alter protein structure and free amino group content (Wang, Zhong, and Wang 2022). HPLC–HCD–MS/MS analysis showed that the glycation sites were all located on the allergic epitopes of OVA. Ma et al. used response surface analysis to optimize the MR parameters of OVA to find the reaction conditions with the lowest allergenicity (Ma, Gao, et al. 2015). The optimization results revealed that temperature was the main factor that significantly reduced the allergenicity of OVA. It could be seen that the effect of the MR on OVA allergenicity depends on many factors. In addition, understanding better the mechanism involved in immunoreactivity of advanced glycation end products by the interaction of MR-modified OVA with antigen presenting cells and the promotion of T cell differentiation, which would help improve the diagnosis of allergy and obtain the best food processing conditions to control the rate of MR.

Polyphenol modification

OVA and polyphenols are cross-linked by non-covalent interaction and covalent interaction, thereby affecting the structure and allergenicity of OVA. Medeiros et al. showed that bee pollen phenol extract and myricetin synergistically inhibited allergic symptoms in OVA-sensitized mice (Medeiros et al. 2008). Apple polyphenols were effective in reducing the allergenicity of eggs and inhibiting antigen presentation, which was associated with reducing the release of mediators from intestinal mast cells and increasing the number of T cells. Oral intake of areca-derived polyphenols diminished OVA-induced allergic responses, including the infiltration and degranulation of mast cells in the duodenum. Moreover, the IgE binding capacity of OVA was also decreased by areca-derived polyphenols treatment (Wang et al. 2013). Zhang et al. demonstrated that dihydromyricetin could attenuate OVA allergic response in OVA-allergic mice by upregulating the rectal temperature and suppressing the IgE receptor (FcεRI)-IgE interaction (Zhang et al. 2019). Furthermore, *Sargassum horneri* extract displayed Th2 immune inhibition under OVA induction by GATA3- and NLRP3-dependent IL-4, IL-5, and IL-13 inhibition, which might provide a strategy for alleviating allergy-mediated diseases (Herath et al. 2021). The cyanidin-3-O-glucoside could efficiently alleviate OVA-induced allergic reactions, suppress OVA-specific IgE and reduce intestinal epithelial damage (Li, Zou, and Liu 2022).

Moreover, the effect of reducing allergenicity of some polyphenol-OVA conjugates was also studied. The combination of OVA and polyphenols changed the protein structures and formed aggregates of different sizes, which affected the allergenicity of OVA (Vapor, Mendonca, and Tomaz 2022). OVA-epigallo-catechin 3-gallate (EGCG) conjugates reduced OVA-induced allergic reactions by decreasing the binding capacity of IgE (Ognjenovic et al. 2014). This might be due to the EGCG could bind some IgE epitopes in OVA and promote cell degranulation. Lu et al. found that the allergenicity was reduced by coupling chlorogenic acid with OVA, which could be explained *via* the change in protein structure and the hiding of IgE epitopes (Lu et al. 2018). Moreover, the cross-linking of OVA with quercetin could reduce its allergenicity *in vitro* and *in vivo*. It was attributed to quercetin's covalent binding to OVA that modulated the Th1/Th2 immune response, decreased IgE binding capacity, and stimulated cell degranulation (Zhang, Hu, et al. 2020).

Enzymatic hydrolysis

Enzymatic disintegration has been an effective method to change food protein allergens (Costa et al. 2022). Benedé et al. found that treating OVA with human fluids (human gastric and duodenal fluids) degraded faster than simulated gastroduodenal fluids and lowered the IgE binding of digestion products (Table 2) (Benedé et al. 2014). It was worth noting that simulated digestive fluids might produce some peptides with stronger IgE-binding features due to the accumulation of large degradation fragments and small molecule peptides. Hwang et al. explored the possibility of ascidian viscera *N*-acetylglucosaminidase to treat OVA allergies. Their

research concluded that the allergenicity of OVA markedly decreased with the increase in the activity of *N*-acetylglucosaminidase (Hwang et al. 2016). Park et al. found that *N*-acetylcelastrol-treated OVA significantly reduced the level of IgE in the serum of OVA allergic mice and decreased the antigenicity of rabbit anti-OVA serum (Park et al. 2017). Moreover, studies found that OVA hydrolysates were effective in preventing the development of allergies (Lozano-Ojalvo et al. 2017). Therefore, enzymatic processing not only offered prospects for producing low-allergic OVA products but also provided options for immunotherapy of OVA-allergic patients.

Enzymatic cross-linking

Glutaminase, peroxidase, and laccase can change protein structure through cross-linking and covalent binding to influence protein allergenicity. Although the enzyme cross-linking agent has great potential application in the food industry, transglutaminase has no apparent advantage in reducing the IgE binding ability of OVA or other food proteins (Ma, Lozano-Ojalvo, et al. 2015). Previous studies showed that modifying OVA with transglutaminase could improve the digestive performance of gastric and duodenal, functional characteristics and mechanical properties, but the allergic properties were not further studied (Giosafatto et al. 2012). Interestingly, polyphenol oxidase played an essential role in reducing OVA-induced allergies. OVA could be cross-linked by using a polyphenol oxidase in the presence of caffeic acid. As a result, the allergenicity of OVA was markedly decreased due to alterations in the structure and the epitopes of OVA (Liu et al. 2018). Further, Tong et al. found that polyphenol oxidase cross-linking obviously reduced the allergenicity of OVA (Tong et al. 2018). The ferulic acid-grafting-laccase-catalyzed cross-linking modification method resulted in a decreased protein IgE binding capacity, which was associated with the cross-linking extent (Li et al. 2021). Thus, the laccase-catalyzed cross-linking method was a promising way to obtain hypoallergenic proteins.

Microbial processing

In recent years, some researchers believed that the defects in the immune tolerance mechanism regulated by intestinal microorganisms could cause allergic reactions (Song et al. 2020). Therefore, the balance of the intestinal microbial region was regarded as important in preventing food allergies. Oral probiotics had a good anti-allergy effect because it could induce Th1 type immunity and enhance regulatory lymphocytes (Kim, Choi, and Ji 2008). In addition, oral heat-treated *Lactobacillus acidophilus* strain L-55 could reduce sneezing and nasal friction caused by OVA (Sunada, Nakamura, and Kamei 2007). Castro et al. found that *Enterococcus faecalis* CECT7121 could effectively inhibit OVA-triggered allergic reactions in mice (Castro et al. 2012). Another study showed that *Lactobacillus plantarum* K37 played an influential role in preventing OVA-induced allergic reactions and improving the asthma-like response of

OVA-allergic mice (Liu et al. 2014). Furthermore, a novel *Lactobacillus rhamnosus* strain was used to regulate intestinal flora and showed great regulatory ability in OVA-allergic mice (Song et al. 2020). Therefore, probiotics could diminish allergic reactions to a certain extent, but further research on the relationship between probiotics and gut microbiota and allergy mechanisms was still needed.

Assembly of OVA

Assembly is the spontaneous formation of highly ordered specific structures by aggregation of molecules that are precise and reproducible, enabling the creation of complex structures that cannot be formed by other methods (Liu, Liu, et al. 2022). Proteins can be assembled into several forms, such as nanoparticles and gels, and their good encapsulation ability can prevent degradation and premature release of encapsulated substances (Visentini, Perez, and Santiago 2019). In this part, we reviewed the assembly of OVA with itself or other biomolecules (Figure 3).

Self-assembly of OVA

Different forms of OVA self-assembly

OVA can be self-assembled into nanoparticles and nanosheets. The nanoparticles were obtained by heat treatment of OVA solution at two different pH values (7.50 and 11.35) (Sponton et al. 2015). The heat treatment with different pH significantly affected the particle size of OVA self-assembly nanoparticles. On the other hand, the nanoparticles assembled by OVA could be used as a carrier of polyunsaturated fatty acids to avoid oxidation and deterioration, thereby enhancing their nutritional value (Visentini, Perez, and Santiago 2019). Surprisingly, after OVA was dissolved in pH

7.0 PBS and continuously shaken for 24 h, the refined nanosheet morphology with folding and wrinkles was obtained (Tufail et al. 2018). It has been reported that shaking could cause the protein to be compressed at the air-water interface, thus pushing the protein chains together and squeezing them into nanosheets. On the contrary, the formation of nanosheets could not be observed if the protein solution failed to form an air-water interface during stirring.

The formation of OVA fibers was affected by several factors, such as pH and ionic strength of the solution, which affect the electrostatic interaction of proteins. At pH 2, the length of OVA self-assembly fiber was proportional to the protein concentration and independent of ionic strength (Veerman et al. 2003). Heating OVA under acidic conditions formed fine chains and gel. On the other hand, the mechanism of OVA fiber formation with salt and salt-free conditions at pH 2 and 90°C was compared. OVA formed more elastic fibers, longer and harder fiber types at low ionic strength (Lara et al. 2012). The protein would self-assemble into fibers by incubating the OVA sample at 60°C, which might be further rearrange to form closed ring fibers. Studies showed that the formation of rings results from end-to-end binding between protein fibers. Moreover, nitric oxide could induce conformational changes and oligomerization of OVA to self-assemble into fibers (You et al. 2015). These micron-sized rigid fibers, with high β -sheet content, were identified for the first time from OVA. Also, additional enzymatic treatment broke the amorphous aggregates formed by heating the OVA and subsequently partially reassembled them into longer OVA fibers (Huyst et al. 2022). Wang et al. discovered that accelerated the formation of ovalbumin fibrils at 85°C. With the duration of heating time, more worm-like and flexible fibers were observed by atomic force microscopy (Wang, Yang, et al. 2022). Some protein fibers formed based on non-covalent interactions (hydrogen bonds

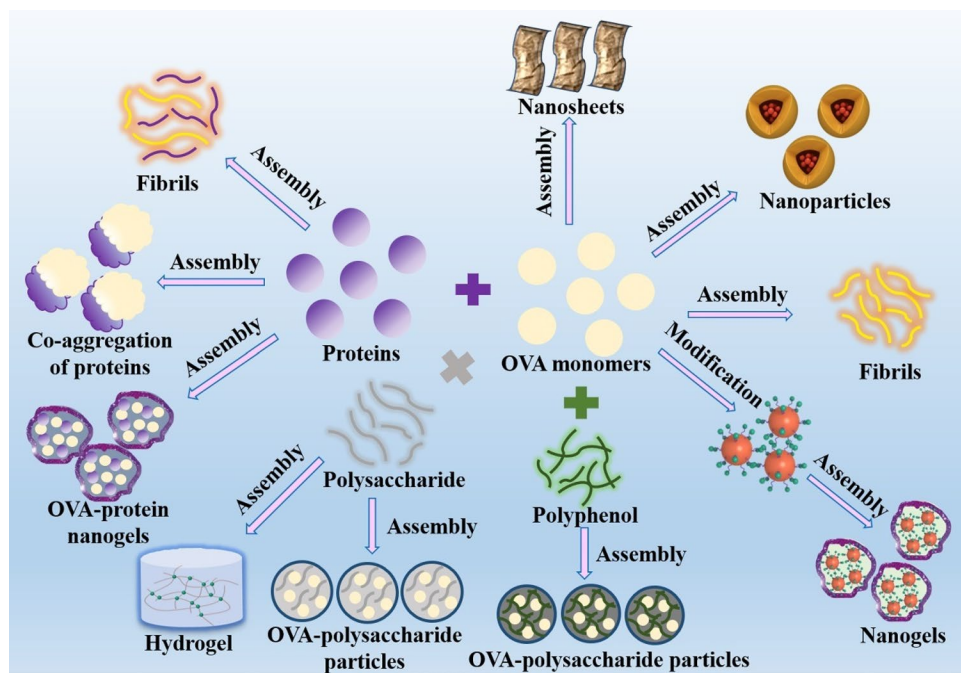


Figure 3. Schematic diagram for the assembly of OVA with itself or other biomolecules.

and hydrophobic interactions) and covalent interactions (sulfur bonds). These results offer a choice for OVA non-disease related fiber formation.

Assembly of modified-OVA into nanomaterials

OVA can be assembled into nanomaterials with different shapes (nanogels, nanoparticles and nanofibers) and physicochemical properties through glycation reaction, acylation modification and interaction of polyphenol. Feng et al. found that more stable spherical OVA-glucan nanogels could be obtained by heating the glycation products near the isoelectric point of OVA (Feng et al. 2016). Zeng et al. used the same method to prepare ovalbumin-pullulan nanogels, which had better colloidal dispersion and particle size (Zeng et al. 2022). The particle size of nanogel was affected by various factors, such as glycation reaction time, conjugation concentration and pH. Li et al. prepared OVA-dextran conjugation by Maillard reaction of dextran and OVA, and then further self-assembled the conjugation with EGCG into conjugated nanoparticles (Li and Gu 2014). Interestingly, the particle size of the nanoparticles was below 300 nm in the simulated intestinal fluid, and the nanoparticles could be maintained for two hours owing to the stability of the nanoparticles in the gastrointestinal tract by glucan.

Succinylation was achieved by a nucleophilic substitution reaction between the ϵ -amino group and the succinyl group of lysine, which changed protein structure (Hu et al. 2021). The increase of negatively charged groups in OVA after acylation led to the decrease of isoelectric point, the rise of solubility and the change of molecular spatial structure, which significantly changed the aggregation and rearrangement of OVA during heat treatment (Hu et al. 2022). Moreover, Hu et al. prepared acylated OVA nanogels by acylation modification and thermally induced self-assembly (Hu et al. 2021). The acylated OVA nanogels had better stability and uniform particle size under high ionic strength, wide pH range, and long storage time. In addition, the free sulfhydryl content and surface hydrophobicity of acylated OVA nanogels increased, which was due to the obvious change of the structure of OVA after acylation modification. Therefore, acylation modification was a convenient and effective method to improve the gel properties and physicochemical properties of proteins.

Polyphenols and OVA could also form nanofibers and nanoparticles. It was reported that EGCG significantly affected the self-assembly behavior and physicochemical properties of OVA nanofibers (Qian et al. 2022). Interestingly, the transformation of OVA from dense linear agglomerates to spherical agglomerates varied with temperature and EGCG concentration, which was closely related to hydrophobic interactions and hydrogen bonds. On the other hand, green nanoparticles could be obtained by self-assembly of EGCG and OVA. The addition of EGCG mainly affected the diameter, surface charge and biocompatibility of OVA nanoparticles (Gou et al. 2018). The diameter of nanoparticles increased significantly with the increase of EGCG/OVA molar ratio, which might be based on the adsorption of EGCG to the corresponding binding sites in OVA

molecules and the physical encapsulation of EGCG between OVA molecules (Ognjenovic et al. 2014). Furthermore, hydrophilic EGCG would hinder the aggregation of OVA molecules with exposed hydrophobic cores, resulting in the formation of loose assemblies with large particle sizes. Still, its functional and antioxidant properties had improved. Chang et al. found that the structure and molecular flexibility of nanoparticles changed by the assembly of ferulic acid and OVA (Chang et al. 2020). However, ellagic acid-OVA binding repressed the formation of protein fibers by the heating treatment, and the inhibition of covalent binding was stronger than that of non-covalent binding (Yan and Zhou 2020).

Assembly of OVA with other biomacromolecules

Assembly of OVA with polysaccharides

The assembly of protein and polysaccharides could obtain the nutritional properties of each macromolecule and ideal functional characteristics (Xiong et al. 2020). The non-covalent binding modes of OVA-polysaccharide included electrostatic interaction, hydrogen bond and hydrophobic interaction, especially electrostatic interaction was the main driving force. Li et al. reported the assembly of OVA with sodium alginate (SA) of different charge densities (SA1 and SA2, the charge density of SA1 was twice of SA2) (Li et al. 2020). Their results found a positive correlation between charge density and OVA/SA1 binding capacity. In another study, high concentrations of OVA-SA complexes exhibited good emulsion stability at 100 °C and pH 2.0–10.0, suggesting that the emulsion stability of OVA-SA complexes was closely related to the concentration, but the salt concentration and temperature had little effect (Zhang, Xiao, and Huang 2020). In addition, the nanogels assembled by the electrostatic attraction of OVA and chitosan had good stability, which could be stored at pH 2–10.5 for a long time without dissociation. The amphiphilic nanoparticles could also be prepared by the pH-driven assembly of OVA and gallic acid-modified chitosan, which had good delivery ability and biocompatibility (Li, Sun, et al. 2022). OVA/CMC nanoparticles were prepared by electrostatic interaction between OVA and carboxymethyl cellulose (CMC 0.7 and CMC 1.2) with different charge densities at pH 4.4 (Xiong et al. 2018a, 2018b). The OVA/CMC 1.2 nanoparticles had more compact structure, smaller size and stronger hydrophobicity than OVA/CMC 0.7. At pH 4–7, the increase in particle size of OVA/CMC nanoparticles was due to the rise in pH and ionic strength.

Moreover, the protein-polysaccharide-polyphenol ternary complex might have better functional properties and a more comprehensive application range than any of the individual macromolecules. Recent studies have shown that the interaction between polysaccharides and OVA-ferulic acid (OVA-FA) led to an increase in the β -sheet content and a decrease in the α -helix and random helix content of OVA (Huang et al. 2022). Compared with OVA-FA, polysaccharide-OVA-FA stabilized emulsion had better storage stability. Chen et al. studied the emulsifying properties

of carboxymethyl cellulose (CMC), tannic acid (TA) and OVA ternary composite food emulsions (Chen et al. 2020). At pH 4.0, CMC increased the electrostatic repulsion between emulsion droplets, thus improving the stability of OVA-TA emulsion.

Assembly of OVA with other proteins

Recently, the assembly of different proteins also receive more and more attention from scholars. The previous study showed that the primary interaction between OVA and lysozyme (LYZ) might be hydrophobic interaction that maintains dynamic equilibrium (Jin et al. 2020). However, the binding between them reduced the bacteriolytic activity of LYZ. Sugimoto et al. also reported that the fiber formed by the assembly of OVA and LYZ inhibited the antibacterial ability of LYZ (Sugimoto et al. 2011). In addition, Liu et al. found that divalent ions could regulate the heat-induced gelation behavior of the OVA-LYZ complex, and the binary protein system could form gels at low protein concentrations (Liu, Jiang, et al. 2022). The aggregates in the gel network increased significantly with the rise of the OVA/LYZ ratio. However, OVA and LYZ solutions did not form obvious aggregates at an electric field strength of 25 kV/cm (Wu et al. 2015). The study demonstrated that the protein interactions could be significantly improved when the OVA/LYZ ratio was 1:1 and the pH was 7.5. However, the interaction between proteins was limited after adding sodium chloride, and even inhibited the formation of protein complexes at a specific concentration. In addition, the gel network structure of the phosphorylated OVA-LYZ complex was wider than that of natural OVA (Jin et al. 2021). There was a synergistic effect of interfacial adsorption when the two proteins are mixed in a certain ratio, which increased the stability of the foam (Jin et al. 2022). Moreover, the ternary

system of ovalbumin, ovotransferrin and lysozyme could form aggregates by electrostatic interactions. Their presence at the air-water interface mitigated the intermolecular sulfhydryl-disulfide exchange reaction of the ternary-protein system. Stable amphiphilic nanogels with different particle sizes were prepared by assembling ovotransferrin and OVA in different ways, which exhibited pH-constant but heat-reversible hydrophobicity (Hu, Yu, and Yao 2007).

Potential applications of OVA

As shown in Figure 4 and Table 3, OVA has great application potential in food preservation, functional food ingredients, and nutrient delivery.

Food preservation

Food contamination caused by pathogens during processing and storage remains a severe problem. Using natural antibacterial substances is attracting more and more attention from consumers. OVA-ligand complexes and OVA-derived peptides showed an excellent prospect of preservation applications in food processing and storage. Mannosylated OVA could increase the permeability of bacterial cell membranes, thus inhibiting the growth of *Escherichia coli* and *Staphylococcus aureus* (Shi et al. 2018). Moreover, the eight antibacterial peptides obtained from OVA hydrolysate showed good antibacterial activity against *Bacillus subtilis*, and some antimicrobial peptides presented antifungal activity against *Candida albicans* (Pellegrini et al. 2004). The OVA-derived peptide TK913 had strong antibacterial activity and low cytotoxicity (Tan et al. 2022). The antimicrobial peptide (Opep2) obtained by pepsin hydrolysis of OVA could interact with bacterial cell membranes to achieve

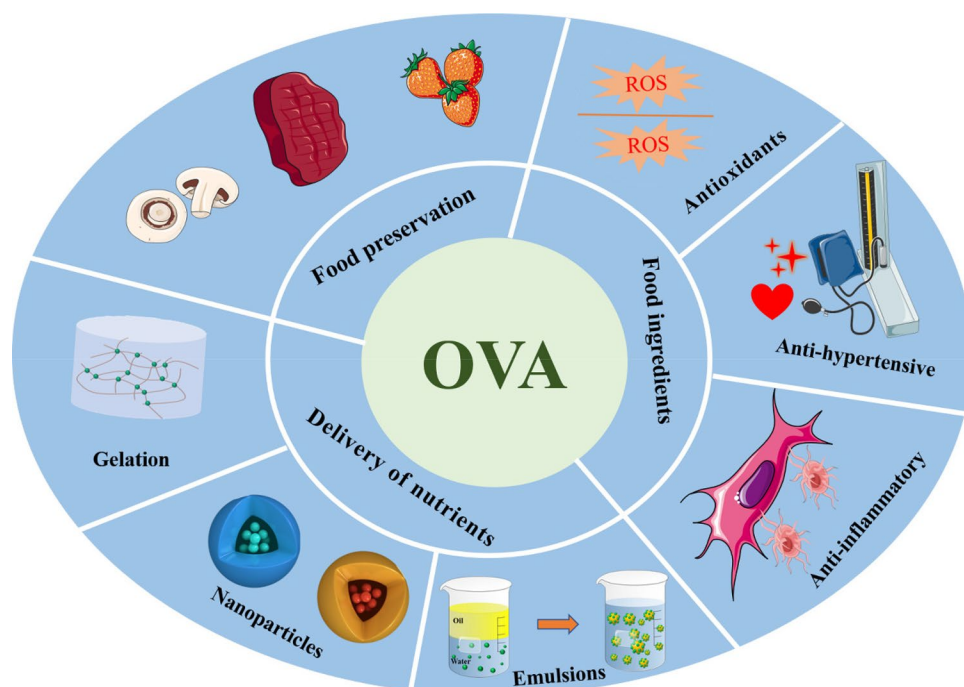


Figure 4. Schematic diagram for potential applications of OVA.

Table 3. Summary of the potential applications of OVA.

Applications		Principle or method	References
Food preservation	Enhance antibacterial and antifungal activity	Induce membrane permeability by mannosylated OVA	Shi et al. (2018)
		Self-assembled antimicrobial peptides based on the OVA-derived peptide TK913	Tan et al. (2022)
		Display antimicrobial activity by OVA-derived peptide	Pellegrini et al. (2004)
		Interact with cell membrane by peptide (Opep2)	Tang et al. (2013)
		Display antifungal activity by OVA-trans-cinnamaldehyde complex	Finos et al. (2021)
Food preservation	Monitor freshness	Monitor mushrooms freshness by anthocyanins-loaded OVA-carboxymethyl cellulose nanocomplexes	Liu, Wu, et al. (2022)
		Monitor pork freshness by anthocyanins-loaded OVA-propylene glycol alginate nanocomplexes	Zhang et al. (2022)
		Improve antioxidant activity by evaluating DPPH radical scavenging activity	Liu et al. (2017)
		Increase the antioxidant activity by the hydrolysates of OVA	Abeyrathne et al. (2014)
			Nimalaratne, Bandara, and Wu (2015), Wang et al. (2018), and Bueno-Gavila et al. (2021)
Functional food ingredients	Antioxidants	Increase the antioxidant activity by OVA-derived peptides	Kim et al. (2020)
		Inhibit the inflammatory activity by the enzymatic products of OVA	Gou et al. (2018)
		Inhibit the inflammation activity by the EGCG-loaded OVA-based nanoparticles	Huang et al. (2015)
		Increase the anti-hypertensive effect by the hydrolysates of OVA	Matoba, Yamada, and Yoshikawa (2003), Miguel et al. (2006), and Khueychai et al. (2018)
		Increase the anti-hypertensive activity by the OVA-derived peptides	Sun et al. (2021)
Delivery of nutrients	Encapsulation via emulsions	Improve the stability of β -carotene by OVA-dextran complexes as emulsifier	Wang, Zhang, et al. (2022)
		Improve the stability and bioaccessibility of curcumin by OVA-pectin as an emulsion stabilizer	Wang et al. (2022a)
		Improve the degree of the bioaccessibility of astaxanthin by OVA fibril-stabilized oleogel-based Pickering emulsions	Zhong et al. (2022)
		Delivery of natto kinase by OVA- flavone complexes	Feng et al. (2016)
		Improve the bioavailability of curcumin by ovalbumin-dextran complexes	Hu et al. (2021)
Hydrogels as nutrients delivery vehicles	Nanoparticles as nutrients delivery systems	Delivery of curcumin by self-assembling acylated ovalbumin	Zeng et al. (2022)
		Delivery of curcumin by the ovalbumin-pullulan complexes	Xu et al. (2021)
		Encapsulation resveratrol by OVA and <i>Porphyra haitanensis</i> polysaccharides nanoparticles	Xiong et al. (2018a, 2018b)
		Delivery of curcumin by OVA-carboxymethyl cellulose nanoparticles	Niu et al. (2021)
		Protection of vitamin D3 by OVA-pectin-sodium alginate composite nanoparticles	Gao et al. (2021)
Delivery of nutrients	Encapsulation hydrophilic riboflavin and hydrophobic quercetin by gallic acid-modified chitosan and OVA prepared nanoparticles	Delivery of polyunsaturated fatty acids by heat-treated OVA nanoparticles	Visentini, Perez, and Santiago (2019)
			Li, Sun, et al. (2022)

Abbreviations: DPPH: 2,2-diphenyl-1-picrylhydrazyl, EGCG: epigallocatechin-3-gall.

antibacterial activity (Tang et al. 2013). Besides, the effective antifungal activity of OVA-trans-cinnamaldehyde complex was confirmed using *Aspergillus niger* as a microbial model (Finos et al. 2021). Liu et al. designed a brilliant colorimetric film to monitor mushrooms' freshness, which changed color (from purple to pink) to monitor the freshness of mushrooms during storage (Liu, Wu, et al. 2022). In another similar study, Zhang et al. prepared an intelligent colorimetric film for monitoring pork freshness (Table 3) (Zhang et al. 2022).

Functional food ingredients

Antioxidants

Oxidative stress was the causative agent of many human diseases such as type 2 diabetes, atherosclerosis, obesity, and cancer. The development of food-derived antioxidants was considered to be an effective means to alleviate diseases associated with oxidative stress and prevent oxidative deterioration of food ingredients. OVA was a good antioxidant due to tyrosine, tryptophan and other sulfur-containing amino acids as hydrogen donors (Liu et al. 2017). Compared to OVA, the hydrolysates of OVA showed stronger hydroxyl radical scavenging capacity and better Fe^{2+} chelating ability (Table 3) (Abeyrathne et al. 2014). The hydrolysates of OVA obtained by pepsin hydrolysis also showed a significant inhibitory effect on lipid peroxidation. Moreover, OVA-derived peptides (AEERYP and DEDTQAMP) exhibited high oxygen radical uptake capacity (Nimalaratne, Bandara, and Wu 2015). The OVA antioxidant peptides got from cooked eggs after simulated gastrointestinal digestion included DSTRTQ, DVYSF and ESKPV (Wang et al. 2018). OVA-derived peptides were gained from OVA hydrolysates *via* artichoke proteases, and the antioxidant activity of these peptides was confirmed (Bueno-Gavila et al. 2021). Therefore, OVA and OVA-derived peptides can be used as natural antioxidants to prevent oxidative damage and food spoilage.

Anti-inflammatory effect

Inflammation was a normal biological response of the organism to harmful stimuli, which was closely related to the immune system. However, uncontrolled inflammatory reactions might develop into chronic inflammatory diseases such as inflammatory gastrointestinal diseases, arthritis, and diabetes. Currently, many drugs are used for treating inflammatory diseases, but their effectiveness is limited (Hossen et al. 2020). The enzyme products of OVA presented excellent anti-inflammatory activity. For example, OVA-trypsin hydrolysates effectively suppressed nitric oxide production in mouse monocytic macrophages and successfully repressed inducible nitric oxide synthase gene expression (Kim et al. 2020). Moreover, EGCG-loaded OVA-based nanoparticles controlled the secretion of proinflammatory mediators and promoted the production of anti-inflammatory factors (Gou et al. 2018). Consequently, OVA may be a promising therapeutic for inflammatory diseases

Anti-hypertensive effect

Angiotensin-converting enzyme (ACE) is very relevant to the system involved in regulating blood pressure, mainly by catalyzing the production of angiotensin II to increase blood pressure. The development of ACE inhibitors is currently the primary approach to treating hypertension. Many proteins and peptides play essential roles in preventing hypertension and maintaining normal blood pressure (Khueychai et al. 2018). Huang et al. used response surface design to optimize pepsin hydrolysis conditions and obtained highly active ACE inhibitory peptides from OVA (Huang et al. 2015). Moreover, the peptide (RADHPF) purified from a chymotryptic digest of OVA showed inhibition of ACE activity and promotion of nitric oxide-dependent vasodilation (Matoba, Yamada, and Yoshikawa 2003). Subsequently, the peptide (RADHPF) was substituted by amino acid to obtain a peptide with higher antihypertensive activity (RPLKPW). Miguel et al. further hydrolyzed OVA-derived peptides (YAEERYPIL and RADHPFL) to get the final peptides (YAEER, YPI and RADHP), which significantly reduced blood pressure in spontaneously hypertensive rats (Miguel et al. 2006). Khueychai et al. obtained the peptide with the highest ACE inhibitory activity (YV) by alkaline hydrolysis of OVA. The ACE inhibitory activity was still maintained after gastrointestinal digestion, suggesting that OVA-derived anti-hypertensive peptides showed great promise in preventing and treating hypertension (Khueychai et al. 2018).

Encapsulation and delivery of nutrients

Encapsulation via emulsions

OVA-based emulsions can encapsulate and control the release of fat-soluble nutrients, such as β -carotene, lutein, curcumin, and unsaturated fatty acids. The stability and digestion of β -carotene could be improved by using OVA-dextran (Dex) complex as the emulsifier. Compared with the OVA-stabilized emulsions, OVA-Dex complex-based emulsions had higher tolerance to the external environmental stresses, indicating that OVA-Dex complex-stabilized emulsions could be utilized as stable food-grade emulsion delivery systems (Table 3) (Sun et al. 2021). Furthermore, the stability and bioaccessibility of high internal phase emulsions loaded with curcumin during gastrointestinal digestion could be improved by using the OVA-pectin (PE) complex as a stabilizer (Wang, Zhang, et al. 2022). Wang et al. improved the bioaccessibility of astaxanthin (AST) by using Pickering emulsion prepared with OVA and candelilla wax-based oleogels (Wang et al. 2022d).

Hydrogels as nutrient delivery vehicles

Hydrogels fabricated from OVA became suitable delivery carriers for hydrophobic and hydrophilic bioactive substances. Zhong et al. reported that hydrogels of OVA solution and flavonoids could protect the thrombolytic activity and stability of nattokinase (Zhong et al. 2022). Unlike free nattokinase, nattokinase/OVA-flavone hydrogels had obvious thrombolytic ability and thermal stability. Notably, OVA

nanogels prepared by Maillard reaction or self-assembly were efficient curcumin delivery systems (Feng et al. 2016). These nanogels enhanced the oral bioavailability of curcumin and exhibited excellent pH stability, storage stability, encapsulation efficiency, and encapsulation capacity (Hu et al. 2021). Moreover, the nanogel delivery system prepared by OVA and pullulan by Maillard reaction could achieve sustainable release of curcumin (Zeng et al. 2022).

Nanoparticles as nutrient delivery systems

It has been reported that nanoparticles prepared from OVA and *Porphyra haitanensis* polysaccharides could effectively encapsulate resveratrol (RES) and control the release of RES in simulated digestion, improving the stability and bioavailability of RES (Xu et al. 2021). Similar studies found that the OVA-carboxymethyl cellulose (CMC) nanoparticles as the carriers could improve the stability, photostability and bioaccessibility of resveratrol (Xiong et al. 2018a, 2018b). Niu et al. prepared a highly salt-tolerant and ultra-long stable OVA-CMC nanoparticle, which could improve the stability and dispersion of curcumin (Niu et al. 2021). Gao et al. fabricated OVA-pectin-sodium alginate composite nanoparticles by the antisolvent precipitation method, which showed good stability and sustained release performance for vitamin D3 in simulated gastric juice (Gao et al. 2021). The OVA-alginate sodium nanoparticles not only encapsulated hydrophobic kaonferol and hydrophilic tannic acid, but also further improved the antioxidant activity and antimicrobial capacity of nanoparticles. Furthermore, nanoparticles prepared by heat-treated OVA could be used as carriers of polyunsaturated fatty acids (Visentini, Perez, and Santiago 2019). The amphiphilic nano-delivery system designed by gallic acid-modified chitosan and OVA had good encapsulation efficiency and sustained release characteristics for hydrophilic riboflavin and hydrophobic quercetin (Li, Sun, et al. 2022). Importantly, this nano-system displayed good biocompatibility and antioxidant activity, providing a meaningful reference for further applications.

Conclusion and perspectives

As the most abundant protein in eggs, OVA is essential in the food industry and other fields. The extraction of OVA has been relatively well established, but other improved methods continue to be explored. Moreover, OVA causes allergic reactions in some populations, especially in infants and children. Currently, different processing technologies and (bio)chemical treatments have been utilized to eliminate. OVA is one of the allergens in eggs, but its nutritional value and application value are not affected. The assembly of OVA with itself or other biomacromolecules can fabricate biomaterials with different structures and functions from natural OVA, which also provides a prospect for further expanding the application of OVA. In addition, OVA and its hydrolysates or peptides can be used for food preservation and functional food ingredients. OVA and other biomolecules can be made into various delivery systems, such as emulsions, hydrogels and nanoparticles.

Some achievements have been reached in the allergenicity, assembly and application of OVA. However, the impact of OVA on human health and applications still require a lot of scientific research. For instance, many processing methods to avoid OVA-induced allergic reactions still need more scientific evidence, such as clinical practice. Further studies on the effect of OVA assembly in terms of allergenicity are needed. Moreover, with the increase of OVA demand, achieving high-value applications has become a vital issue to be addressed: for example, (1) preparation of different nutrient delivery protection systems using OVA assembly products as raw materials; (2) OVA and other biopolymers together to prepare multifunctional biomaterials.

Credit authorship contribution statement

Bin Ma: Conceptualization; Software; Visualization; Writing—original draft. **Xing Fu:** Conceptualization; Investigation; Writing – review & editing. **Ping Zhu:** Conceptualization; Validation. **Zhaoxin Lu:** Conceptualization; Visualization. **Jiafeng Niu:** Conceptualization; Supervision. **Fengxia Lu:** Conceptualization; Investigation; Writing – review & editing; Supervision.

Disclosure statement

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