

Review

## Use of $\alpha$ -Lactalbumin [ $\alpha$ -La] from Whey as a Vehicle for Bioactive Compounds in Food Technology and Pharmaceuticals: A Review

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### Abstract

Whey protein is a byproduct of cheese, casein, and Greek yogurt produced in Europe, North America, and Australasia. It is a substantial source of functional proteins and peptides for the worldwide food industry.  $\alpha$ -Lactalbumin ( $\alpha$ -La) is a globular protein that can be isolated from WPI (whey protein isolates) using techniques such as chromatography/gel filtration, membrane separation, etc.  $\alpha$ -La is used in the elaboration of functional foods and is a very good source of peptides with anticancer, antimicrobial, antiviral, antihypertensive, immunomodulating, opioid, mineral-binding, and antioxidant bioactivities. Nanotubes and nanoparticles generated from this protein are utilized as vehicles for the transport of active compounds, and thus, can be used in foods and pharmaceutical industries. The contaminant



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effects of whey, characteristics of  $\alpha$ -La, production technologies, and its applications in nanotechnology are reviewed here.

### Keywords

Whey;  $\alpha$ -lactalbumin; bioactive compounds; encapsulation; nanotechnology

## 1. Introduction

Milk is one of the most important foods because of its high nutritional content. It is a good source of lipids, proteins, amino acids, vitamins, and minerals [1]. OECD/FAO [2] has reported an expansion of 1.4% in global milk production after a total of 880 million tons of milk was produced during 2020. Traditionally, the demand for milk is higher in urban centers, whereas the demand for fermented dairy products is superior in rural areas. Processed dairy products are becoming increasingly important in many countries, including the regions where animal protein demand is increasing faster than production.

OECD/FAO Agricultural Outlook reported the data of per capita consumption of processed and fresh dairy products in milk solids for different countries during the 2017–19 period (see Table 1) [2].

**Table 1** Per capita consumption of processed and fresh dairy products in milk solids during 2017–2019 (kg/capita/year).

Country or Region	Fresh Dairy Products	Processed Dairy Products
European Union	11.2	15.8
United States	9.0	15.4
India	19.2	2.8
Pakistan	34.6	3.5
China	2.4	1.5
Sub-Saharan Africa	3.1	0.6
World	9.0	4.2

The world milk production is anticipated to grow at 1.6% per year (to 997 Mt by 2029) over the next decade, and this is faster than the rate of most other agricultural goods [2]. The maximum amount of milk is consumed in the form of fresh dairy products, including pasteurized and fermented products. Greek yogurt is a very popular fermented dairy food. However, its production generates large amounts of acid whey as a byproduct (one liter of milk used to produce Greek yogurt generates 666 mL of acid whey). The post-processing treatment of this primary waste stream is one of the main concerns for the dairy industry [3, 4].

The byproduct from the elaboration of hard and semi-hard cheeses is known as sweet whey and has a pH between 5.9 and 6.6. Fresh acid-curd cheeses such as quarg, cottage, cream, fromage frais, and ricotta are the products obtained by the coagulation of milk, cream, or whey via acidification or a combination of acid and heat [5]. The manufacture of quarg, cottage, and cream cheeses and Greek yogurt yields acid whey with a pH between 4.3 and 4.6. The approximate composition of whey

includes water (94–95%), lactose (3.8-4.2%), proteins (0.8–1%), minerals (0.7-0.8%), and fat (0.05%) [6]. Whey proteins are mainly globular proteins that are highly soluble and heat-labile. Alpha-lactalbumin ( $\alpha$ -La) and beta-lactoglobulin ( $\beta$ -Lg) are the most abundant components constituting approximately 20-25% and 50-55% of the whey proteins, respectively. They are responsible for the functional properties of whey, such as foaming, emulsion, and gel formation [7, 8].

In recent years, whey has been widely used as a bioactive ingredient for healthy tailored dairy beverages. These beverages are mostly associated with fruits or other functional ingredients possessing prebiotic properties or fermented with probiotic bifidobacteria and lactic acid bacteria [9].

Whey must be processed as soon as possible after its production to avoid the growth of bacteria responsible for protein degradation and lactic acid formation. Whey proteins can easily be recovered by different methods. The whey proteins obtained by ultrafiltration or ion exchange have good functional properties and can be highly nutritional, as in the case of whey protein isolates (WPI). Whey proteins have also been used for the prevention and treatment of abdominal obesity [10]. The most common techniques used for the membrane filtration of dairy products are microfiltration (MF), ultrafiltration (UF), and reverse osmosis (RO). These technologies differ in terms of particle size, molecular weight, and the components that they separate [11–13].

Whey protein concentrates are produced from the skim milk permeate in the MF process. They can be further concentrated through UF using diafiltration, ion exchange, or electrodialysis to remove the salts and the remaining lactose to produce WPI with up to 90% of protein content [14, 15]. The contaminant effects of whey, characteristics of  $\alpha$ -La, production technologies, and its applications in nanotechnology are reviewed here.

## 2. Contaminant Effect of Whey Remnant

All types of milk, cream, and most other dairy products and byproducts have a very high oxygen demand, and their release into the environmental water sources causes serious pollution. This can happen because of spills, process leaks, overfilled containers, containment failures, wrong drainage connections, and blocked drains. Biological Oxygen Demand (BOD) represents the amount of oxygen consumed by microorganisms while they decompose organic matter under aerobic conditions at a specific temperature. The BOD of whey is between 20,000 and 50,000 mg of  $O_2/L$  [16]. This value is around 100 times higher than that of domestic sewage (400 mg of  $O_2/L$ ). Therefore, the necessity to treat and use these dairy effluents is essential.

On the other hand, Chemical Oxygen Demand (COD) is defined as the number of oxygen equivalents consumed in the chemical oxidation of organic matter by a strong chemical oxidant [17]. Natural Resources Wales [18] and Bylund [12] have reported the COD and BOD of the main dairy products (see Table 2). The waste load equivalents of specific milk constituents are 1 kg of milk fat = 3 kg COD; 1 kg of lactose = 1.13 kg COD; and 1 kg of protein = 1.36 kg COD [19]. Whey protein is a very valuable component that can be utilized in the manufacture of many food products, and hence, prevent its wastage as an environmental pollutant.

**Table 2** COD and BOD of the main dairy products.

Dairy product	COD (mg/L)	BOD (mg/L)
Whole milk	220 000	120 000

Skim milk	105 000	70 000
Raw whey	82 000	40 000

### 3. $\alpha$ -Lactalbumin

$\alpha$ -La is a globular protein (123 amino acids, 14.2 kDa) with one calcium-binding site, four disulfide bonds, and an isoelectric point between 4.2-4.6 [20]. It is one of the two components of the enzyme lactose synthase, which catalyzes the final step in lactose biosynthesis in the lactating mammary gland [20]. It is a protein that regulates the production of lactose in the milk of most mammalian species. This protein provides vital essential amino acids such as tryptophan, lysine, and cysteine, and therefore, is important for the rapidly growing neonate [21–24].

$\alpha$ -La is attractive because of its physical characteristics like a clean flavor profile, high water solubility, and relative heat stability (which, when combined, allow for diverse food applications). Some biological properties derived from its structure are also important. This includes the capacity of  $\alpha$ -La to form a complex with oleic acid at low pH values and render anticancer properties (BAMLET) [25, 26].

The use of  $\alpha$ -La in infant and standard (whole protein) formulas has been limited due to its allergenic potential. It causes about 30-35% of the IgE-mediated cow's milk allergy [27]. This problem can be reduced if enzymatic digestion is used before incorporating the protein into foods. Several peptides released from  $\alpha$ -La during digestion have been shown to elicit biological effects such as antitumor, antibacterial, antihypertensive, immunomodulatory, opioid, mineral-binding, and antioxidative activities [15]. It has also been reported that some of the peptides formed during hydrolysis by trypsin, chymotrypsin, or pepsin might possess specific activity against herpes simplex and HIV-1 virus [28].

Some researchers have reported the binding between  $\alpha$ -La and three fat-soluble vitamins (A, D<sub>3</sub>, and E). However, this protein has also been shown to effectively bind other hydrophobic bioactive compounds such as retinol, genistein, kaempferol, curcumin, EGCG (epigallocatechin gallate), capsaicin, and trans-resveratrol in high-affinity pockets for transportation inside the body [29-31]. It is well known that protein-based micro- and nanoparticles are suitable for use as carriers for bioactive compounds found in foods such as peptides, vitamins, functional lipids, and antioxidants [32].

The functionality of  $\alpha$ -La has been studied in terms of its emulsifying, gelling, and foaming properties [33, 34] that allow its use in different areas like food additives, nutritional or pharmaceutical applications, and protein-fortified beverages. A combination of various emergent technologies has permitted the preparation of  $\alpha$ -La in significant amounts with different purity levels (up to 87%) and allowed its use as an important nutrient and ingredient of functional foods [5].

### 4. Methods to Obtain $\alpha$ -Lactalbumin

Different methods have been used to isolate whey protein: affinity chromatography, membrane filtration (including MF, UF), size-exclusion chromatography, ion exchange, and variations in pH, etc. Membrane filtration is the main method used for the isolation of this protein [35].

The fractionation of a protein mixture with an ultrafiltration membrane is not easy since the sizes and MW of the proteins are close together [36]. Isolation and purification of  $\alpha$ -La from whey can be

achieved using different methods. The method reported by Heine, Klein, and Miyashita [37] involved the extraction of  $\alpha$ -La from acidified, heat-treated whey using an organic solvent. The  $\alpha$ -La was then precipitated from the solvent using a base.

Lucas et al. [36] extracted  $\alpha$ -La from acid casein WPC at pH 7 by limiting the  $\beta$ -Lg transmission with inorganic membranes that were chemically modified by a polyethyleneimine coating carrying positive charges.

Both proteins ( $\alpha$ -La and  $\beta$ -Lg) have close molecular weights (14.2 and 18.6 kDa, respectively). Hence, their direct fractionation using conventional industrial technologies such as membrane filtration is difficult [38]. However, recent technologies such as microfiltration and ultrafiltration at high shear rates and aqueous two-phase extraction can be applied to isolate whey proteins in lesser time and obtain better results in their purification [39, 40]. Muller et al. [41] proposed a pre-purification of  $\alpha$ -La by UF of acid casein whey with the limited transmission of  $\beta$ -Lg. Ultrafiltration steps were carried out with mineral membranes that increased the purity of  $\alpha$ -La in the filtrate and also retained the bovine serum albumin and immunoglobulin fractions. Ben Ounis et al. [42] reported the elimination of minor protein components from whey protein isolates by heparin affinity chromatography.

## 5. $\alpha$ -Lactalbumin in Nanotechnology

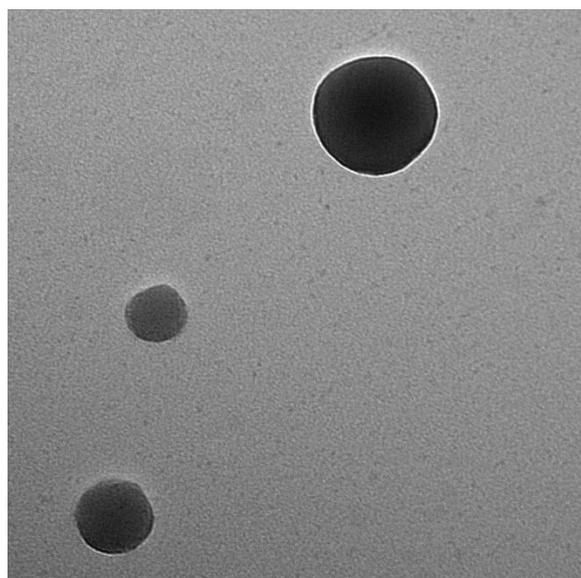
Nanotechnological methods are designed to produce materials of various types at the nanoscale level. This field is used in different areas like pharmacy, medicine, engineering, materials, and foods. Food nanotechnology has been used as a new tool for pathogen detection, disease prevention, food packaging, and delivery of bioactive compounds to target sites [43]. Nanoparticles and nanotubes are the most common shapes obtained in the case of  $\alpha$ -La [44]. The amino acid composition of  $\alpha$ -La is one of the factors responsible for its solubility, viscosity, emulsification, foaming, and protein nanoparticle formation, similar to that of other albumins [45].

Partial hydrolysis of bovine  $\alpha$ -La with *Bacillus licheniformis* protease (BLP) induces the formation of nanotubular structures with an average diameter of 20 nm and a cavity of about 8 nm, in the presence of calcium ions by a self-assembly process. The presence of this cavity enables the  $\alpha$ -La nanotubes to function as vehicles for encapsulating molecules such as vitamins, bioactive compounds, colorants, and enzymes. Fuciños et al. [46] encapsulated caffeine at high efficiency using  $\alpha$ -La-based nanotubes. Additionally, the growth of nanotubes induces the formation of stiff transparent protein gels due to the well-arranged networks formed by the strands. These gels can be used for the entrapment, transportation, and delivery of colorants and bioactive compounds in the food and pharmaceutical industries [47].

Nanoparticles (NPs) are a wide class of materials that include particulate substances, which have at least one dimension less than 100 nm [48]. WPI nanoparticles (NPs) have been prepared by the desolvation process using ethanol as the anti-solvent. The size of the WPI nanoparticles ranged between 10 and 100 nm and they possessed the potential to stabilize emulsions [49]. WPI NPs have also been used to encapsulate 3,3'-diindolylmethane, a bioactive compound found in cruciferous vegetables with antioxidant, anticancer, and anti-inflammatory properties [50].

In another study, Arroyo-Maya et al. [51] reported spheroidal nanoparticles prepared from bovine  $\alpha$ -La cross-linked with glutaraldehyde in the presence of acetone. The NPs had sizes between 100 and 160 nm, and their morphology, as determined by transmission electron microscopy (TEM),

is shown in Figure 1. These nanostructures displayed excellent pH stability. Further, the overall structure and size of  $\alpha$ -LA NPs underwent only minor changes within the pH interval of 3.0 – 9.0 at 25 °C.



**Figure 1** Morphology and size of  $\alpha$ -La nanoparticles obtained by the desolvation method with acetone as observed by TEM. Magnification 100,000 X (adapted from [50]).

Thus, this variety of architecture renders  $\alpha$ -La a potential vehicle for the introduction of challenging lipophilic compounds such as capsaicin (CAP) into foods and beverages. The low solubility of capsaicin otherwise makes this molecule hard to introduce in foods other than high-fat foods. [31].

Carvalho et al. [52] reported a high efficiency (> 45%) process for riboflavin nanoencapsulation in  $\alpha$ -La NPs. The system presented instability only after 120 days, a period, which is acceptable for applications in food technology. There are only a few reports on riboflavin nanoencapsulation, and their entrapment efficiencies are also around 45% [53, 54].  $\alpha$ -La NPs have also been used for the controlled release of methotrexate, an antimetabolite of the antifolate type, used in the treatment of cancer and rheumatoid arthritis [55]. The above information confirms the fact that  $\alpha$ -La and milk proteins, in general, are excellent encapsulation devices and delivery vehicles for bioactive compounds for foods and pharmaceuticals due to their structural and physicochemical properties [56, 57].

## 6. Concluding Remarks

$\alpha$ -La has many potential applications in food technology, pharmaceuticals, and nanotechnology. It has been used as a wall material for nanoparticles, as a vehicle for bioactive compounds, and as a substrate for the generation of bioactive peptides. In the case of WPI and  $\alpha$ -La nanoparticles, their stability at different pH values, their size dependence on the preparation conditions, and their safety make them an attractive wall material for the encapsulation of bioactive compounds in the development of functional food products. This can generate benefits for human health. Current

investigations include the generation of nanoparticles with different purposes and specific action sites.

### **Author Contributions**

A.P.C.G, I.J.A.M and H.H.S conceived the idea, A.P.C.G performed the review of the literature, A.P.C.G, I.J.A.M and H.H.S analyzed the data and A.P.C.G and H.H.S wrote the paper.

### **Competing Interests**

The authors declare that no competing interests exist.

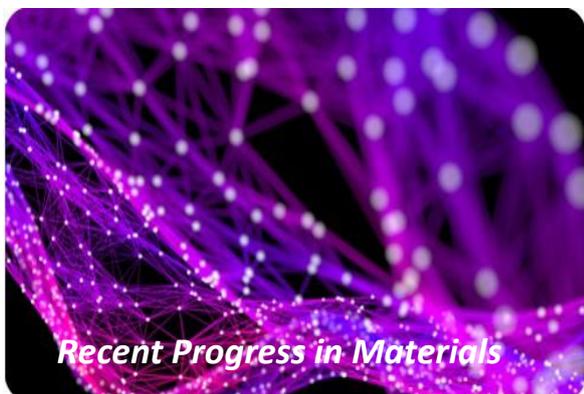
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