Delivery carrier of curcumin based on nanotechnology: A review

Dawei Zong1,a

1 Biochemistry Department, Allegheny College, Meadville, PA, 16335, USA

a Corresponding author: zongd@allegheny.edu

Abstract. Curcumin is a polyphenolic compound derived from the rhizome of turmeric. It has been widely used as a medicine, condiment and food additives. Curcumin has several biological activities such as anti-oxidation, anti-inflammatory, liver protection, anti-tumor, anti-atherosclerosis, inhibition of obesity, anti-aging, neuroprotection, and anti-senile dementia, it has been applied in functional food in recent years. In view of the current shortcomings of curcumin, such as poor water solubility, instability, and low bioavailability, improving its bioavailability will be the main research direction in the future. This paper mainly discussed the source and physicochemical properties of curcumin, as well as the research progress of delivery carrier of curcumin including nanoparticles of protein matrix, nanoparticles of polysaccharide matrix and nanoparticles of protein polysaccharide composite matrix. Besides, it discussed the application of nanoparticles in improving the solubility, stability, and bioavailability of curcumin. The paper might contribute to the development and research of functional food.

1. Introduction

Turmeric is a flowering plant of the ginger family which are used in cooking. It is known as a spice because turmeric is one of the main components of curry powder[1]. It has been traditionally used in medicine. Some studies have shown that turmeric has anti-inflammatory, antioxidant, and perhaps anticancer properties [2]. Curcumin is the major active component of turmeric, which has long been used to treat a variety of diseases [3]. Recently, curcumin is believed to help to prevent or treat cancer [4]. Due to antioxidant properties which means it could decrease swelling and inflammation [5], curcumin is regarded as a cancer treatment in part because inflammation appears to play a role in cancer. Some lab tests show that curcumin seems to block the growth of certain kinds of tumors [6]. In some laboratory and animal research, curcumin could slow the spread of cancer and protect healthy cells from damage by radiation therapy [7]. Therefore, research about curcumin is ongoing.

However, curcumin has a major deficiency so that it is hard to be applied to further clinical trials. Its oral bioavailability is very poor [7]. First, curcumin has low water solubility. The water solubility of native curcumin is just 0.00134mg/ml [8]. Because of degradation caused by dissociation of the phenolic proton, curcumin is unstable at neutral and basic pH [9]. Also, curcumin is vulnerable to degradation by light, heat and oxygen so it is very difficult to preserve it. At
pH 7.4, the degradation can be blocked by antioxidants but its molecule is still unstable in the small intestine [10]. Poor absorption cooperating with extensive metabolism of curcumin limits markedly the oral bioavailability.

In order to solve the problem and extend the applications of curcumin, many new technologies, such as nanotechnology, emulsification technology, cyclodextrin inclusion technique, as well as chemical modification technology, were used to improve the water solubility of curcumin, increase its stability to light, heat and oxygen [11], and improve its bioavailability [12]. Compared with other technologies, nanotechnology can prepare the delivery carrier, which has a very small particle size, to carry curcumin across the cell membrane [13]. It is able to achieve the effect of targeting and controlled release. Also, it has a high encapsulation efficiency and loading capacity so that curcumin will have better stability and bioavailability [14]. In recent years, nano-composites, nano-emulsions, nano-liposomes, nano-gels and other delivery carriers prepared by using nanotechnology as materials such as starch, oil, protein and polysaccharides not only have the advantages of nano-carriers, but also have several advantages such as high biocompatibility, in vivo degradability, and safe and non-toxic [15]. In the development of curcumin delivery carrier, it has important application value, so the application of curcumin delivery carrier based on natural bio-macromolecules and nanotechnology is very broad.

2. Nano-delivery carrier of curcumin

There are many biomolecular polymers that can be used to prepare nanoparticles in nature. Due to several advantages such as a wide range of sources, renewable, in vivo degradation, safety, better biocompatibility and so on, the preparation of nanoparticles by polysaccharides and protein-based materials is the most widely studied.

Natural polysaccharides commonly used in the preparation of nanoparticle delivery vehicles include starch, chitosan, sodium alginate and pectin. Chitosan is the only natural cationic animal polysaccharide. Curcumin has a negative charge on its surface so chitosan can form nanoparticles with curcumin by emulsion method under ionic salt induction and electrostatic interaction [16] [5]. Through this method, the chitosan-curcumin nanoparticle, prepared by Yadav et al, has a particle size of only 50 nm. It has a better stability than natural curcumin. Also, the chitosan-curcumin nanoparticle has the ability to chelate heavy metal ions, so it has good application value in preventing heavy metal poisoning. In order to further increase the stability of the nanoparticles and the loading of curcumin, two or more polysaccharides may be used as materials. Then, the composite nanoparticle, formed by interaction between polysaccharide molecules, can be used to deliver curcumin. Bhunchu et al [16] prepared sodium alginate-chitosan nanoparticles encapsulating curcumin by emulsification and ion gelation and this nanoparticle can be stored at 4 °C for 3 months without change. Also, the embedding rate and loading of curcumin increased significantly, as the proportion of chitosan increased.

Proteins commonly used in the preparation of nanoparticle delivery vehicles include animal proteins such as gelatin, whey protein isolate, casein, lactoferrin; and vegetable proteins such as soy protein isolate and zein. There are many advantages of protein as a carrier of curcumin. In addition to its own safe, non-toxic and digestible degradation, protein molecules are large, curcumin can be embedded inside the molecule, and curcumin can be adsorbed on the surface of the molecule [17]. In addition, the protein also has certain emulsion stability in aqueous solution, which can be used to stabilize curcumin nanoparticles [18]. Yadav’s research shows that gelatin can stabilize the curcumin nanoparticles which prepared by the anti-solvent precipitation method [18]. Also, gelatin can prevent the aggregation of curcumin and reduce the particle size of curcumin nanoparticles from 195 nm to 93 nm. However, sodium alginate, sodium carboxymethyl cellulose, cellulose methyl ester,
etc. alone are not ideal for stabilizing curcumin nanoparticles \[19\]. Pan et al dissolved curcumin in an aqueous solution of sodium caseinate and prepared sodium curcuminated nanoparticles loaded with curcumin by spray drying \[20\]. This method can increase the water solubility of curcumin by 40 times. The antioxidant activity of curcumin-sodium caseinate nanoparticles and the ability to inhibit cancer cell proliferation are also significantly increased. Bollimpelli et al used lactoferrin and curcumin to prepare composite nanoparticles with a particle size of 43-60 nm \[1\]. Its cell uptake rate is high, but the embedding rate is low, only 61.3%, because the interaction between lactoferrin and curcumin molecules is weak.

Because curcumin is a hydrophobic molecule (log P = 2.5), it does not interact well with most proteins in aqueous systems, but it is able to form stable nanoparticles with hydrophobic proteins through hydrophobic interactions. Zein contains more than 50% hydrophobic groups. Even though it is insoluble in water, it is easily soluble in 60%-90% ethanol solution. Zein is easy to prepare nanoparticles by anti-solvent precipitation method \[21\]. Therefore, it is an ideal material for preparing curcumin nanocarriers. However, the isoelectric point of zein is 6.2, and the zein particle dispersion alone can easily aggregate in pH neutral or human environment and affect the transfer of curcumin \[17\]. In order to improve the stability of zein nanoparticles, many researchers have tried to use other biomolecular materials such as polysaccharides to complex with zein to modify their surface properties and particle structure \[22\]. There are many reports on preparation of biomolecule polymer nanoparticles based on zein and polysaccharides, and the enzymatic transfer of curcumin. In addition, some studies have shown that nanoparticle prepared by the combination of zein hydrolysate and soybean soluble polysaccharide can also be used as a carrier of curcumin. This nanoparticle can increase the water solubility of curcumin from 11 ng/mL to 135 μg/mL, and the complex nanoparticle reconstitution rate is over 90%.

At present, methods for preparing zein-polysaccharide complex mainly include anti-solvent precipitation method, current body driven atomization method, electrostatic deposition method et al. The advantage of the current body driven atomization method is that the particle size range can be regulated and less solvent is consumed. Electrostatic deposition requires proteins and polysaccharides with positive and negative opposite charges to allow layer-by-layer assembly into nanoparticles. The nanoparticle prepared by the anti-solvent precipitation method has a relatively small particle size range, does not require complicated operation equipment, and has a wider application range. The interaction mode, particle size, and embedding effect of curcumin are different between different polysaccharides and zein. However, the nanoparticles formed by protein-polysaccharide complexation have a small particle size and high embedding rate. After embedding, curcumin is more stable to environmental factors such as light, heat, oxygen and pH than curcumin embedded with protein nanoparticles alone. Besides, its digestion absorption rate and bioavailability are also improved.

In addition to polysaccharides, there are other biomolecular polymers that can also complex with zein to form nanoparticles and exhibit specific structural properties. Shellac is a natural polyester polymer formed by hydroxy fatty acid and sesquiterpene acid. It is certified by the FDA as a safe substance and can be used as a carrier for enteric-targeted functional active ingredients \[5\]. Also, it is a substance allowed in GB 2760-2014. Sun et al used zein and shellac to make composite particles for embedding curcumin by anti-solvent co-precipitation method \[23\] \[24\]. The embedding rate of composite particles (93.2%) was significantly higher than that of zein alone (82.7%). It can effectively protect curcumin from photo and thermal degradation, and molecular cross-linking occurs when the amount of shellac is high. The particle size of the composite nanoparticles gradually becomes larger and becomes micro-particles of crosslinked network structure.
3. Application of curcumin nanocarrier

Curcumin compounds include three types: curcumin (C21H20O6), demethoxycurcumin (C20H18O5), and bis-demethoxycurcumin (C19H16O4). Because of their highly similar structure and physiological activity, most of the curcumin products used in foods are a mixture of the three. Nanocarriers have good protection and delivery to all three curcumins. Curcumin can be used in a variety of foods such as frozen drinks, cooked nuts and seeds, cocoa products, chocolate and candy, food product fillings, carbonated drinks, jellies, and puffed foods.

Based on the efficacy of curcumin on some chronic diseases such as cardiovascular disease, diabetes and hyperlipidemia, it can be foreseen that curcumin nanocarriers have great potential in the development and utilization of functional foods. For example, it can be used into developing health milk, functional beverages, solid instant granules, capsules, etc. In addition to better exerting the physiological activity of curcumin itself, the curcumin nanocarrier can also prepare emulsion beverages by its unique physical and chemical properties. For example, a curcumin nanoemulsion made by high pressure homogenization is applied to milk, and the droplet size of the nanoemulsion is 90 nm to 122 nm. Milk containing curcumin nanoemulsion maintains physical stability for 3 months at room temperature. Moreover, the milk fat oxidation rate is also significantly lower than ordinary milk. The oil-in-water Pickering emulsion prepared by phytoglobulin-curcumin nanoparticles mainly relies on the interfacial action of nanoparticles to prevent emulsion droplets from agglomerating so that use of emulsifiers in foods is reduced. Therefore, curcumin nanocarriers have a wide range of applications in the food field and have huge market potential.

4. Conclusion

Curcumin has a long history of application in food and medicine, but its low solubility, poor stability and low bioavailability have always been the bottleneck restricting the development and utilization of curcumin. Based on nanotechnology, the nano-transport carrier of curcumin is prepared from edible natural sources of protein, polysaccharides and lipids, which not only increases the water solubility of curcumin but also protects curcumin from factor degradation such as light, heat, oxygen, etc. The stabilization of curcumin in the food system can prolong the retention time of curcumin in the gastrointestinal tract, achieve a sustained release effect, and ultimately improve the bioavailability of curcumin in the human body.

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