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APPLICATIONS OF CYCLODEXTRINS IN FOOD SCIENCE. A REVIEW

Adrián Matencio[#], Silvia Navarro-Orcajada, Francisco García-Carmona and José Manuel López-Nicolás*

Departamento de Bioquímica y Biología molecular-A, Facultad de Biología, Universidad de Murcia - Regional Campus of International Excellence "Campus Mare Nostrum", E-30100 Murcia, Spain

adrian.matencio@um.es

* Corresponding author: Tel: +34 868 883**4777**
E-mail: josemln@um.es

ABSTRACT

Background: The food industry is constantly attempting to develop better products that will have a positive effect on health (commonly known as functional foods). In this respect, cyclodextrins (CDs) could be of interest because they are tasteless, non-caloric and odourless molecules with several valuable characteristics, such as a capacity to separate chiral compounds and solubilize or stabilize bioactive compounds (BaC).

Scope and Approach: This review represents a revision of the state-of-the-art of CDs and their uses in the food industry.

Key Findings and Conclusions: We analysed their metabolism and regulatory aspects of current applications of CDs: as carriers, for removing components, to produce or extract BaC, their use as nanosensors or in food packaging. We study how inclusion complexed are formed referring to the most common techniques and parameters Moreover, how inclusion complexes are formed will be studied with reference to the most common techniques and parameters. In conclusion, their applications in the food and other industries will increase in the coming years without a doubt.

Keywords: Cyclodextrins; Food industry; nutraceuticals; packaging; “free products”; nanosensor.

HIGHLIGHTS

1. The paper reviews the state-of-the-art of CDs as used in the food industry.
2. The mechanism, metabolism, pharmacokinetics and regulatory aspects were discussed.
3. Different applications are reviewed, including formulations, production and packaging.
4. Products containing CDs that are already on the market are described.

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58 **CONTENTS**

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1. INTRODUCTION

Antoine Villiers would not have suspected the number of applications of their cyclodextrins (CDs) that would be discovered in just over one hundred years (Antoine Villiers, 1891).CDs are a torus-shaped oligosaccharides made up of α-(1,4) linked glucose units, obtained from the degradation of starch by the enzyme Cyclodextrin Glucosyltransferase (CGTAse). Although the most common CDs are the natural α, β and γ- forms (**Fig**. 1A, which contain six, seven and eight glucose units, respectively), CDs containing up to nineteen units have been characterized(French et al., 1965; Pulley, 1961). However, these novel CDs are not used commonly because of their propensity to collapse. Even smaller CDs with 3 or 4 glucose units have recently been synthesized with the same type of linkage of natural CDs (Ikuta et al., 2019).

The CD ring is a conical cylinder of an amphiphilic nature, with a hydrophilic outer part (formed by the hydroxyl groups) and a predominantly lipophilic cavity, which can contain water(Pereva et al., 2019). Although both inorganic and organic salts and neutral molecules can form complexes with CDs (Fourmentin, Crini, &Lichtfouse, 2018), they are more generally used to complex (**Fig.** 1B) poorly-soluble drugs or bioactive compounds (BaC), creating so-called “inclusion complexes”, novel BaC/CD nanoparticles. In solution, the equilibrium between free and complexed BaC is dynamic, meaning that when the solution is diluted or another BaC is added, the first BaC is easily released.

In general, the generation of CD/BaC nanoparticles improves the apparent solubility of the drug, which increases its final concentration and possibly its bioactivities(Shieh& Hedges, 1996). Among previously cited benefits of using CDs are:

1. Increased stability under abiotic (light, oxidants...) or biotic (enzymatic degradation) conditions.
2. The ability to control the release of molecules (e.g. volatiles).
3. The elimination of undesirable tastes and odours.
4. Chiral separation.
5. Controlling chemical reactions.
6. The selective purification of molecules.
7. Dietary fibre(EFSA, 2012) .

To improve the properties of CDs, different chemically obtained derivates (e.g. Hydroxylpropyl-β-CD or Methyl-β-CD) and materials containing CDs (e.g. CD-nanosponges or CD-based nanoparticles) have been obtained. Although these have improved capacities compared with natural CDs(Salazar et al., 2018; Sherje et al., 2017) even Hydroxylpropyl-β-CD is considered *orphan drug* for Niemann Pick type C (Matencio, Navarro-Orcajada, González-Ramón, et al., 2020), only natural CDs (Szente&Szejtli, 2004) are permitted as food additives (E-457, E-458 and E-459).

Due to their interesting applications in the pharmaceutical and nutraceutical industries and similar fields, the number of publications on CDs has rapidly increased, for example only in 2018, 1530 research articles were published with CDs in the title and the word “cyclodextrin” appears in 4800 patents. Furthermore, Jansook et al. (2018) have published that the CD annual production is over 10,000 metric tonnes (information from Roquette, France), of which 20% is used in food applications (Jansook, Ogawa, &Loftsson, 2018). Such data attest to the importance of CDs in the food industry.

In spite of the importance of CDs in food, the last exhaustive review on their use in food science was published in 2009 (Astray et al., 2009), with partial updates (dos Santos et al., 2017; Fenyvesi et al., 2016a). Although, a review focusing on beverages was published in 2020(Astray et al., 2020), there is a clear need for a fresh review of the uses and applications of CDs in food science. For this reason, the purpose of the present contribution is to provide, a general overview of the use of CDs and modified CDs in the food and nutraceutical industries, with special attention paid to functional food production.

2. METABOLISM, PHARMACOKINETICS AND TOXICOLOGY

In nature, only CGTase is able to convert starch into CDs, although other enzymes can help in their industrial production (Biwer, Antranikian, &Heinzle, 2002; Tonkova, 1998).However, various enzymes or processes in our body may degrade CDs into glucose derivatives: Starting in the mouth (when you eat something containing CDs),salivary α-amylase can rapidly hydrolyse dextrins, although rapid transport to the stomach means that the degree of degradation is insignificant. Of the three natural CDs (α-, β- and γ-CD), the first two are essentially stable towards α-amylase, and γ-CD is rapidly digested(John Marshall & Miwa, 1981; Kurkov & Loftsson, 2013).

Unspecific pH-dependent degradation can occur in the stomach; however, inclusion complexes present lower degradation (Singh et al., 2010). After the stomach, in the neutral pH environment of the small intestine pancreatic amylase continues the hydrolysis reaction. While α- and β-CDs are mainly digested by bacteria in the colon (where α-CD is degraded more rapidly than β-CD), γ-CD is almost completely digested in the gastrointestinal tract. Finally, undigested CDs are metabolized by microbiota in the lower section of the digestive system, where

155 they are degraded almost completely, a fact that has led to their being used as
156 prebiotics (Fenyvesi et al., 2016a).The rest is eliminated in the faeces. In general,
157 the bioavailability of natural and common CDs derivatives is very low, which
158 makes them safe when administered orally (Arima et al., 2011; Jansook et al.,
159 2018; Kurkov & Loftsson, 2013).

160 Dextrins can also be administered parenterally, and study of their
161 pharmacokinetics has led to the publication of monographs such as the European
162 Pharmacopoeia (*European Pharmacopoeia (Ph. Eur.) 9th Edition* | *EDQM*). The
163 urinary clearance of linear dextrin and CDs decreases with increasing molecular
164 weight. Indeed, molecules of less than 15 KDa are almost totally excreted (≥ 90
165 %) by urine without much modification (Kurkov&Loftsson, 2013).The
166 pharmacokinetics of i) HPβ-CD, ii) sulfobutylether β-CD sodium salt and iii)
167 Sugammadex sodium salt has been studied in rats, in which $t_{1/2}$values of 1.9, 1.6
168 and 1.7, respectively were found. More than 90% of CD is excreted by urine within
169 24h; although the kidneys of affected subjects may maintain CD levels for longer
170 periods (Frijlink et al., 1990; Hamilton et al., 2018; Jansook et al., 2018; Kurkov
171 & Loftsson, 2013; Luke et al., 2012; Matencio, Alcaráz-Gómez, et al., 2018).

172 As regards the toxicity of CDs, most studies are concerned with their
173 medical application. A high orally administered dose of CDs could generate
174 diarrhoea and caecum enlargement, and even affect to the bioavailability of some
175 substances, to prevent which, the European Commission has published a guide
176 to help scientists in drug development(EMA, 2017). On the other hand, the
177 toxicology of HPβ-CD has been studied in greater depth due to its classical use
178 as a medical excipient (Gould & Scott, 2005), and even its degree of substitution
179 has been studied (P. Li et al., 2016). The results of the last study showed that the

best option to lower toxicity levels would be to use at lower degrees of substitution, although more studies are necessary in this respect.

3. REGULATORY OF CDS IN FOOD SCIENCE.

Before we approach our last objective using CDs- for human consumption and as nutraceuticals - we should first take a look at the current regulations that govern their use, including the quantity and type of CDs permitted. When used as supplements in food products, natural CDs are considered food additives (E-457, E-458 and E-459) and recognized as “Generally recognized as safe” (GRAS). The recommendation of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) established the maximum advisable level of β-CD in foods at 5 mg/kg/day. On the other hand, there is no Acceptable Daily Intake (ADI) for α- and γ-CD due to their favourable toxicological profiles. The European Food Safety Authority (EFSA) permitted the health status claimed for α-CD dietary fibre, and its ability to reduce of post-prandial glycaemic responses (EFSA, 2012). In addition, the dosage of β-CD was re-evaluated in 2016 with no modifications recommended (Mortensen et al., 2016). Furthermore, a recent review focused on the safety and recommended levels of CDs in foods (Fenyvesi et al., 2016a) also suggested no modification to the above levels was necessary. However, no regulations apply to BaC/CD nanoparticles in food products.In these cases, the regulation of both ingredients, BaC and CD, is considered. However, we think that this should be re-considered.

When a drug is administrated orally, the excipient (in this case CD), must be considered as an “active compound” and its safety must be evaluated (Jansook et al., 2018). Although they are not directly tested, the formulation of new drugs must be evaluated in the context of the application. Generally, GRAS

molecules are directly approved for use as excipient (in this case, natural CDs). In this respect, the American Food and Drug administration (FDA) has published a list of inactive pharmaceutical ingredients for downloading (https://www.fda.gov/Drugs/InformationOnDrugs/ucm113978.htm).The list indicates the route, dosage form and maximum concentration recommended. In addition, the European Medicines Agency (EMA) has published several reports on the use of CDs in pharmaceutical products (https://www.ema.europa.eu/en/cyclodextrins), among others. A question and answer document on CDs and their uses (EMA, 2017), provides information about safety: for example, in general around 200 mg/kg/day of CD is recommended for oral administration. Finally, The Japanese Pharmaceutical Codex (JPC) has published several applications of CDs in its Pharmacopoeia (医薬品医療機器レギュラトリーサイエンス財団, 2017).

4. FORMATION OF INCLUSION COMPLEXES

When a molecule enters the inner cavity of a CD a nanoparticle, known as "inclusion complex", is formed. This type of non-covalent interaction involves a *host* and a *guest*, the latter of which is totally or partially included by the host. The cavity volumes of α-, β- and γ-CD measured 0.174, 0.262 or 0.427 nm^3, respectively (Astray et al., 2009). The stability of the inclusion complex can be described in terms of its complexation constant (K_F) or dissociation constant (K_D):

$$CD + BaC \overset{K_F}{\rightarrow} CD - BaC \quad (1)$$

$$CD - BaC \overset{K_D}{\rightarrow} CD + BaC \quad (2)$$

This is not easy to evaluate and sometimes requires a combination of several techniques, as mentioned in two recent reviews (Mura, 2014, 2015), the

information they contained helping us to select the most interesting CDs for use in our work.

The methods are generally based on the variations in any physical or chemical property of the guest molecule that may be considered useful for following complex formation (Table 1).

In recent years of chemoinformatic techniques such as molecular docking or molecular dynamics have increased for their capacity to predict inclusion complexes (Brocos et al., 2010; F. Garrido et al., 2020; Khuntawee et al., 2015; Matencio, Hernández-García, et al., 2017; Matencio, Bermejo-Gimeno, et al., 2017; Matencio et al., 2019; R. Wang et al., 2015), and interfaces that work with CDs have been developed to facilitate input and output analysis (Montenegro Rabello et al., 2019), and there are even libraries of computational molecular dynamics simulations of cyclodextrins (Mixcoha et al., 2016).

In detail, molecular docking is a method which predicts the preferred orientation of one molecule (host) towards a second molecule (guest), when they bind to each other to form a stable complex. In turn, knowledge of the preferred orientation may be used to predict the strength of association or binding affinity between two molecules using, for example, scoring functions (Tao et al., 2020). On the other hand, molecular dynamics is a computer simulation method for analysing the physical movements of atoms and molecules. The atoms and molecules can interact for a fixed period of time, revealing the dynamic "evolution" of the system. In the most common version, the trajectories of atoms and molecules are determined by numerically solving Newton's equations of motion for a system of interacting particles, where forces between the particles and their

potential energies are often calculated using interatomic potentials or molecular mechanics force fields (Durrant& McCammon, 2011).

4.1 Cyclodextrin/guest mechanism, thermodynamic and structural interactions

The complexation generally induces the release of water from the cavity, and any solvents or salts present might affect the complexation. Among the different processes, steric hindrance, and the substitution of unfavourable interactions by favourable new ones usually determine the energy state of the nanoparticle. Interactions that may contribute to nanoparticle formation include electrostatic/coulomb forces, van der Walls interactions, hydrogen bonding, and hydrophobic effects, among others, although their impact depends on several factors such as type of guest, the solvent used, etc. (Jansook et al., 2018; Schönbeck & Holm, 2019).

Such changes are related to the classical thermodynamic parameters, enthalpy, entropy and binding free energy. In general, attractive electrostatic and van der Walls forces are assumed to result in enthalpy-driven binding, while hydrophobic attraction seems to be characterized by a large gain in entropy.

Several CDs can be used to complex a guest, and so, the different cavities of CDs and any modifications must be analysed. In general, β-CD and derivatives are the most useful (Jansook et al., 2018). However, for the food industry only the three natural CDs can be used, the cavity constituting the main difference between them, although β-CD is usually the most used.

As regards the effect of polarity, the most important factors to consider are structure, solvent and temperature. In general terms, hydrophobic molecules form complexes with CDs, although neutral or polar molecules, ions or gases are

also able to form such complexes (Fourmentin et al., 2018b). The solvent is important, since the presence of organic solvents might decrease the complexation constant due to the higher solubility of the molecule (Charumanee et al., 2016). On the other hand, the presence of a minimal quantity of water is necessary to form the inclusion complex (Kamihira et al., 1990).

5. APPLICATIONS OF CDS IN FOODS

As mentioned above, the need for an update concerning the application of CDs in food science has led us to provide some guidance for the community involved. A selection of the most interesting applications is presented below.

5.1 Production or extraction of bioactive compounds using CDs.

The capacity of CDs to complex bioactive compounds can be used to displace the Le Châtelier equilibrium or even to protect the freshly synthesized compound.

It is common to use CDs in the production of bioactive compounds (**Fig**. 2) from plant cell cultures to act as elicitors and so obtain higher yields (García-Pérez et al., 2019; Pinho et al., 2014). For example CDs are used to produce polyphenols, such as stilbenes (Komaikul et al., 2019) or flavonoids (García-Pérez et al., 2019), alone or, to take advantage of the resulting synergetic effects, in combination with elicitors such as methyl jasmonate or salicylic acid (Perassolo et al., 2016; Xu et al., 2015); indeed, the complex formed between methyl jasmonate and salicylic acid with CDs have been evaluated (López-Nicolás et al., 2013; Matencio, Bermejo-Gimeno, et al., 2017; Nishioka et al., 1984)and in combination with the bioactive compounds produced in the cell culture(Oliva et al., 2018). Additionally, the use of CDs has been extended to other types of organism such as cyanobacteria in order to increase the production of antifungal

303 products (Shishido et al., 2015). The use of CDs in combination with enzymes
304 (Bonnet et al., 2010)has also been studied in recent years. For example, in one
305 study, using CDs, the biotechnological production of phenylethylamine-
306 betaxanthin and indoline-betacyanin, two of the most promising betalain
307 derivatives was studied obtaining higher production, around 51 and 26% of both
308 derivatives, respectively(Matencio, Guerrero-Rubio, Gandía-Herrero, et al.,
309 2020); while, CDs can also be used directly for chemical synthesis (Kokkirala et
310 al., 2011), this is not the case with food products.

311 The use of CDs for the extraction of both hydrophobic and hydrophilic
312 substances has been studied (Gao et al., 2016). For example, polyphenols can
313 be extracted from many plants, including pomegranate or green pepper
314 (Athanasiadis et al., 2018; Diamanti et al., 2017; Favre et al., 2020) or catechins
315 (López-Miranda et al., 2016).

316 **5.2 Using CDs to produce "free" products and induce organoleptic**
317 **modifications.**

318 The growing tendency for consumers to look for "-free" products (sugar-
319 free, gluten-free, etc.) have highlighted the ability of CDs to remove some
320 compounds from a given food matrix (**Fig**. 3). For example, advantage is taken
321 of the capacity of CDs to complex cholesterol in order to extract it from food
322 products, thus creating low cholesterol products (Ahn&Kwak, 1999; Alonso et al.,
323 2019a, 2019b; Lee et al., 1999).

324 In addition, unpleasant flavours can be reduced by adding CDs: for
325 example the beany flavour of soy milk, and bitter components, and fish or goaty
326 flavours (Hadi et al., 2015; Serfert et al., 2010; Suratman et al., 2004; Ünlüsayin
327 et al., 2016; C. Wang et al., 2018). In addition, volatile fragrance complexes may

change the organoleptic profile of the product (Abril-Sánchez et al., 2019; Ciobanu et al., 2013) because, although complexation prolongs the half-life of volatiles in the matrix, the odour becomes less intense. Some allergens or toxins could also be complexed – a potential that could be more widely used in industry but which is not (Ayesh& Essa, 2002; Hou et al., 2015).

Due to the physicochemical properties of CDs, their use as emulsifiers is a very promising application in the food industry. In particular, CDs have proved to be effective in the formation of particle-stabilized emulsions, also known as Pickering emulsions. In this sense, it has been described that oil/water Pickering emulsions with natural CDs can provide less oxidized oil and fewer undesired flavours (Moriyama et al., 2013). Soybean oil and kenaf seed oil are examples of common oils that have been tested in this kind of emulsions with CDs (Cheong & Nyam, 2016; Inoue et al., 2010). In a recent study (Xi et al., 2018), the amphiphilic properties of β-CD were enhanced by esterification with octadecenyl succinic anhydride leading to more stable emulsions. Furthermore, Pickering emulsions made with CDs have been suggested for producing special foods for elderly people with dysphagia (Moriyama et al., 2013).

5.3 Formulation of CD nanoparticles as carriers of bioactive compounds for functional foods.

Every month studies appear on the subject of novel nanoparticles formed by CDs containing drugs or bioactive compounds for possible use in functional food. Since 2018, 1750 articles and patents have been published with the word “cyclodextrin” in the title, pointing to the high potential of these molecules.

In general terms, CDs interact with bioactive compounds, thereby enhancing their solubility or stability: for example, complexes of natural CDs with

353 antioxidants, vitamins, saponins, fatty acids or carotenoids (dos Santos et al.,
354 2017; dos Santos Lima et al., 2019; Fenyvesi et al., 2016a; López-Nicolás et al.,
355 2014; Matencio, Hernández-Gil, et al., 2017; Matencio, García-Carmona, et al.,
356 2017a). Of the most recently, formed nanoparticles, the most interesting
357 complexes and their possible applications will be discussed below.

358 In the case of vitamins, an interesting combinatorial use of the hydrophobic
359 Vitamin E and cholesterol complexed with CDs has been successfully tested to
360 improve sperm motility, cryopreservation and quality (Benhenia et al., 2016,
361 2018)and for reducing lipid peroxidation. Complexes with soluble vitamins
362 (vitamin C, nicotinic acid and vitamin L1) have also been evaluated (Saha et al.,
363 2016; Vázquez et al., 2019).An interesting application is the use of pH-responsive
364 CD nanoparticles to release compounds like polyunsaturated fatty acids
365 according to their pH(Xi et al., 2019). The pH-induced protonation/deprotonation
366 of carboxyl groups ensured that the emulsions remained steady at pH ≤4 but were
367 unsteady under neutral conditions.

368 As regards antioxidants, a large number of publications have appeared in
369 recent years about nanoparticles formed by several antioxidants with CDs from
370 natural extracts (Rakmai et al., 2018) or complexed molecules from sources such
371 as polyphenols or essentials oils (Matencio et al., 2016; Matencio, García-
372 Carmona, et al., 2017b; Yildiz et al., 2018; Zhang et al., 2016). In general, the
373 complexation of antioxidants with CDs increases the total concentration of the
374 substance and, consequently, their antioxidant capacities (Celebioglu et al.,
375 2018; Das et al., 2019; López-Nicolás et al., 2014), which can be used by the
376 food industry to fortify products (Ho et al., 2017; Matencio, Navarro-Orcajada,
377 Conesa, et al., 2020). On the other hand, CDs can also be used as *secondary*

antioxidants, whereby an oxidising substrate is complexed by a CD, preventing its oxidation (Crini et al., 2018; López-Nicolás et al., 2014), a quality widely used to reduce the browning of some juices (Andreu-Sevilla et al., 2011).

Although only the three natural CDs α-, β- and γ-CD are authorized as food additive, several derivatives such as hydroxypropyl-β-CD (HPβ-CD) and methyl-β-CD (Mβ-CD) are commonly used as excipients because of their lower toxicity and wider applicability in drugs complexes (Jansook et al., 2018). A variety of novel CD-based matrixes with BaCs have been synthetized, for example polymeric CD based materials (Dhakar et al., 2019; Matencio, Dhakar, Bessone, et al., 2020; Swaminathan et al., 2016; Yao et al., 2019), or nano-derivatives such as amphiphilic CDs(Varan et al., 2017).

5.4 Cyclodextrin effect on hydrocolloid properties.

The use of CDs in different hydrocolloids such as carrageen or starch not only improves the properties of the substance, but also changes the properties of the hydrocolloid. Some interesting examples use approved food additives like carrageen and, include the study of the influence of CDs on carrageen hydrogel properties (Y. Wang et al., 2019; Yuan et al., 2016, 2018, 2019). It is highlighted the case of κ-carrageenan/Konjac glucommanan compound gel, which hardness was strengthened in the presence of 0.5 – 1.5 % (w/w) of CDs and then, gradually decreased at higher CDs concentrations. In this study, Methyl-βCD (Mβ-CD) was the most significant among all the selected CDs on the formation and characteristics of κ-carrageenan/Konjac glucommanan compound gel (Yuan et al., 2019). In another study, the influence of CDs on the rheological and structural properties of κ-carrageenan gel was investigated. The gelling temperature (Tg) and the plasticity were improved. The authors showed that the influence of CDs

403 on κ-carrageenan gelation was mainly through (i) the exclusion of CDs from κ-
404 CA in the sol state, (ii) the regular rearrangement of κ-carrageenan random coils
405 influenced by CDs in the sol state, (iii) the binding of CDs to the κ-carrageenan
406 surface by hydrogen bonds in the gel (Yuan et al., 2018).

407 The influence of β-CD on the retrodegradation of rice starch was
408 evaluated. Retrogradation of normal rice starch was reduced more by β-CD than
409 by glycerol monostearate by the amylose-β-CD complex formation. β-CD
410 significantly lowered the crystallizing rate and increased the Avrami exponent of
411 amylose recrystallisation (Tian et al., 2009).

412 Finally, when CDs are used with guar or xanthan gum they are able to
413 enhance the viscosity of both hydrocolloids (Rao et al., 2014). In other study, a
414 novel self-assembling biopolymer was created between xanthan gum and β-CD,
415 this system exhibits superior mechanical and thermal stability, and also tolerance
416 to elevated brine salinity and hardness (Wei et al., 2015)

417 **5.5 Cyclodextrins for developing novel nanosensors.**

418 In the food industry it is important to know the quantity of a nutrients or
419 bioactive compounds in products, and, for this purpose novel measurement
420 methods with increased sensitivity have been developed. In this respect, the
421 many properties of CDs such as their capacity of chiral recognition of isomers or
422 to amplify their signals, means that they can be used as a platform for developing
423 novel nanosensors (**Fig**. 4).

424 For example, modified CDs have recently been used with grapheme
425 quantum dots to separate tyrosine enantiomers (Dong et al., 2017), after
426 obtaining β-CD quantum dot derivatives for inclusion in an electrode.

Not only hydrophobic molecules can form complexes with CDs, but ions too, can be encapsulated, a property that can be used to create sensors. A recent work analysed Zn^{2+} and CN^- in a solution using magnetic CDs (Q. Li et al., 2015). A modified fluorescein was used to selectively bind the Zn^{2+} ion in preference to others. The magnetic CD used showed high selectivity and an increased fluorescent signal. Moreover, the CDs completely recovered their activity for at least four more cycles. In this sense, a novel cholesterol nanosensor has been studied (Y. Li et al., 2019), and natural CDs can be used to lay the foundations of nanosensors to measure ellagic acid in a ternary complex with borax (Matencio, Navarro-Orcajada, et al., 2018).

The use of CDs in water treatment involves using natural, chemically modified or polymeric CDs to detect contaminants (Fourmentin et al., 2018a; Salazar et al., 2018). The most common strategy is to create different chemosensors focus on coloured or fluorescent CDs (modified with a chromophore or fluorophore). CDs have demonstrated their capacity to recognize and enantio-separate different water contaminants such as pesticides or 1-adamantanol. Indeed, masks can be also modified with CDs to catch contaminants (Alzate-Sánchez et al., 2016).

CDs can be used in chiral chromatography to separate isomers, a technique widely used in the gas chromatography of essential oils (Fourmentin et al., 2018a; Pragadheesh et al., 2015). CD columns are commercially available, in which the degree of substitution or the type of CD contributes to the separation of isomers.

5.6 CDs in food packaging

451 The food industry is constantly searching for ways to make food products
452 safer and more long-lasting, while maintaining quality and minimising any
453 environmental impact. One of the results in this respect is the development of
454 *active* and *smart* packaging, in which compounds are added to the packages in
455 order to extend the shelf life of the food or provide information on the state of the
456 food in real time. Applications of CDs in active packaging are abundant (**Fig. 5**),
457 although they are less used in smart packaging. Despite that, some promising
458 studies have been published, such as using p-methyl red in α-CD, which
459 produces a colour change in the event of leakage (Kuwabara, 2007). Additionally,
460 as CDs are starch-based oligosaccharides and therefore biodegradable
461 (Marshall & Miwa, 1981), if the material used is also easy-to-degrade (e.g.
462 chitosan, cellulose or polylactic acid) (Mohamed et al., 2020), the whole package
463 could be considered biodegradable.
464 CDs can be incorporated in food packages alone (the so-called “empty
465 cyclodextrins”) or complexed with a BaC acting as delivery systems
466 (Szente&Fenyvesi, 2018). Empty CDs in packaging can be used to encapsulate
467 hydrophobic compounds either from inside the package or from the outside. They
468 have been used to reduce the migration of plasticizers (Kwak et al., 2011) and
469 trichloroanisol (a contaminant from bottle corks (Angermaier, 2006)), to capture
470 undesirable volatile molecules, such as hexanal from fried peanuts (López-de-
471 Dicastillo et al., 2011) or sulphur off-flavours(Shin et al., 2018), and even to
472 reduce cholesterol in milk (López-de-Dicastillo et al., 2011). Meanwhile, inclusion
473 complexes in packaging can keep and controlled release a BaC in the inner
474 cavity, acting as preservatives and hence reduce the use of food additives, or in
475 the outer surface of the package to provide protection against environmental

476 factors. It has been described how an increase in humidity levels in the
477 headspace of packaged fresh-cut vegetables or fruits, which is associated with
478 spoilage, may trigger the release of BaC when using CDs as carriers (Ayala-
479 Zavala et al., 2008). In this sense, the quality and shelf life of fresh-cut pineapple
480 and papaya have been increased with the use of edible coatings that incorporate
481 *trans*-cinnamaldehyde in β-CD (Brasil et al., 2012; Mantilla et al., 2013), and the
482 same applies to fresh-cut onion using filter paper containing ally lisothiocyanate
483 in β-CD (Piercey et al., 2012).

484 Among such inclusion complexes used for food packaging, the most
485 studied are those that incorporate antimicrobial BaCs to increase the useful life
486 of the packaged foods by decreasing the growth of bacteria and/or fungi. Most of
487 the reviewed research on this matter involves the encapsulation of essential oils
488 or their major bioactive ingredients in HPβ-CD or natural CDs, with β-CD being
489 the most predominant. Such complexes have demonstrated their ability to extend
490 shelf life and maintain the quality of packaged meat (Aytac, Ipek, et al., 2017;
491 Chen et al., 2019; Higueras et al., 2014; Lin et al., 2017, 2018; XiaoYun et al.,
492 2018), mushrooms (Cheng et al., 2019; Pan et al., 2019), and fruits
493 (Buendía−Moreno et al., 2020; da Rocha Neto et al., 2019; Wen et al., 2016). In
494 packaged fruits, some authors associated the improvement of shelf life with the
495 dual effect of BaC release and ethylene adsorption (Buendía−Moreno et al.,
496 2020).

497 The ripening of packaged fresh fruits and vegetables can be controlled by
498 encapsulating ripening agents or inhibitors. For instance, mango ripening was
499 modulated by packaging them with ethylene and α-CD complexes (Capozzi et

al., 2018), while, similar effects were observed using 1-methylcyclopropene in α-CD (Wood et al., 2017) and hexanal in γ-CD (Lang, 2019).

Antioxidant compounds are also commonly used for active packaging with CDs: for example, HPβ-CD complexes with curcumin(Aytac&Uyar, 2017) or ferulic acid (Sharif et al., 2018), β-CD with gallic acid (Rezaee et al., 2018) or retinyl acetate (Lemma et al., 2015), and γ-CD with quercetin(Aytac et al., 2018) or α-tocopherol (Aytac, Keskin, et al., 2017). Only the last mentioned authors tested the package with a real food (meat), while Rezaee et al. (2018) and Sharif et al. (2018) checked the release of the BaCin acid, alcoholic and fatty food simulants, which consisted of 3 % acetic acid, 10 % ethanol or 95 - 96 % ethanol in water, respectively.

Volatile fragrances such as vanillin (Kayaci&Uyar, 2012), geraniol(Kayaci et al., 2014), D-limonene (Mallardo et al., 2016) and 2-phenyl ethanol (Zarandona et al., 2020) have been successfully integrated into polymers with natural CDs.

Moreover, CDs in packaging can also provide thermal protection to volatile or thermo-sensitive molecules during polymer processing (Fenyvesi et al., 2016b; Sharif et al., 2018), increasing the amount of added BaC (Poverenov et al., 2013) and, enhance the UV-light barrier property of packages (Cheng et al., 2019; Ye et al., 2017). In some cases, there is no other way that can be used to retain the BaC in the matrix (Chen et al., 2019; Zarandona et al., 2020).

Empty CDs or inclusion complexes can be embedded homogeneously in the packaging material or be applied in a separate coating to limit their effect to one direction through the package (inwards or outwards) (Szente&Fenyvesi, 2018). A wide variety of carrier materials (natural or synthetic) and techniques can be applied to create the packaging. For example, the use of electrospun

525 nanofibres is increasing because of their appealing characteristics, such as high
526 surface-to-volume ratio, nanoporosity, and safety (Noruzi, 2016): Mixed with
527 inclusion complexes they can improve the thermal stability and shelf life of foods,
528 and ensure the slow release of some BaCs, such as eugenol (Kayaci et al., 2013).

529 **5.7 Market products with CDs.**

530 Although most applications of CDs are connected with the pharmaceutical
531 industry, where they are used as drug excipients(Jansook et al., 2018), some
532 food products also containthem: for example, α-CD is used for direct weight
533 control purposes and some products such as Calorease™, a natural supplement
534 that has been clinically researched to help control cholesterol and triglyceride
535 levels and maintain a healthy weight through diet and exercise (Comerford et al.,
536 2011; Fenyvesi et al., 2016a; Jarosz et al., 2013). In New Zealand Cyclopower™,
537 which is based on encapsulating the bioactive compounds found in manuka
538 honey and in propolis inside cyclodextrins, allow the controlled release of the
539 bioactive compounds where they are needed most in the body. Although the
540 current cost of CDs prevents the use of all the potential applications mentioned
541 in the literature, production costs are continuously falling, and they will surely be
542 more widely used in the near future.

543 **6. CONCLUSIONS**

544 Although CDs have been used for several years, the way in which they are
545 currently used in the food industry is changing: the classical (although equally
546 important) role as of a “carrier” to stabilize bioactive compounds is giving way to
547 novel applications: i) CDs as nutritional supplement in the form of prebiotic, and
548 for weight and lipid control, ii) in active and smart food packaging, enabling the
549 controlled release of antimicrobials, antioxidants, etc., iii) as nanosensor to

measure bioactive compounds and, iv) forming novel nanoparticles for functional food uses, v) its use with hydrocolloids and vi) as enhancers of the extraction or production enhancers of bioactive compounds.

As an evident prospect from this review, the versatility of cyclodextrins is wide and promising. Traditional and chemically derived CDs find novel applications and uses every day. Several research groups are increasing the number of CDs and CD-based materials available for use in fresh applications. As the costs of this technology are decreasing (CD production, protocols…),and novel applications are constantly being found, their application in the food, pharmaceutical and other industries (not only in scientific research) will undoubtedly increase in forthcoming years.

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FIGURE CAPTIONS

Fig. 1: (A) Structure of β-CD. (B) Schematic illustration of an inclusion complex between Piceatannol (a bioactive compound) and β-CD. Molecular docking image was obtained from published data(Matencio et al., 2016).

Fig.2: Graphical representation of the production or extraction of bioactive compounds using CDs.

Fig.3: Graphical representation of the use of CDs to produce “free” products and induce organoleptic modifications.

Fig.4: Graphical representation of cyclodextrins for developing novel nanosensors.

Fig. 5: Graphical representation of the applications of CDs in food packaging

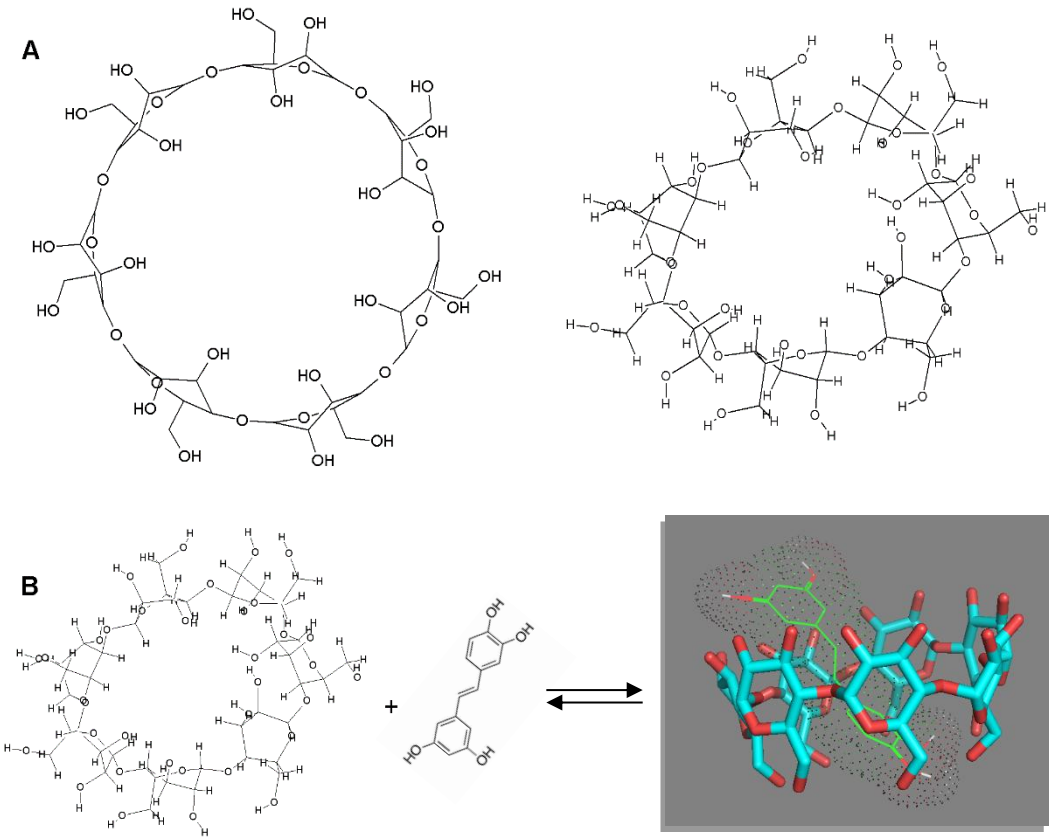
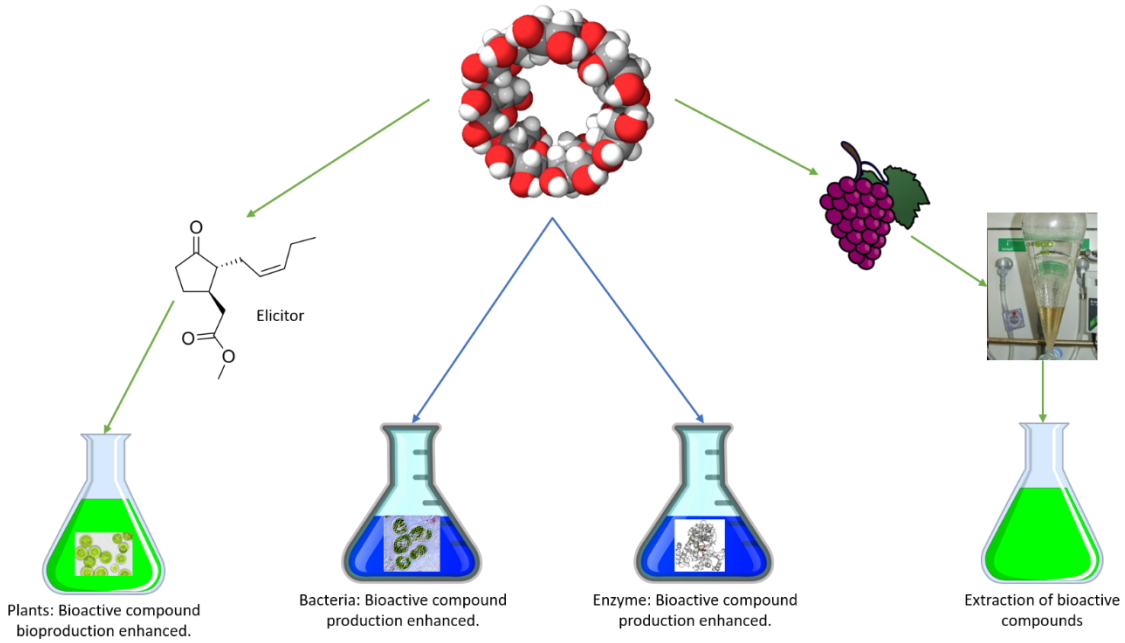


Fig 1.



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1298 Fig. 2

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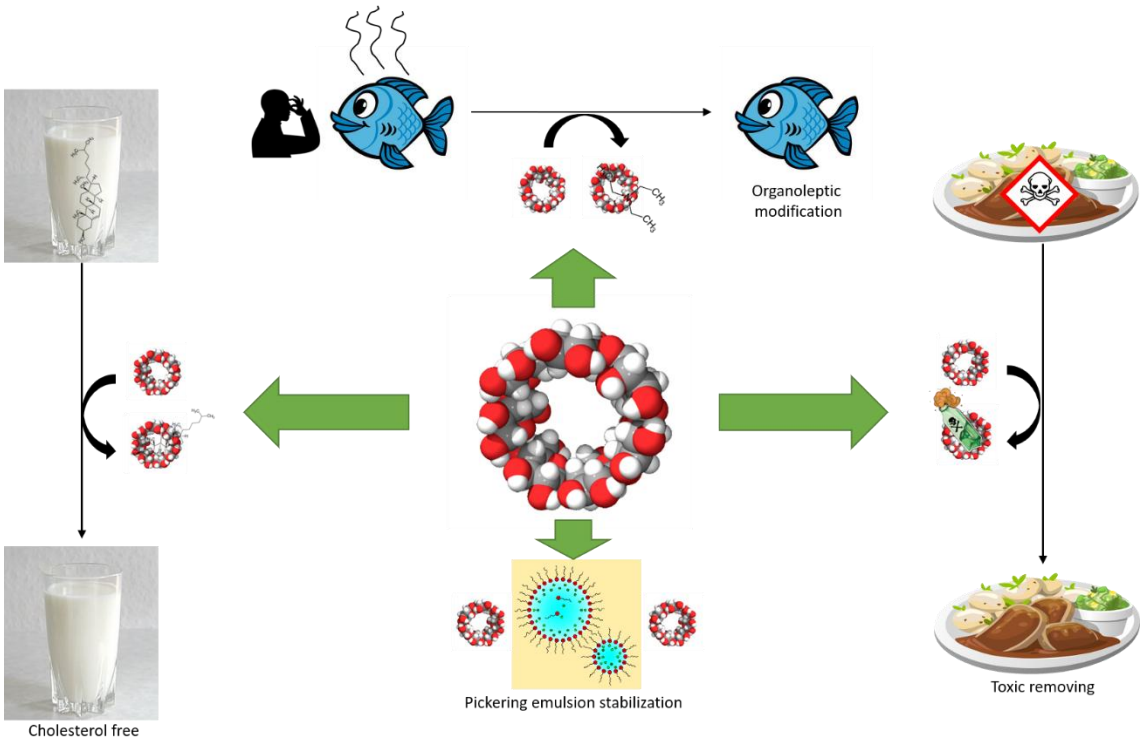

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1301 Fig. 3

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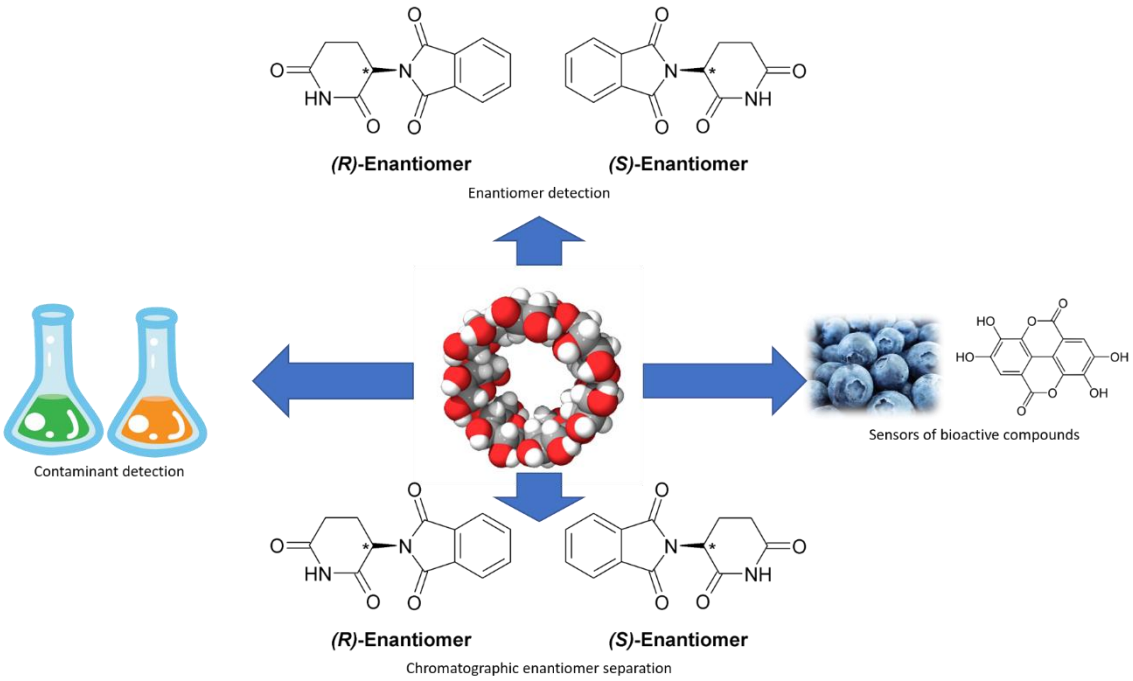

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1306 Fig. 4

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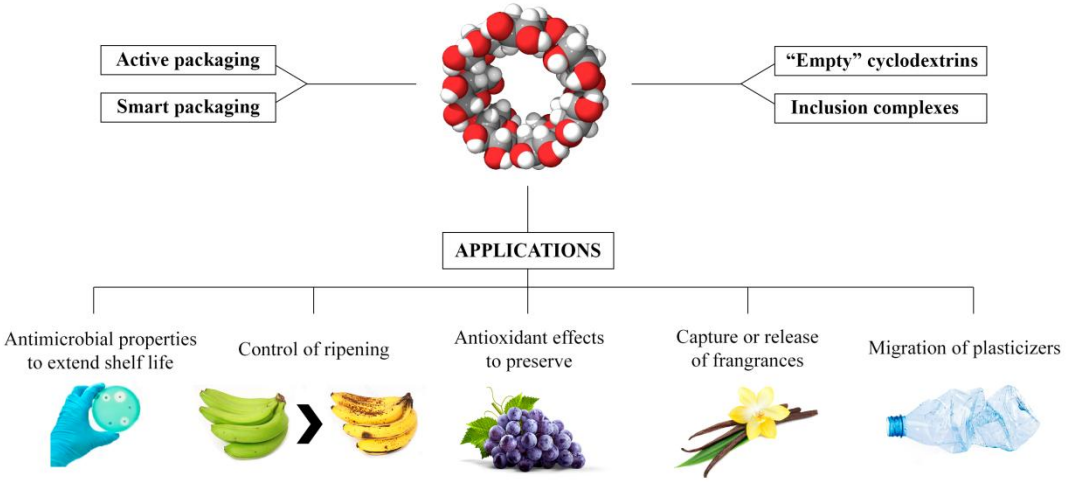

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1309 Fig. 5

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TABLES

Table 1: Different methods to characterize CD inclusion complexes.

Technique basis	Technique
Spectroscopic	Ultraviolet/Visible (UV)
	Circular dichroism
	Fluorescence
	Nuclear magnetic resonance (NMR)
	Electrons spin resonance (ESR)
	Fourier-transform infrared (FTIR)
Electroanalytical	Polarography
	Voltammetry
	Potentiometry
	Conductimetry
Separative	High performance liquid chromatography (HPLC)
	Capillary electrophoresis (CE)
	Gas chromatography
Thermal	Differential scanning calorimetry (DSC)
	Thermal gravimetric analysis (TGA)
	Isothermal titration calorimetry
Microscopy	Hot Stage microscopy (HSM)
X-Ray	Single crystal X-ray diffraction (SCXRD)
	Powder X-ray diffraction (PXRD)
	Polarimetry

1316 **Graphical Abstract**

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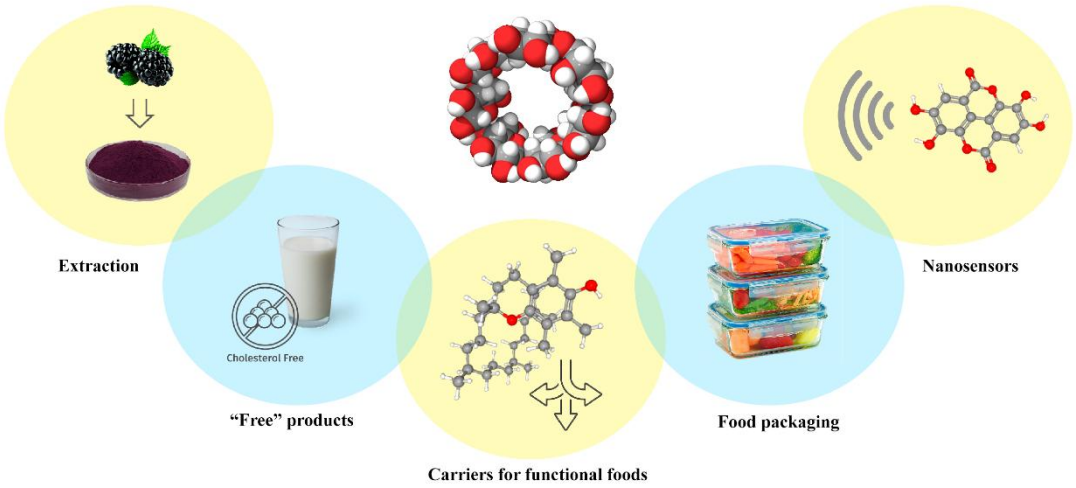

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