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Chitosan-tripolyphosphate nanoparticles designed to encapsulate polyphenolic compounds for biomedical and pharmaceutical applications – A review

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ABSTRACT

Plant-based polyphenols are natural compounds, present in fruits and vegetables. During recent years, polyphenols have gained special attention due to their nutraceutical and pharmacological activities for the prevention and treatment of human diseases. Nevertheless, their photosensitivity and low bioavailability, rapid metabolism and short biological half-life represent the major limitations for their use, which could be overcome by polyphenols encapsulation (flavonoids and non-flavonoids) into chitosan (CS)-tripolyphosphate (TPP) based nanoparticles (NP). In this review, we particularly focused on the ionic gelation method for the NP design. This contribution exhaustively discusses and compares results of scientific reports published in the last decade referring to ionic gelation applied for the protection, controlled and site-directed delivery of polyphenols. As a consequence, CS-TPP NP would constitute true platforms to transport polyphenols, or a combination of them, to be used for the designing of a new generation of drugs or nutraceuticals.

1. Naturally occurring polyphenols: from benefits to limitations

Bioactive compounds are defined as those that occur in nature and are part of the food diet [1]. Natural-derived bioactives from plants are phytochemicals capable of regulating metabolic processes and promoting good health [2–4]. Particularly, vegetables or fruit diets were proven to provide essential bioactive molecules that were able to exert key roles in human health. These plant-derived bioactive molecules include enzymes, amino acids, vitamins, essential oils, minerals, fibers and polyphenols [5]. In this context, studies on polyphenols have been growing particularly in the last two decades [6]. In those years we have become witnesses of a revolution in the exploration of phenolic compounds due to their potential plethora of health benefits as numerous scientific reports proposed [7].

Polyphenols are a broad group of plant secondary metabolites whose family contains at least 10,000 different compounds. In the last decades, a burgeoning research field has paid attention to the study of the benefits of diverse polyphenols in the prevention and treatment of multiple chronic disorders, such as neurodegenerative, retinal, cardiovascular and intestine disease, diabetes mellitus, arthropathies, stroke, hypertension, atherosclerosis, obesity, cancer, viral and bacterial infections, among others [7–21]. In general terms, antioxidant, anti-inflammatory, antibacterial, anti-fungal, anti-viral, and anti-tumor activities were reported for polyphenols [22].

Polyphenols can be classified into two large groups, flavonoids and non-flavonoids, according to the presence of one or more hydroxyl groups linked to a benzene ring [23–26]. Fig. 1 summarizes the two groups in which polyphenols are divided, their respective chemical structures, and the main source from which they can be extracted.

Flavonoids share a structure that consists of a general structural

Abbreviations: CS, chitosan; DD, degree of deacetylation; EE, encapsulation efficiency; IG, ionic gelation; LC, loading capacity; MW, molecular weight; NP, nanoparticle/s; TPP, sodium tripolyphosphate; CS-TPP NP, CS-TPP based NP designed via by IG.

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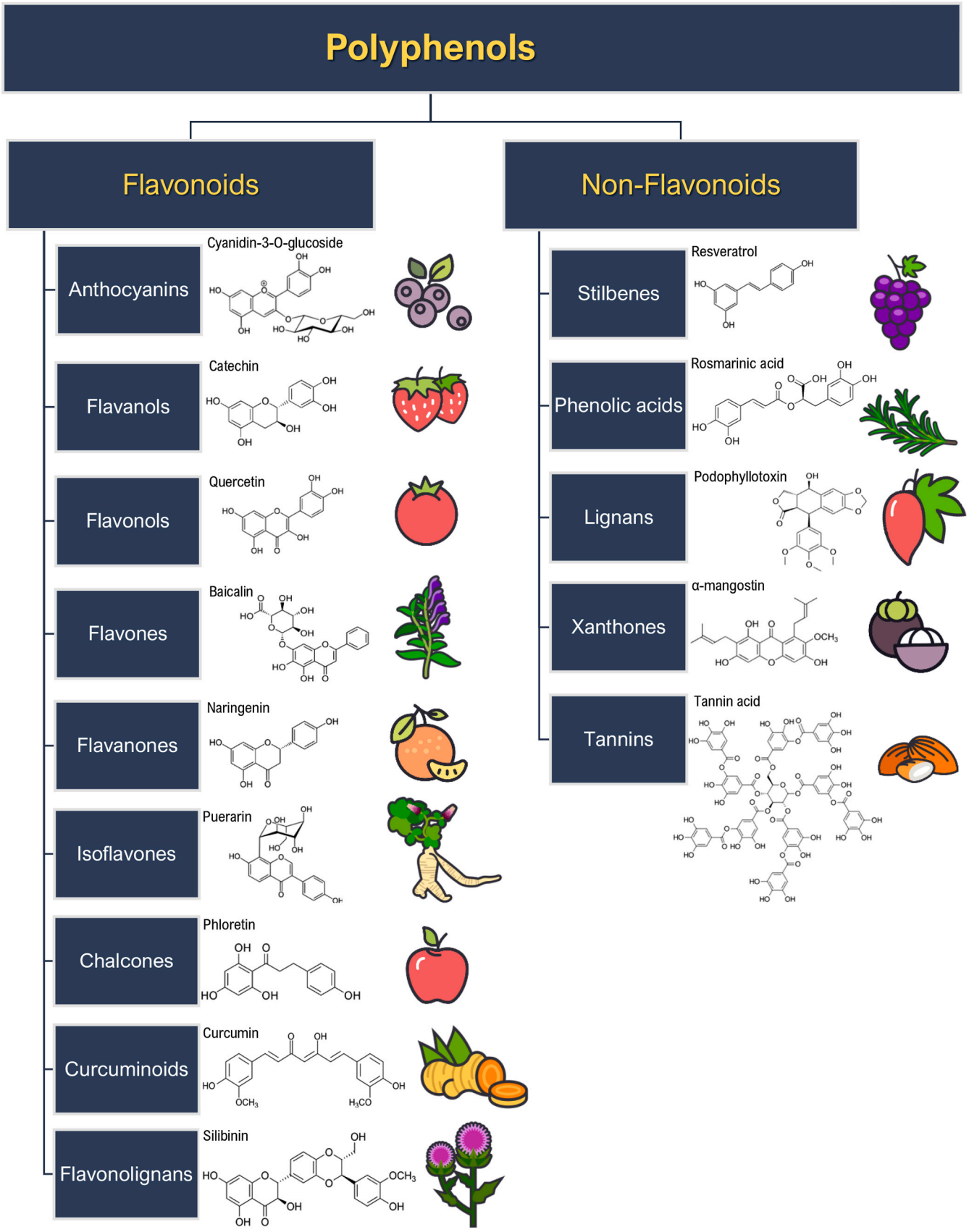

Fig. 1. Classification of polyphenols. Polyphenols are categorized into two main subgroups, flavonoids and non-flavonoids, according to the occurrence of one or more hydroxyl groups linked to a benzene ring.

backbone of two benzene rings linked through a linear three-carbon chain (C6-C3-C6) [18,22–24,27]. The basic flavonoid structure is an aglycone with a fifteen-carbon skeleton consisting of the two benzene rings (A and B) linked via a heterocyclic pyran ring (C). Flavonoids occur as aglycones, glycosides, and methylated derivatives [28]. Depending on the connection position of the B and C rings as well as the degree of saturation, oxidation, and hydroxylation of the C-ring hydroxylation pattern, flavonoids can be further sub-classified as flavonols, flavones, flavanones, flavanols, isoflavones, chalcones and anthocyanins [29–31]. The various subclasses of flavonoids vary in the level of oxidation and pattern of substitution of the C-ring, while individual compounds within a class differ in the pattern of substitution of the A- and B-rings [32]. The chemical nature of the flavonoids in plants makes them relatively resistant to heat, oxygen, dryness, and moderate degrees of acidity, but they can be easily modified by light. Photostability of the flavonoid molecule depends on the nature of the hydroxyl group attached to C3 of the C-ring. The absence of glycosylation of this hydroxyl group results in high photostability of the molecule [33].

Remarkably, Sepahpour et al., mentioned that even though curcuminoids are not classified as a flavonoid, they behave similarly to flavonoid compounds when they react with $AlCl_3$ in the total flavonoid content method. That is to say, after the reaction, $AlCl_3$ forms acid-stable complexes with the keto groups and hydroxyl groups of flavonoids [34]. Hence, many reports include curcuminoids among the group of flavonoids [23,35,36]. In a similar way, flavonolignans are naturally occurring hybrid molecules, biogenetically originated from ubiquitous flavonoids and monolignols. Flavonoid portions of flavonolignans are divided into four types: flavonol-, flavanonol-, flavanone- and flavone-type; meanwhile the counterpart involves molecules such as sinapyl alcohol, coniferyl and p-coumaryl [37,38]. Therefore, in this review, for more convenience and clarity, curcuminoids and flavonolignans will be included in the flavonoid group of polyphenols.

Non-flavonoids group involves structurally diverse compounds, among which are classically included stilbenes (C6-C2-C6), phenolic acids (divided into two main types, benzoic acid and cinnamic acid derivatives based on C1-C6 and C3-C6 backbones) and lignans (C6-C3-C3-C6) [18,22–24,29]. Additionally, xanthones (C6-C6-C6) and tannins (C6-C1) were incorporated into this second group [5,24]. All of the mentioned compounds have at least two aromatic rings in the structure, while only tannins have more than two aromatic rings [5].

Currently, polyphenols research gained attention for its impact on nutraceutical and pharmaceutical industries due to their potential benefits for human health. The therapeutic approach to alternative compounds extracted from plants is an option for a concerted search of new drugs. Hence, while science looks at polyphenol bioactives with promising eyes, many large pharmaceutical companies are reluctant to accept these compounds for some key reasons [4,39]. The major issues with the enforcement of polyphenols are their low bioavailability, water insolubility, instability, rapid metabolism and short biological half-life, which have caused problems in clinical trials [4,40–42].

The efficiency of polyphenol intake depends on their bioavailability and molecular integrity. Those characteristics vary for each phenolic compound; however, the chemical structure principally affects the rate and the extent of their absorption before the concentration could do [43,44]. In the case of oral administration, a small proportion of those compounds are absorbed due to the insufficient gastric residence time, low permeability and/or low solubility. That is to say, the polyphenol instability in the gastrointestinal tract (enzymes, occurrence of other nutrients, microbiota, pH) limits its bioavailability, and, as a consequence, the potential health benefits [17,44]. On the other hand, polyphenols are susceptible to environmental factors (e.g. heat, moisture, oxygen, light irradiation: UV, visible, and solar), which makes them unfavorable for topical use because of degradation as a result [17,42,45–48] (Fig. 2).

To date, several encapsulation technologies have been designed to overcome polyphenol limitations by enhancing the solubility, stability, bioavailability and controlled release in order to direct them precisely towards a physiological target [4,17,41,44,45,48–53]. The usage of encapsulated polyphenols as a replacement for their free form is the source of a copious number of reports.

2. Polysaccharides as encapsulation biomaterials

Nanoencapsulation, defined as the encapsulation of compounds into generated submicronic structures, has the potential to protect the components of interest that are sensitive to environmental conditions or processes that may be injurious or unfavorable. In this way, incompatibility can be reduced, and physicochemical properties such as solubilization can be improved. Increased bioavailability of the bioactive compounds that are poorly absorbable and their protection during the processing of the matrix in which it is included can be achieved by nanoencapsulation processes [54].

In recent years, there has been a growing interest in the design of site-directed or site-specific delivery systems based on polymeric

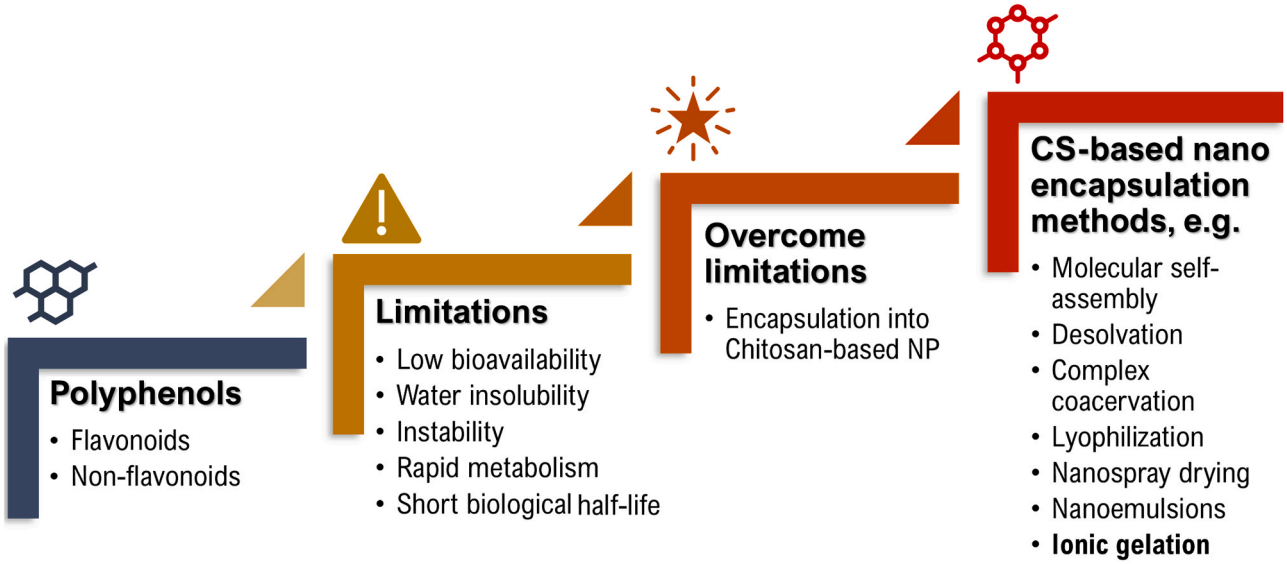

Fig. 2. Schematic representation of polyphenols-associated limitations and nano-formulations to overcome it.

structures. Polysaccharides are among the most abundant substances in nature; they are relatively inexpensive and widely known to obtain, which makes them natural replacements for synthetic polymers. They are also safe, non-toxic, and biodegradable materials. Their different compositions give them endless application possibilities (molecular weight, charge, polarity, solubility, etc.) [55] that increase, in most cases, the bioavailability of the encapsulated bioactive compound [56,57]. Several attempts have been made to develop encapsulation systems using these materials as encapsulating agents for the subsequent "site-specific" release of compounds with biological importance, in food, as well as in the pharmaceutical and cosmetic fields [58,59].

There are several factors that must be considered when selecting appropriate polysaccharides - or a combination of them - to manufacture a delivery system based on these materials. It is important to establish the conditions of the solution and the environment in which the molecules are found, which allows the intermolecular association and the relation with other molecules present in the solution bosom. This requires knowing the physicochemical properties of the species involved, such as the transition temperatures of dehydration events, glass transition, aggregation, electrical properties, *pKa*, sensitivity to mono- or polyvalent ions, or the susceptibility to chemical or enzymatic reactions [60].

The molecular structure of polysaccharides depends on their monomer sequence, the prevailing environmental conditions, and their physicochemical and rheological history. These chemical differences translate into different molecular properties, such as MW (molecular weight), degree of branching, structure, flexibility, electrical charge, and interactions. In turn, these molecular differences lead to differences in functional properties, such as solubility, gelation, water retention capacity, emulsification, and surface activity [61].

Polysaccharides are biomaterials that can be neutral (*e.g* starch, cellulose), anionic (*e.g* alginate, carrageenan, xanthan) and even cationic (*e.g* chitosan) [62–67]. The electrical charge of polysaccharides depends on the nature of the ionic groups along the chain, as well as the conditions of the solution. In this context, it is important to establish the electrical characteristics of the molecules used, i.e. ζ-potential versus solution pH; in the case of electrostatic interactions this principle can be used to assemble specific polymeric structures [56,68,69].

The magnitude of the electric charge depends on the pH in relation to the *pKa* of the charged groups. Those of an anionic nature tend to be neutral at pHs sufficiently lower than *pKa*, and negative at higher pHs, while cationic ones tend to be neutral at higher pHs and positive at lower pHs. The most common charged groups are sulfates, as in carrageenans; carboxyl groups as in pectin, alginate and carboxymethylcellulose; and amines, as in CS. The electrical charge of polysaccharides can be altered by interactions with other ionic species in their environment. These interactions usually involve mono- or multivalent ions such as sodium or calcium, which bind to charged groups in the biopolymer chain, altering the total charge.

3. Chitosan: a versatile polysaccharide for NP design

CS has been considered the biopolymer of the 21st century because in recent decades, its study and its consequent uses have grown exponentially [70]. The precursor of CS, chitin, is a linear homopolysaccharide formed by N-acetyl-β-D-glucosamine units. CS is obtained after a process of deproteinization and removal of a large number of acetyl groups from the chitin structure (deacetylation), thus exposing the amino groups, which are responsible for the versatility of this biopolymer [59,71,72]. The degree of deacetylation (DD) and MW are the most important characteristics of the polysaccharide structure and define its possible applications. CS is considered when the DD of the molecule is greater than 50%. The characteristics of its molecules allow the CS to be used in different forms: in solution, films, hydrogels, fibers, nanoparticles, nanocapsules, microspheres, among others [73,74]. From a regulatory point of view, this polysaccharide has the GRAS (Generally Recognized as Safe) category granted by the US Food and Drug Administration (FDA) to be used as a dietary supplement to prevent fat absorption, in bandages for various wounds [75,76] and for tissue engineering [77].

As the absorption of most active drug ingredients is controlled by a passive diffusion process, its increment is crucial to maintain the concentration gradient as steep as possible. This fact represents the driving force that maximizes the absorption of the component of interest. To achieve this goal, the delivery system must be kept in intimate contact with the absorption membrane during the adequate time, which can be ensured by using mucoadhesive delivery systems. CS is capable of easily adhering to the mucus surface and open tight junctions between epithelial cells. This property is possible because of its abundant bioactive hydroxyl and amino groups, which determine the changeable solubility, chemical reactivity, and bioactivity of CS. Most importantly, the toxicity level of CS is very low, and its oral LD50 value is greater than that of sucrose [78]. The low toxicity of chitosan depends on the DD, surface charge, and solubility.

In general terms, nanoscale refers to structures between 1 and 100 nm that exhibit unique size dependent properties [64]. Then, NP refers to particles that fall into the nanoscale. In practice, this criteria is extended to larger particles, usually less than 500 nm size. Broadly speaking there are two strategies or approaches for NP generation. In the *top-down* strategy, the process begins with macroscopic scale materials, which are reduced until the desired particle size is obtained. For the second strategy, on the contrary, the assembly of smaller components is sought to achieve more complex structures [79]. This approach is commonly associated with milling, crushing, homogenization and extrusion, which involve the disruption of solids or liquids into smaller particles. To this end, compression, impact, and shear forces are regularly used [65]. Although this strategy is used in the industry to generate biopolymeric particles, in many cases, the development of particles with well-defined structural properties that safeguard the physicochemical integrity of bioactives, results really complex [66]. The *Bottom-up* approach is characterized by the construction of particles by the self-assembly or self-organization of molecules due to changes in the solution external conditions, such as pH, ionic strength, temperature, or biopolymers concentration. This strategy allows the formation of very small particles with a high degree of control over their size, morphology, etc. Some of the most representative techniques to generate CS-based nanostructures by the *bottom-up* approach are listed in Fig. 2 and briefly described below.

3.1. Molecular self-assembly

When an amphiphilic material is dissolved in an aqueous solution, self-aggregates can form spontaneously, through intra- or intermolecular associations between the hydrophobic domains, mainly to minimize interfacial free energy. This process is triggered by intrinsic changes in the solution, such as pH, ionic strength, or the presence of co-solutes, or extrinsic ones such as store temperature, or treatments like irradiation. The NP thus formed exhibit unique characteristics, depending on the hydrophobic / hydrophilic constituents. In many cases, core-shell type structures are obtained: a hydrophobic center surrounded by a hydrophilic crown [67].

3.2. Desolvation

A polysaccharide is desolvated through changes in charge or by the addition of a desolving agent, inducing a coacervation effect. Among the most common desolvation agents are certain alcohols and salts, depending on the drug to be encapsulated [67].

3.3. Complex coacervation

It occurs when two polyelectrolytes of opposite charges are mixed,

consequently a new structure (NP) mediated by electrostatic interactions between the two species is formed and a phase separation mechanism takes place. Thus, a rich phase of mixed polymeric NP called coacervate, and a depleted supernatant phase are formed. This method allows the encapsulation of various drugs and bioactive compounds in the aqueous phase at low temperatures, preserving their activity [64].

3.4. Lyophilization

It is a physical entrapment process of bioactive molecules which consists of the dehydration ofheat sensitive materials. It involves freezing, sublimation, and desorption of water from the polymer solution. This technique gives rise to samples with a high degree of porosity, which can be reconstituted with relative ease [66].

3.5. Nanospray drying technology

The solution containing the biopolymers for the NP construction is propelled through a grid with micrometric pores which vibrates at ultrasonic frequencies. This produces an aerosol of small, charged droplets, which are dried by hot air flow. A fine powder constituted by the NP is obtained [80,89]. Analogous to lyophilization, it is another way of physical entrapment of bioactives [57].

3.6. Nanoemulsions

An emulsion is able to not only to protect active substances from environmental stressors, but also delay deteriorative reactions [81,82]. These complex systems can be obtained by ultrasound (US) process, which has been used to successfully prepare nanoemulsions with small droplet diameter, greater stability and low poly-dispersity [83]. The effect of ultrasound on the preparation of nanoemulsions depends on multiple factors including ultrasonic power, frequency, and time. US has been widely used to form the CS-surfactant nanostructure assembly [84].

3.7. Ionic gelation

The IG technique is the most studied formulation method for preparing CS NP. It is built on electrostatic interaction among the positively-charged amino-sugar monomeric units of CS and negatively-charged polyanions, e.g., TPP, glutaraldehyde, genipin, and glyoxal, hexametaphosphate, or dextran sulfate [85]. The IG method is widely reported for the administration of various drugs in literature. In this review, we mainly considered discussing CS-based NP (CS-TPP NP) constructed via the IG approach, using TPP ion as a crosslinking agent. The main reasons for this focusing are based on the fact that the CS-TPP NP generation process is unexpensive in comparison to other technologies mentioned above. This relatively low-cost technique allows the encapsulation of bioactive compounds in a high-speed manner. Particularly, since it does not require high temperatures, organic solvents or sonication, it is especially useful for labile compounds. Another advantage of the IG method is the ease with which the degree of crosslinking and, therefore, the 'buffering' activity can be manipulated. In addition, CS-based NP are biodegradable and do not show considerable toxic effects in either in vitro or in vivo studies [86,87].

4. CS-TPP interactions: the ionic gelation method for the NP synthesis with biomedical purposes

The ability of polyelectrolytes to cross-link in the presence of counter ions and form hydrogel beads/spheres is the base of the IG method. The formed NP are obtained spontaneously under mild control conditions without involving high temperatures, organic solvents, or sonication. TPP ($Na_5P_3O_{10}$) is a multivalent polyanion with low toxicity and cost, and, unlike other cross-linkers, this ion presents no severe constraints for handling and storage [62,88]. TPP is the salt sodium penta-anion polyphosphate, which is the conjugate base of triphosphoric acid. TPP interacts with the amino groups of long polymer molecules and form a three-dimensional network of ionically cross-linked regions leading to the formation of inhomogeneous systems, as well-defined NP or not-controlled aggregates depending on CS characteristics, and the concentration of CS and TPP [63]. Fig. 3 schematically shows the underlying concept of IG given between CS and TPP. Upon TPP solution addition, NP can be formed immediately through inter and intramolecular linkages between TPP phosphates and amino groups of CS (Fig. 3). NP characteristics can be affected by the CS nature, DD and MW, and superficial charge. Solution characteristics also affect the NP formation as the strength of TPP crosslinking is sensitive to both the abundance of CS ionized amine groups and presence of monovalent salt; the dissolution/disintegration stability of CS-TPP particles is expectedly sensitive to both, pH (which affects the abundance of ionized chitosan amine groups) and ionic strength (which affects the CS-TPP binding strength) [90]. Therefore, the handling of features such as CS:TPP ratio, CS concentration and solution pH allow to exert control on both the particle size distribution and ζ-potential.

In summary, the interaction of CS with TPP leads to biocompatible cross-linked CS based structures, which can be used to efficiently transport bioactive compounds, i.e., NP as carriers. Nevertheless, the crosslinking density, crystallinity, and hydrophilicity of the crosslinked CS system can allow controlling the bioactive release and extending the range of applications of such bioactives.

5. . Polyphenols encapsulated into CS-TPP NP constructed via IG

The purpose of this contribution is to offer the state of art for polyphenols encapsulated into CS-TPP NP by using IG technique. These NP constitute real carriers for the most common bioactive polyphenolic compounds allowing to exert their protection and controlled release. To this end, a comprehensive literature search was performed using the available search engine systems in science: PubMed, Scopus and Google Scholar for the articles published during the last 10 years. Those investigations were summed up in Table 1 (flavonoids) and Table 2 (non-flavonoids). What one can see is the progressive increase in the number of reports on the subject (Fig. 4). This trend has become outstandingly popular in Asia, which accounted for more than 70% of the reports we have found, followed by North America, Europe, Oceania, South America, and Africa, respectively. Particularly, it is notable for the limited number of european reports, considering the importance of the Mediterranean diet in many of the countries of such continent [91,92]. On the other hand, we believe that the large number of reports concerning to polyphenols encapsulation in Asia is related to the traditional Asian plant-based diet. Particularly, isoflavones intake in asiatic countries is ~10 times greater than in western countries; green tea is an important source of many flavonoids in oriental cultures. Additionally, most polyphenols occur in abundance in tropical fruits and vegetables that are widely cultivated in Asia [93–95]. On the other hand, and in accordance with Food and Agriculture Organization 2020 reports, the total crustacean production (shrimps, lobsters, crabs, and others) in Asia constituted nearly 90% of the total world production [96]. Moreover, crustaceans derived porducts are obtained and consumed in China, Thailand, and Japan in large quantities, which makes crustacean shell waste readily available in this region. North America is projected to witness significant expansion, due to the rise in adoption of CS-based biomedical and pharmaceutical products, involving weight loss supplements and bandages. Anyway, the high percentage of crustacean consumption in Asia might explain the large-scale utilization of shrimp wastes to avoid excessive environmental pollution. The global CS market is propelled by the growth of crustacean waste from the seafood industry, which is the main industrial source of chitin [97,98].

The reports concerning to in vitro (prokaryotic and eukaryotic cells) and in vivo (animals) studies are deeply increasing over time. An

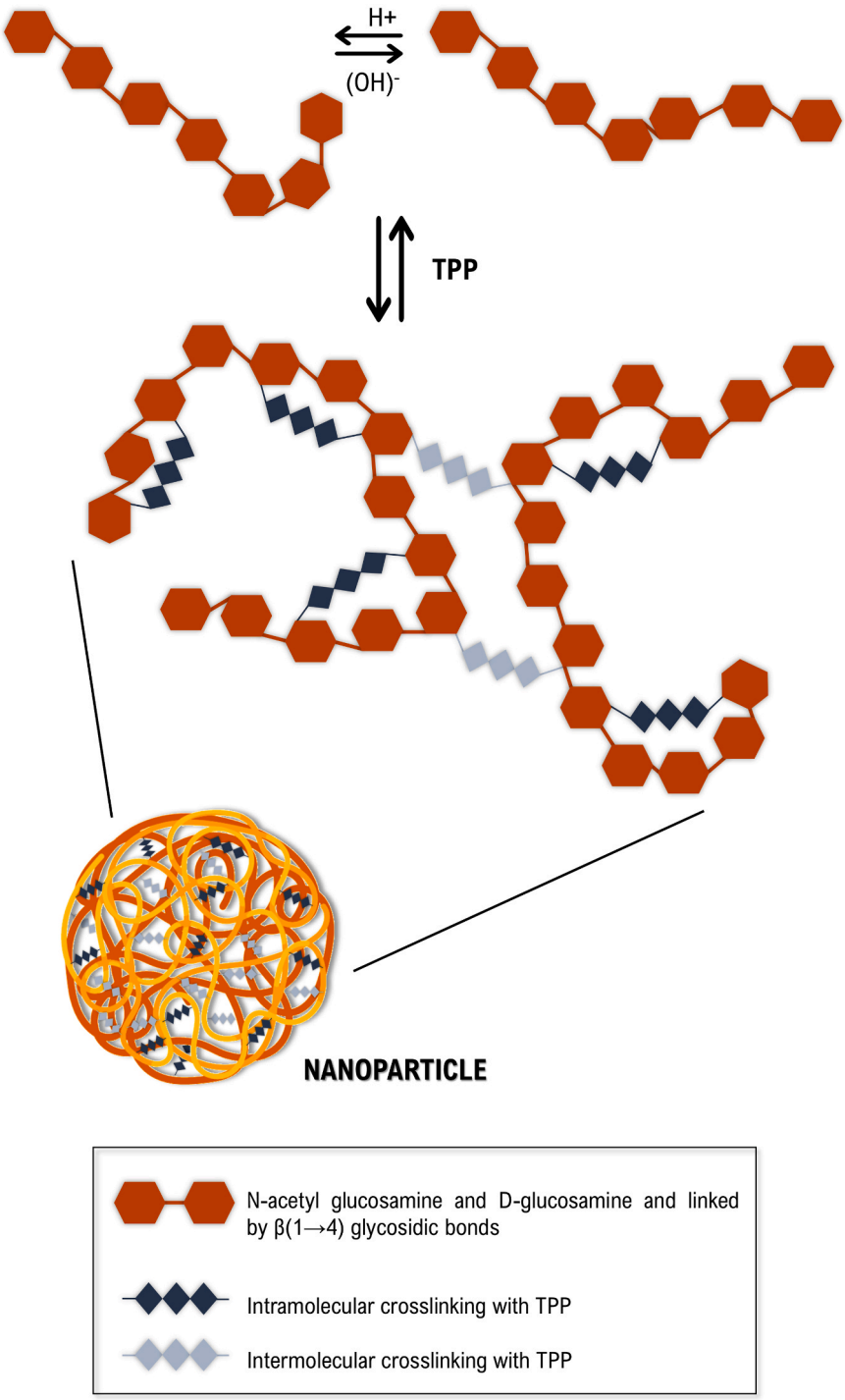

Fig. 3. Ionic gelation. CS-based NP can be developed spontaneously by mixing a solution of CS with TPP, a polyanionic cross-linker, to establish inter- and intramolecular bonds.

exhaustive analysis, having into account intrinsic aspects of CS such as MW and DD, and characteristics of the NP such as size, charge, polydispersity index, particle size efficiency, and encapsulation efficiency were considered for this review.

5.1. Flavonoids

5.1.1. Flavonols

Fruits, vegetables, and beverages such as tea and red wine are major sources of flavonols in the human diet. These compounds possess a hydroxyl group at the C3, which may also be glycosylated, a C2-C3 double bond and a ketone in C4 of the C-ring [30]. Since they are very diverse in methylation and hydroxylation patterns, flavonols are an extensive subgroup of natural flavonoids whose source is wide; including onion, broccoli, apples and black grapes [31].

Greater concentrations of flavonols are found mainly in foods that are characterized by a high skin:volume ratio, such as grape wines and cherry tomatoes [43]. In leafy vegetables and fruits, flavonols are almost exclusively present as glycosides. Flavonol glycosides are located mainly in the leaves, flowers, and outer parts of plants such as skin and peel. Only trace amounts of flavonols are found in plant parts below the soil surface with the notable exception of onions [43]. Certain flavonol

Table 1
Flavonoid polyphenols encapsulated by ionic gelation method in CS-TPP NP. The symbol (-) represents data not informed or unavailable. The particle sizes were indicated in nm unless otherwise specified.

Subgroup	Active compound	CS source	CS MW	CS DD (%)	Particle size	CS:TPP Ratio	EE (%)	Application field
Flavanols	**Catechin and EGCG**	Sigma	Low	85	163–165	2.2:1	–	Food additive – Drug delivery
	Catechin and EGCG	Sigma	Low	85	440	2.2:1	–	Food additive – Drug delivery
	EGCG	Sigma	Low	85	440	2.2:1	–	Food additive – Drug delivery
	EGCG	Polysciences (Warrington, PA)	–	–	150–200	5:1	–	Treatment of prostate cancer
	EGCG	Polysciences (Warrington, PA)	–	–	150–200	5:1	–	Treatment of human melanoma
	EGCG	Crab shell, Zhejiang A. Biotech. Co. (China)	100 kDa	95	143–185	4:1	40–90	Treatment of breast cancer
	EGCG	Sigma	Low	–	415	40:1	–	Treatment of hepatic fibrosis
	Catechin	Sigma	–	85	134	7:1	–	Food additive
	Catechin and Catechin-Zn	Squid pens	160 kDa	86	208–591	5:1	50–89	Food additive and packaging
Curcuminoids	**Curcumin**	Sigma	Low	75–85	261	3:1	78	Drug delivery for colon cancer treatment
	Curcumin	–	–	–	160	10:1	75	Drug delivery
	Curcumin	Sigma	–	–	197	2:1	85	Treatment of cervical cancer
	Curcumin	Crab Shell	–	–	≥ 250	8:1	–	Food additive
	Curcumin	Sigma	–	–	49	3:1	–	Treatment of breast cancer
	Curcumin and EGF	–	–	–	235	5:1	83	Fotodynamic therapy for carcinoma
Flavonols	**Quercetin**	Sigma	165–175 kDa	–	100	2:1.5	–	Protection of liver from mycotoxins
	Quercetin	Macklin (Shanghaii)	–	–	184	2:0.7	91	Prevention of UVB radiation-induced skin damage
	Quercetin	Yarrow Chem Products (India)	–	–	114,6	2:1	80	Treatment of cancer
	Quercetin	Sigma	Low	–	179	5:1	96	Treatment of colon cancer
	Quercetin	–	–	–	361	–	90	Cutaneus wound healing
	Quercetin	Sigma	–	–	744	–	62	Treatment of cancer
	Quercetin and Myricetin	Sigma	50–190 kDa	–	124–153	2:1	82–89	Prevention of age-related diseases
	Quercetin and Glibenclamide	Sigma	190–310 kDa	75–85	370	2.8:1	94–97	Treatment of diabetes
	Kaempferol	Sigma	Low	75–85	192	3:1	78–93	Antibiofilm agents
	Rutin	Sigma	Low	92	528	4:1	58	Food additive
	Rutin	–	–	–	100	7.5:1	–	Treatment of cancer
Anthocyanins	**Anthocyanin**	Primex ehf (Siglufjordur, Iceland)	149 kDa	97	~34 μm	–	–	Food additive
	Anthocyanin	CV. ChemiMix Pratama (Indonesia)	–	–	28	–	–	Food additive
	Anthocyanin	Sigma	Medium	75–85	197	–	66	Food additive
	Anthocyanin + sinapic acid	Sigma	Low	–	160–1093	–	–	Food additive
	Cyanidin-3-O-glucoside	–	–	–	288	5:1	45	Protection Against UVB-induced photodamage
Flavonolignans	**Silibinin**	Sigma	–	–	237	4:1	83	Treatment of prostate cancer
	Silibinin	Sigma	Low	–	208	3:1	49	Treatment of lung cancer
	Silibinin	Sigma	50 – 190 kDa	> 75	189	2.5:1	87	Treatment of glioma
	Silymarin	Central Inst. of Fish. and Tech. Kochi (India)	–	–	104	4:1	83	Hepatoprotective activity – Liver targeting
Chalcones	**α-Arbutin / β-Arbutin**	Sigma	Low	95	147–284	5:1.2	68–71	Cosmetics drug delivery
	Phloretin	Sigma	–	–	80–100	–	–	Prevention of oral cancer
	Phloretin	Sigma	50 kDa	75	80–100	1.9:1	–	Treatment of oral cancer
Flavones	**Chrysin**	Sigma	Medium	75–85	355	5:1	81	Antimicrobial
	Baicalin	Guoyao Chem. Reag. Co. Ltd. (China)	–	–	316	5:1	91	Chemotherapeutic drug delivery
Flavanones	**Naringenin**	Sigma	–	–	447	5:1	70–80	Therapeutic drug delivery
	Naringenin	Sigma	–	–	233	2:1	72	Treatment of neurotoxicity
	Naringin	Shrimp shells	–	–	93	4:1	–	Bone tissue engineering
	Hesperetin	Himedia, Chennai, Tamil Nadu, (India)	–	–	450	5:6	98	Treatment of colorectal cancer
	Hesperidin	Sigma	–	–	184	10:1	78	Parkinson's disease Brain targeting
Isoflavones	**Puerarin**	Laboratory-made	20–30 kDa	–	126	2.8:1	95	

(*continued on next page*)

Table 1 (*continued*)

	Genistein	Sigma	Low	92	788	4:1	77	Drug delivery for oral administration Treatment of colon cancer

Subgroup	Active compound	Biological properties assessed	Assessed in:	References
Flavanols	**Catechin and EGCG**	–	–	[131]
	Catechin and EGCG	Intestinal absorption	Mouse jejunum model	[132]
	EGCG	Intestinal stability and plasma exposure	Swiss Outbred mice	[133]
	EGCG	Release studies - Antiproliferative	Tumor xenograft in mice	[136]
	EGCG	Antiproliferative - Proapoptotic	Tumoral cells and tumor xenograft in mice	[137]
	EGCG	Antiproliferative - Cellular uptake	Breast cancer cells	[138]
	EGCG	–	–	[139]
	Catechin	Antioxidant (DPPH)	–	[134]
	Catechin and Catechin-Zn	Antimicrobial	Bacteria	[135]
Curcuminoids	**Curcumin**	Mucoadhesion	–	[164]
	Curcumin	Antibacterial - Skin infection prevention	BALB/c mice	[165]
	Curcumin	Cellular uptake - Apoptotic - Antiproliferative	Tumoral cells	[166]
	Curcumin	Antimicrobial testing	Bacteria	[168]
	Curcumin	Apoptotic- Anticarcinogenic	Breast cancer cells	[167]
	Curcumin and EGF	Cell viability - ROS production	Tumoral cells	[169]
Flavonols	**Quercetin**	Antioxidant - Gene expression - DNA fragmentation	Sprague-Dawley rats	[111]
	Quercetin	Cytotoxicity - Skin permeation - Skin damage - Cellular uptake	Mammalian cells and C57BL/6 mice	[106]
	Quercetin	Citotoxicity - NP biodistribution - Antioxidant - Tumor size	Mammalian cells and tumor xenografts in mice	[102]
	Quercetin	Microvasculature - Mitosis - Apoptosis	Tumors in Wistar rats	[103]
	Quercetin	Wound contraction - Cytokine, molecular and histological studies	Wistar rats	[108]
	Quercetin	Cytotoxicity - Antimicrobial and antifungal - Epigenetic analysis	Tumoral cells - Bacteria – Phatogenic fungus	[105]
	Quercetin and Myricetin	Antioxidant (DPPH) and antimicrobial testing	Bacteria	[238]
	Quercetin and Glibenclamide	Artificial skin-permeation	–	[107]
	Kaempferol	Antioxidant (DPPH, FRAP) - Quorum sensing inhibition	Bacteria	[109]
	Rutin	Release studies in simulated gastric and intestine fluids	–	[110]
	Rutin	Cytotoxicity - Apoptosis	Breast cancer cells	[104]
Anthocyanins	**Anthocyanin**	–	–	[153]
	Anthocyanin	–	–	[239]
	Anthocyanin	Antioxidant (DPPH, FRAP) - Simulated gastrointestinal digestion	–	[152]
	Anthocyanin + sinapic acid	Antioxidant - Color stability pigments	–	[151]
	Cyanidin-3-O-glucoside	Epidermal damage - Apoptosis - Skin moisture and histology	Photodamage mouse model	[157]
Flavonolignans	**Silibinin**	Antiproliferative	Prostate cancer cells	[181]
	Silibinin	Antiproliferative	Lung cancer cells	[182]
	Silibinin	Citotoxicity - Cellular uptake - Gene expression	Glioma cells	[183]
	Silymarin	CCl_4-induced hepatotoxicity	Swiss Albino mice	[180]
Chalcones	**α-Arbutin / β-Arbutin**	–	–	[173]
	Phloretin	Antioxidant - Anticarcinogenic	DMBA-induced cancer in hamsters	[177]
	Phloretin	Apoptotic - Antioxidant	Human oral cancer cells	[176]
Flavones	**Chrysin**	Antibiofilm (MPA, EPS, MATH)	Bacteria	[118]
	Baicalin	–	–	[117]
Flavanones	**Naringenin**	Biocompatibility - Antiproliferative - Antioxidant	Lung cancer cells	[123]
	Naringenin	–	–	[127]
	Naringin	Antinflamatory - Anticoagulant - Antioxidant - Antiproliferative - Osteoblast differentiation	Tumoral cells	[124]
	Hesperetin	Cellular uptake – Antitumoral - Colony formation – Apoptosis - Gene expression	Colon adenocarcinoma cells	[125]
	Hesperidin	–	–	[126]
Isoflavones	**Puerarin**	Intestinal absortion	Sprague–Dawley rats	[145]
	Genistein	Antiproliferative – Antiangiogenic	Colorectal adenocarcinoma cells - Chick embryos	[143]

glycosides are absorbed more rapidly than others because the attached sugar moiety on flavonol glycosides affects the rate of absorption [99].

Kaempferol, quercetin, myricetin and fisetin are examples of well-studied flavonols [100]. The main flavonols in onions (quercetin-3, 4′-glucoside, quercetin-4′-glucoside, quercetin-3-glucoside) are more readily absorbed than the principal flavonols found in green and black tea (quercetin-3-rhamnoglucoside or rutin) [101]. The incorporation of these compounds is found to be associated with extensive health benefits which include antioxidant and anti-viral properties, and a reduced risk of vascular disease [31,102]. From 2012–2021, literature searches result in several studies involving flavonol encapsulations in CS-TPP NP. The application fields of these studies focused on cancer therapy [102–105],

Table 2
Non-flavonoid polyphenols encapsulated by IG method in CS-TPP NP. The symbol (-) represents data not informed or unavailable. Particle sizes were indicated in nm unless otherwise specified.

Subgroup	Active compound	CS source	CS MW	CS DD (%)	Particle size	CS:TPP Ratio	EE (%)	Application field
Stilbene	**Resveratrol**	Sigma	Medium = 190–310 kDa High = 310–375 kDa	–	160; 206 (μm)	1:1.5 and 1:3	94–99	Food additive - Drug delivery
	Resveratrol	Aladdin (China)	179 kDa	≥ 95	172–217	1:1	11–15	Antitumoral
	Resveratrol	Sigma	150–190 kDa	93	407	2.5:1	72	Drug delivery (oral)
	Resveratrol	Sigma	150–190 kDa	93	951	5:1	–	Food additive and packaging
	Resveratrol	Amicogen Co. (South Korea)	20 kDa oligochitosan	–	126–266	–	85	Food additive
	Resveratrol	Prawns, INTI-Mar del Plata (Argentine)	300 kDa	81.5	144	2.4:1	59	Nutraceutics - Drug delivery (ocular)
Phenolic acids	**Chlorogenic acid**	Sigma	150–190 kDa	86.6	210	1.4:1	59	Food additive
	Chlorogenic acid	Sigma	150–190 kDa	86.6	134	3:1	60	Drug delivery - Antitumoral
	Rosmarinic acid	Sigma	Low	85	200–1030	10:1	50	Drug delivery
	Rosmarinic acid	Sigma	Low	85	300	7:1	51	Pharmaceutical science
	Rosmarinic acid	Sigma	Low = 107 kDaHigh = 624 kDa	75–85 and > 75	300–600	7:1	89	Food additive
	Rosmarinic acid	Sigma	86 kDa	86	236	7:1	60	Nutraceutics - Drug delivery (ocular)
	Ellagic acid	Sigma	60–90 kDa	85	176	4:1	94	Antitumoral
	Ellagic acid	India Sea Foods	140 kDa	85	80	–	49	Anti–hemorrhagic agent for surgery
	Ellagic acid	Sigma	–	> 75	275	–	66	Nutraceutics - Drug delivery
	Ferulic acid	Sigma	Low	85	125	5:1	63	Drug delivery - Antitumoral
	Ferulic acid	Sigma	190–310 kDa	75–85	213	4:1	56	Drug delivery - Antidiabetic
	Gallic acid	Crabs, Polymar Ciência e Nutriç ão (Brazil)	480 kDa	85	140	5:1	82	Food additive - Drug delivery
	Gallic acid	Sigma	–	80–85	65	–	51	Drug delivery - Antidiabetic
	Protocatechuic acid	Sigma	150–190 kDa	90	30–35	6:1	56	Food and agriculture science
	Betulinic Acid	Merck	20 kDa	–	102	1.3:1	93	Leishmaniasis
	Hydrocaffeic acid	Sigma	150–190 kDa	75–85	100–150	3:1	25–30	Nutraceutics - Drug delivery
	Sinapic acid	Sigma	150–190 kDa	75–85	100–115	4:1	58–62	Bone regeneration
Xanthone	**Alpha-mangostin**	Merck	Low = 62 kDa Medium = 116 kDa High = 326 kDa	–	600	–	99	Nutraceutics - Drug delivery
	Alpha-mangostin	–	300 kDa	77	308–420	3:1	87	Drug delivery
	Alpha-mangostin	Padjadjaran University, (Indonesia)	–	–	326–398	1.4:1	99	Nutraceutics - Drug delivery
Lignans	**Podophyllotoxin**	Sigma	–	99	150–174	5:1	52	Drug delivery - Antitumoral
Tannins	**Tannic acid**	Shrimps, Zhejiang Yuhuan Ocean Bioch. Co. (China)	200 kDa	92	78	5:1	–	Food additive and packaging

Subgroup	Active compound	Biological properties assessed	Assessed in:	References
Stilbene	**Resveratrol**	–	–	[240]
	Resveratrol	Antioxidant - Antiproliferative	Hepatocarcinoma cells	[189]
	Resveratrol	Biocompatibility	Mammalian cells	[190]
	Resveratrol	Antioxidant (ABTS) - Antimicrobial	Bacteria	[188]
	Resveratrol	–	–	[241]
	Resveratrol	Biocompatibility	Mammalian cells	[45]
Phenolic acids	**Chlorogenic acid**	Antioxidant (ABTS)	–	[196]
	Chlorogenic acid	Antioxidant - Antiproliferative	Human renal adenocarcinoma	[197]
	Rosmarinic acid	–	–	[242]
	Rosmarinic acid	–	–	[198]
	Rosmarinic acid	Antimicrobial	Bacteria	[199]
	Rosmarinic acid	Biocompatibility		[200]

(*continued on next page*)

Table 2 (*continued*)

			Mammalian cells - Chick embryos	
	Ellagic acid	Antiproliferative	Human oral cancer cells	[202]
	Ellagic acid	Blood coagulation and clot retraction	Rat whole blood	[203]
	Ellagic acid	Antioxidant - Antiapoptotic	Mammalian cells	[204]
	Ferulic acid	Pro-apoptotic - Antiproliferative	Human cervical cancer cells	[206]
	Ferulic acid	Antidiabetic effects tested through associated indicators	Diabetic rat model	[207]
	Gallic acid	–	–	[210]
	Gallic acid	Inhibition of α - glucosidase enzyme	–	[211]
	Protocatechuic acid	Antifungal	*Pyricularia oryzae* rice blast fungal	[213]
	Betulinic Acid	Antiparasitic	Amastigotes - Mammalian cells – Mice	[215]
	Hydrocaffeic acid	Biocompatibility	Mammalian cells	[217]
	Sinapic acid	Osteoblast differentiation and osteogenesis signaling	Mammalian cells - Rats	[219]
Xanthone	**Alpha-mangostin**	–	–	[227]
	Alpha-mangostin	Antimicrobial	Bacteria	[228]
	Alpha-mangostin	–	–	[229]
Lignans	**Podophyllotoxin**	Pro-apoptotic and anti-proliferative	Liver and breast cancer cells	[223]
Tannins	**Tannic acid**	Antioxidant (DPPH) - Antimicrobial	Bacteria	[233]

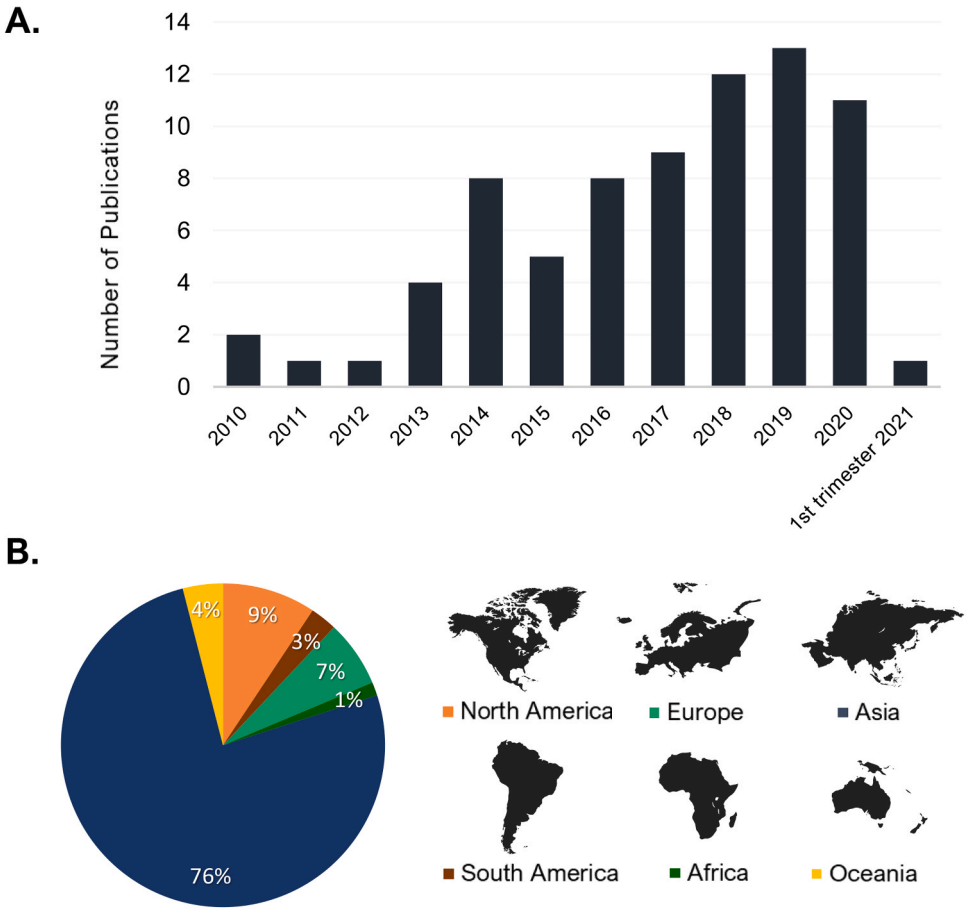

Fig. 4. Polyphenol-loaded CS-TPP reports. (A) Number of publications throughout the years. (B) Worldwide distribution of publications.

skin drug delivery [106–108], antibiofilm agent [109] and food additive [110], among others.

Numerous medicinal plant formulations are used to treat liver disorders in traditional therapy. Exposure to aflatoxin B1, a mycotoxin commonly found as a contaminant in cereals and oilseeds, produced detrimental consequences for animal and human health closely related to high reactive oxygen species (ROS) production, including hepatocellular carcinoma. With the aim to protect the liver from mycotoxins, Abdel-Wahhab et al. formulated CS-TPP NP which were used in combination with quercetin. Notably, the authors carried out animal

experiments by using CS-TPP NP alone (of ~100 nm size), without quercetin entrapment, in combination with quercetin oral administration. FT-IR analysis showed that anionic phosphate groups of TPP interacted with the cationic amino groups of CS. *In vivo* experiments were conducted in aflatoxin B1-induced Sprague-Dawley rats, orally fed with CS-TPP NP plus quercetin. Other rat groups were treated with required controls (i.e., CS-TPP NP alone and quercetin alone) and different CS-TPP NP doses were tested. After treatments, animal sera and livers were subjected to analysis to verify their hepatoprotective activity against aflatoxin B1-induced cytotoxicity. Gene expression and DNA damage analysis from liver tissues indicated that quercetin and/or CS-TPP NP, at the two tested doses, reversed oxidative stress especially in the group treated with the high dose of CS-TPP NP and quercetin. It was concluded that CS-TPP NP, beside the protective role that they exert by their own, enhanced the antioxidant effect of quercetin against the cytogenetic injures of aflatoxin B1 [111].

The encapsulation of quercetin in CS-TPP NP was performed, for exerting its protective effects against UVB radiation, which induces damage in human skin [106]. Quercetin loaded CS-TPP NP of ~184 nm mean size, positive charged (37 mV) with a high EE (~91%) and a loading capacity (LC) equal to 13.15% were obtained and evaluated for its biological effects in both in vitro and in vivo systems. These NP were efficiently uptaken by HaCaT cells and easily permeated through the epidermis layer of C57BL/6 mice dorsal skin displaying better stability, and low cytotoxicity. Encapsulated quercetin was more efficient in inhibiting the NF-kB/COX-2 signaling pathway as well as ameliorating the skin edema caused by UVB radiation. This nanoformulation was proposed for topical use against photodamage since quercetin percutaneous absorption and retention in the skin resulted enhanced by this methodology; thus, providing a method to get rid of quercetin low hydrophilicity and further improve its anti-UVB effect.

The entrapment of rutin, a pigment with powerful antioxidant properties, was carried out by CS-TPP IG for the promotion of its stability during delivery [104,110]. With the aim to be applied as a food additive, rutin was entrapped in CS:TPP submicron particles [110]. After the screening of the best conditions (i.e., CS:TPP ratio), positive charge (59 mV) and particle size of 528 nm were obtained. These particles were considered optimal for the promotion of mucoadhesion and for the easier absorption across the intestinal wall. The particles presented an encapsulation efficiency (EE) equal to 58%, showing a good retention of rutin through simulated gastric juices (pH = 1.40) and a ~20% maximum release of the bioactive content in simulated intestinal conditions (pH = 7.7). Authors related this moderate release with the presence of bile salts and the pH of simulated intestinal fluids, both of which would alter the hydrogen bonding between the rutin and CS, and the electrostatic bonding between CS and TPP. More recently, by using a high CS:TPP ratio (7.5:1), rutin was encapsulated in CS formulations of nanometric size (100 nm). With the aim to be used as cancer treatment, these NP were tested in human breast cancer cells showing induction of apoptosis and notable cytotoxic effects [104].

5.1.2. Flavones

Flavones have a double C2-C3 bond and a ketone in C4 of the C-ring. Most flavones of vegetables and fruits have a hydroxyl group in C5 of the A-ring. The hydroxylation in other positions may vary according to the taxonomic classification of the particular vegetable or fruit [112]. Flavones occur in a wide variety of fruits, vegetables, and beverages. In their native forms, they are found as both O- and C-glycosides, with O-glycosides being more common and usually better absorbed [113].

Celery, parsley, pepermint, chamomile are among the major sources of flavones [113]. The peels of citrus fruits are rich in the polymethoxylated flavones tageretin, nobiletin and sinensetin [114]. Luteolin and apigenin are well-studied compounds belonging to this subclass of flavonoids [100,113,114]. However, as far as we know, their use for bioactive entrapment into CS-TPP NP is not described in the literature of the ten last years. The antioxidant and anti-inflammatory effects of these flavonoids explain their chemopreventive and chemotherapeutic applications in the treatment of inflammatory-related diseases [115]. The C2-C3 bond in flavones seems to be important for the anti-proliferative activity of these flavonoids, since flavones are typically more potent than flavanones [116].

Baicalin and its aglycone, baicalein, are flavones found in edible medicinal plants, *Scutellaria baicalensis* and *Oroxylum indicum* in abundant quantities. The roots of *Scutellaria baicalensis* are widely used in traditional Chinese medicines for clinical treatment of hepatitis, hyperlipidemia, atherosclerosis, hypertension, dysentery, common cold and other respiratory disorders [115]. Baicalin is regarded as a drug with chemotherapeutic potential, but its solubility in water is poor and its oral bioavailability limited. In order to improve its bioactive properties, baicalin was loaded in CS-TPP NP [117]. The NP showed a LC of 13.2%, with high EE (91%), spherical structure and a mean size of 316 nm. The authors assayed many factors that may affect EE and drug loading, including CS and baicalin initial concentration, CS:TPP ratio, pH, stirring speed and dropping speed. The two main factors affecting EE and LC were CS:TPP ratio and CS concentration, although other effects were not negligible. The optimal CS:TPP ratio for obtaining the highest LC and EE was 5:1, similar to that obtained as optimal for chrysin, another flavone [118]. Authors showed that IG is a suitable method for the preparation of baicalin loaded CS-TPP NP and could be used as a potential carrier of low MW chemotherapeutic drug, constituting a simple and effective method for baicalin delivery [117].

Chrysin is a well-studied flavone, constituent of *Orocylumineicum vent*, with well-known biological effects. Like baicalin, its therapeutic potential has not been fully exploited due to its poor solubility and bioavailability. Biofilms are aggregations of densely packed microbial cells embedded inside an exopolysaccharide matrix giving a protective barrier for microbials, which become recalcitrant to antimicrobial agents and host defenses. In a recent report, chrysin was encapsulated into CS-TPP NP with the aim to be used as an anti-biofilm therapeutic agent [118]. Chrysin loaded CS-TPP NP were characterized and investigated for their anti-biofilm activity against *Staphylococcus aureus*. CS:TPP in the ratio of 5:1 was found to be the best formulation for the NP formation. The mean size of NP was ~355 nm, with spherical geometry and an intermediate polydispersity index equal to 0.4. Release studies revealed that ~90% of the chrysin was loosed from the NP within 10 h after its suspension in a medium containing PBS and DMSO at 37 °C. After treatment with chrysin loaded CS-TPP NP, decreases in exopolysaccharide production and in the cell surface hydrophobicity were reported. Both parameters were markers for the inhibitory effect on the initial stages of biofilm development. An enhanced inhibitory effect was achieved with chrysin-loaded CS-TPP NP compared to single chrysin and CS alone (used as control treatments) with a higher reduction in the thickness of the biofilm matrix determined by microscopic examination. Taken together, these results highlighted the potential application of these formulations in combating infections associated with *Staphylococcus aureus*.

5.1.3. Flavanones

Flavanones occur in around 42 larger plant families, especially in Compositae, Leguminosae, and Rutaceae [119]. These phytochemicals lack the double bond between C2 and C3 in the C-ring of the flavonoid skeleton, which is present in flavones and flavonols [120]. Depending on the species, flavanones can be found in all vegetative parts of plants and in generative organs with high concentrations in the peel of fruits [116].

Extraction of phenolic compounds from Citrus peels has attracted considerable scientific interest with the aim to use them as natural antioxidants mainly in foods to prevent the oxidative alteration of lipids [116]. Citrus flavonoids exert interesting pharmacological effects as antioxidant, anti-inflammatory, blood lipid-lowering and cholesterol lowering agents [121]. Oranges, lemons and grapes are enriched with flavanones like hesperetin, naringenin and eriodictyol, which are examples of this class of flavonoids [30]. The antioxidant activity of

flavanones is dependent on the number and spatial arrangement of phenolic hydroxyl groups present in the molecular structure [122]. Among flavanones, naringenin and hesperetin aglycones and their glycosides are of particular interest because of their high prevalence in foods [116].

The encapsulation into CS-TPP NP was employed for the protection of flavanones like naringenin, naringin, hesperetin and hesperidin with the aim to be applied in the treatment of different human diseases during the last years [123–127]. By using in vitro cell cultures, lung cancer A549 and fibroblast 3T3 lines, Kumar et al., demonstrated that encapsulated naringenin into CS-TPP NP fabricated with commercial CS presented anti-proliferative effects for tumor cells also resulting non-cytotoxic for normal cells. An in vitro system for free radical scavenging assessment showed that naringenin loaded CS-TPP NP possessed higher potential to scavenge ROS than the single bioactive compound. Different initial bioactive concentrations were assayed, and the highest EE was achieved (70%) when 0.5 mg/ml concentration of naringenin was used in 5:1 CS:TPP ratio solutions, showing a good performance for the designed system. *In vitro* release studies showed that the percentage release of naringenin from CS-TPP NP was relatively low (~15%) indicating that the CS-NP were able to retain a great amount of this bioactive in simulated gastric fluids, thereby increasing the bioavailability of the drug [123].

Another related flavanone, naringin, was loaded in CS-TPP NP of ~100 nm mean size by using a laboratory made-CS from shrimp shells from the local market [124]. The naringin used was prepared by its extraction from grapefruit rind. The composition of the extracts was confirmed by use of a naringin standard and HPLC chromatography, showing that naringin is a dominant phenolic compound in this fruit. Biological experiments, which included the analysis of collagen and calcium deposition in mouse mesenchymal stem cells, suggested the ability of naringin loaded CS-TPP NP to promote osteoblast differentiation and bone formation. In the same work many beneficial effects, like anti-inflammatory, anti-coagulant, and antioxidant properties, were verified for naringin loaded CS-TPP NP. Even more, these formulations showed potential anti-tumor activity since they turned out to be cytotoxic to HeLa and lung cancer (A549) cells in culture [123].

On the other hand, using Human Colon Adenocarcinoma cells (HCT15), Lazer et al. [125] showed an improved anti-tumor effect of hesperetin, after its loading in CS-TPP NP. For NP tumoral targeting, the authors conjugated CS with folic acid prior to hesperetin encapsulation, since cancer cells are known for over-expressing the folate receptors [125]. Concerning the optimal NP size for suitable penetration and retention in tumors, it is known that NP with large sizes tend to distribute around tumor blood vessels rather than penetrate into tumor parenchyma, while smaller particles can penetrate deeply but with poor tumor retention [128]. The hesperidin loaded CS/folate-TPP NP showed a size of ~450 nm, which was considered compatible with passively targeting to cancer cells [125]. Also, hesperidin loaded NP inhibited the colony formation and induced apoptosis in tumor cells by regulating the expression of proapoptotic genes. This finding constitutes a promising carrier for drug treatment of colorectal cancer.

5.1.4. Flavanols

Flavanols, also called catechins or flavan-3-ols, are the 3-hydroxy derivatives of flavanones [29]. These polyphenols are found abundantly in fruits, vegetables, and tea leaves. Collectively named “catechins”, the main occurring in green tea are (-)-epicatechin (EC), (-)-epicatechin-3-gallate (ECG), (-)-epigallocatechin (EGC), and (-)-epigallocatechin-3-gallate (EGCG). Between these groups, EGCG and EGC are found in the highest amounts in green tea and have been the subject of most of the studies [129]. Having several health benefits, EGCG is a major constituent of green tea infusion, but it is susceptible to degradation, which largely depends on temperature and pH conditions, among other factors [130].

After oral ingestion of catechins, harsh environmental conditions decrease their bioavailability rendering necessary the search of protective systems for its delivery. In the last years, several NP systems based on CS-TPP have been used to stabilize catechins to use them as food additive and/or packaging applications [131–135] and for human disease treatment [136–139].

In three consecutive published works [131–133], catechins (specifically +(−)catechin and EGCG) were encapsulated in CS-TPP NP for their protection upon oral delivery. Particles with a mean size of 440 nm were obtained showing a LC of ~4 μg/ml for the bioactive encapsulation [132]. Using a system transport across the mouse jejunum [132] and an in vivo model with mouse stomach and jejunum [133], it was demonstrated that encapsulated catechins increased the bioactive content in plasma and its intestinal stability and absorption in Swiss Outbred mice. These results demonstrated the ability of catechin loaded CS-TPP NP to protect the bioactive from hazardous stomach fluids.

Uncaria gambier is an important Indonesian crop cultivated as a source of catechins. In order to maintain and improve the stability of catechins towards temperature and pH changes, gambier leave extracts were used for its encapsulation in CS-TPP NP [134]. In this work, NP presented a mean size of 137 nm and showed good emulsion stability with improved antioxidant potential. In another study, CS-TPP NP of different sizes (208–591 nm) were obtained to encapsulate catechin or catechin–zinc complex by IG technology [135]. After loading, an improved antibacterial activity of the designed nanosystems against *Escherichia coli* and *Listeria innocua* were determined. Besides, the smallest particle showed the highest antibacterial activity. In this study, the inclusion of zinc rendered an increased bioactivity than the polyphenol alone. These preparations have great potential to be used for food and other applications through either direct addition or incorporation into packaging materials.

In the field of cancer therapy, two consecutive published studies described EGCG encapsulation in CS-TPP NP with the aim to improve its therapeutic efficacy [136,137]. Khan et al. demonstrated in an in vivo model of prostate cancer, an increased anti-tumoral activity for EGCG loaded CS-TPP NP prepared for oral consumption [136]. After injection of tumor xenografts in athymic nude mice and oral administration of EGCG loaded CS-TPP NP with a size of < 200 nm, a significant inhibition of tumor growth and a decrease of secreted prostate-specific antigen levels were observed compared with single EGCG or CS-TPP NP (control treatments). Also, in tumor tissues of mice treated with EGCG loaded CS-TPP NP there was a significant increase in apoptotic markers and inhibition of proliferation signals, like reduction in Ki-67 marker and proliferating cell nuclear antigen. A suitable behavior was found in release studies since encapsulated EGCG showed slow discharge from NP in simulated gastric juice (pH~ 1.5) and a faster offload in simulated intestinal fluid (pH~ 6.8). The authors introduced the concept of nanochemoprevention by encapsulating useful bioactive food components for their slow and sustained release [136]. In a similar way, but for the treatment of human melanoma, in vitro and in vivo models were assayed to test the efficacy of EGCG loaded CS-TPP NP [137]. Both models, MEL928 cultured cells and implantation of tumor xenografts in athymic nude mice demonstrated that encapsulated EGCG improved its anti-proliferative capacity and decreased the proapoptotic activity compared to therapeutical use of sole EGCG [137].

5.1.5. Isoflavones

The main dietary sources of isoflavones for humans are soybean and soybean products, which are found almost exclusively in legumes. Soy foods provide an important dietary source of these bioactive non-nutrients, among which genistein and daidzein are the main ones. Isoflavones occur predominantly as glycosides in plants and consequently are highly polar and water-soluble compounds [140]. Chemically isoflavones are flavonoids in which the B-ring is linked in C3 of the C-ring with a C2-C3 double bond and a ketone in C4 of the C-ring [30].

Isoflavones are considered to be chemoprotective and they can be used as an alternative therapy for a wide range of hormonal disorders,

including several cancer types, like breast cancer and prostate cancer, cardiovascular diseases, osteoporosis, or menopausal symptoms [141]. Structurally related to human estrogens, they exert estrogenic and/or antiestrogenic effects. Based on their chemical structure and actions, isoflavones are named phytoestrogens. Isoflavones, as well as flavonols and flavones, were found to be the most active classes of flavonoids with a dose dependent-anti-angiogenic activity [142]. Among all the flavonoids subclasses, isoflavones exhibit the highest bioavailability [120]. Although daidzein is the one of most well-known isoflavone, as far as we know, there is no available information about designed systems for daidzein encapsulation based on CS-TPP.

In a recent work, genistein was entrapped into CS-TPP NP with the aim to improve cancer targeting and the bioactive miscibility and absorption in aqueous environments [143]. Spherical particles of submicron size (788 nm) were obtained, with an EE and a LC of 76.8% and 32.6%, respectively. Cell cycle flow cytometry and caspase-3 gene expression analyses revealed the apoptotic death of human colorectal cancer cells (HT-29) after application of genistein loaded CS-TPP NP. These NP notably inhibited the growth and proliferation of HT-29 cells without affecting the viability of normal ones, like human dermal fibroblasts (HDFs). Besides, the anti-angiogenic potential of genistein loaded CS-TPP NP was evaluated using a chick chorioallantoic membrane assay (CAM), which implies the incorporation of NP by injection in a chorioallantoic sac of fertilized chicken eggs and further imaging analysis of membrane vasculatures developed through ti me. Results showed that encapsulated genistein was also anti-angiogenic, in addition to anti-proliferative, constituting in this way a promising carrier for the colon delivery of the bioactive for therapeutic treatment.

Puerarin is an important bioactive compound isolated from the root of the leguminous plant *Pueraria lobata*, which is well known as Gegen in traditional Chinese medicine. It is available in common foods and is used in alternative medicine. The beneficial effects of puerarin on the various medicinal purposes may be due to its wide spectrum of pharmacological properties such as vasodilation, cardioprotection, neuroprotection, antioxidant, anti-tumor, anti-inflammation, alleviating pain, promoting bone formation, inhibiting alcohol intake, and attenuating insulin resistance [144]. However, puerarin is a drug with low oral bioavailability, mostly excreted in its original form through feces, and only a small part is absorbed into the blood and distributed to various tissues and organs [145]. Recently, using laboratory prepared CS, puerarin was encapsulated in CS-TPP NP for oral delivery [145]. The CS concentration, pH of the CS solution, TPP concentration and other factors were assessed to obtain the required NP characteristics. Optimal puerarin loaded CS-TPP NP were obtained with a CS:TPP ratio equal to 3:1, showing high EE (95%) with a mean diameter size of 130 nm. Employing Sprague-Dawley rats, an in situ single-pass intestinal perfusion model was used to investigate the bioactive absorption in the intestine. It was found that puerarin loaded CS-TPP NP significantly improved the bioavailability of the bioactive compound.

5.1.6. Anthocyanins

Anthocyanins are glycosides of anthocyanidins, the latter of which are composed of a flavylium cation backbone hydroxylated at different sites [146]. Anthocyanins are regarded as flavonoids despite its positive charge at the oxygen atom of the C-ring [147]. The glycosides of cyanidin, pelargonidin, malvidin and delphinidin are the most widely spread anthocyanins. The most usual glycosylation position is C3 of the C-ring to produce 3-O-β-glucosides, such as cyanidin-3-O-glucoside, which has been increasingly studied in the last years [146].

Anthocyanins can be recovered from all tissues of higher plants [146]. These molecules are natural food colorants with antioxidant effects. They are commonly found in vegetables and fruits, such as eggplant and berries, respectively [148,149]. In the elderberry fruit anthocyanins account for ~70% of total phenolic compounds [150]. These pigments are red in an acidic environment and blue in alkaline conditions [147], although their stability in alkaline conditions is relatively small. Several approaches have been attempted to enhance the stability of anthocyanins [149]. Nevertheless, the literature on anthocyanin encapsulation in CS-TPP NP is scarce at present.

A study showed that nanoencapsulation in CS-TPP increased the color stability and antioxidant activity of anthocyanins, and this effect was enhanced by copigmentation [151]. In a recent work, using anthocyanins from *Aronia melanocarpa*, similar results were reported, with NP size of 197 nm, a positive ζ-potential of 43 mV and high EE (66%) [152]. However, another study reported low yield and stability of CS-TPP microcapsules in comparison with those prepared using CS-cellulose nanocrystal [153]. Besides, CS-TPP encapsulation generated significantly bigger particle sizes (~34 μm) than CS-cellulose nanocrystal capsules of 65 nm. The authors ascribed this difference in size to both the occurrence of relatively big gaps within the CS-TPP capsule size, and the aggregation of small CS-TPP microcapsules with a less charged surface [153].

On the other hand, the antioxidant effect of anthocyanins has been linked to several health benefits: anticancer, neuroprotective, antiobesity, anti-inflammatory, among others [154–156]. Liu et al. reported that cyanidin-3-O-glucoside loaded CS-TPP NP reduced UVB-induced epidermal damage through regulation of p53-mediated apoptosis in a mouse model; this skin protection was more effective with cyanidin-3-O-glucoside loaded CS-TPP than with the single bioactive. It should be noted that cyanidin-3-O-glucoside loaded CS-TPP NP had a homogeneous size (288 nm) and spherical shape without agglomeration. These NP not only improved the skin moisture of mice, but they also reduced the LPO (lipid peroxidation), MDA (malondialdehyde) and 8-Ohdg (8-hydroxy-2'-deoxyguanosine) levels induced by UVB [157].

5.1.7. Curcuminoids

Turmeric extracts, obtained from *Curcuma longa*, contain two bioactive components: volatile oil and curcuminoids; both present in oleoresin extracted from roots [158]. The curcuminoids are a mixture of curcumin, chemically a diferuloylmethane mixed with its two derivatives, demethoxycurcumin and bisdemethoxycurcumin [31], which are natural phenols responsible for turmeric's yellow color. Curcuminoids and their derivatives have been shown to possess a wide range of biological activities including antioxidant, anti-inflammatory, anticancer, antimicrobial, neuroprotective, cardioprotective and radioprotective effects [35,159,160].

Among the properties of curcuminoids, it is remarkable that they can modulate the expression of genes and the activity of enzymes involved in lipoprotein metabolism that lead to a reduction in plasma triglycerides and cholesterol and elevate HDL-C (high-density lipoprotein cholesterol) concentrations [159]. Likewise, curcuminoids supplementation modulates oxidative stress-parameters including plasma activities of SOD (superoxide dismutase) and catalase, as well as serum concentrations of GSH (glutathione peroxidase) and lipid peroxides [161]. However, the health promoting effects of these phytochemicals have been called into question because serum levels are low when curcuminoids are administered orally in purified forms [162]. To resolve this apparent discrepancy between turmeric bioactivity and curcuminoid bioavailability, it has been proposed that curcuminoid metabolites, including degradative or reduced products, may be the bioactive moieties responsible for mediating polyphenol effects [163].

It is noticeable that the curcuminoid encapsulation in CS-TPP NP is a method of choice among the strategies developed to improve the delivery of curcumines in food applications and cancer therapeutics [164–169]. As we can note in Table 1, all studies cited provide EE for curcumin higher than 75% into ≤ 300 nm sized NP. CS, obtained from crab shell collected from the local fish markets, was used to encapsulated curcumin by TPP crosslinking, to improve its antibacterial activity in drug delivery systems [168]. The drug releasing ability of curcumin loaded CS-TPP NP in the presence of different solvent system was evaluated using agar well diffusion method against *Pseudomonas*

aeruginosa. The in vitro bioactive release assay showed an improved antibacterial activity when ethanol and acetic acid were used as solvent for curcumin loaded CS-TPP NP [168].

Curcumin was also encapsulated for the enhancement of its therapeutic effects on cervical [166] and breast [167] cancer treatments. Khan et al. prepared curcumin loaded CS-TPP NP positively charged (~71 mV) with a mean diameter size of ~197 nm. The EE and LC of this formulation system were found to be ~85% and 5.6%, respectively. The binding of curcumin to CS-TPP NP was pH dependent and optimal at pH 5.0 with a maximum value of 85.12 μg/100 μg of CS. The binding of curcumines at lower pH constituted an additional advantage for their stability since CS usually dissolves under acidic solutions. *In vitro* experiments, using cancer cell lines (SiHa, HeLa, Caski and C33a), demonstrated increased pro-apoptotic and antiproliferative activities after the application of curcumin loaded CS-TPP NP [166]. The authors correlated the higher cytotoxicity effect of these nanocarriers on tumoral cells with their higher cellular uptake as compared to the effect exerted by the non-encapsulated curcumin. The enhanced cellular internalization and sustained release of entrapped curcumin showed that curcumin loaded CS-TPP NP could be considered as an efficient delivery system for therapeutic treatment of tumors. Recently, Sadoughi et al. investigated the effect of Cold Atmospheric Plasma (CAP) treatment, which is useful for biomaterials surface modification and functionalization, on improving the curcumin solubility in aqueous solutions. This CAP modified-curcumin loaded on CS-TPP NP enhanced the drug delivery system and rendered it a proper candidate for breast cancer treatment [167].

Photodynamic therapy is regarded an effective therapy for cancers as it is minimally invasive. The combination of photosensitizers with a specific light source produces ROS that damage tumor cells. With the aim to employ curcumin as a photosensitizer for carcinoma-photodynamic therapy, Tsai et al. manufactured curcumin loaded CS-TPP NP [169]. In this way the low curcumin solubility would be overcome. Prior to encapsulation, curcumin was conjugated with EGF (Epidermal growth Factor) to exert the simultaneous loading of both components. Since cancer cells are known to over express EGFR (EGF receptor), this strategy focused on specific targeting of curcumin in tumors. The authors employed normal and EGFR-overexpressing gastric cancer cells (MKN45) to compare the effects of curcumin and curcumin loaded CS-TPP NP on cell viability and ROS intracellular production and showed that curcumin encapsulation and EGF-mediated targeting improved the effect of the bioactive as a photosensitizer agent for carcinoma-photodynamic therapy.

5.1.8. Chalcones

Chalcones are a subclass of flavonoids present in significant amounts in tomatoes, pears, strawberries, bearberries, and certain wheat products. Since they are characterized by the absence of C-ring on the basic flavonoid skeleton structure, they can also be referred to as open-chain flavonoids. The closed C-ring by itself may not be critical to the activity of flavonoids, given that chalcones are active antioxidants [170]. Major examples of chalcones include phloridzin, arbutin, phloretin and chalconaringenin [30]. Even though some authors regard arbutin as a chalcone [30,171,172], arbutin is, in terms of its structure, a glycoside of hydroquinone [173].

Chalcones possess interesting biological properties, including antioxidant, anti-inflammatory, anti-microbial, analgesic, anti-anxiety and anticancer activities [171,174]. α- and β-arbutin are extensively used whitening agents that inhibit tyrosinase enzyme activity in the skin [173]. CS-TPP NP have proven to be useful for the delivery of these molecules. Both α- and β-arbutin loaded CS-TPP NP presented colloidal stability as determined by ζ-potential. These arbutin loaded NP possessed different characteristics according to the initial concentration of the bioactive compound to be encapsulated. The optimal EE and LC were achieved when the concentration of either α-arbutin or β-arbutin was 0.4%. Furthermore, in vitro release studies of each bioactive compound encapsulated in CS-TPP NP showed a considerably higher percentage of release [173].

Phloretin, a dihydrochalcone present in apples, exhibits anticancer activity in a wide variety of human cancer cells and by different mechanisms (e.g. cell cycle arrest, autophagy) [175]. The anticancer effects of nanoencapsulated phloretin was determined using in vitro and in vivo models [176,177]. Phloretin loaded CS-TPP NP increased mitochondrial-mediated apoptosis through the induction of oxidative stress, exhaustion of cellular antioxidants and cell cycle arrest in human oral cancer cell lines [176]. Moreover, these NP augmented the cellular uptake, sustained release and the bioavailability of phloretin [176]. More recently, phloretin loaded CS-TPP NP exerted antioxidant and anticarcinogenic effects on 7,12-dimethylbenz[*a*]anthracene (DMBA)-induced oral cancer in hamsters [177]. Thus, phloretin loaded CS-TPP NP notably decreased the levels of lipid peroxidation and restored the levels of enzymatic and non-enzymatic antioxidants in DMBA-treated animals [177]. Not only that, but tumor incidence, cancer cell proliferation and tumor size were significantly diminished after treatment with the encapsulated phloretin [177].

5.1.9. Flavonolignans

Flavonolignans, termed as “non-conventional lignans” or “hybrid lignans”, are biogenetically related to lignans and neolignans as they have similar biosynthetic pathways. Formally, flavonolignans are derived from two phenylpropanoid units, but have an additional structural part that places them under the flavonoids group [112]. Flavonolignans in *Silybum marianum* are structurally diverse constituents isolated from its fruits and seeds that have been found to exhibit antioxidant, lipid-lowering, antihypertensive, antidiabetic, antiatherosclerotic, anti-obesity properties [178]. Extracts of milk thistle have been recognized for centuries as remedies for liver and gallbladder disorders. The active ingredients of milk thistle fruits are flavonolignans, collectively known as silymarin.

Silymarin is a mixture of flavonolignans extracted from the seeds, commercialized in standardized form, and widely used in drugs and dietary supplements. Silymarin is comprised of silybin, isosilybin, silydianin and silychristine. Its poor bioavailability is mainly due to extensive metabolism, poor water solubility and low permeability across intestinal epithelial cells. Silymarin has been widely investigated for its pharmacological activities, among which the hepatoprotective effects stand out [178–180]. The encapsulation of sylimarin was performed with the aim to improve its hepatoprotective properties by prolonging its retention time after oral delivery [180]. The IG method using CS-TPP was optimized using a central composite design to minimize the particle size and maximize the drug EE. Only 53% of silymarin was released from NP in 24 h showing a sustained release behavior of formulated NP. The optimized formulation was evaluated for an in vitro study that involved the use of Swiss Albino mice in a CCl_4 (carbon tetrachloride)-induced hepatotoxicity model. CCl_4 is a known-hepatotoxic agent that elicits liver injury. After 24 h of CCl_4 induction, animal blood and liver samples were evaluated for toxicity markers (serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase and alkaline phosphatase activities). The overall results suggested that silymarin loaded CS-TPP NP could successfully enhance its hepatoprotective effect. The enhanced ability of CS-entrapped sylimarin for passive liver targeting would be attributable to small NP size, larger surface area and the sustained release via oral administration.

Silibinin is a major biologically active component in silymarin; widely used for treatment of various acute and chronic liver toxicities, inflammation, fibrosis, and oxidative stress. Various studies indicate that silibinin is also active against different carcinomas. However, its hydrophobic nature limits its bioavailability compromising in vivo biological activities. There are contributions that deal with the fabrication and evaluation of silibinin loaded CS-TPP NP, with the aim of being employed in cancer treatment [181–183]. Pooja et al. prepared silibinin-loaded CS-TPP NP using commercial CS. Data obtained

suggested that optimum interaction (inter and intramolecular) between CS and TPP occurred with a 4:1 polysaccharide-TPP ratio. The optimized silibinin loaded CS-TPP NP showed a mean diameter of ~263 nm with a ζ-potential of ~37 mV, showing a relatively high EE (~83%). No chemical interactions between silibinin and CS were observed in FTIR analysis, indicating that the bioactive was only physically encapsulated into the biopolymer matrix. NP were evaluated for their cytotoxic activities by using an in vitro model. Encapsulated silibinin displayed an increase in the dissolution rate and better cytotoxicity against human prostate cancer cells (DU145) [181]. A different approach was carried out for encapsulation of silibinin. In this study, hydrophobically-modified CS-TPP NP were generated [182]. The formulation included a palmitoyl group incorporated into the CS molecule, which in turn formed a hydrophobic core, where the silibinin could be associated by hydrophobic interactions. The FTIR profile and electron microscopy correlated the successful formation of nanosized particles (208 nm) with moderate EE values (~50%). After cytotoxicity evaluation, using A549 lung cancer cells, it was possible to demonstrate an enhanced anti-proliferative effect for silibinin loaded CS-TPP NP, which was attributed to the hydrophobic modification of the CS-NP system since non-modified-CS showed a lesser anti-proliferative effect.

5.2. Non-Flavonoids

5.2.1. Stilbenes

A few unrelated plant species produce stilbenes, a little family of plant secondary metabolites, which is derived from phenylpropanoid [184]. Stilbenes present a high diversity in their phenolic structures, which is a determining component of their absorption and metabolism rates [185]. They are characterized by two aromatic rings joined by a double bond. These compounds have two configurations, *trans* or *cis* since the styrene double bond does not permit free rotation. In plants, they are accumulated in both free and glycosylated forms, as well as methoxylated or in the form of oligomers (viniferins). A reduced number of plant species can produce stilbenes are phytoalexins. Those plants usually produce these molecules in response to abiotic (environmental stresses like ultra-violet light, cold, salinity, drought, and ozone exposures) or biotic (pathogen or herbivore attack) stresses [184,186]. Examples of stilbenes isolated from different plants include resveratrol, piceatannol, gnetol, oxyresveratrol, pinosylvin, pinostilbene pterostilbene, rhapontigenin, isorhapontigenin, arachidin, and piceid (resveratrol-3-O-β-glucoside) [185]. However, as far as we know, the wide-ranging pharmacological and biomedical applications of encapsulated stilbenes were only described for resveratrol [45,187]. Resveratrol is mainly found in red wine, skin of red grapes, bilberries, blueberries, cranberries, dark chocolate, pistachios, peanuts, and seeds. Notably, the reports related to encapsulation employed *trans*--resveratrol, since it constitutes the biologically active form [45]. The first report to be emphasized, focuses on resveratrol loaded CS-TPP NP with application in the food industry. The developed particles had a size that was around the micrometer scale (951 nm) with a ζ-potential value of 48 mV, which is usually believed to have enough repulsive force to attain better physical colloidal stability. It was proved the additive effect of antimicrobial CS together with anti-oxidative and anti-microbial property properties of resveratrol, which positively acted as a brand-new packaging material. The aforementioned system prevents both, the gram-negative, *Escherichia coli*, and the gram-positive one, *Staphylococcus aureus* growth on foils surfaces [188]. On the other hand, fluorescent FITC conjugated-nanosized carriers for resveratrol have been proved to be incorporated into hepatocellular carcinoma cells SMMC 7721 and exhibited anti-proliferative activity. On the contrary, and as expected for antitumor drugs, lower cytotoxicity on normal hepatocyte cells L02 was detected. Notably, the cumulative drug release from NP in a mimetic tumor tissue condition (pH = 6.5) was greater with respect to the physiological condition (pH = 7.4). Consequently, this work suggested the potential use of resveratrol loaded CS-TPP NP for chemotherapy [189]. Similarly, the cellular uptake of resveratrol was improved through its efficient encapsulation (72%) within CS-TPP NP (407 nm). Those analysis were carried out in human colorectal adenocarcinoma Caco-2 cells, whereby the authors finally determined that resveratrol loaded CS-TPP NP inhibited tumoral cell growth [190].

Oxidative stress and inflammation play a key role in many ocular pathologies (e.g., age-related macular degeneration, glaucoma, diabetic retinopathy, cataract, among others). Considering that resveratrol has gained interest in the scientific community for its antioxidant and anti-inflammatory characteristics, Buosi et al. proved that resveratrol loaded CS-TPP NP were efficiently internalized in normal human retinal pigment epithelial ARPE-19 cells. These positive spherical ζ-potential (32 mV) CS-TPP NP were synthesized with a laboratory-produced CS (DD = 81.5%) whose source of chitin came from the processing of *Pleoticus muelleri* prawns. After their uptake, those NP escape from the endo/lysosomal degradative pathway, which is crucial for efficient nanocarrier delivery systems. These CS-TPP NP did not result cytotoxic, nor immunogenic [45]. In conclusion, nanocarriers for resveratrol delivery opened the chance of its application for ophthalmic use [45,76,191,192].

5.2.2. Phenolic acids

The group of "phenolic acids" includes compounds having one carboxylic acid group. They are found in high concentrations in a variety of plant-based foods, namely seeds, skins of fruits and leaves of vegetables. Phenolic acids are characterized by their high antioxidant and anti-inflammatory activities. Many experimental evidences describe the protective role of phenolic acids in degenerative diseases such as cancer, neurodegeneration, cardiovascular, cancer, diabetes and many more [193–195].

Among the encapsulation reports into CS-TPP based NP, the group of phenolic acids is the most represented non-flavonoid group of compounds. This section of the review will be initiated with the chlorogenic acid, an antioxidant widely distributed in fruits like pears, berries, apple, lettuce, spinach, carrots, tomatoes, sweet potato, coffee beans, tea, etc. [194]. As far as we know, two papers referred to chlorogenic acid loaded CS-TPP NP. In the first published article, the particles obtained displayed a size and ζ-potential of 210 nm and 33 mV, respectively. In addition, with an EE of chlorogenic acid of about 59%, ABTS assay indicated that the radical scavenging activity of this bioactive was retained in the NP. Hence, synthesized chlorogenic acid loaded CS-TPP NP with sustained release property could consequently improve the fortification of food-matrices targeted for health benefits through effective delivery of the bioactive in the body [196]. In a recent work, Rajan et al., managed to synthesize chlorogenic acid loaded CS-TPP carriers with a stable and monodispersed profile in the nanoscale (134 nm) with low polydispersity index (0.2). Authors determined the incorporation and cytotoxic effect of those NP on a human kidney cancer cell line (786-O). Also, an improved antioxidant activity of chlorogenic acid due to the encapsulation in CS-TPP NP was confirmed. Hence, after physicochemical characterizations and biological assays, authors confirmed that CS-TPP NP could be used as a drug/bioactive delivery vector in pharmaceutical applications [197].

Rosmarinic acid is a phenolic compound generally admitted as a free radical scavenger. It has been documented that rosmarinic acid provides safety as antibacterial and antiviral activity. It can act as an anti-inflammatory and anti-mutagenic agent with the capability to reduce atopic dermatitis symptoms. Anti-tumoral and neuroprotector properties were also reported [198]. Madureira et al. generated rosmarinic acid loaded CS-TPP NP with low and high MW CS. All particles showed slight variations in the particle size in the range between 300 and 600 nm, with a ζ-potential value in the range 20–30 mV, which indicates a moderate colloidal stability. The tested rosmarinic acid loaded CS-TPP NP had high antimicrobial activity. The most susceptible bacteria resulted to be *Escherichia coli* O157 and *Bacillus cereus*, whereas the worst efficiency was obtained for *Salmonella typhimurium*. As a

consequence, authors proposed that those carriers were an optimal candidate for its inclusion in functional food matrices [199]. On the other hand, da Silva et al. developed carriers with a size range between of 200–300 nm with a ζ-potential ranged from 20 to 30 mV. Authors performed an extensive in vitro study for the biocompatibility of rosmarinic acid loaded CS-TPP NP. In this sense, mucoadhesive NP did not exert cytotoxicity against human ocular cell lines (HCE: corneal epithelium; ARPE-19: retinal pigment epithelium). Remarkably, authors performed an elegant cytotoxicity assay by using chorioallantoic membrane from chick embryos ("Hen's Egg Test"), as an alternative of the in vivo rabbit ocular test ("Draize Test"). Results indicated that rosmarinic acid loaded CS-TPP NP were not irritating since they did not prompt vasoconstriction, haemorrhage or coagulation in the HET-CAM cells within the time of incubation [200].

Ellagic acid is found in fruits and vegetables including strawberries raspberries, blackberries, cranberries, pecans, walnuts, wolfberry, pomegranates, and other plant foods. It is one of the better studied phytochemicals. It has antioxidant, anticancer and antimutagenic properties [201]. Arulmozhi et al. reported an effective ellagic acid entrapment (94%) into spherical shaped nano-sized particles. In this report, an enhanced anti-proliferative activity of ellagic acid loaded CS-TPP NP was determined in human oral cancer KB cell line, revealed by DNA fragmentation analysis. Those results could constitute a novel formulation to overcome the current limitations of ellagic acid and opens the possibility for its use in oral cancer therapy [202]. The effectiveness of ellagic acid loaded CS-TPP NP in promoting blood coagulation was reported for the first time by Gopalakrishnan et al. The employed NP appeared as clusters with an average particle size of ~80 nm and a 49% of EE of ellagic acid was achieved. The release profile revealed an initial burst release (84%) within the first 12 h due to the loosely associated and surface-bound bioactive molecules. After that, a gradual release occurred up to 108 h possibly due to the tight association of ellagic acid within the CS matrix. Biological assays denoted that ellagic acid loaded CS-TPP NP promoted rapid blood coagulation as well as clot retraction as a consequence of the synergistic properties of both ellagic acid and CS. Hence, the results suggested that ellagic acid loaded CS-TPP NP constituted a novel anti-hemorrhagic system that could be further investigated for biomedical applications [203]. Ellagic acid has a high effectiveness to mitigate neuronal oxidative stress and related pathologies, including Parkinson disease. Ahlawat et al. introduced a sustainably resourced ionic gelation method to overcome the limitations in solubility and biodisponibility of ellagic acid by employing the CS-TPP pair. A positive ζ-potential of 24 mV was recorded for the 275 nm-sized ellagic acid loaded CS-TPP NP. Results from this report emphasized 66% of EE for ellagic acid into CS-TPP nanocarriers. In addition, ellagic acid CS-TPP NP were neuroprotectant against the rotenone neurotoxin induced-oxidative stress and apoptosis in neuronal SH-SY5Y cells [204].

Ferulic acids are generally found in wheat, oats, rice, and pineapple, grasses, grains, vegetables, flowers, fruits, leaves, nut, peanuts, beans, seeds of coffee, artichoke. Ferulic acids display a wide range of biomedical effects including antioxidant, anti-inflammatory, antimicrobial, antiviral, antiallergic, hepatoprotective, anticarcinogenic, antithrombotic, vasodilatory effect, and aids to enhance the viability of sperms [205]. So far, only the research group of Vikas Pruthi has explored the biological effects of the ferulic acid loaded CS-TPP NP. The researchers showed NP with a positive ζ-potential value (22.5 mV) and an average particle diameter of 125 nm, which exhorted strong anti-proliferative activity against human ME-180 cell line derived from cervix tumor [206]. In the other report, authors explained that phenolic phytochemicals usually remain confined to NP core through hydrophobic interactions and H-bonds. The outer polar surfaces of these CS-based NP keep stable in dispersion medium through surface charges and hydration properties. NP ζ-potential was equal to +14 mV. With the aim to generate stable ferulic acid loaded CS-TPP NP, researchers tested a range of ferulic acid concentrations with a fixed CS:TPP ratio (4:1). The higher bioactive working concentration 0.1056 mg/ml had the maximum EE (56%). Spherical ferulic acid-loaded CS-TPP NP enhanced the bioactive plasma retention time and/or its bioavailability compared to free ferulic acid. These NP also exhibited improved anti-diabetic potential indicated by the anti-hyperglycemic effect in streptozotocin induced diabetes of Wistar albino rats model [207]. Consequently, ferulic acid CS-TPP NP could constitute a potent therapeutic agent for medicine and clinical use.

In nature, gallic acid and its derivatives are present in almost every part of the plant, such as fruit, leaf, bark, wood, seed, and root. They are found in blackberry, strawberry, blueberry, grapes, mango, cashew nut, plums, hazelnut, tea, wine, walnut, etc. [208]. Several beneficial effects are reported for gallic acid, including antioxidant, anti-inflammatory, and antineoplastic properties. This compound has been reported to have therapeutic activities in gastrointestinal, neuropsychological, metabolic, and cardiovascular disorders [209]. Regarding gallic acid encapsulation in CS-TPP nanocarriers, two reports were found after our comprehensive search [210,211]. Lamarra et al. used a CS from crab shells with a DD of 85% to acquire gallic acid loaded CS-TPP NP (~140 nm) with good stability confirmed by the ζ-potential value (+25 mV). FTIR analysis revealed the presence of both hydrogen bond and ionic interactions of CS-TPP, which allowed the encapsulation and the improvement of the stability of the bioactive. TEM analysis verified the existence of nanosized particles as well as showed a roughly spherical shape. The authors suggested that their NP formulation could be a potential candidate for the encapsulation and controlled release of bioactives, such as gallic acid, to be applied in food preservation [210]. Diabetes mellitus is a chronic metabolic disorder caused by dysfunction of insulin that causes hyperglycemia. According to Purbowatiningrum et al., a therapeutic option to reduce hyperglycemia following meal is to avoid the absorption of glucose by inhibiting carbohydrate glycolytic enzymes, such as α-glucosidase. In this report, gallic acid loaded CS-TPP NP with a 51% of EE and the α -glucosidase inhibition test revealed a partial inhibition of such enzyme [211].

Protocatechuic acid has been investigated due to its effects on human health such as antioxidant activity, anti-inflammatory, anti-fatigue, anticancer, anti-arrhythmia, antiviral, antimicrobial, analgesic, neuro- and nephro-protector. Protocatechuic acid is widely present in nipa palm nut, buckwheat, mustard, currents, mango, grapes, kiwi fruit, strawberries, chokeberries, blackberries, Jujube fruit, olives, dates, chicory, cauliflower, and lentils [212]. Protocatechuic acid loaded CS-TPP NPs present an average particle size of 30–35 nm, greatly below 500 nm, which is the requirement for the penetration into fungal cells. More precisely, NP can completely interact on Pyricularia oryzae's cell membrane, easily penetrate the cell layer and destroy this fungus. Hence, this formulation could be taken into account in the preservation of food systems [213].

The betulinic acid can be found in a wide variety of botanical sources, e.g., *Betula* spp., *Ziziphus* spp., *Syzygium* spp., *Diospyros* spp., *Paeonia* spp., among others. Particularly, betulinic acid is present in leaves, steam bark, woods, aerial roots, roots, fruits, twigs, seeds, and callus tissues derived from the stem. Betulinic acid exhibited a variety of biological and medicinal properties such as inhibition of human immunodeficiency virus (HIV), antibacterial, antimalarial, anti-inflammatory, anthelmintic, antinociceptive, anti-tumoral [214]. The antiparasitic effects of betulinic acid against Leishmaniasis were reported. Mehrizi et al. prepared spherical betulinic acid loaded CS-TPP NP with a size of 124 nm, a bioactive LC of 93%, a slow drug release profile and an optimal cellular uptake without any cytotoxicity. The therapeutic effects and the frequency of its side effects in the treatment of Leishmania major-infected Balb/c mice were improved after betulinic acid nanoencapsulation since the parasite was inhibited in a large extent [215]. Since betulinic acid is a low-cost derived compound, authors suggested that its nanoformulation could be a proper alternative for current Leishmaniasis treatment regimens.

Caffeic acid is a naturally phenolic acid found in several plant foods

such as cabbage, carrots, tomatoes, and berries. Also, it is present in numerous beverages such as coffee, wine, and fruit juices. As a natural product, it possesses several biological and physiological activities: antioxidant, anti-obesity, anti-mutagenic, and anti-tumoral [216]. Soliman et al. designed hydrocaffeic acid loaded CS-TPP NP (100–150 nm) that could not aggregate or precipitate over a wide pH range (4−10), unlike CS-TPP NP which aggregate at pH > 6.5. The obtained NP were able to induce reversible tight junction opening in Caco-2 cell monolayers, a widely used in vitro model to evaluate the intestinal paracellular permeability of macromolecules. In addition, hydrocaffeic acid loaded CS-TPP NP did not significantly affect Caco-2 viability. The authors concluded that their nanocarriers could be used for protein or hydrophilic bioactives delivery with poor oral absorption [217].

Sinapic acid is a phytochemical found in various edible plants such as vegetables, cereals, and oilseed crops, spices, citrus, and berry fruits. Sinapic acid has been reported as effective against a variety of pathological conditions such as infections, oxidative stress, inflammation, diabetes, neurodegeneration, anxiety and cancer [218]. Balagangadharan et al. recently reported a sinapic acid EE range of 58–62% into CS-TPP NP. Also, the sinapic acid release profile resulted to be prolonged over time (25 days). The positive ζ-potential values of the NP translate into their effective adherence with negatively charged cellular membranes. In this sense, biological test revealed that sinapic acid loaded CS-TPP NP stimulated mouse mesenchymal stem cells (mMSCs) differentiation towards osteoblasts. Particularly, the authors explored the molecular mechanism involved in this differentiation demonstrating the triggering of TGFβ1/BMP/Smad/Runx2 signaling pathways. In support of the in vitro results, the release of sinapic acid from the CS-TPP NP promoted bone regeneration in vivo (male albino-wistar rats). Collectively, data support the potential of sinapic acid encapsulated in CS matrix for bone regeneration treatment [219].

5.2.3. Lignans

Lignans are formed from two phenylpropane units [220,221]. These non-flavonoids compounds are found in quite low concentrations in numerous grains, seeds, fruits, and vegetables, and in higher concentrations in sesame and flax seeds [37,222]. Lignans are bioactive compounds exhibiting various biological properties, including anti-inflammatory, antioxidant, antiviral, anti-tumor activities, and can act as cathartic and anti-helminthic agents. Additionally, it has been suggested that lignans decrease the risk of cardiovascular disease [220].

Podophyllotoxin is a non-alkaloid toxin of the lignan family [221]. At the present time, search exploration threw one report in which podophyllotoxin was encapsulated by ionic gelation. Since podophyllotoxin offers a broad-spectrum of anticancer activities, Chen et al. analyzed the effect of podophyllotoxin loaded CS-TPP NP on tumoral-derived HepG-2 and MCF-7 cells. Upon contact with cancer cells, nanocarriers (50–74 nm) with positive ζ-potential (42 mV) allowed effective uptake and internalization. Also, releasing curves of podophyllotoxin at different pH (7.4, 6.8 and 3.7) demonstrated an early fast release phase (~15–20% within 0.25 h) in all cases. However, for greater times, the release was more effective at pH = 3.7. Notably, the antiproliferative efficacy of the encapsulated podophyllotoxin was improved in comparison to its free form. In this sense, podophyllotoxin loaded CS-TPP NP induced the decrease of CyclinD1 gene expression, the critical target of proliferative signals in G1 stage of cellular cycle. Also, cell cycle was arrested in the G2/M phase, which eventually leads to cell death. Particularly, the loss of the mitochondrial membrane potential, the caspase-3 up regulation and the down regulation of Bcl-2 and Survivin genes, indicated that the intrinsic apoptotic signaling pathway was involved [223].

5.2.4. Xanthones

Xanthones are found in lichens, fungi, and higher plants. They exhibit a variety of pharmacological and health benefits, such as antioxidant, anti-inflammatory, antidiabetic, anticancer and neuroprotective [224,225]. In this subgroup of non-flavonoids, three studies were reported in the last few years. In the published papers, the bioactive α-mangostin was incorporated into submicron CS-TPP carriers.

α-Mangostin is a major xanthone in fruit pericarps, bark, and dried sap of the mangosteen tree (Garcinia mangostana Linn.), which is commonly called “Queen of fruits and Food of Gods”. Mangosteen, whose main xanthone components are α- and β-mangostin, is a well-known tropical Asian delicious fruit mainly in Malaysia, Thailand and Indonesia [224]. α-mangostin has hydrophobic characteristics; its poor aqueous solubility and low oral bioavailability hamper its therapeutic application [225,226]. Krisanti et al. employed CS with low, medium, and high molecular weight for NP generation by applying the ionic gelation concept. In all cases, the EE for α-mangostin resulted in 98–99%. Particularly, the obtained NP made with the high MW CS presented lower mucoadhesion since this CS presents low DD leading to a weak interaction with mucin [227]. One year later, Sitti et al. published that the nano-mangosteen peel extract showed a stronger antibacterial activity against *Staphylococcus aureus*, *Bacillus cereus*, and *Shigella flexinery*. Authors determined that α-mangostin loaded into CS-TPP NP present a size range of 308–420 nm with a very low polydispersity index; however, the encapsulated bioactive did not show satisfactory antibacterial activity [228]. Remarkably, Herdiana et al. designed a CS-TPP NP coated with Eudragit® S 100 [229]. Eudragit® S 100 is a pH-sensitive polymer usually used for the improvement of bioactive compounds delivery at the colon level [230]. α-mangostin encapsulation into nanosized CS-TPP NP (326–398 nm) was categorized as good quality entrapment because the EE was close to 100%; however, this report did not show any application in the biomedical or food science fields [229].

5.2.5. Tannins

Tannins are found in a variety of plants used as feed and food, such as sorghum, barley, millets, peas, fava beans, carobs, pigeon peas, winged beans, and other legumes. Also, tannins are present in almonds, apples, bananas, blackberries, cranberries, dates, grapes, hawthorns, raspberries, strawberries, plums, peaches, pears, and persimmons. The anticarcinogenic and antimutagenic potentials of tannins have been related to their antioxidant properties, which are crucial for cellular protection from oxidative damage. The generation of superoxide radicals was described to be inhibited by tannins and related compounds. The antimicrobial activities of tannins are well supported. The growth of many fungi, yeasts, bacteria, and viruses was inhibited by tannins [231,232].

Notably, the only published report in which tannin acid was encapsulated into CS-TPP NP employed a CS (DD 92%), obtained from chitin from shrimp shells. The obtained positive-charge CS-TPP NP exhibited an average diameter about 80 nm and spherical morphology. Additionally, tannin acid-loaded CS-TPP NP were encapsulated in polyvinyl alcohol (PVA)/poly-acrylic acid (PAA) electrospinning films obtained by electrostatic spinning technology. The antibacterial and antioxidative properties of these engineered tannins loaded CS-TPP NP were also discussed. Films showed an excellent moisture-resistant property as well as efficient antioxidant and antibacterial properties. All the studied films showed bacteriostatic activity against *Staphylococcus aureus* and *Escherichia coli*. Remarkably, the incorporation of Ag ions onto electrospinning films exhibited higher inhibitory effects on the growth of microorganisms. Hence, authors conclude that their findings provided a reference for the preparation of antibacterial packaging materials for food [233].

6. Concluding remarks and perspectives

The current review recapitulates the role of CS-TPP NP, prepared by the IG method, for the delivery of polyphenolic bioactive compounds in exerting a better control or prevention of different pathologies. Due to

some physiological barriers like enzymatic degradation, low absorption, and rapid clearance, polyphenols could not reach specific target sites and be unable to fulfill their effect. To overcome or minimize these difficulties, several biomaterials have been used for bioactives encapsulation, protection and delivery achieving their desired outcome. Among these biomaterials, CS, a biopolymer of polysaccharide nature, is being extensively used. For instance, PubMed, a free access search engine that allows to consult mainly the contents of the MEDLINE database, returns a total of 450 publications with the words "CS plus TPP" for the last ten years (from 2010 until the first trimester of 2021). In recent years, owing to its mucoadhesivity and low toxicity (among other characteristics), CS has become an extremely useful biopolymer in health and nutrition settings. It has been called "the polymer of future". Into this frame, it is not a surprise that CS has received extensive attention in the past few decades because of its huge potential and advantages as a carrier for bioactive compounds.

In order to highlight general aspects about the IG methodology based on the interaction between CS and TPP, the most relevant information that can be extracted from Tables 1 and 2 is summarized below. Of note, commercial CS, i.e. commercial ones of analytical grade, prevails as the encapsulating material of choice in the analyzed reports. Among 67 studies analyzed only 10 used CS developed at a laboratory scale, although this choice possibly responds to factors of a practical nature, such as the availability and homogeneity of the starting material. Alternatively, an own production of this polymer, added to a correct characterization of the derived product would add functional variability and reduce the production costs of nanoformulations based on CS as well. Likewise, the latter would make it possible to take advantage of local fishing waste and provide to this production an added value from the eco-environmental point of view.

In general terms, low or medium MW CS with a high DD has been employed across the research works. One can conclude that the higher the DD, the more free-NH_3^+ groups on the molecular chain and a better solubility in acid media. In terms of the interactions between polyphenols and CS, a great number of reactive sites in the polysaccaride chain will be able to establish weak chemical bonds with specific sites of bioactive to be delivered. Another point to consider is the infrequent use of high MW CS. The latter issue is noteworthy since few papers are immersed in the use of this type of CS at the expense of using the commercial classic CS of low MW. However, there exists evidence demonstrating that the crosslinking of high MW CS provides a beneficial and efficient polymeric network for controlled drug delivery [234].

The IG approach can be carried out at room temperature and the eventual size of the NP can be adjusted by changing the CS/TPP ratio, which is a central property that directly affects the drug encapsulation efficiency and its delivery. In this sense, more than 80% of works used CS:TPP ratios $\leq$ 5:1 to successfully obtain nanosized particles, among which 5:1 ratio was the most frequently reported. Only 9 of 67 papers reported CS:TPP ratios oscillating between 5:1 and 10:1 and rarely using amounts beyond this latter ratio. There may be a threshold in the minimum amount of TPP necessary to obtain optimal crosslinking in order to achieve NP that are neither excessively nor weakly compacted. Also, under the conditions described so far for IG approach, it was possible to obtain NP of the suitable sizes for different applications, since 53% of them had sizes smaller than 200 nm, with a 33% of particle sizes ranging 200–500 nm and the rest with particle sizes greater than 500 nm (Tables 1 and 2).

On the other hand, it should be noted that TPP is a food additive having the GRAS status (European food additive number E451). CS could be combined with TPP for the design of new nanosized materials and structures, increasing the biological performance of the encapsulated bioactive compound. CS based drug carriers often possess good mechanical properties and controlled drug release efficiency. These nanostructures produced by IG method can easily bind to cells as visualized by the different in vitro or in vivo biological tests, as included in Tables 1 and 2. The product engineered by CS-TPP combination results innocuous and non-toxic in comparison to other crosslinking agents employed with the same aims, e.g. glutaraldehyde, formaldehyde [235]. Consequently, these properties point to CS-TPP NP as a good candidate for the development of conventional and novel drug delivery systems. Their size allows them to be administered to the body via local application, enterally (orally) or parenterally. Particularly, the oral route is remarkably complex in expression of anatomical features physiology throughout the gastrointestinal tract (GIT). For instance, the mucus layer varies in composition and pH in the main sections of the GIT. The pH profile promptly shifted from highly acid (range 1.0–2.5) in the stomach to nearly pH 6 in the duodenum. The pH progressively raises in the small intestine from pH 6 to about pH 7.4 in the terminal ileum. The pH drops to 5.7 in the caecum, although again gradually rises, reaching pH 6.7 in the rectum. These pH changes must be taken into account for the oral delivery of bioactives in NP. In this sense, CS is stable in neutral condition due to the presence of amino and hydroxyl groups in the glucosamine unitthat can form inter- and intramolecular hydrogen bonds to form aggregates. The aggregate structure decomposes under acidic conditions due to electrostatic repulsion between the protonated amine groups in its structure. To maintain the stability of CS in the gastrointestinal tract or against enzymatic degradation, it is necessary to form cross-links with the amino groups [85], which can accomplished by TPP crosslinking. After ingestion, CS-based NP become attached to the GIT mucosa due to their muco-adhesive properties, and also, are capable to physically penetrate it. A posteriori, they are transported through the circulation to different organs. Such system facilitates the dissolution rate of poorly water-soluble drugs and prolongs the therapeutic effect at specific sites of target organs [236]. Many uses of CS-TPP NP require control over its stability until dissolution. To help elucidate how this stability depends on the choice of supramolecular gelling chemistry, Worthen et al. carried out an exhaustive analysis. The authors indicated that CS-TPP NP are very sensitive to pH, dissolving within an hour at low pH levels (e.g., stomach pH 1.2). In such environment, TPP protonates and, due to its lower anionic charge and weaker binding, provides only a stabilizing effect. On the other hand, in weakly acidic media, CS-TPP NPs turn out to be the most stable NPs compared to other type of NPs, such as those derived from alkaline solution or cross-linked with surfactant. In turn, CS-TPP NP remain intact for several weeks at an acidic pH of 5.0 [237].

In summary, the CS-TPP NPs could constitute platforms for the encapsulation of bioactive compounds. Different bioactives could even be combined for synergistic action on specific cells and/or organs. The overall innovative potential of CS jointly with its friendly nature should be evidenced in the translation of therapies from the laboratory design to pharma, food, or nutraceutical applications. The undeniable potential as a tool in biomedicine must be studied and understood before its clinical use.

CRediT authorship contribution statement

Mariana Carolina Di Santo, Cecilia Luciana D' Antoni, Ana Paula Domínguez Rubio, Agustina Alaimo, Oscar E. Pérez: Contributed to the review, Data searching data, Writing, Editing. **Oscar E. Pérez**: Supervision, Funding acquisition. All authors have given their consent to participate in this report and submit it to Biomedicine & Pharmacotherapy.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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