Contents lists available at ScienceDirect

Biotechnology Advances

journal homepage: http://ees.elsevier.com

Research review paper

Towards green nanoscience: From extraction to nanoformulation

Amaia Huguet-Casquero [a,b], Eusebio Gainza [b], Jose Luis Pedraz [a,c,*]

[a] NanoBioCel Group, Laboratory of Pharmaceutics, University of the Basque Country (UPV/EHU), School of Pharmacy, Paseo de la Universidad 7, Vitoria- Gasteiz 01006, Spain
[b] Biosasun S.A, Iturralde 10, Etxabarri-Ibiña, Zigoitia 01006, Spain
[c] Biomedical Research Networking Center in Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Vitoria-Gasteiz, Spain

ARTICLE INFO

Keywords
Green nanotechnology
Green nanoscience
Ecofriendly
Nanoparticle
Polyphenols
Antioxidant
Green chemistry
Nanocarrier
Nanocapsule

ABSTRACT

The use of nanotechnology has revolutionized many biotechnological sectors, from bioengineering to medicine, passing through food and cosmetic fields. However, their clinic and industrial application has been into the spotlight due to their safety risk and related side effects. As a result, Green Nanoscience/Nanotechnology emerged as a strategy to prevent any associated nanotoxicity, via implementation of sustainable processes across the whole lifecycle of nanoformulation. Notwithstanding its success across inorganic nanoparticles, the green concept for organic nanoparticle elaboration is still at its infancy. This, coupled with the organic nanoparticles being the most commonly used in biomedicine, highlights the need to implement specific green principles for their elaboration. In this review, we will discuss the possible green routes for the proper design of organic nanoparticles under the umbrella of Green Nanoscience: from the extraction of nanomaterials and active compounds to their final nanoformulation.

1. Introduction

Over the past decade, there has been an explosion of interest on the consumption of the so called "natural products" and mainly phytochemicals, in nutraceutical, cosmetic and pharmaceutical fields. Among them, natural antioxidants and, specially, polyphenols have garnered special interest. Despite plenty of preclinical data attest their pleiotropical health-promoting activities, their extraction and further formulation processes are often linked with such a negative environmental impact that renders the term "natural" meaningless. High energy consumption together with the use of large amounts of hazardous organic solvents have an important influence on that. As a result, from an eco-friendly and toxico-pharmacological viewpoint, the search for new green methods arose as an urgent necessity. In this framework, Collins (1995) was pioneering in the introduction of the term "Green chemistry" in early 90's. This led to the delivery of several governmental initiatives around the world that aid to promote the importance of sustainability when designing new products and processes, both at industrial and laboratory levels. Soon after, Anastas and Warner (2010) defined the now well-known 12 principles of Green Chemistry (Fig. 1) that facilitated the application of this novel concept. From then on, scientists have been striven so hard to deploy those goals in several chemical industrial processes. With this aim, Chemat et al. (2012) coined and described for the first time the term "Green extraction" as "*the discovery and design of extraction processes which will reduce energy consumption, allows use of alternative solvents and renewable natural products, and ensure a safe and high quality extract/product*". Additionally, the authors proposed the new six principles for "Green extraction of natural products" (Fig. 1). Particularly, they focused on the relevance of using renewable matters, offering alternative solvents and reducing energy consumption in order to achieve a high quality and safe final product. However, the inherent instability of bioactive compounds in general, and polyphenols in particular, limits its application (Fig. 2). In this sense, the development of new nano-scale delivery systems has emerged as a promising strategy. Notwithstanding the competitive edges offered by nano-drug delivery systems for the encapsulation of labile compounds, they still

Abbreviations: DES, deep eutectic solvents; DMSO, dimethyl sulfoxide; EGCG, epigallocatechin gallate; EGP, egg phosphatidylcholine; GRAS, Generally recognized as safe; HME, hot melt emulsification; HPH, high pressure homogenization; HPMC, hydroxypropylmethylcellulose; LNC, lipid nanocapsules;; MCT, medium chain triglycerides; NaCas, sodium caseinate; NLC, nanostructured lipid carrier; NP, nanoparticle; OVA, ovalbumin; PBS, phosphate buffered saline; PEF, pulsed electric fields; PEG, polyethylene glycol; PIT, phase inversion temperature; PLA, poly (d-l-lactic acid); PLGA, poly(glycolic acid); SAA, supercritical assisted atomization; SAILA, supercritical assisted injection in a liquid antisolvent; SAS, supercritical antisolvent; ScCO2, supercritical carbon dioxide; SCF, supercritical fluid; SEDS, solution-enhanced dispersion by supercritical fluids; SLN, solid lipid nanoparticle; T80, tween 80; T20, tween 20; TA, tannic acid; TPGS, α-tocopheryl polyethylene glycol 1000 succinate; TPP, tripolyphosphate.

* Corresponding author.
E-mail address: joseluis.pedraz@ehu.es (J.L. Pedraz)

https://doi.org/10.1016/j.biotechadv.2020.107657
Received 1 July 2020; Received in revised form 22 September 2020; Accepted 3 November 2020
Available online xxx
0734-9750/

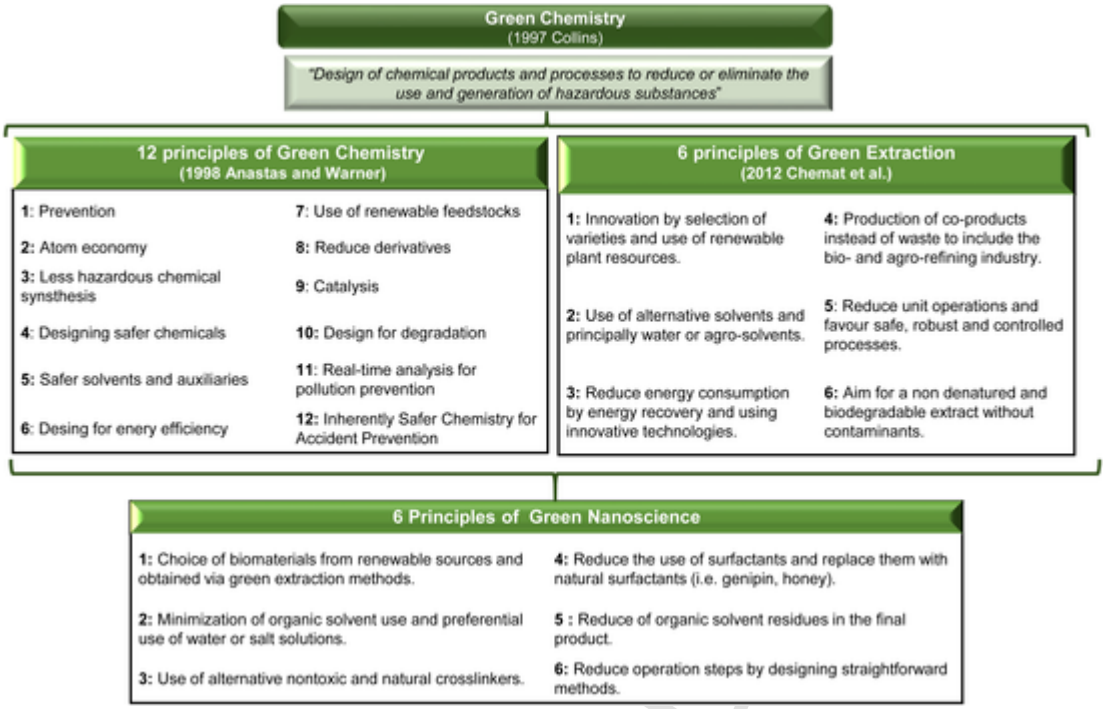

Fig. 1. Definitions and principles of Green Chemistry, Green extraction and Green nanoscience (Anastas and Warner, 2010; Chemat et al., 2012; Collins, 1995; Hutchison, 2016).

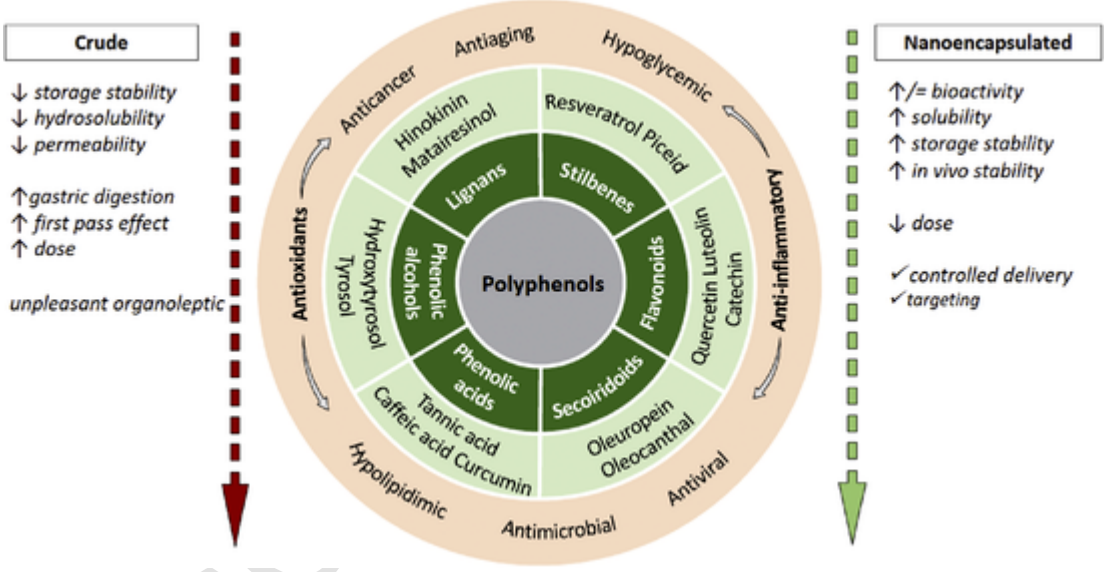

Fig. 2. Main polyphenols classification and bioactivities. Limitations of crude form and advantages of nanoencapsulation. **Adapted with permission from* Luo et al. *(2020). Copyright 2020 American Chemical Society.*

have some tackles to overcome particularly in view of the use of toxic as well as hazardous manufacturing processes that aid no favor for their scale-up to industry and clinics.

As De la Guardia said, "*to move safely from the bench to the real world, it could be a good starting point to work on nanomaterials with an intrinsic absence of toxic components; thus moving to a green nanotechnology*" (de la Guardia, 2014). To attain this purpose, the reduction or elimination of toxic solvents during the nanoformulation process together with the use of green excipients are imperative. Unfortunately, solvent based methods (nanoprecipitation, solvent evaporation, solvent injection, solvent diffusion, antisolvent precipitation) account for more than 50% of all nanoparticle (NP) fabrication processes. These methods emerged as a solution to encapsulate labile compounds with compromised bioavailability and often endowed with lipophilic nature. Moreover, many of them are low-cost and straightforward approaches offering good encapsulation yields for lipophilic and hydrophilic compounds. Naturally, their use is limited by the toxicological issues arisen from the utilization of organic solvents (i.e. isopropanol, acetone, acetonitrile, dimethyl sulfoxide, eythylacetate, tetrahydrofluorane) which ultimately, give rise to the need of special equipment for the removal of residual solvents thus requiring an important investment for companies (Davidov-Pardo et al., 2015; Li et al., 2019).

Given this scenario, there are several underpinning aspects that should be taken into account towards greening nanotechnology. As a

result, Hutchison (2016) introduced the term Green nanoscience as an approach to "*design products and processes at the molecular level that enhance product performance while minimizing impacts on health and the environment*" (Fig. 1). In this regard, a large number of studies report the green synthesis of inorganic NPs (metal or mineral based NPs), but few have been conducted in the field of organic nanocarrier systems (lipid, protein, polysaccharide based NPs). Approved nanomedicine products till 2019 were 29, from which 58.6% were organic NPs and 41.4% inorganic NPs Khalil et al. (2020), thereby highlighting the importance of Green Nanoscience in organic NPs. Therefore, in an attempt to facilitate the implementation of the Green Nanoscience concept in this field, this work is aimed at the establishing six new principles (Fig. 1) focused on greening the process of nanoencapsulation: from the choice for sustainable biomaterials to the industrial scale-up.

In light of all these considerations, this review focuses on the evaluation of renewable nanomaterials available for the development of novel nanomedicines via Green Nanoscience. Even though we will focus on the encapsulation of natural polyphenols, the strategies presented in this review could be applied to any other compound of natural origin. Since Green Nanoscience principles should apply across the entire lifecycle of the product, we will give an overall sustainable evaluation of the process: from polyphenol extraction to nanoencapsulation.

2. Green extraction of natural compounds

Excellent reviews describing green extraction methods for polyphenols have been recently published (Chemat et al., 2019, 2020). Therefore, in the first section of this review, we will give a brief update on the novel green extraction methods of these bioactive compounds. For years, pure organic solvents and hydroalcoholic solutions have been the solvents of choice in polyphenol dissolution and conventional extraction (i.e. soxhlet and solid-liquid extraction methods). However, their negative impact in security, health and environment has been largely described elsewhere (i.e. flammability, health-toxicity, accumulation in the atmosphere) (Moreira et al., 2019). As a result thereof, deep eutectic solvents (DES) were proposed as greener solvent agents and still remain as a promising choice. Unfortunately, despite being low-cost and highly biodegradable, DES still need to be better studied in order to be effectively scaled-up (Ruesgas-Ramón et al., 2017). Similarly, ionic liquids (IL) were also presented as an environmentally friendlier option compared to conventional solvents but their classification as "green solvents" is still a matter of debate. Whilst the first generation of ILs were rapidly discarded due to their demonstrated toxicity and high price, those from second and third generation can be easily prepared and obtained from renewable sources leading to biodegradable, low toxic and low cost solvents provided that their elaboration process is accurately designed for instance via high-throughput computational models. For a detailed discussion on the greenness and/or toxicity of DES and ILs, recent comprehensive literature reviews be found elsewhere (Emami and Shayanfar, 2020; Juneidi et al., 2018; Kudłak et al., 2015; Sivapragasam et al., 2020).

Low yield is another limiting factor for conventional methods and thus several pre-treatment technologies have emerged to overcome this issue (Table 1). Despite their competitive perks for polyphenol extraction, these approaches still challenge some important shortcomings. With regard to mechanochemical extraction, only laboratory and pilot-scale studies have been conducted up to day, and it is unlikely to be suitable for industrial production due to the lack of a continuous process (FDA, 2019). Similarly, the industrialization of enzyme assisted extraction is limited by its expensiveness (Gligor et al., 2019). As for pulsed electric fields (PEF) and instant controlled pressure, they offer high extraction yields and have been proven to be suitable for an industrial setting. However, most reported studies lose sight of green notion by following pre-treatment strategies with solvent-based extraction processes and thus greater efforts should be made to tackle this issue. Accordingly, a recent study showed similar extraction yields on PEF-pretreated fish waste followed either by water or methanol extraction techniques, thus confirming the possibility to design environmentally friendly processes for the extraction of natural antioxidants (Franco et al., 2020). Additionally, pressure-driven membrane processes have been largely studied for the recovery of polyphenols and other bioactive compounds from vegetable liquid matrices. These green engineering processes include principally microfiltration, nanofiltration, ultrafiltration and reverse osmosis techniques which offer the opportunity to concentrate, separate and purify solutions whilst avoiding the use of chemicals and preserving the quality of the extracted compounds (Cassano et al., 2017; Conidi et al., 2018; Giacobbo et al., 2017). Excellent polyphenol recovery rates have been obtained by these methods which have sometimes shown superior yields with aqueous solutions compared to alcoholic solutions thereby contributing to the greenness of the whole extraction process (Mello et al., 2010).

Beyond trying to improve the conventional existing methods, the design and implementation of new green chemistry-based extraction techniques seems to be a more fruitful strategy. As a matter of fact, scientific community has proposed several innovative methods with successful results even at industrial scale. Table 1 presents a summary of those green pretreatment and extraction strategies to obtain natural-source polyphenols. Whilst non-thermal methods are performed at room temperature, thereby reducing energy consumption and ensuring the preservation of thermosensitive compounds, thermal methods are often non convenient for thermosensitive bioactives.

3. Towards green nanotechnology: the challenge of greening nanoformulation processes

There is an ever-growing list of different types of nanocarriers offering a number of advantages for polyphenol delivery. Unlike the extraction processes, the "green" awareness has recently arrived to the nanotechnology world. Natural occurring lipids, biopolymers (proteins and polysaccharides) as well as synthetic polymers have been extensively used in polyphenol nanoencapsulation studies. Most of these biomaterials can be obtained from renewable sources thus accomplishing with one of the main important principles to become green excipients and, at the same time, promoting green nano-processing. Whilst synthetic polymers suffer from regulatory hurdles, most of the naturally occurring compounds are generally recognized as safe (GRAS) by the European Medicines Agency (EMA), the Food and Drug Administration (FDA) and/or the European Food Safety Authority (EFSA), thereby facilitating the regulatory acceptance of the final nanoformulation in terms of time and cost of registration.

With specific regard to protein-NPs, most of the published studies opt for desolvation methods (i.e. nanoprecipitation, antisolvent precipitation) in which organic solvents such as acetone, isopropanol or, as an eco-friendlier alternative, ethanol, are used to promote protein aggregation in the form of NPs (Li et al., 2019). Despite its simplicity, low-energy requirement and good encapsulation yields for several lipophilic and hydrophilic polyphenols, the need of extremely increased amounts of highly concentrated organic solvent solutions (70-85% v/v) lead to the search of greener alternatives unless justified. Similarly, polysaccharide nanomedicines are usually obtained through nanoprecipitation by large dilution of the polymer phase in highly flammable and toxic solvents (i.e. ethylacetate, tetra- hydrofluorane, dymethilsulfoxide) (Mosaiab et al., 2019). Therefore, despite being a low-cost and straightforward method, it should be considered unsuitable from an eco-friendly viewpoint. With regard to lipid-based NPs, whilst some elaboration methods (i.e. solvent evaporation, solvent injection or displacement, solvent diffusion) are based on the use high quantities of organic solvents, the vast majority offers eco-friendlier alternatives. In

Table 1
Description of green strategies for polyphenol isolation and recent application examples.

Classification	Method	Mechanism	Limitations	Application
Pre-treatment methods	Instant Controlled Pressure	Pressure drop to vacuum leads to the disruption of cell membranes and the release of internal metabolites of the humidified sample at 180°C.	Ulterior solvent-based extractions is usually applied, high energy consumption.	Olive leaves, orange by-products, green bean coffee, grape stalk powder, pomegranate peel (Chemat et al., 2020; Kamal and Allaf, 2013; Louati et al., 2019; Mkaouar et al., 2015; Ranjbar et al., 2016; Sánchez-Valdepeñas et al., 2015).
	Mechanochemical extraction	Breakdown of cells by means of high energy micronization forces (permeabilization, destruction or disintegration).	Unlikely to be suitable for industrial productions due to the lack of a continuous process.	Flavonoids and other polyphenols (Chemat et al., 2020; Wu et al., 2017a, 2017b).
	Enzyme-assisted extraction	Hydrolytic degradation of plant cell wall via specific enzymes or complex of enzymes.	Scale-up is a challenge due to the economic cost of enzymes for industrial volumes of raw materials	Fruit samples in drink industry. Likely to be expanded in nutraceuticals and cosmetic industry (Gligor et al., 2019).
	Pulsed Electric Fields	Electroporation phenomena: application of high-voltage (Kv/cm) short –time pulses (μs) results in the formation of pores, increasing cell membrane permeability and leading to the diffusion and extraction of intracellular actives.	Ulterior solvent-based extractions are usually applied.	Panax ginseng roots, banana skin , apple pieces ,fresh carrots, lemon waste residues, fish industry waste, cinnamon (Chemat et al., 2020; Franco et al., 2020; Hendrawan et al., 2019; Kim et al., 2019; López-Gámez et al., 2020; Pashazadeh et al., 2020; Peiró et al., 2019; Ribas-Agustí et al., 2019).

Classification	Method	Mechanism	Limitations	Application
Non-thermal extraction	**High Pressure Assisted methods**	Uniform application of high hydraulic pressure induces damage of the sample.	Algae polyphenols might be inactivated	Stinging nettle, açai pulp, black garlic, algae (de Jesus et al., 2020; Moreira et al., 2020; Tapia-Salazar et al., 2019; Zhao et al., 2019a, 2019b).
	Non-thermal plasma	Generation of plasma discharges (ionized gas or gases) at low or atmosphere pressure	Might decrease antioxidant activity of extracts, challenging regulatory approval, low control, safety should by studied.	Fruits, onion, lettuce (Muhammad et al., 2018).
	Extrusion	Compression step to extrude liquids.	Non declared.	Agrifood by-products (Chemat et al., 2020).
	Ultrasound assisted	Acoustic cavitation induces acceleration mass and heat transfer to the targeted material.	long time and energy output might increase temperature.	Bay leaves, olive leaves, olive tree pruning biomass (Martínez-Patiño et al., 2019; Piccolella et al., 2019; Zurob et al., 2020).
	Supercritical carbon dioxide	Solid-liquid or liquid-liquid extraction using $ScCO_2$ as solvent.	Expensive machinery	Olive leaves, mango by-products (Baldino et al., 2018; Meneses et al., 2015; Žugčić et al., 2019).
	Pressure-driven membrane	Application of hydrostatic pressure within the two sides of a permeoselective membrane, leading to the selective transport of solutes and fluids.	Possible membrane fouling ? or not declared?	Olive leaves and pulp, artichoke leaves and stems, pommegranate juice, pequi fruit extract, wine lees (Conidi et al., 2017; de Santana Magalhães et al., 2019; Giacobbo et al., 2017; Romani et al., 2017).

Classification	Method	Mechanism	Limitations	Application
Thermal extraction	**Microwave assisted**	Frequencies ~2450 MHz induce a heating.	Limited choice of solvents, inhomogeneous heating	Polar polyphenols (i.e. oleuropein derivatives, rutinoside, apigenin) (Žugčić et al., 2019).
	Ultrasonic & Microwave	Application of cavitation and microwaves.	Not declared	Coriander seeds, olive leaves, tea leaves, peony flowers (Chemat et al., 2020; Žugčić et al., 2019).
	Subcritical water extraction	Dielectric constant of water at 100-374°C and 1-22MPa conditions is equivalent to methanol, enhances its diffusivity, mass transfer and solvation properties.	Not declared	Medicinal plants and fruits (Cvetanović et al., 2017; Nastić et al., 2018).
	Solar energy hydro & steam distillation	Solar radiation as heating energy.	Process can took even 14 days.	Orange peel, olive mill waste water (Hilali et al., 2019; Sklavos et al., 2015).

view of these considerations, encouraging scientists on the benefits of the application of Green Nanoscience principles (Fig. 1) arises as an urgent necessity ranging from the selection of green excipients and the design of green processes to the development of green NPs. A description on the mechanisms of those nanoformulation methods that can be driven towards greenness is given in the appendix section. In the following sections, with the aim to highlight the possibility to apply Green Nanoscience principles presented in Fig. 1, we will evaluate the existing works on polyphenol nanoencapsulation that have followed some of these strategies.

3.1. Protein-based nanomedicines

Based on the nature of the proteins they can be water-soluble, soluble in hydroalcoholic solutions or in salt solutions. Naturally, several studies take advantage of the combination of two different proteins (i.e. zein and albumin), proteins with one polysaccharide (i.e. zein and chitosan, zein/caseinate/alginate) or even with lipids to further synergistically exploit their functions. In their comprehensive review, (Martínez-López et al., 2020) recently reported a more detailed classification of the proteins employed in nanomedicine. Thanks to their amphiphilic nature, protein-based NPs offer the possibility to accommodate a wide range of different compounds. Nonetheless, as a rule of nature, protein NPs are endowed with several advantages but also important limitations as depicted in Fig. 3. One of the major challenges in the development of protein-NPs is to prevent microbial contamination upon storage as well as the presence of endotoxins and/or prions which hamper the translation of these NPs to the clinic (Singh et al., 2019). Though there are several sterilization strategies to overcome these challenges, special attention should be given to their impact on the physico-chemical properties of the final nanoformulation (Vetten et al., 2014). Additionally, the physico-chemical properties of the proteins (i.e. molecular weight, isoelectric point) play an important role on the choice of the proper nanoparticle synthesis method and the resulting particle size and yield of the process. Overall, since most proteins can be solubilized in non-hazardous solvents, protein-NP elaboration could be conducted under eco-friendly conditions if carefully designed. However, a number of research studies still consider the use of toxic stabilization substances (i.e. glutaraldehyde) to control the particle size and prevent agglomeration phenomena.

3.1.1. Production methods

3.1.1.1. Via Self-assembly Self-assembly emerged as a green alternative which can be applied to the manufacturing of most of the protein-based NPs. For instance, gelatin-based NPs can be obtained by simply blending the aqueous protein solution with catechins or ellagitanins, without chemical modification of the protein, by means of hydrophobic interactions (Chen et al., 2010; Li and Gu, 2011; Martínez-López et al., 2020; Morán et al., 2018). This methodology could be further exploited for the encapsulation of other hydrophilic or amphiphilic molecules but low encapsulation yields are usually obtained (<10%) (Morán et al., 2018). As a result, aiming at reducing reaction times while increasing encapsulation efficiencies, temperature, pH and chaotrope treatments have been proposed for the induction of self-assembly. Ethanol-based induction has been also proposed for instance for the elaboration of silk-fibroin NP (Martínez-López et al., 2020). However, considering the green and organic solvent-free perspective of this review we will not consider this self-assembly variant. A summary

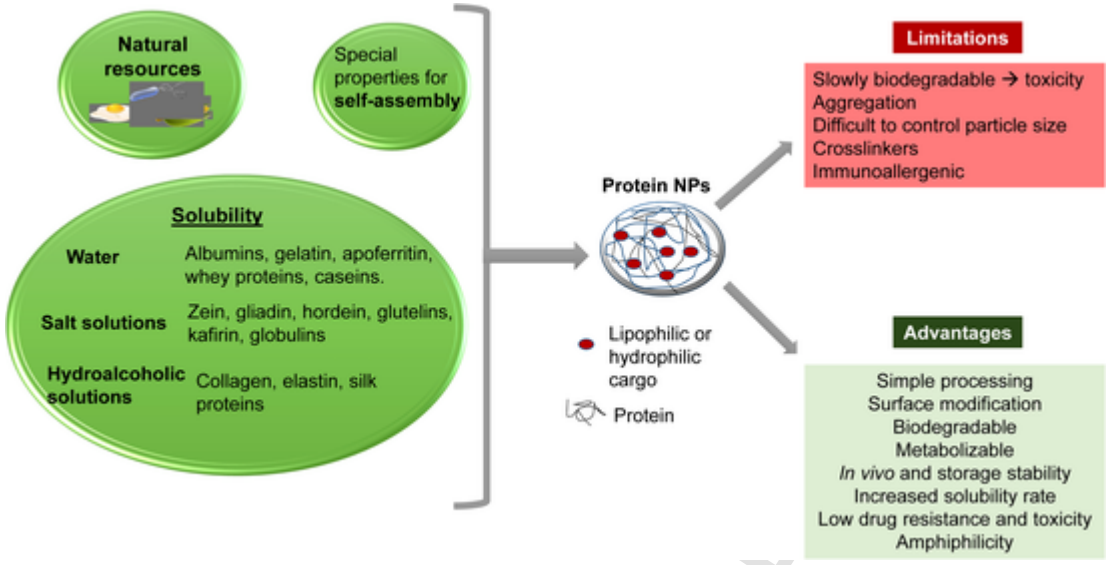

Fig. 3. Protein-based nanoparticles: main advantages and limitations.

of polyphenol-loaded protein NPs via these disassembly/reassembly green techniques is displayed in Table 2.

3.1.1.2. Temperature-induced self-assembly Temperature-driven self-assembly is based on the denaturation of proteins at certain temperatures (denaturation point temperature). As an example, elastin-like NPs elaboration is easily controlled by an increase in temperature (~ 4°C to 42°C) which leads to NPs with a narrow size distribution and micelle-like morphology (Fujimoto et al., 2010). Albumin-based NPs have been also driven by heat induction. For instance, Gou et al. (2018), on the basis of the inherent properties of ovalbumin (OVA), proposed a green method for the encapsulation of the major polyphenol of green tea: epigallocatechin 3-gallate (EGCG). Briefly, OVA and EGCG solutions were individually prepared in phosphate buffer (pH 6.6). OVA was subjected to thermal denaturation (80°C, 20min) and EGCG solution was immediately added. The blend was vortexed for 30 s, cooled down for 3 min and further sonicated (1 min, 25% amplitude). The NPs were recovered by washing and centrifugation and freeze-dried. Similarly, other authors heated β-lactoglobulin (75°C) and bovine serum albumin (BSA) (65-69°C) for the encapsulation of amphiphilic (caffeine) and lipophilic (dimethylcurcumin) polyphenols, respectively (Das et al., 2017; Guo et al., 2017). All in all, this technique offers the possibility to be performed under solvent-free, low-energy and mild pH conditions through simple operating steps.

3.1.1.3. pH-induced self-assembly This method takes advantage of the dissociation-reconstitution properties of some proteins at wide pH windows to encapsulate lipophilic or hydrophilic compounds, increasing its solubility, and effectively preserving their bioactivity (Fig. 4). Particularly, zein, walnut and whey proteins unfold at alkaline conditions (~ pH 11.5-12) whereas other proteins such as ferritin are disassembled at acid pH conditions (~ 2-3.6) (Moghadam et al., 2020; Pan and Zhong, 2016; Zhang et al., 2019). It is worth noting that, for this method to be effective, polyphenols should have deprotonable hydroxyl groups at the unfolding pH conditions of the protein. As an example, walnut-curcumin complex formulations obtained by solvent-free alkaline to neutral pH-driven method have shown to increase curcumin encapsulation efficiency from 2.5 to 60%, and the loading capacity from 1.3 to 30 μg/mg. The authors suggested that curcumin might have been grafted onto the hydrophobic fragments of the unfolded protein at alkaline pH and then entrapped in the refolded protein structure. Interestingly, curcumin-walnut NPs displayed enhanced hydrosolubility and antioxidant capacity compared to free curcumin, along with a sustained release behaviour within the gastrointestinal fluid. Moreover, NPs were shown to preserve the well-known anticancer effects of this phenol in vitro (Moghadam et al., 2020). Additionally, Zhang et al. (2019) showed that the pH-driven method offers better features in the final zein/casein/alginate nanoformulation compared to the antisolvent technique whilst, at the same time, avoids the need of ethanol for zein dissolution. Similarly, other authors have applied this method for the encapsulation of curcumin into other proteins (zein, soybean proteins, sodium caseinate (NaCas), whey proteins) and polysaccharides (gum arabic) to form core-shell nanostructures with improved thermal, salt and pH-stability of the polyphenol. Particularly, gum arabic coatings seemed to give the best pH and salt stability, whereas NaCas and soybean protein gave the best thermal stability and loading capacities up to 27% (Peng et al., 2020; Zhan et al., 2020). In the specific case of ferritin, the pH-driven method allows to take advantage of the cage-structure of this protein to accommodate hydrophobic, hydrophilic and amphiphilic biomolecules. The research group of Yang has extensively studied the dissociation-reconstitution abilities of different ferritin proteins at extreme acid (pH~ 2)/basic (pH~12) and neutral pH conditions, respectively, for the encapsulation of different polyphenols. More specifically, they have shown that red bean apoferritin yields better encapsulation rates (12.9%) for the hydrophilic polyphenol EGCG compared to the recombinant soybean seed H-2 ferritin (6.98%) (Yang et al., 2018b). As for the hydrophobic polyphenol curcumin, they have demonstrated that human-ferritin based nanocarriers result in significantly high encapsulation efficiencies (up to 30.3 %) compared to conventional formulations (Pandolfi et al., 2017). In the case of globulins and caseins, this process is preferentially followed by the addition of a crosslinker to further improve their in vivo stability (Martínez-López et al., 2020). Beyond this, other proteins that do not need stabilization compounds offer greener approaches simply based in pH-shifting assembly with efficient encapsulation results. This issue will be discussed in section 3.1.2.This method has been also applied for the synthesis of protein/polysaccharide complex NPs and lipid-based systems. Since extreme pH shifting could negatively influence on the bioactivity, storage, sensory and physicochemical properties of some sensitive bioactive cargo, Meng et al. (2018) proposed to subject ferritin to PEF-treatment prior to its disassembly. Interestingly, they showed that PEF-ferritin was disassembled at slightly less extreme acid condition (pH 3.6) than conventional ferritin resulting in similar particle size (about 12 nm) and higher encapsulation efficiencies (13.8%). Therefore, protein pre-treatment with PEF or similar procedures hold

Table 2
Summary of phenolic compounds encapsulation in protein-based NPs via self-assembly solvent-free methods.

Self-assembly inducer	Protein matrix	Polyphenol cargo	Encapsulation Efficiency	Reference
Stirring	Gelatin	Ellagitanins	84.3 % and 73.9%	(Li and Gu, 2011)
Temperature				
	OVA	EGCG	98.1%	(Gou et al., 2018)
	β-lactoglobulin	caffeine	13.54%	(Guo et al., 2017)
pH (basic/neutral)	Walnut proteins	curcumin	60.7%	(Moghadam et al., 2020)
	Whey protein and zein	curcumin	84.62%	(Zhan et al., 2020)
	NaCas	curcumin	up to 91%	(Peng et al., 2020)
	Whey protein		up to 69%	
	Soybean protein		up to 81%	
	Gum Arabic		up to 83%	
	Zein-NaCas	none	-	(Pan and Zhong, 2016)
	Zein-rhamnolipid	curcumin	82-96%	(Dai et al., 2019)
	Zein-NaCas-alginate	propolis	86.5%	(Zhang et al., 2019)
pH (acid/neutral)	Apoferritin and H2 ferritin	EGCG	9.69%	(Yang et al., 2018b)
	H2-Ferritin	Curcumin	95%	(Pandolfi et al., 2017)
	PEF-Ferritin	rutin	13.7%	(Meng et al., 2018)
Urea	Soy conglicin	curcumin	61-79%	(Liu et al., 2019)
	Ferritin	EGCG	17.6%	(Yang et al., 2017)
Guanidine hydrochloride	Ferritin	Rutin EGCG	10.1% 16.9%	(Yang et al., 2018a)

OVA: ovalbumin; EGCG: epigallocatechin gallate; NaCas: sodium caseinate; PEF: pulsed electric fields.

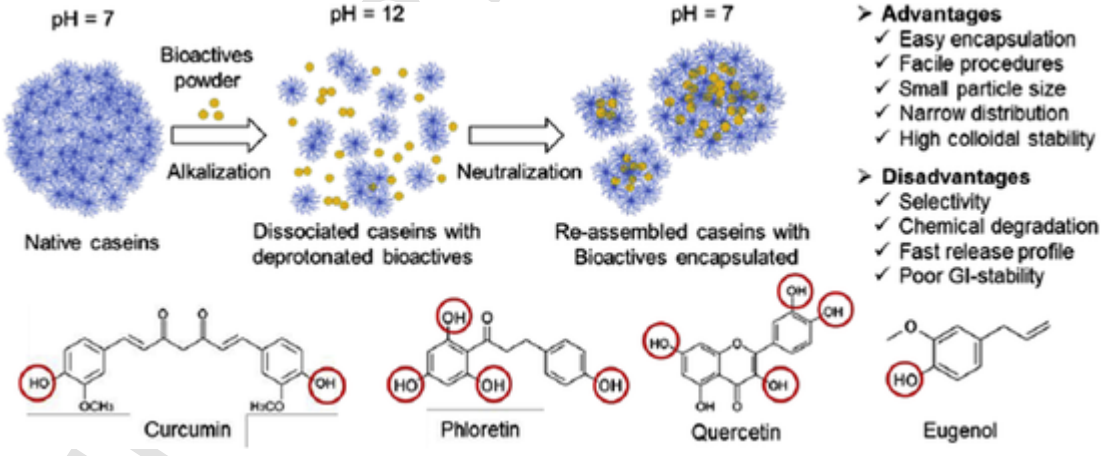

Fig. 4. Example scheme of pH-driven self-assembly of proteins for the elaboration of nanoparticles (NPs). On top, illustrative summary of pH-driven nanoencapsulation of polyphenols into casein NPs. On bottom, examples of lipophilic polyphenols that can be encapsulated by this technique within casein NPs. Red circles indicate deprotonable hydroxyl groups at alkaline conditions that allow their co-dissolution with the dissociated casein micelles. **Reprinted with permission from* Luo et al. (2020). *Copyright 2020 American Chemical Society.*

great promise to further widen the applicability of the pH-induced method to labile polyphenols.

3.1.1.4. Chaotropic treatment assembly This approach arises as an attempt to tackle the limitations that heat and pH driven methods offer to pH and/or thermo-sensitive phenolic compounds, respectively. In this regard, soybean-globulin based NPs and apoferritin-based NPs can be prepared under the presence of chaotropes such as urea or guanidine hydrochloride which at low concentrations induce structural changes in the native structure of proteins allowing its disassembly and further reassembly after withdrawal via dialysis (Liu et al., 2019; Yang et al., 2017, 2018a). More specifically, chaotropes disturb protein structures via non-covalent forces leading to their disassembly into protein subunits. Chaotropic-driven assembly has shown to effectively encapsulate inside the protein core hydrophobic (rutin, curcuminoids) as well as hydrophilic (EGCG, anthocyanins, chlorogenic acid) compounds without needing alcohol assistance.

3.1.1.5. Supercritical-fluid (SCF) methods Despite being regarded as a "green" method (Chakravarty et al., 2019; Kankala et al., 2018) enough relevance should be given to the solvents used for the solution medium preparation, taking into account that amid all organic solvents ethanol is the eco-friendliest option. Actually, the phase behaviour is a key factor in the optimization of SCF techniques and thus in the final properties of the obtained particles (Costa et al., 2018). As for protein-based NPs, supercritical anti-solvent (SAS) processes and variations like supercritical assisted atomization (SAA) are the most used for zein, BSA as well as silk-fibroin based NP elaboration (Adami et al., 2017b; Martínez-López et al., 2020). Methanol (100%) is usually the solvent of choice for SAS owing to its ability to render smaller and more uniform particle sizes and thus a large flow rate of CO_2 to remove the toxic solvent residues is usually needed to obtain adequate results (Elzoghby et al., 2017; Luo and Wang, 2014; Reverchon, 2002). Aimed at overcoming this problem, Palazzo et al. (2019) recently proposed the application of Supercritical Assisted Injection in a Liquid Antisolvent method (SAILA) which enabled the use of ethanol 80% as solvent media. However, it is worth noting that oppositely to other SAS-based processes the SAILA technique produces a liquid suspension thereby requiring a post-processing to obtain dry particles. It was Reverchon who in 2001, patented the SAA process for the elaboration of dry microparticles and nanoparticles which indeed offers the advantage of using lesser CO_2 compared to other SCF techniques (Reverchon, 2001). Up to day, this technique has not yet been implemented for protein-based NPs. Other researchers have also described the elaboration of zein and silk-fibroin NPs via solution-enhanced dispersion by supercritical fluids (SEDS) (Hu et al., 2012; Li and Zhao, 2017). In line with this, Xie and co-workers demonstrated the efficacy of SEDS method to encapsulate curcumin into low-sized (<100nm) silk-fibroin NPs while enhancing its dissolution properties as well as its antifungal and anticancer activities in vitro (Xie et al., 2015, 2017; Xue et al., 2019). Despite allowing to almost totally remove organic solvent residues from the final product, SEDS method still triggers in the use of inflammable and hazardous solvents such as hexafluoroisopropanol, dichloromethane or dimethylsulfoxide, which ultimately are not in compliance with the Green Chemistry principles and hamper its eco-friendly and safety scale-up. Moreover, controlling particle size still remains a challenge.SCF-driven nanonization of polyphenols without the need of any additive (surfactants, polymers) has been also studied for trans-resveratrol and dihydromyricetin nanoformulations (Ha et al., 2020; Xu et al., 2020). All in all, SCF gives the advantage of reducing the presence of solvent traces in the final product thus promoting its future clinical use, but further efforts should be made to drive the choice for greener solvents (i.e. ethanol) as well as for those techniques using lesser amounts of CO_2 (i.e. SAA vs SEDS or SAS).

3.1.1.6. Complex coacervation/Heteroprotein complexation This method takes advantage of the ability of proteins to interact electrostatically with oppositely charged polymer electrolytes (protein, polysaccharide or lipid) for the synthesis nanoparticles (Pathak et al., 2017). In this section we will discuss the complex coacervation between two proteins, namely heteroprotein complexation. The physico-chemical properties of the proteins (molecular weight, chain brains, charge distribution and size and the mobility of the protein chains) as wells as processing conditions (pH, ionic strength, protein stoichiometry, total protein concentration, temperature etc) have an important impact on the coacervation process (Croguennec et al., 2017; Moschakis and Biliaderis, 2017; Pathak et al., 2017). Despite few examples are found for the synthesis of protein nanoparticles via this strategy more have been reported to form particles in the micron-range. For instance, gelatin and sodium caseinate heteroprotein complex has been applied for the microencapsulation of several bioactive compounds such as probiotics (Zhao et al., 2020) and lactoferrin-lactoglobulin complexation has been shown to effectively load vitamin B9 resulting in particles with good stability and sizes around 3-20μm (Chapeau et al., 2016). Indeed, lactoferrin is one of the most studied proteins in heteroprotein complexation (Liu et al., 2018). Recently (Zheng et al., 2020) proposed the elaboration of soy protein-lactoferrin complexes of around 50-150 nm. Other authors have also reported the synthesis of lactoferrin-βlactoglobulin complexes exhibiting a droplet size ~10-20 nm (Yan et al., 2013). From a green perspective, this method offers the advantage of being performed under mild operating conditions (mild temperature, low energy consumption) together with an aqueous environment, free of organic solvents. Nonetheless, to our knowledge, this strategy has not yet been studied for the encapsulation of polyphenols.

3.1.1.7. High-energy based methods Ultrasonic-assisted synthesis has been reported for the elaboration of β-lactoglobulin and casein based NPs (Sahlan Dienayati et al., 2017; Wijayanto et al., 2017; Wu et al., 2017a, 2017b). However, high polydispersity indexes are usually obtained by the solely application of ultrasounds. Interestingly, Wijayanto et al. (2017) proposed an organic solvent-free and almost totally green procedure for eugenol (in the form of clove oil) encapsulation in casein based NPs via ultrasound assisted nanoprecipitation. Briefly, eugenol was extracted under green conditions, via hydrodistillation, from clove leaf powder. For the protein phase, casein was extracted from pasteurized milk through a pH and temperature induced decantation method. For nanoencapsulation, authors applied the polar and non-polar properties of casein as a surfactant, and the non-polar properties owned by the clove oil without the need of organic solvents leading to the formation of nanoparticles with an encapsulation efficiency of around 64% and a particle size of ~ 677 nm. With the aim to obtain a uniformly sized product, Sahlan Dienayati et al. (2017) combined the sonochemical assisted nanoprecipitation with an intensive homogenization process by means of a High Pressure Ball Mill Homogenize equipment. They suggested that the proposed device was suitable for large-scale manufacturing propolis-loaded casein micelles with 80 nm in size and encapsulation efficiencies around 80%.Leed jet homogenization has also been proposed as an additional step to further narrow the particle size distribution of whey-protein based particles (Murray and Phisarnchananan, 2016). Electrospray deposition has been applied for the elaboration of several protein-based particles (gliadin, zein, whey or elastin-like proteins) without the need of surfactants while leading to high payloads. Nonetheless, only when working with hydrosoluble proteins (i.e. whey) and cargo (i.e. olive leaf extracts) organic solvents can be avoided (Soleimanifar et al., 2020). Based on a similar phenomenon and totally circumventing the use of organic solvents electrohydrodynamic spraying allows the encapsulation of non-water soluble molecules into silk-fibroin NPs (Qu et al., 2014). Despite avoiding organic solvents, the number and complexity of the operational steps might humper the scale-up of this method.

3.1.1.8. Other techniques Few studies in the field of protein-based NPs have been performed by nanospraydrying probably due to the difficulty to obtain narrow size distributed particles. As a matter of fact, Pedrozo et al. (2020) proposed the encapsulation of rutin, as a model of poorly water soluble flavonoid, by means of nanospray-drying. Due to the nature of rutin, ethanol (50% v/v) solution was needed for the feed solution preparation. Nano-sized particles with spherical shape and negative zeta potential (-32 mV) were obtained, but particle size distribution was too broad (300 ± 210 nm) probably due to aggregation, and the obtained encapsulation efficiencies were significantly low (32± 9 %). Interestingly, the antioxidant activity of rutin was not disturbed.As an intermediate approach towards greening NP formulation methods the emulsification technique can be considered. Albumin, hordein, silk-fibroin and gelatin based NPs have been elaborated by this strategy (Martínez-López et al., 2020). The industrialization of this technique was conveniently endorsed by American Bioscience, Inc. who developed and patented the well-known Nab®-Technology currently applied for the commercialized albumin-based NPs (Abraxane®). Despite its success for the encapsulation of the lipophilic drug paclitaxel, chloroform and ethanol are needed during the process and thus other authors have proposed greener alternatives such as an organic solvent-free hydration process for the synthesis of paclitaxel-BSA-liposomes (Fu et al., 2009.; Zhao et al., 2019a, 2019b). In the case of hordein NPs, emulsification is usually carried out by suspending the protein in an oil phase containing the lipophilic cargo by means of a homogenizer and then passing the nanoemulsion through a microfluidizer system. Notwithstanding the low solubility in water of hordein at neutral pH, organic solvents are avoided via pH-driven hydration prior to the emulsification of the protein (Wang et al., 2011). Therefore, again, pH-shifting methodology to improve protein hydration seems a promising strategy towards the elaboration of particles with non-hydrosoluble proteins. Soybean protein based nanoemulsions have been also prepared by the ultra-high pressure homogenization for the encapsulation of tea polyphenols (Tian et al., 2019). On the other hand, gelatin offers the eco-friendly advantage of being water soluble and thus only hydrosoluble cargo can be encapsulated via emulsification. The aqueous protein-drug solution can be emulsified with an organic solution of polymethylmethacrylate or, as a greener option, an oil (sesame oil), and particles are stabilized via crosslinking (Martínez-López et al., 2020).

3.1.2. Stabilization of protein-NPs

Beyond their possible allergenic potential, one of the major limitations of protein-based NPs is their tendency to aggregation and, for certain proteins, their instability against gastric enzymes. As a matter of fact, protein-NPs have been, for years, subjected to chemical crosslinking for their stabilization. In this regard, conventional toxic cross-linkers such as glutaraldehyde and glycoxal should be replaced by safer alternatives such as sodium tripolyphosphate, transglutaminase, natural surfactants (i.e. saponin, rhamnolipid, genipin) or polysaccharide-based coatings (chitosan, alginate) (Dai et al., 2019; Kharat et al., 2018; Martínez-López et al., 2020; Moghadam et al., 2020). Additionally, the synthetic Pluronic F127, F68 and F88 are non-toxic and FDA-approved hydrophilic surfactants that have gained special interest within the stabilization of protein-NPs (Ganguly et al., 2020). More specifically, gelatin-F127 combination has shown to overcome the individual drawbacks of these two compounds (protein and non-ionic surfactant) related to their instability under physiological conditions and rapid clearance (Das et al., 2020). Likewise, there are some molecules similar to surfactants, the so-called hydrotropes, that have shown to prevent protein aggregation and nucleation upon storage (Dey et al., 2015). In line with this, (Das et al., 2019) demonstrated the ability of sodium deoxycholate to improve the stability of albumin-based NPs after 30 days of storage and, at the same time, increase their curcumin loading capacity compared to the nanoformulation free of hydrotrope. Interestingly, whilst surfactants are added via emulsification processes, hydrotropes only require mild mixing techniques. With regard to polysaccharide coatings, they can be added by simple electrostatic interactions or, more strongly, by transglutaminase treatments (Yang et al., 2019). Even the stabilization by simply incorporating a basic amino acid or cyclodextrin has been proposed (Peñalva et al., 2018, 2019).

3.2. Polysaccharide-based nanomedicines

Unlike some proteins, polysaccharides generally display very low toxicity and non-immunoallergenic potential as well as high biocompatibility. Despite being sensitive to enzymatic degradation their breakdown by-products have shown to be recycled by cells (Mosaiab et al., 2019). These polymers are available in high quantity within a wide range of renewable sources (i.e. animal, algal, plant and microbial), and their processing methods are usually cheap and easy to perform (Fig. 5A). Their functional groups endow polysaccharide-based NPs with good hydrosolubility and bioadhesion abilities which ultimately could extend the residence time of loaded cargo and its absorption within the human body (Fig. 5B). Additionally, most of the polysaccharide-based NPs can be used for stimuli-responsive drug release via appropriate crosslinkage. However, the heterogeneity in the obtained NPs is still a challenge (Barclay et al., 2019). Nonetheless, all of these features support the use of these inexpensive polymers as effective biomaterials for the design of green nanodelivery systems. Natural polysaccharides are found in, but not limited to, their cationic (amine groups), neutral or anionic (carboxylate and/or sulphate groups) forms (Fig. 5A). In any event, most of them can be chemically modified to tailor the desired superficial charge and physicochemical characteristics of NPs (Kim et al., 2006; Negm et al., 2020).

3.2.1. Production methods

Excellent reviews have been reported in regards to polysaccharide-based NPs, starting with chitosan-based nanocarriers by Janes et al. (2001) and Prabaharan and Mano (2005). Science evolves rapidly and thus shortly after Liu et al. (2008) gave a detailed review on new initiatives emerged for the design of polysaccharide-based NPs. From then till now, other authors have described the wide range of applications that these natural-based delivery systems can offer in food, pharmaceutical and cosmetic sectors (Barclay et al., 2019; Mosaiab et al., 2019; Yang et al., 2015).

Based on the chemical structure of polysaccharides, they can interact via three specific methods with other polymers: covalent crosslinking, polyelectrolyte complexation and ionic crosslinking (Fig. 5C). These three approaches are based on the gel transition phenomena that occurs when a system of branched polymers (proteins, polysaccharides, synthetic polymers) is linked until a unique macroscopic molecule is formed (gel point) leading to the increase of the mixture viscosity. All these interactions have been conveniently exploited for the elaboration of polysaccharide-based and polysaccharide-protein based NPs and also as an extra-step for surface modification of polymeric, protein or lipid NPs.

With regard to ionic gelation, despite it might be performed solely using polysaccharide-based polymers, the true is that most studies conveniently exploit the competitive perks that polysaccharide-protein combinations can offer (Liang et al., 2016). For instance, Liang et al. (2016) have recently proposed the fabrication of EGCG-loaded NPs by ionic gelation combined with heat-induced denaturation and a coating process. In this work, the protein coat led to a nanoformulation with promising features for intestinal targeting after oral administration, since β-lactoglobulin is able to withstand pepsin hydrolysis in stomach but suffers a degradation in the intestinal fluid thus releasing loaded cargo (Izadi et al., 2016; Reddy et al., 1988).

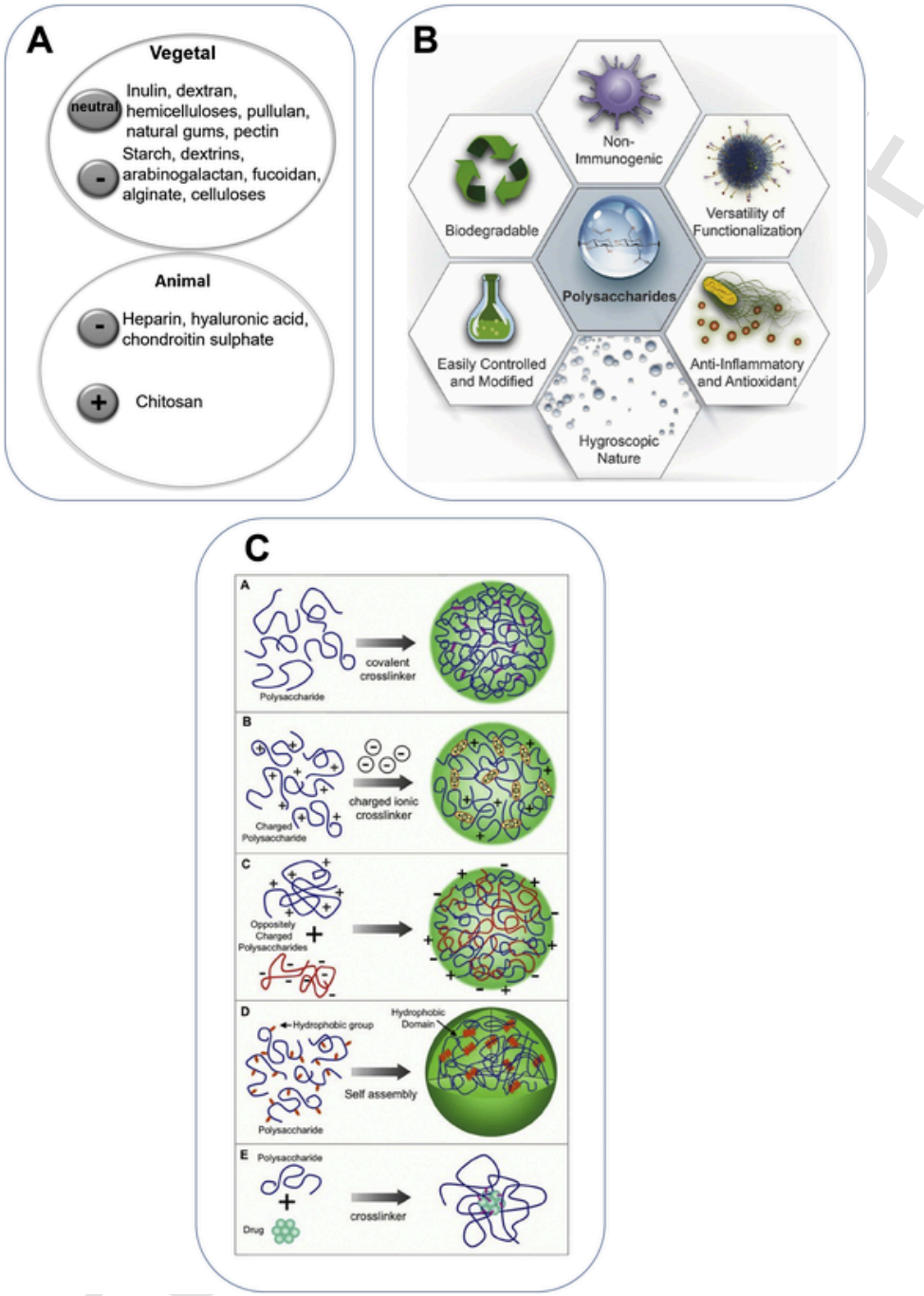

Fig. 5. Polysaccharide nanomaterials classification (A), main advantages (Miao et al., 2018) (B), and nanoformulation methods [A. Covalent cross-linking, B. Ionic cross-linking, C. Polyelectrolyte complexation, D. Self-assembly of hydrophobically modified polysaccharides and E. Polysaccharide–drug conjugate] (Mizrahy and Peer, 2012) (C).

On the other hand, polyelectrolyte complexation offers a number of simple manners to combine negative-charged biopolymers (alginate, gum Arabic, pectin) and positive charged biopolymers (gelatin, chitosan) (Akbari-Alavijeh et al., 2020; Fathi et al., 2014). It can be also performed with any other combination of oppositely charged polymers such as proteins, protein-polysaccharide, as well as with pre-gelated polysaccharides (i.e. calcium alginate) (Sarmento et al., 2007).

The most competitive edge of polysaccharide-based NPs is their ability to form stimuli-responsive networks for one or more factors (i.e. pH, light, temperature) via specific crosslinkage. In this framework, Tan et al. (2019) have recently published an excellent work proposing a novel ecofriendly strategy for the elaboration of double-core-shell protein-polysaccharide nanostructures as carriers of poorly stable hydrophilic compounds and offering pH/redox stimuli response delivery. With this purpose, they applied the sonochemical assisted covalent crosslinking method followed by the electrostatic interaction technique through successive interfacial polyelectrolyte complexation and cross-linking with the remaining non-cross-linked protein. They proved that this method was effective for polysaccharide-based NPs (carrageenan, dextran sulfate, pectin, xanthan gum), polysaccharide-polysaccharide combinations (pectin-chitosan, xanthan gum-chitosan) as well as protein-polysaccharide complexation (BSA-chondroitin sulfate). No organic solvent nor specifically designed machinery were used thus facilitating

their industrial scale-up. More importantly, stimuli-responsiveness of the NPs was obtained via nontoxic products (proteins).

Based on the ultrasound-assisted ionic crosslinking approach, the research group of Manconi proposed a green strategy that combined polysaccharides and phospholipids to give rise to novel nanovesicles formation. The so-called hyalurosomes and polymer glycerosomes offered superior physico-chemical properties and hold great promise as lipophilic drug carriers in skin and lung delivery, respectively (Lai et al., 2020). A brief summary of recent work on green approaches for polyphenol encapsulation into polysaccharide based NPs is displayed in Table 3.

3.2.1.1. Self-assembly via hydrophobic modification of polysaccharides Self-assembly of hydrophobically modified polysaccharides can be considered as green approach that allows the avoidance of organic solvents for its performance. Nonetheless, polymer modification procedure aside from being time-consuming normally needs the use of various risk solvents. For instance, Xie et al. (2014) reported the elaboration of PEGylated carboxymethyl chitosan/calcium phosphate hybrid anionic NPs through self-assembly. For NP elaboration, the method was adequate from an eco-friendly and health-safety viewpoint since non-toxic solvents were needed. However, for the PEGylation of the chitosan a time-consuming (83h) and non-ecofriendly (DMSO, chloroform, acetone) process was proposed. Similarly, Vasquez et al. (2014) reported a simple and eco-friendly method for self-assembly of chitosan-O-PEG Graft Copolymers aided by extrusion forces. Unfortunately, the problem still remained on the transformation of chitosan into a polymerizable organosoluble precursor. All in all, the application of Green Chemistry principles for chitosan modification is imperative.As it can be seen, self-aggregation might be aided by external forces such as sonication, extrusion or high pressure homogenization (HPH) (Wang et al., 2007). Accordingly, Catalán-Latorre et al. (2018) proposed the elaboration of an innovative nanovesicle via green self-assembly. The proposed process seems a great alternative for curcumin and related hydrophobic compounds encapsulation without needing organic solvents for their solubilization and under mild conditions (room temperature), thereby holding great promise for industrial scale up. The new formulation was named as Nutriosome, referring to the use of a commercially available dextrin named Nutriose® and the vesicle nature of the final formulation ("some"). The nanovesicles, were made up of soy phosphatidylcholine and two hydrosoluble polysaccharides (dextrin and hydroxypropylmetylcellulose), and were endowed with high encapsulation efficiencies for curcumin (88%). Moreover, freeze-dried nutriosomes were shown to be stable for 60 days under 25°C in air or under vacuum.

3.2.1.2. Other techniques Recently, Gonzatti and co-workers loaded α-galactosylceramide, a naturally occurring antitumor agent, into positively charged polymeric NPs obtained through a rapid green nanospraydrying process, in the absence of organic solvents (Gonzatti et al., 2019). Particularly they used Eudragit® EPO, a commercially available cationic copolymer made by acrylates, as pH-stimuli responsive carrier. To our knowledge, there is no data available about polyphenol encapsulation into polysaccharide-particles via nanospraydrying and thus it could be an interesting approach for upcoming studies. As for SCF technology, SAS is the most used variant for the encapsulation of polyphenols that require organic solvent assistance (Di Capua et al., 2017a; Ha et al., 2019; Zhou et al., 2012). Recently, Ubeyitogullari and Ciftci (2019) proposed a novel and one-step green SCF approach for the impregnation of curcumin into starch NPs. They used ethanol as solvent and the resulting food-grade particles increased up to 173-fold the amount of curcumin available for absorption after simulated gastric digestion, compared to free curcumin (Fig. 6). It is worth noting that for these kind of atomization based techniques most of the polysaccharides need to be modified to lower the liquid feed viscosity (i.e. glycol chitosan) (Akbari-Alavijeh et al., 2020). On the other hand, microfluidics have also been proposed for polysaccharide-based NPs elaboration (Chiesa et al., 2018) with better control of the particle preparation procedure. However, this is still a field under exploration and few studies have been reported to date.

3.2.2. Stabilization of polysaccharide-NPs

Environment-responsive properties are strongly useful for the design of smart NPs and the nature of the cross-linking agent directly influences on them. Despite its hazard nature, glutaraldehyde is still used for dual pH/light and pH/thermo-responsive chitosan-NP elaboration (Meng et al., 2013). Fortunately, since the cytotoxicity of this compound was demonstrated, scientific community has strived to find safer and more biocompatible alternatives such as dopamine, natural and nontoxic acids (i.e. critic acid, succinic acid, malic acid, tartaric acid), the naturally occurring genipin (Heimbuck et al., 2019; Lin et al., 2017) and more recently some polyphenols. In particular, tannic acid (TA), a polyphenol found in some plants, has been proposed to assist the cross-linking of polymers giving rise to the formation of pH-sensitive NPs via solvent-free approaches. Additionally, TA has been showed to endow protein NPs with better resistance to digestion as well as enhanced antioxidant activity (Jia et al., 2020; Zou et al., 2017). In accordance with this, Qin et al. (2019) proposed an interesting strategy for the incorporation of this natural antioxidant into starch particles by the fabrication of a metal-phenolic network through a simple and environmentally friendly ultrasonic assisted self-assembly method.

Table 3
Green polysaccharide-based nanoparticles for polyphenol encapsulation

Polymer	Method	Polyphenol	Encapsulation efficency	Solvent	Stabilization agent	Reference
Water soluble chitosan	Simple coacervation + Us	Retinol	63-76%	Ethanol (coacervation agent)	-	(Kim et al., 2006)
Chitosan + Gum Arabic	Complex coacervation	Curcumin	90%	Acetic acid (for chitosan dissolution)	Tween 80	(Tan et al., 2016)
Sodium hyaluronate + soy phosphatidylcholine	Us + Ionic crosslinking	Curcumin	76-79%	-	-	(Manca et al., 2015a)
TrimethylChitosan chloride/sodium Hyaluronate	Us + Ionic crosslinking	Curcumin	74%	-	Glycerol	(Manca et al., 2015b)
HPMC + Nutriose	Self-assembly	Curcumin	91%	-	-	(Catalán-Latorre et al., 2018)

HPMC: hydroxypropylmethylcellulose, US: ultrasonication.

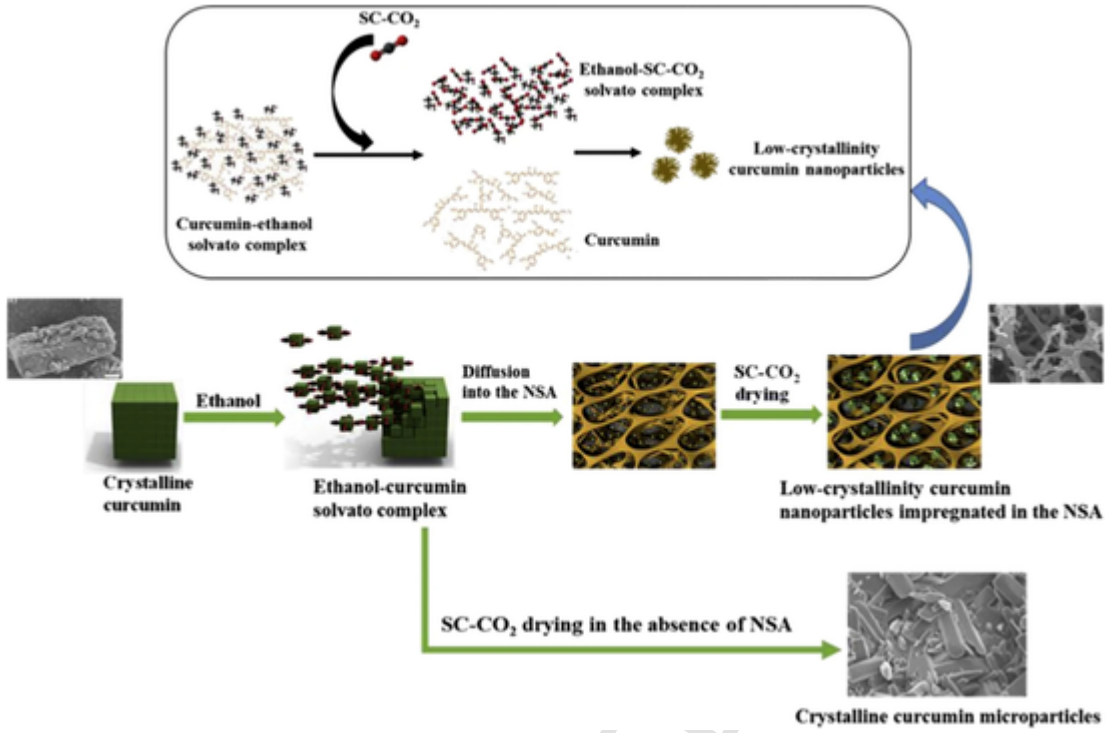

Fig. 6. Illustration of the simultaneous elaboration of nanoporous starch aerogels (NSA) and low-crystallinity curcumin nanoparticles via green supercritical carbon dioxide ($ScCO_2$) (Ubeyitogullari and Ciftci, 2019).

Even TA alone has been used as a nanocarrier for the design of pH-responsive nanoantibiotics (Abouelmagd et al., 2019).

Unlike covalent crosslinkers ionic ones are usually nontoxic. Alonso and coworkers were pioneers in applying ionic crosslinking to form nano-drug delivery systems and, more specifically, exploiting the ability of tripolyphosphate (TPP), a nontoxic multivalent anion, to form a gel with the cationic chitosan (Calvo et al., 1997). From then on, TPP has been the most used ionic crosslinker and a number of studies report the bounties of TPP-chitosan NPs in drug delivery. Other crosslinkers include: sodium sulfate, calcium chloride and cyclodextrins (Mosaiab et al., 2019). With regard to calcium chloride, Riyajan and Nuim (2013) used this ionic crosslinker for the elaboration of carboxymethylcellulose and sodium alginate NPs loaded with curcumin. Interestingly, they showed that the higher the amount of calcium chloride the lower the aggregation of the NPs.

Aimed at overcoming the tendency to aggregation of polysaccharide-based NPs, surfactants are usually employed. Interestingly, natural honey with antibacterial and wound healing features, has been recently used in green ionotropic gelation methods as a stabilizer agent. For instance, Thomas et al. (2020) applied honey for the stabilization of rifampicin loaded pH-sensitive calcium-cross-linked alginate NPs and proved its non-toxicity in wistar rats. Similarly, Geetha et al. (2016) showed the efficacy of honey as a coating agent for the synthesis of calcium-cross-linked alginate NPs with metal-biosorbent properties. The ability of honey to stabilize alginate nanoparticles was confirmed with the spectrophotometry data revealing that only a weak intermolecular attraction force and no chemical interaction between honey and alginate had taken place. Moreover, they demonstrated that the method was also useful for the production of chitosan, albumin and casein NPs. Thus, honey holds great interest for the stabilization of polysaccharide-based NPs with stickiness and aggregation problems acting as a non-toxic natural coating agent with the possibility to offer additional pharmacological effects (Hixon et al., 2019).

3.3. Synthetic Polymer-based nanomedicines

Beyond naturally occurring biopolymers synthetic ones have gained special interest in drug delivery mainly due to its ability to mimic natural biomolecules by multivalent interactions with specific proteins (i.e. lectins). They are nontoxic, able to avoid gut and liver enzymatic degradation, offer efficient targeting properties and can increase the solubility of the system. Some polymers such as polymethylacrylate need organic solvents for the dissolution (i.e. ethyl acetate, trichloroethylene), but more recently certain ionic liquids have been proposed as a greener alternative (Ali et al., 2015). Copolymers, formed by the addition of two polymerizable monomers, as well as the polymerization of copolymers (di-, tri-blocks) have been also proposed as nanomaterials. Fig. 7A displays a summary of the most common synthetic polymers in nanomedicine. Above all, polyethyleneglycol (PEG) is the most used for polymer di-block or triblock elaboration via PEGylation (i.e. PLGA/PEG, PLGA/PEG/PLGA). PEGylation can be used to reduce immunogenicity and toxicity, prolong circulation time, change biodistribution and optimize activities. These features along with their ease for surface modification and their long circulation time make di-block copolymers favorable materials for the design of nanodrug delivery systems. It is worth noting that despite its synthetic nature, these polymers can be obtained via green strategies (i.e. enzyme-assisted ring opening polymerization) from renewable sources (i.e. lactic acid, plant oils) as has been extensively demonstrated by the research group of Kobayashi (2017). Unfortunately, few studies report the origin of the polymeric nanomaterial and thus it is difficult to evaluate the overall greenness of the process.

3.3.1. Production methods

Double emulsion and microfluidics are the most greener approaches for synthetic-polymer based NPs elaboration. Farokhadz and co-workers synthetized the first polymeric (PLA-PEG diblock) drug loaded NPs by means of microfluidics and more specifically via hydrodynamic fo-

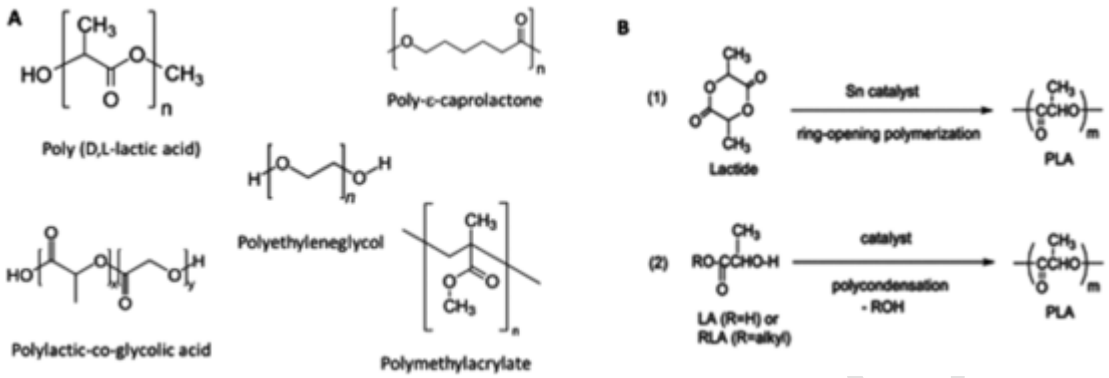

Fig. 7. Main synthetic polymers used in nanomedicine (A) and green synthesis of Poly (D-L-lactic acid) (PLA) (B) (Kobayashi, 2017).

cusing (Karnik et al., 2008). Despite acetonitrile was still needed for the preparation of the polymer solution, the quantity was low (5 w/v %). From then on, their method has been used to produce a wide range of NPs and even the usually problematic lipid-polymer NPs. Accordingly, Morikawa et al. (2018) took advantage of microfluidics mixing to elaborate curcumin-loaded PEGylated PLGA NPs, yielding encapsulation efficiencies of around 50%. Among these microengineered technologies, membrane emulsification has been largely applied for the production of polymeric micro/nanoparticles via dispersion of a polymer-containing organic solution (dispersed phase) into an aqueous solution (continuous phase) while passing through the pores of a membrane (Piacentini et al., 2018). Composition of the phases and operating conditions strictly determine the size, uniformity and reproducibility of the generated droplets as well as the greenness of the method. More specifically, mild conditions have been strictly correlated not only with the reduced energy consumption and waste generation but also with the production of uniform particles (Albisa et al., 2018; Piacentini et al., 2020). Moreover, according to (Albisa et al., 2018), the commonly used organic solvents in the dispersed phase (i.e. chloroform or DCM) can be effectively substituted by the greener and less-toxic solvent ethyl acetate whilst enhancing the uniform distribution of particle sizes and the profitability of the overall production process. Supercritical Fluid Extraction of Emulsions (SFEE) also offers the advantage to form synthetic polymer-based nanoparticles with controlled size and morphology allowing the encapsulation of hydrophilic nor lipophilic compounds. Concerning polyphenols, Tirado et al. (2021) have recently proposed the formation of hydroxytyrosol-loaded polymer nanoparticles via SFEE. The authors employed ethyl acetate as solvent and it was almost totally removed from the final product (<50 ppm) thereby accomplishing with the food and pharmaceutical industry limits (5,000 ppm). However, it should be underlined that SFEE needs an increased amount of CO_2 to remove the organic solvent from the particles and particles are obtained in an aqueous suspension. Therefore, the major limitations of this technique are the need for a recycling process to recover CO_2 together with a post-processing step for particle drying which leads to a non-continuous process hampering its industrial implementation. SAS has been also proposed for the encapsulation of several polyphenols employing ethanol as solvent. However, particles often range from nanometer to some microns (Kurniawansyah et al., 2017; Ozkan et al., 2019). In opposite, SAA, a variation of SAS, allows to effectively control the particle size while producing dried particles. This technology has been successfully applied for the protection of hydrophobic polyphenols such as curcumin and luteolin within poly(vinylpyrrolidone)-NPs while effectively controlling the particle size (below 400 nm) and enhancing the dissolution rate of the bioactive molecules compared to the unprocessed compounds (Adami et al., 2017a; Di Capua et al., 2017b).

On the other hand, Carbone et al. (2015) proposed a novel and simple eco-friendly alternative for the encapsulation of amphiphilic and hydrophilic drugs in aqueous core surface-modified PLA-nanocapsules. Particularly, they used a modified version of the conventional phase inversion temperature (PIT) method which avoided the use of large amounts of surfactants, employed low energy for heating and circumvented organic solvents assistance.

3.4. Lipid-based nanomedicines

Lipid-based drug delivery systems arise as an alternative to overcome the toxicological and allergenic aspects displayed by polymeric and protein based carriers. Thanks to their natural-derived lipid composition they are often endowed with a moderately facilitated regulatory acceptance process as well as biodegradable and biocompatible properties. Moreover, their surface can be engineered to effectively reach the desired targeted tissue/organ (Pyo et al., 2017).

Lipid nanomedicines are commonly classified as a function of its nanostructure and their historical discovery (Fig. 8). It could be said that liposomes are the cornerstone of all other lipid-based nanocarriers (Barenholz, 2012; Weissig, 2017). Early after their discovery, a new generation of cholesterol-based vesicles was developed namely, niosomes. Their amphiphilic character allows the accommodation of a variety of drugs for which they offer a number of advantages ranging from improved oral bioavailability and skin-delivery to enhanced osmotic stability and activity. Nonetheless, their limited shelf life along with their ease for drug expulsion led to the search of novel formulations. Particularly ethosomes together with transethosomes emerged as the second generation, but involve the presence of high quantities of ethanol in the final formulation (25-45%). Afterwards, more complex and even inimitable structures obtained through solvent-free methods were proposed: cubosomes and hexosomes. Despite the apparent competitive edges offered by these sophisticated vesicles, there is still a lack of knowledge on their precise physical properties and cellular behavior, and their scale-up feasibility has been called into question by the industry (Van Tran et al., 2019). In respect to the latter, the incorporation of solvents such as ethanol or ethyl acetate has been proposed to obtain larger volumes (Magana et al., 2019).

On the base of lipid nanoemulsions the first generation of lipid-based carriers, namely, solid lipid nanoparticles (SLN) was developed (Gasco, 1993; Stefan and Rainer, 1994). The reason why they attracted so much interest lies in the fact that they did not require organic solvents for their preparation and were able to remain solid at human body temperature thus exhibiting high in vivo stability. Despite this, the true was that they displayed a lower drug loading capacity than conventional liposomes, mainly because of the restricted solubilization of actives in solid lipids compared to liquid ones. Moreover, cargo expulsion was evidenced upon storage (Pyo et al., 2017). As a

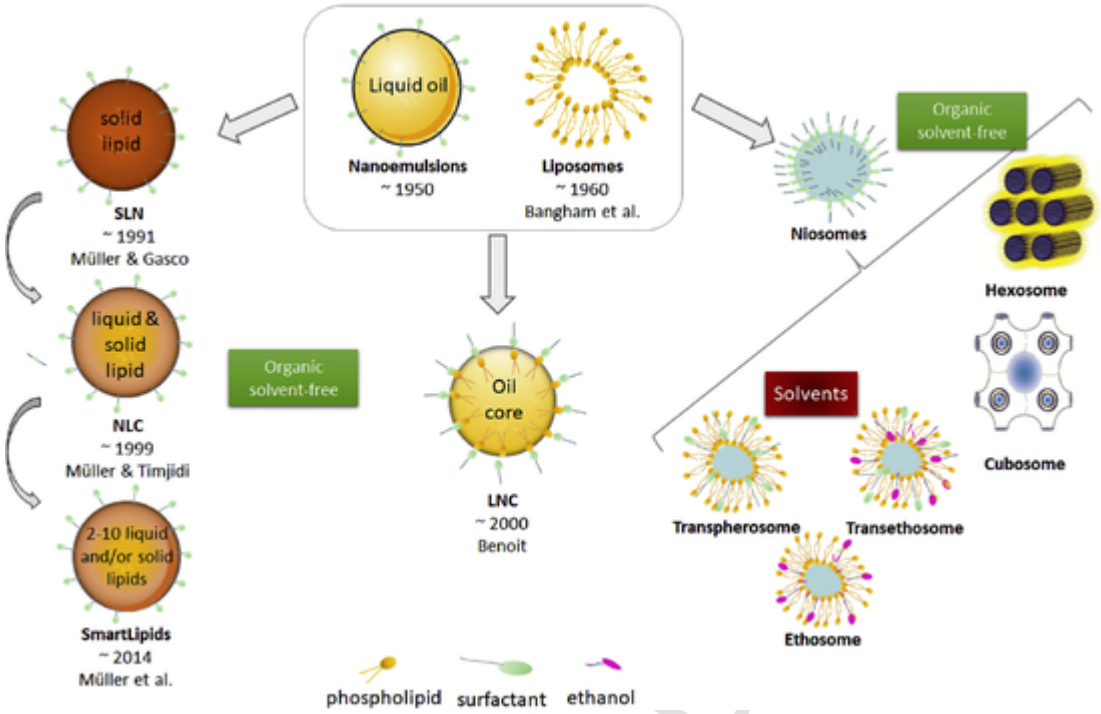

Fig. 8. Summary of lipid based nanoparticles and nanovesicles. Adapted from Rostamabadi et al. (2019).

result, Timjidi and Müller introduced a liquid lipid to form the matrix of the nanocarriers, leading to the invention of the second generation of lipid NPs: Nanostructured Lipid Carriers (NLCs). The philosophy of these formulations was to obtain a less ordered lipid matrix as well as the better solubility of the cargo within the liquid lipid (Müller et al., 2002, 2011). Shortly afterwards, Müller proposed the third generation of lipid NPs which were called as Smart Lipids (Ding et al., 2017). These innovative particles were aimed at further increasing the active loading capacity of lipid nanocarriers by combining up to 10 different solid and/or liquid lipids to form the carrier core. This chaotic lipid core was shown to enhance the storage stability of NLCs at room temperature even up to one year.

In the very early 2000's, the research group of Benoit (France) patented the first core-shell lipid nanostructure and its reverse-phase method of elaboration (Heurtault et al., 2003). The so-called lipid nanocapsules (LNC), still protected by valid patents (Huynh et al., 2009), are endowed with high encapsulation efficiencies (>90%) for several lipophilic and amphiphilic bioactive compounds, and there is no need for organic solvents for their preparation.

3.4.1. Production methods

Ganesan and Narayanasamy (2017) have recently highlighted the possibility to tailor lipid nanocarriers preparation techniques towards green strategies. From an ecofriendly viewpoint, the main limitation of lipid NPs is the essential need of surfactants to keep an emulsion with adequate hydrophilic-lipophilic balance which ultimately determines the size and stability of the particles (Long et al., 2020). Among the examples of surfactants and co-surfactants lecithin and biliary salts are the most used. Alcohols such as butanol have been also proposed but should be discarded due to their toxicity that ultimately humpers the regulatory process of the product (Müller et al., 2000). Otherwise, most of the lipid NPs can be obtained through eco-friendly processes without organic solvents unless indispensable for the dissolution of the active cargo. A summary of solvent-free methods for the elaboration of lipid NPs and nanovesicles is given in Table 4.

3.4.1.1. High pressure homogenization (HPH) Cold and hot HPH have been used for years in the development of SLNs, NLCs and SmartLipids, and the dispersion step has been also conducted by means of ultrasonication (Ding et al., 2017; Gainza et al., 2015; Vairo et al., 2020). Thanks to its versatility, either hydrophilic nor lipophilic cargo can be encapsulated by HPH methods yielding high encapsulation efficiency rates. To enhance the encapsulation efficiency of hydrophilic compounds, water from the aqueous phase can be replaced by liquids in which the drug is low-soluble (i.e. oils or PEG). In line with this, a green HPH method has been proposed for the encapsulation of curcumin (lipophilic and thermosensitive) into NLCs. Briefly, egg phosphatidylcholine (solid lipid) was dispersed in a polyol solution (60°C, 15 min) and homogenized by means of HPH (800-1000 bar, 10 min). Liquid triglycerides were then added and the mixture was passed again by HPH. Finally, the curcumin solution was included and the blend was passed again through HPH keeping temperature below 40°C to avoid thermal degradation of the polyphenol (Akhlaghi et al., 2019). This process offered a high curcumin-loading efficacy (around 70%) along with a narrow size distribution of the particles of around 58 nm which might be further optimized by controlling the number of HPH cycles. Similarly, Alavi et al. (2019) proposed an interesting eco-friendly HPH method that prevented the use of organic solvents and surfactants thanks to the dispersion of the lipid phase into a glycerol or sucrose solution. This approach could be further applied for the green encapsulation of lipophilic polyphenols.

3.4.1.2. Hot melt emulsification Lipophilic and hydrophilic phenolic compounds have been nanoencapsulated by this technology. For instance, Huguet-Casquero et al. (2020b, 2020c) have recently proposed the encapsulation of olive polyphenols (oleuropein) into olive oil based NLCs via hot melt emulsification. Moreover, they proposed a green HPLC method for the quantification of the olive polyphenol, thereby promoting the implementation of Green Nanoscience across the whole lifecycle of the product development process (Huguet-Casquero et al., 2020a). Similarly, hot melt emulsification by means of high shear homogenization in an UltraTurrax followed by ultrasonication

Table 4
Recent ecofriendly and organic solvent-free studies on polyphenol-loading lipid nanoparticles or applicable to polyphenols.

Nanostructure	Method	Lipid matrix	Surfactants	Polyphenol	Encapsulation efficiency	Reference
NLC	HPH	EGP, MCT	Polyol	Curcumin	68%	(Akhlaghi et al., 2019)
NLC	HME-Us	Olive oil, Precirol	T 80, Poloxamer	Oleuropein	99%	(Huguet-Casquero et al., 2020b)
SLN	Membrane contactor	Gelucire 44/14	T 20	none	-	(Charcosset et al., 2005)
Nanoemulsion	Us-emulsification	MCT, oil	T80	Curcumin	-	(Kharat et al., 2020)
Nanoliposomes	Microfluidics + pH-driven method	Sunflower lecithin	PBS	Curcumin, Quercetin, Resveratrol	100%, 54% and 93%	(Peng et al., 2019)
Niosomes	Microfluidic mixer	Cholesterol	T85 or Span 80	Curcumin (ethanol)	60%	(Obeid et al., 2019)
Nanoemulsion	HPH	Palm oil, sunflower oil	T20, T 80	Catechins	-	(Gadkari and Balaraman, 2015)
SLN	Hot homogenization	Stearic acid	NaCas and pectin	Curcumin	-	(Xue et al., 2018)

EGP: egg phosphatidylcholine; TPGS: α-tocopheryl polyethylene glycol 1000 succinate; T80/T20: Tween80/20; NaCas: sodium caseinate; SLN: solid lipid nanoparticle; NLC: Nanostructured lipid carrier; Us: ultrasounds; MCT: medium chain triglycerides; HPH: high pressure homogenization; HME: hot melt emulsification, PBS: phosphate buffer.

has been proposed for the encapsulation of resveratrol in SLNs without the need of organic solvent assistance (Loureiro et al., 2017).As for lipid nanovesicles, their elaboration is generally associated with the need of large amounts of hydroalcoholic solutions. In an attempt to tackle the excessive amount of water used for the elaboration of transpherosomes as well as to reduce the amount of ethanol needed, Manconi et al. (2019) recently proposed a novel eco-scalable method in which the lipid phase (phospholipid, lipophilic flavonoid) is subjected to two sonication assisted hydration steps with ethanol, propylene glycol, glycerol and a minimum amount of water (4%).

3.4.1.3. Microemulsion Several modifications have been proposed during the last year to Gasco's method (Gasco, 1993). For instance, Koziara et al. (2005) used microemulsion precursors (emulsifying wax + surfactant) for oil phase preparation. Interestingly, the low melting points of these precursors allowed to formulate SLNs at mild temperatures and the process was reduced to one step and one container, becoming more amenable for large-scale productions.

3.4.1.4. Coacervation In the specific case of lipid-NPs, this inexpensive method is based on the interaction, at certain temperature, of an acid solution (coacervation solution) with the oil phase (fatty acid alkaline salts) in the presence of a specific amphiphilic polymeric stabilizer. In this way, NPs are formed by simple precipitation after lowering the pH (~ pH 4) and further cooling (~15°C) (Battaglia et al., 2010). Preliminary studies on the Krafft point of the fatty acid alkaline salt are essential to determine the temperature of the process. Lipophilic polyphenol-loaded SLNs have been elaborated by this method, and the possibility to add the lipophilic cargo without the need for organic solvent pre-dispersion has been demonstrated (Battaglia et al., 2010; Clemente et al., 2018; Hao et al., 2012).

3.4.1.5. Phase inversion temperature (PIT) method PIT is the method par excellence for LNC elaboration. Carbone et al. (2016), have recently proposed the application of this approach for the encapsulation of alpha lipoic acid, an amphiphilic natural antioxidant, in lipid based NPs and nanocapsules. Interestingly, they showed that coating with cationic lipids leads to promising delivery systems for the ocular route with high stability (Carbone et al., 2017).

3.4.1.6. SCF technology SFEE, SAA and SAILA methods have been reported mainly for liposome and SLN elaboration. With regard to liposomes a special technique named Supercritical Assisted Liposome Formation (SuperLip) has gained special interest for the encapsulation of hydrosoluble polyphenols. Basically, a droplet of water is formed and further surrounded by one or several double layers of natural phospholipids. Nonetheless, ethanol is used needed for phospholipid feed solution preparation. This method has shown to offer good particle size distributions whereas encapsulation efficiencies might differ from above 90% for theophylline and caffeine, to below 60% for olive polyhenols. Given the variety of lipid nanoformulation processes that totally circumvent the use of organic solvents while effectively encapsulate hydrosoluble polyphenols, the choice for SuperLip technique over others should be properly justified (Trucillo et al., 2018).

3.4.1.7. Spray drying Spray-drying of lipid particles has been largely employed as a drying process of pre-formed lipid NPs (SLN, NLC, LNC) for which the main limitation is the melting of the lipid core. Additionally, when producing lipid nanocarriers via nanospray-drying, an increased amount of organic and hazardous solvents (i.e. chloroform) is usually necessary to dissolve the lipid phase. Conversely, oil encapsulation into protein or dextrin wall materials via spray drying can be tailored free of organic solvents, but this is beyond the scope of this review (Alcántara et al., 2019; Arpagaus et al., 2018). Recently, an interesting work reported a novel organic solvent-free method for SLN preparation via ultrasound-assisted emulsification and further nano-spray drying which offer superior physico-chemical properties than those obtained with organic solvents (Xue et al., 2017). This work again highlights that organic solvent-free processing is not at odds with efficiency. Furthermore, they also overcame the problematic use of surfactants by replacing them with others from natural origin (i.e. pectin and NaCas). Practically, they presented a hybrid method combining the pH-driven unfolding of NaCas with the emulsification of a solid lipid in the presence of a surfactant-aqueous phase. This strategy further served for loading several lipophilic compounds such as curcumin, while circumventing the use of hazardous solvents and non-eco-friendly surfactants (Xue et al., 2018).

3.4.1.8. Electrospray technique The electrospray technique has been proposed for the elaboration of SLN and nanoliposomes. As for polyphenols, Reddy et al. (2019) dissolved 200 mg of a drug-lipid blend (L-phosphatidylcholine, cholesterol, curcumin) in 1 ml of dichloromethane and passed the mixture through a syringe, sprayed it at 15kV in N_2 atmosphere to remove the residual solvent and collected the resulting particles in phosphate buffer. Despite organic solvent was still needed for the preparation of the lipid phase, it was in lower amounts than in conventional solvent-based methods.

3.4.1.9. Membrane contactor SLN, NLC and nanoliposomes can be formed by this method that circumvents the use of organic solvents and increased amounts of surfactants. However, to our knowledge, only seven studies report the encapsulation of bioactive cargo into lipid nano-sized particles by this technology (Charcosset et al., 2005; Cor-

rias and Lai, 2011; D'oria et al., 2009; Jaafar-Maalej et al., 2011; Laouini et al., 2011, 2014; Li et al., 2011), which in fact has been mainly exploited for lipid micro-particle elaboration via microemulsion membrane techniques (Bazzarelli et al., 2017; Piacentini et al., 2019). The rationale for this might lie in the difficulty to obtain particles below ~700 nm which despite being in the nanometer scale are mainly considered microparticles.

3.4.1.10. Microfluidics Fine-tuned liposomes, SLN, niosomes and PEGylated liposomes have been obtained by several microfluidic approaches. In an attempt to tackle the superior cost of these particular systems, Barba et al. (2020) patented a novel device offering semi-continuous and rapid elaboration of large batches of nanoliposomes under mild conditions whilst minimizing energy waste, costs and time. Recently, Peng and collaborators proposed the application of a pH-driven method for the encapsulation of ionizable polyphenols into nanoliposomes by means of a high pressure microfluidizer (~11,700 bar) that allowed the avoidance of surfactants and organic solvents (Peng et al., 2019). Weitz and co-workers also developed a generic, solvent-free one-step microfluidic double emulsion approach to simultaneously accommodate a hydrophilic drug (into the core) and a hydrophobic active (within the shell) with high efficiency that could be further exploited for the encapsulation of hydrophilic phenolic acids (Windbergs et al., 2013). The elaboration of curcumin-loaded niosomes with reduced organic solvent use and greater encapsulation efficiencies (60%) than conventional elaboration methods has been also reported (Obeid et al., 2019).

3.4.2. Stabilization of lipid-NPs

As aforementioned, the addition of surfactants is essential to confer physical stability to the final lipid-NP dispersion and during storage. Aside from this, however, one of the main hurdles for the synthesis of lipid-NPs is the presence of water in the final lipid-NP dispersion that ultimately leads to the growth of microbes and long-term physical instability. There are two alternatives toward the preservation on lipid-NP dispersions: (1) to remove water via drying of the particles, or (2) to maintain the water content and add preservatives. With regard to the former, freeze drying and spray-drying offer the opportunity to obtain dried lipid particles. Whilst spray-drying is limited by the melting point of the lipid dispersion that should be generally > 70°C, when freeze-drying the addition of a cryoprotectant compound to avoid particle aggregation is imperative. Carbohydrates, hydrosoluble sugars and certain polymers have been proposed as good cryoprotectant candidates. Nonetheless, special attention should be given to the choice of the proper cryoprotectant since it often impairs the initial properties of the lipid-NPs. With regard to sugars, trehalose has shown to be the most suitable to preserve the structure of lipid-NPs after lyophilization even up to one year (Beloqui et al., 2016; Moreno-Sastre et al., 2016). Likewise Avicel RC5291, a mixture of polymeric carbohydrates, has shown to effectively favor the shelf-life of NLCs (Varshosaz et al., 2012).

On the other hand, when it is preferred to preserve the lipid-NPs in water dispersion, a preservative agent is added (i.e. benzoic acid, parabens, aromatic alcohols…). However, these agents can significantly alter the physical stability of lipid-NPs (i.e. changes in pH, conductivity modification or surface adsorption leading to particle agglomeration). Ideally, the preservative should be non-charged, as hydrophilic as possible, and should have low affinity to the surface of the particles (Obeidat et al., 2010).

Unfortunately, while several studies can be found in regard to the physical stability of lipid-NPs there are few of them reporting the microbiological quality of the nanoformulations which indeed is a critical factor towards the industrial and clinic scale-up of these nanoparticles.

4. Conclusions and further remarks

Besides regulatory and eco-friendly aspects, the main issue for greening NP preparation concerns their scale up to industrial and clinical settings. In this vein, the application of the six principles of Green Nanoscience (Fig. 1) is proposed as a novel strategy to overcome some of the main challenges of current nanomedicines and nano-food ingredients. Particularly, we have presented the following key aspects that every researcher in the field of nanotechnology should bear in mind:

(1) Use of natural and/or green nanomaterials obtained from renewable by-products if possible.
(2) Chose a nanoformulation method that avoids or minimizes the use of toxic solvents and/or surfactants and/or crosslinkers
(3) Chose minimum operational step based methods for nanoformulation.
(4) Chose mild-conditions based methods if possible.
(5) If stabilizers are needed chose natural and non-toxic ones.
(6) When working with lipophilic drugs, look for alternative solvents for their dissolution/dispersion.
(7) If organic solvents are imperatively needed chose a nanoformulation method that ensures the total removal from the product (i.e. supercritical fluid based methods).

Moreover, despite being beyond the scope of this review, eco-friendly analytical methods to further study the physico-chemical properties of NPs should be also addressed under the umbrella of Green Chemistry. Likewise, sterilization of NPs is a key factor towards the clinical translation of any nanomedicine which impact on the environment and the physical stability of the formulation should be carefully evaluated (Vetten et al., 2014). Naturally, all these recommendations should be followed in line with the special requirements of each drug/bioactive type for an optimal therapeutic efficacy.

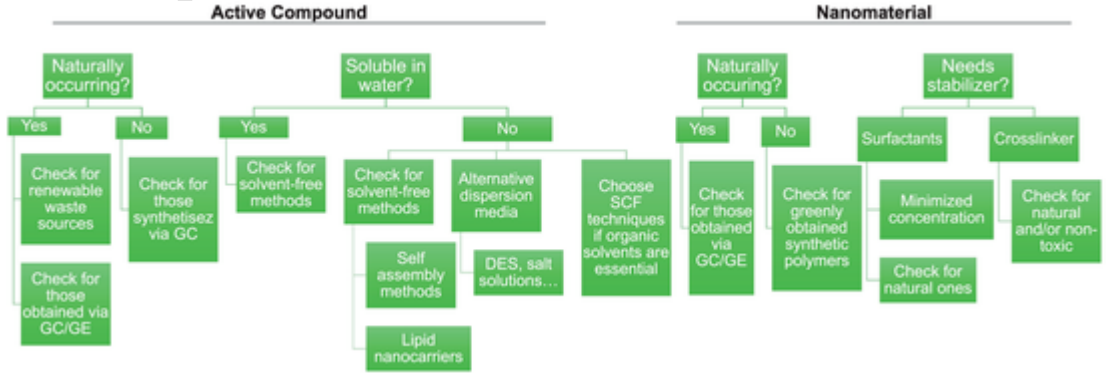

Fig. 9. Decision-tree for green nanoformulations. (GC/GE: Green Chemistry/Green Extraction).

All in all, we have highlighted that the concept and principles of Green Nanoscience must involve the entire lifecycle of NP production. In this line, we strongly hope that the present review could serve as a basic guideline for the choice of the most appropriate nanoformulation method which could promote the future industrialization, clinical scale up and commercialization of the NPs whilst also ensuring a reduced environmental impact. In an attempt to facilitate the application of the Green Nanoscience principles to NP elaboration, a decision tree is given in Fig. 9.

Uncited reference

Prabaharan and Mano, 2005

Acknowledgements

The authors wish to thank the ICTS "NANBIOSIS" and the Drug Formulation Unit (U10) of the CIBER in Bioengineering, Biomaterials, and Nanomedicine (CIBER-BBN) at the University of Basque Country (UPV/EHU).

Funding

This work was supported by the Spanish Ministry of Economy and Competitiveness [grant number DI-15-07513], the R&D projects of BIOSASUN, the University of the Basque Country (UPV/EHU) and the Basque Country Government (Grupos Consolidados) [ref. IT907-16 to J.L.P.].

References

Abouelmagd, S.A., Abd Ellah, N.H., Amen, O., Abdelmoez, A., Mohamed, N.G., 2019. Self-assembled tannic acid complexes for pH-responsive delivery of antibiotics: role of drug-carrier interactions. Int. J. Pharm. 562, 76–85. doi:10.1016/j.ijpharm.2019.03.009.

Adami, R., Di Capua, A., Reverchon, E., 2017. Supercritical Assisted Atomization for the production of curcumin-biopolymer microspheres. Powder Technol. 305, 455–461. doi:10.1016/j.powtec.2016.10.020.

Adami, R., Liparoti, S., Della Porta, G., Del Gaudio, P., Reverchon, E., 2017. Lincomycin hydrochloride loaded albumin microspheres for controlled drug release, produced by Supercritical Assisted Atomization. J. Supercrit. Fluids 119, 203–210. doi:10.1016/j.supflu.2016.09.017.

Akbari-Alavijeh, S., Shaddel, R., Jafari, S.M., 2020. Encapsulation of food bioactives and nutraceuticals by various chitosan-based nanocarriers. Food Hydrocoll. 105, 105774. doi:10.1016/j.foodhyd.2020.105774.

Akhlaghi, S., Rabbani, S., Alavi, S., Alinaghi, A., Radfar, F., Dadashzadeh, S., Haeri, A., 2019. Green formulation of curcumin loaded lipid-based nanoparticles as a novel carrier for inhibition of post-angioplasty restenosis. Mater. Sci. Eng. C 105, 110037. doi:10.1016/j.msec.2019.110037.

Alavi, S., Akhlaghi, S., Dadashzadeh, S., Haeri, A., 2019. Green formulation of triglyceride/phospholipid-based nanocarriers as a novel vehicle for oral coenzyme Q10 delivery. J. Food Sci. 84, 2572–2583. doi:10.1111/1750-3841.14763.

Albisa, A., Piacentini, E., Arruebo, M., Sebastian, V., Giorno, L., 2018. Sustainable production of drug-loaded particles by membrane emulsification. ACS Sustain. Chem. Eng. 6, 6663–6674. doi:10.1021/acssuschemeng.8b00401.

Alcántara, M.A., de Lima, A.E.A., Braga, A.L.M., Tonon, R.V., Galdeano, M.C., Mattos, M. da C., BrĀgida Iraidy Santa, A, Rosenhaim, R., Santos, N.A. dos, Cordeiro, A.M.T. de M, 2019. Influence of the emulsion homogenization method on the stability of chia oil microencapsulated by spray drying. Powder Technol. 354, 877–885. doi:10.1016/j.powtec.2019.06.026.

Ali, U., Karim, K.J.B.A., Buang, N.A., 2015. A review of the properties and applications of poly (Methyl Methacrylate) (PMMA). Polym. Rev. 55, 678–705. doi:10.1080/15583724.2015.1031377.

Anastas, P.T., Warner, J.C., 2010. Green chemistry: principles and practice. Chem. Soc. Rev. 39, 301–312. doi:10.1039/B918763B.

Arpagaus, C., Collenberg, A., Rütti, David, Assadpour, E., Jafari, S.M., 2018. Nano spray drying for encapsulation of pharmaceuticals. Int. J. Pharm. 546, 194–214. doi:10.1016/j.ijpharm.2018.05.037.

Baldino, L., Della, G., Sesti, L., Reverchon, E., Adami, R., 2018. The journal of supercritical fluids concentrated oleuropein powder from olive leaves using alcoholic extraction and supercritical CO 2 assisted extraction graphical abstract. J. Supercrit. Fluids 133, 65–69. doi:10.1016/j.supflu.2017.09.026.

Barba, A.A., Dalmoro, A., Bochicchio, S., De Simone, V., Caccavo, D., Iannone, M., Lamberti, G., 2020. Engineering approaches for drug delivery systems production and characterization. Int. J. Pharm. 581, 119267. doi:10.1016/j.ijpharm.2020.119267.

Barclay, T.G., Day, C.M., Petrovsky, N., Garg, S., 2019. Review of polysaccharide particle-based functional drug delivery. Carbohydr. Polym. 221, 94–112. doi:10.1016/j.carbpol.2019.05.067.

Barenholz, Y., 2012. Doxil® — The first FDA-approved nano-drug: lessons learned J. Control. Release; Past, Curr. Futur. Appl. liposomes - Gd. Challenges Oppor. Nanomedicine 160, 117–134 (Chezy). doi:10.1016/j.jconrel.2012.03.020.

Battaglia, L., Gallarate, M., Cavalli, R., Trotta, M., 2010. Solid lipid nanoparticles produced through a coacervation method. J. Microencapsul. 27, 78–85. doi:10.3109/02652040903031279.

Bazzarelli, F., Piacentini, E., Giorno, L., 2017. Biophenols-loaded solid lipid particles (SLPs) development by membrane emulsification. J. Memb. Sci. 541, 587–594. doi:10.1016/j.memsci.2017.07.029.

Beloqui, A., Solinís, M.Á., Rodríguez-Gascón, A., Almeida, A.J., Préat, V., 2016. Nanostructured lipid carriers: promising drug delivery systems for future clinics. Nanomedicine 12, 143–161. doi:10.1016/j.nano.2015.09.004.

Calvo, P., Remuñán-López, C., Vila-Jato, J., Alonso, M.J., 1997. Novel hydrophilic chitosan-polyethylene oxide nanoparticles as protein carriers. J. Appl. Polym. Sci. 63, 125–132. doi:10.1002/(SICI)1097-4628(19970103)63:1<125::AID-APP13>3.0.CO;2-4.

Carbone, C., Musumeci, T., Lauro, M.R., Puglisi, G., 2015. Eco-friendly aqueous core surface-modified nanocapsules. Colloids Surfaces B Biointerfaces 125, 190–196. doi:10.1016/j.colsurfb.2014.11.038.

Carbone, C., Manno, D., Serra, A., Musumeci, T., Pepe, V., Tisserand, C., Puglisi, G., 2016. Innovative hybrid vs polymeric nanocapsules: the influence of the cationic lipid coating on the "4S". Colloids Surfaces B Biointerfaces 141, 450–457. doi:10.1016/j.colsurfb.2016.02.002.

Carbone, C., Arena, E., Pepe, V., Prezzavento, O., Cacciatore, I., Turkez, H., Marrazzo, A., Di Stefano, A., Puglisi, G., 2017. Nanoencapsulation strategies for the delivery of novel bifunctional antioxidant/ĪƒĪ¼1 selective ligands. Colloids Surfaces B Biointerfaces 155, 238–247. doi:10.1016/j.colsurfb.2017.04.016.

Cassano, A., De Luca, G., Conidi, C., Drioli, E., 2017. Effect of polyphenols-membrane interactions on the performance of membrane-based processes. A review. Coord. Chem. Rev. 351, 45–75. doi:10.1016/j.ccr.2017.06.013.

Catalán-Latorre, A., Pleguezuelos-Villa, M., Castangia, I., Manca, M.L., Caddeo, C., Nácher, A., Díez-Sales, O., Peris, J.E., Pons, R.B., Escribano-Ferrer, E., Fadda, A.M., Manconi, M., 2018. Nutriosomes: prebiotic delivery systems combining phospholipids, a soluble dextrin and curcumin to counteract intestinal oxidative stress and inflammation. Nanoscale 10 (4), 1957–1969 JID - 101525249. doi:10.1039/c7nr05929a.

Chakravarty, P., Famili, A., Nagapudi, K., Al-Sayah, M., 2019. Using supercritical fluid technology as a green alternative during the preparation of drug delivery systems. Pharmaceutics 11. doi:10.3390/pharmaceutics11120629.

Chapeau, A.L., Tavares, G.M., Hamon, P., Croguennec, T., Poncelet, D., Bouhallab, S., 2016. Spontaneous co-assembly of lactoferrin and β-lactoglobulin as a promising biocarrier for vitamin B9. Food Hydrocoll. 57, 280–290. doi:10.1016/j.foodhyd.2016.02.003.

Charcosset, C., El-Harati, A., Fessi, H., 2005. Preparation of solid lipid nanoparticles using a membrane contactor. J. Control. Release 108, 112–120. doi:10.1016/j.jconrel.2005.07.023.

Chemat, F., Vian, M.A., Cravotto, G., 2012. Green extraction of natural products: concept and principles. Int. J. Mol. Sci. 13, 8615–8627. doi:10.3390/ijms13078615.

Chemat, F., Abert-Vian, M., Fabiano-Tixier, A.S., Strube, J., Uhlenbrock, L., Gunjevic, V., Cravotto, G., 2019. Green extraction of natural products. Origins, current status, and future challenges. TrAC - Trends Anal. Chem. 118, 248–263. doi:10.1016/j.trac.2019.05.037.

Chemat, F., Abert Vian, M., Fabiano-Tixier, A., Nutrizio, M., Jambrak, Anet Režek, Munekata, P.E.S., Lorenzo, J.M., Barba, F.J., Binello, A., Cravotto, G., 2020. A review of sustainable and intensified techniques for extraction of food and natural products. Green Chem. 22, 2325–2353. doi:10.1039/C9GC03878G.

Chen, Y.C., Yu, S.H., Tsai, G.J., Tang, D.W., Mi, F.L., Peng, Y.P., 2010. Novel technology for the preparation of self-assembled catechin/gelatin nanoparticles and their characterization. J. Agric. Food Chem. 58, 6728–6734. doi:10.1021/jf1005116.

Chiesa, E., Dorati, R., Pisani, S., Conti, B., Bergamini, G., Modena, T., Genta, I., 2018. The microfluidic technique and the manufacturing of polysaccharide nanoparticles. Pharmaceutics 10. doi:10.3390/pharmaceutics10040267.

Clemente, N., Ferrara, B., Gigliotti, L.C., Boggio, E., Capucchio, T.M., Biasibetti, E., Schiffer, D., Mellai, M., Annovazzi, L., Cangemi, L., Muntoni, E., Miglio, G., Dianzani, U., Battaglia, L., Dianzani, C., 2018. Solid lipid nanoparticles carrying temozolomide for melanoma treatment. Preliminary In Vitro and In Vivo studies. Int. J. Mol. Sci.. doi:10.3390/ijms19020255.

Collins, T.J., 1995. Introducing green chemistry in teaching and research. J. Chem. Educ. 72, 965. doi:10.1021/ed072p965.

Conidi, C., Cassano, A., Caiazzo, F., Drioli, E., 2017. Separation and purification of phenolic compounds from pomegranate juice by ultrafiltration and nanofiltration membranes. J. Food Eng. 195, 1–13. doi:10.1016/j.jfoodeng.2016.09.017.

Conidi, C., Drioli, E., Cassano, A., 2018. Membrane-based agro-food production processes for polyphenol separation, purification and concentration. Curr. Opin. Food Sci. 23, 149–164. doi:10.1016/j.cofs.2017.10.009.

Corrias, F., Lai, F., 2011. New methods for lipid nanoparticles preparation. Recent Patents Drug Deliv. Formul. 5, 201–213. doi:10.2174/187221111797200597.

Costa, C., Casimiro, T., Aguiar-Ricardo, A., 2018. Optimization of supercritical CO2-assisted atomization: phase behavior and design of experiments. J. Chem. Eng. Data 63, 885–896. doi:10.1021/acs.jced.7b00820.

Croguennec, T., Tavares, G.M., Bouhallab, S., 2017. Heteroprotein complex coacervation: A generic process. Adv. Colloid Interface Sci. 239, 115–126. doi:10.1016/j.cis.2016.06.009.

Cvetanović, A., Švarc-Gajić, J., Gašić, U., Tešić, Ž., Zengin, G., Zeković, Z., Đurović, S., 2017. Isolation of apigenin from subcritical water extracts: optimization of the process. J. Supercrit. Fluids 120, 32–42. doi:10.1016/j.supflu.2016.10.012.

D'oria, C., Charcosset, C., Barresi, A.A., Fessi, H., 2009. Preparation of solid lipid particles by membrane emulsification-Influence of process parameters. Colloids Surfaces A Physicochem. Eng. Asp. 338, 114–118. doi:10.1016/j.colsurfa.2009.01.003.

Dai, L., Zhou, H., Wei, Y., Gao, Y., McClements, D.J., 2019. Curcumin encapsulation in zein-rhamnolipid composite nanoparticles using a pH-driven method. Food Hydrocoll. 93, 342–350. doi:10.1016/j.foodhyd.2019.02.041.

Das, R.P., Singh, B.G., Kunwar, A., Ramani, M.V., Subbaraju, G.V., Hassan, P.A., Priyadarsini, K.I., 2017. Tuning the binding, release and cytotoxicity of hydrophobic drug by Bovine Serum Albumin nanoparticles: influence of particle size. Colloids Surfaces B Biointerfaces 158, 682–688. doi:10.1016/j.colsurfb.2017.07.048.

Das, R.P., Gandhi, V.V., Singh, B.G., Kunwar, A., Kumar, N.N., Priyadarsini, K.I., 2019. Preparation of albumin nanoparticles: Optimum size for cellular uptake of entrapped drug (Curcumin). Colloids Surfaces A Physicochem. Eng. Asp. 567, 86–95. doi:10.1016/j.colsurfa.2019.01.043.

Das, R.P., Singh, B.G., Kunwar, A., 2020. Preparation of a size selective nanocomposite through temperature assisted co-assembly of gelatin and pluronic F127 for passive targeting of doxorubicin. Biomater. Sci.. doi:10.1039/d0bm00725k.

Davidov-Pardo, G., Joye, I.J., McClements, D.J., 2015. Encapsulation of resveratrol in biopolymer particles produced using liquid antisolvent precipitation. Part 1: Preparation and characterization. Food Hydrocoll. 45, 309–316. doi:10.1016/j.foodhyd.2014.11.023.

de Jesus, A.L.T., Cristianini, M., dos Santos, N.M., Maróstica Júnior, M.R., 2020. Effects of high hydrostatic pressure on the microbial inactivation and extraction of bioactive compounds from açaí (Euterpe oleracea Martius) pulp. Food Res. Int. 130, 108856.

de la Guardia, M., 2014. The challenges of green nanotechnology. Bioimpacts 4, 1–2. doi:10.5681/bi.2014.009.

de Santana Magalhães, F., de Souza Martins Sá, M., Luiz Cardoso, V., Hespanhol Miranda Reis, M., 2019. Recovery of phenolic compounds from pequi (Caryocar brasiliense Camb.) fruit extract by membrane filtrations: comparison of direct and sequential processes. J. Food Eng. 257, 26–33. doi:10.1016/j.jfoodeng.2019.03.025.

Dey, J., Kumar, S., Aswal, V.K., Panicker, L.V., Ismail, K., Hassan, P.A., 2015. Effect of sodium salicylate and sodium deoxycholate on fibrillation of bovine serum albumin: comparison of fluorescence, SANS and DLS techniques. Phys. Chem. Chem. Phys. 17, 15442–15451. doi:10.1039/c5cp01666e.

Di Capua, A., Adami, R., Izzo, L., Reverchon, E., 2017. Luteolin/dextran-FITC fluorescent microspheres produced by supercritical assisted atomization. J. Supercrit. Fluids 130, 97–104. doi:10.1016/j.supflu.2017.07.034.

Di Capua, A., Adami, R., Reverchon, E., 2017. Production of luteolin/biopolymer microspheres by supercritical assisted atomization. Ind. Eng. Chem. Res. 56, 4334–4340. doi:10.1021/acs.iecr.7b00211.

Ding, Y., Pyo, S.M., Müller, R.H., 2017. SmartLipids® as third solid lipid nanoparticle generation - stabilization of retinol for dermal application. Pharmazie 72, 728–735. doi:10.1691/ph.2017.7016.

Elzoghby, A., Freag, M., Mamdouh, H., Elkhodairy, K., 2017. Zein-based nanocarriers as potential natural alternatives for drug and gene delivery: focus on cancer therapy. Curr. Pharm. Des. 23, 5261–5271. doi:10.2174/1381612823666170622111250.

Emami, S., Shayanfar, A., 2020. Deep eutectic solvents for pharmaceutical formulation and drug delivery applications. Pharm. Dev. Technol. 25, 779–796. doi:10.1080/10837450.2020.1735414.

Fathi, M., Martín, Á., McClements, D.J., 2014. Nanoencapsulation of food ingredients using carbohydrate based delivery systems. Trends Food Sci. Technol. 39, 18–39. doi:10.1016/j.tifs.2014.06.007.

Food and Drug Administration. Centre for Drug Evaluation and Researh (CDER), 2019. Quality considerations for conitnuous manufacturing. In: Guidance for Industry. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/quality-considerations-continuous-manufacturing (Accessed on July 17,2020).

Franco, D., Munekata, P.E.S., Agregán, R., Bermúdez, R., López-Pedrouso, M., Pateiro, M., Lorenzo, J.M., 2020. Application of pulsed electric fields for obtaining antioxidant extracts from fish residues. Antioxidants 9. doi:10.3390/antiox9020090.

Fu, Q., Sun, J., Zhang, W., Sui, X., Yan, Z., He, Z., 2009. Nanoparticle albumin-bound (NAB) technology is a promising method for anti-cancer drug delivery. Recent patents anti-cancer drug Discov. JID -101266081. doi:10.2174/157489209789206869.

Fujimoto, M., Hara, M., Hayashi, T., Furuta, M., 2010. Effect of heating process on the formation of nanoparticles of elastin model polypeptide, (GVGVP)251, by gamma-ray crosslinking. Polym. Bull. 64, 707–716. doi:10.1007/s00289-009-0220-2.

Gadkari, P.V., Balaraman, M., 2015. Extraction of catechins from decaffeinated green tea for development of nanoemulsion using palm oil and sunflower oil based lipid carrier systems. J. Food Eng. 147, 14–23. doi:10.1016/j.jfoodeng.2014.09.027.

Gainza, G., Chu, W.S., Guy, R.H., Pedraz, J.L., Hernandez, R.M., Delgado-Charro, B., Igartua, M., 2015. Development and in vitro evaluation of lipid nanoparticle-based dressings for topical treatment of chronic wounds. Int. J. Pharm. 490, 404–411. doi:10.1016/j.ijpharm.2015.05.075.

Ganesan, P., Narayanasamy, D., 2017. Lipid nanoparticles: Different preparation techniques, characterization, hurdles, and strategies for the production of solid lipid nanoparticles and nanostructured lipid carriers for oral drug delivery. Sustain. Chem. Pharm. 6, 37–56. doi:10.1016/j.scp.2017.07.002.

Ganguly, R., Kumar, S., Kunwar, A., Nath, S., Sarma, H.D., Tripathi, A., Verma, G., Chaudhari, D.P., Aswal, V.K., Melo, J.S., 2020. Structural and therapeutic properties of curcumin solubilized pluronic F127 micellar solutions and hydrogels. J. Mol. Liq. 314, 113591. doi:10.1016/j.molliq.2020.113591.

Gasco, M.R., 1993. Method for Producing Solid Lipid Microspheres Having a Narrow Size Distribution. US5250236A.

Geetha, P., Latha, M.S., Pillai, S.S., Deepa, B., Santhosh Kumar, K., Koshy, M., 2016. Green synthesis and characterization of alginate nanoparticles and its role as a biosorbent for Cr(VI) ions. J. Mol. Struct. 1105, 54–60. doi:10.1016/j.molstruc.2015.10.022.

Giacobbo, A., Meneguzzi, A., Bernardes, A.M., de Pinho, M.N., 2017. Pressure-driven membrane processes for the recovery of antioxidant compounds from winery effluents. J. Clean. Prod. 155, 172–178. doi:10.1016/j.jclepro.2016.07.033.

Gligor, O., Mocan, A., Moldovan, C., Locatelli, M., Crișan, G., Ferreira, I.C.F.R., 2019. Enzyme-assisted extractions of polyphenols: a comprehensive review. Trends Food Sci. Technol. 88, 302–315. doi:10.1016/j.tifs.2019.03.029.

Gonzatti, M.B., Sousa, M.E.P., Tunissi, A.S., Mortara, R.A., de Oliveira, A.M., Pereira Cerize, N.N., Keller, A. de C., 2019. Nano spray dryer for vectorizing α-galactosylceramide in polymeric nanoparticles: a single step process to enhance invariant Natural Killer T lymphocyte responses. Int. J. Pharm. 565, 123–132. doi:10.1016/j.ijpharm.2019.05.013.

Gou, S., Chen, Q., Liu, Y., Zeng, L., Song, H., Xu, Z., Kang, Y., Li, C., Xiao, B., 2018. Green fabrication of Ovalbumin nanoparticles as natural polyphenol carriers for ulcerative colitis therapy. ACS Sustain. Chem. Eng. 6 (10), 12658–12667. doi:10.1021/acssuschemeng.8b01613.

Guo, Y., Harris, P., Kaur, A., Pastrana, L., Jauregi, P., 2017. Characterisation of β-lactoglobulin nanoparticles and their binding to caffeine. Food Hydrocoll. 71, 85–93. doi:10.1016/j.foodhyd.2017.04.027.

Ha, E.S., Sim, W.Y., Lee, S.K., Jeong, J.S., Kim, J.S., Baek, I.H., Choi, D.H., Park, H., Hwang, S.J., Kim, M.S., 2019. Preparation and evaluation of resveratrol-loaded composite nanoparticles using a supercritical fluid technology for enhanced oral and skin delivery. Antioxidants 8. doi:10.3390/antiox8110554.

Ha, E.S., Park, H., Lee, S.K., Sim, W.Y., Jeong, J.S., Baek, I.H., Kim, M.S., 2020. Pure Trans-resveratrol nanoparticles prepared by a supercritical antisolvent process using alcohol and dichloromethane mixtures: effect of particle size on dissolution and bioavailability in rats. Antioxidants 9. doi:10.3390/antiox9040342.

Hao, J., Wang, F., Wang, X., Zhang, D., Bi, Y., Gao, Y., Zhao, X., Zhang, Q., 2012. Development and optimization of baicalin-loaded solid lipid nanoparticles prepared by coacervation method using central composite design. Eur. J. Pharm. Sci. 47, 497–505. doi:10.1016/j.ejps.2012.07.006.

Heimbuck, A.M., Priddy-Arrington, T., Padgett, M.L., Llamas, C.B., Barnett, H.H., Bunnell, B.A., Caldorera-Moore, M., 2019. Development of responsive Chitosan–Genipin hydrogels for the treatment of wounds. ACS Appl. Bio Mater. 2, 2879–2888. doi:10.1021/acsabm.9b00266.

Hendrawan, Y., Larasati, R., Wibisono, Y., Umam, C., Sutan, S.M., Choviya Hawa, L., 2019. Extraction of phenol and antioxidant compounds from kepok banana skin with PEF Pre-treatment. IOP Conf. Ser. Earth Environ. Sci. 305, 12065. doi:10.1088/1755-1315/305/1/012065.

Heurtault, B., Saulnier, P., Benoit, J.P., Proust, J.E., Pech, B., Richard, J., 2003. Lipid Nanocapsules, Preparation Process and use as Medicine.

Hilali, S., Fabiano-Tixier, A., Ruiz, K., Hejjaj, A., Ait Nouh, F., Idlimam, A., Bily, A., Mandi, L., Chemat, F., 2019. Green extraction of essential oils, polyphenols, and pectins from orange peel employing solar energy: toward a zero-waste biorefinery. ACS Sustain. Chem. Eng. 7, 11815–11822. doi:10.1021/acssuschemeng.9b02281.

Hixon, K.R., Klein, R.C., Eberlin, C.T., Linder, H.R., Ona, W.J., Gonzalez, H., Sell, S.A., 2019. A critical review and perspective of honey in tissue engineering and clinical wound healing. Adv. Wound Care 8, 403–415. doi:10.1089/wound.2018.0848.

Hu, D., Lin, C., Liu, L., Li, S., Zhao, Y., 2012. Preparation, characterization, and in vitro release investigation of lutein/zein nanoparticles via solution enhanced dispersion by supercritical fluids. J. Food Eng. 109, 545–552. doi:10.1016/j.jfoodeng.2011.10.025.

Huguet-Casquero, Amaia, López-Méndez, T.B., Gainza, E., Pedraz, J.L., 2020. Development and validation of an eco-friendly HPLC-DAD method for the determination of oleuropein and its applicability to several matrices: olive oil, olive leaf extracts and nanostructured lipid carriers. Green Chem. 22, 3495–3505. doi:10.1039/D0GC00965B.

Huguet-Casquero, A., Moreno-Sastre, M., López-Méndez, T.B., Gainza, E., Pedraz, J.L., 2020. Encapsulation of oleuropein in nanostructured lipid carriers: Biocompatibility and antioxidant efficacy in lung epithelial cells. Pharmaceutics 12. doi:10.3390/pharmaceutics12050429.

Huguet-Casquero, A., Xu, Y., Gainza, E., Pedraz, J.L., Beloqui, A., 2020. Oral delivery of oleuropein-loaded lipid nanocarriers alleviates inflammation and oxidative stress in acute colitis. Int. J. Pharm. 586. doi:10.1016/j.ijpharm.2020.119515.

Hutchison, J.E., 2016. The road to sustainable nanotechnology: challenges, progress and opportunities. ACS Sustain. Chem. Eng. 4, 5907–5914. doi:10.1021/acssuschemeng.6b02121.

Huynh, N.T., Passirani, C., Saulnier, P., Benoit, J.P., 2009. Lipid nanocapsules: a new platform for nanomedicine. Int. J. Pharm. Challenges Nanotechnol. Deliv. Imaging 379, 201–209. doi:10.1016/j.ijpharm.2009.04.026.

Izadi, Z., Divsalar, A., Saboury, A.A., Sawyer, L., 2016. β-lactoglobulin-pectin nanoparticle-based oral drug delivery system for potential treatment of colon cancer. Chem. Biol. drug Des. 88, 209–216 JID - 101262549. doi:10.1111/cbdd.12748.

Jaafar-Maalej, C., Charcosset, C., Fessi, H., 2011. A new method for liposome preparation using a membrane contactor. J. Liposome Res. 21, 213–220. doi:10.3109/08982104.2010.517537.

Janes, K.A., Calvo, P., Alonso, M.J., 2001. Polysaccharide colloidal particles as delivery systems for macromolecules. Adv. Drug Deliv. Rev. Nanoparticulate Syst. Improv. Drug Deliv. 47, 83–97. doi:10.1016/S0169-409X(00)00123-X.

Jia, C., Cao, D., Ji, S., Zhang, X., Muhoza, B., 2020. Tannic acid-assisted cross-linked nanoparticles as a delivery system of eugenol: The characterization, thermal degradation and antioxidant properties. Food Hydrocoll. 104, 105717. doi:10.1016/j.foodhyd.2020.105717.

Juneidi, I., Hayyan, M., Hashim, M.A., 2018. Intensification of biotransformations using deep eutectic solvents: overview and outlook. Process Biochem. 66, 33–60. doi:10.1016/j.procbio.2017.12.003.

Kamal, I., Allaf, K., 2013. Optimization of instant controlled pressure drop dic-assisted-solvent extraction of total phenols of green coffee beans. J. Food Stud. 2 (42), 61. doi:10.5296/jfs.v2i1.2013.

Kankala, R.K., Chen, B.Q., Liu, C.G., Tang, H.X., Wang, S.B., Chen, A.Z., 2018. Solution-enhanced dispersion by supercritical fluids: an ecofriendly nanonization approach for processing biomaterials and pharmaceutical compounds. Int. J. Nanomed. JID - 101263847. doi:10.2147/IJN.S166124.

Karnik, R., Gu, F., Basto, P., Cannizzaro, C., Dean, L., Kyei-Manu, W., Langer, R., Farokhzad, O.C., 2008. Microfluidic platform for controlled synthesis of polymeric nanoparticles. Nano Lett. 8, 2906–2912. doi:10.1021/nl801736q.

Khalil, I.A.H., Arida, I.A., Ahmed, M., 2020. Introductory chapter: overview on nanomedicine market. In: Khalil, I.A.H. (Ed.), Current and Future Aspects of Nanomedicine, Current and Future Aspects of Nanomedicine. IntechOpen, pp. 1–8. doi:10.5772/intechopen.91890.

Kharat, M., Zhang, G., McClements, D.J., 2018. Stability of curcumin in oil-in-water emulsions: impact of emulsifier type and concentration on chemical degradation. Food Res. Int. 111, 178–186. doi:10.1016/j.foodres.2018.05.021.

Kharat, M., Skrzynski, M., Decker, E.A., McClements, D.J., 2020. Enhancement of chemical stability of curcumin-enriched oil-in-water emulsions: impact of antioxidant type and concentration. Food Chem. 320, 126653. doi:10.1016/j.foodchem.2020.126653.

Kim, D.-G., Jeong, Y.-I., Choi, C., Roh, S.-H., Kang, S.-K., Jang, M.-K., Nah, J.-W., 2006. Retinol-encapsulated low molecular water-soluble chitosan nanoparticles. Int. J. Pharm. 319, 130–138. doi:10.1016/j.ijpharm.2006.03.040.

Kim, Y.N., Kwon, H.J., Lee, D.U., 2019. Effects of pulsed electric field (PEF) treatment on physicochemical properties of Panax ginseng. Innov. Food Sci. Emerg. Technol. 58, 102232. doi:10.1016/j.ifset.2019.102232.

Kobayashi, S., 2017. Green polymer chemistry: new methods of polymer synthesis using renewable starting materials. Struct. Chem. 28, 461–474. doi:10.1007/s11224-016-0861-3.

Koziara, J.M., Oh, J.J., Akers, W.S., Ferraris, S.P., Mumper, R.J., 2005. Blood compatibility of cetyl alcohol/polysorbate-based nanoparticles. Pharm. Res. JID - 8406521. doi:10.1007/s11095-005-7547-7.

Kudłak, B., Owczarek, K., Namieśnik, J., 2015. Selected issues related to the toxicity of ionic liquids and deep eutectic solvents—a review. Environ. Sci. Pollut. Res. 22, 11975–11992. doi:10.1007/s11356-015-4794-y.

Lai, F., Caddeo, C., Manca, M.L., Manconi, M., Sinico, C., Fadda, A.M., 2020. What's new in the field of phospholipid vesicular nanocarriers for skin drug delivery. Int. J. Pharm. 583, 119398. doi:10.1016/j.ijpharm.2020.119398.

Laouini, A., Jaafar-Maalej, C., Sfar, S., Charcosset, C., Fessi, H., 2011. Liposome preparation using a hollow fiber membrane contactor - application to spironolactone encapsulation. Int. J. Pharm. 415, 53–61. doi:10.1016/j.ijpharm.2011.05.034.

Laouini, A., Andrieu, V., Vecellio, L., Fessi, H., Charcosset, C., 2014. Characterization of different vitamin e carriers intended for pulmonary drug delivery. Int. J. Pharm. 471, 385–390. doi:10.1016/j.ijpharm.2014.05.062.

Li, Z., Gu, L., 2011. Effects of mass ratio, pH, temperature, and reaction time on fabrication of partially purified pomegranate Ellagitannin-Gelatin Nanoparticles. J. Agric. Food Chem. 59, 4225–4231. doi:10.1021/jf200024d.

Li, S., Zhao, Y., 2017. Preparation of zein nanoparticles by using solution-enhanced dispersion with supercritical CO(2) and elucidation with computational fluid dynamics. Int. J. Nanomed. 12, 3485–3494. doi:10.2147/IJN.S135239.

Li, Y., Fessi, H., Charcosset, C., 2011. Preparation of indomethacin-loaded lipid particles by membrane emulsification. Adv. Sci. Lett. 4, 591–595. doi:10.1166/asl.2011.1245.

Li, X., Maldonado, L., Malmr, M., Rouf, T.B., Hua, Y., Kokini, J., 2019. Development of hollow kafirin-based nanoparticles fabricated through layer-by-layer assembly as delivery vehicles for curcumin. Food Hydrocoll. 96, 93–101. doi:10.1016/j.foodhyd.2019.04.042.

Liang, J., Yan, H., Yang, H.-J., Kim, H.W., Wan, X., Lee, J., Ko, S., 2016. Synthesis and controlled-release properties of chitosan/β-Lactoglobulin nanoparticles as carriers for oral administration of epigallocatechin gallate. Food Sci. Biotechnol. 25, 1583–1590. doi:10.1007/s10068-016-0244-y.

Lin, Y.-H., Lu, K.-Y., Tseng, C.-L., Wu, J.-Y., Chen, C.-H., Mi, F.-L., 2017. Development of genipin-crosslinked fucoidan/chitosan-N-arginine nanogels for preventing Helicobacter infection. Nanomedicine 12, 1491–1510. doi:10.2217/nnm-2017-0055.

Liu, Z., Jiao, Y., Wang, Y., Zhou, C., Zhang, Z., 2008. Polysaccharides-based nanoparticles as drug delivery systems. Adv. Drug Deliv. Rev. 60, 1650–1662 2008 Ed. Collect. doi:10.1016/j.addr.2008.09.001.

Liu, F., Zhang, S., Li, J., McClements, D.J., Liu, X., 2018. Recent development of lactoferrin-based vehicles for the delivery of bioactive compounds: Complexes, emulsions, and nanoparticles. Trends Food Sci. Technol. 79, 67–77. doi:10.1016/j.tifs.2018.06.013.

Liu, L.-L., Liu, P.-Z., Li, X.-T., Zhang, N., Tang, C.-H., 2019. Novel Soy β-conglycinin core-shell nanoparticles as outstanding ecofriendly nanocarriers for curcumin. J. Agric. Food Chem. 67, 6292–6301. doi:10.1021/acs.jafc.8b05822.

Long, Y., Huang, W., Wang, Q., Yang, G., 2020. Green synthesis of garlic oil nanoemulsion using ultrasonication technique and its mechanism of antifungal action against Penicillium italicum. Ultrason. Sonochem. 64, 104970. doi:10.1016/j.ultsonch.2020.104970.

López-Gámez, G., Elez-Martínez, P., Martín-Belloso, O., Soliva-Fortuny, R., 2020. Enhancing phenolic content in carrots by pulsed electric fields during post-treatment time: Effects on cell viability and quality attributes. Innov. Food Sci. Emerg. Technol. 59, 102252. doi:10.1016/j.ifset.2019.102252.

Louati, I., Bahloul, N., Besombes, C., Allaf, K., Kechaou, N., 2019. Instant controlled pressure-drop as texturing pretreatment for intensifying both final drying stage and extraction of phenolic compounds to valorize orange industry by-products (Citrus sinensis L.). Food Bioprod. Process. 114, 85–94.

Loureiro, J.A., Andrade, S., Duarte, A., Neves, A.R., Queiroz, J.F., Nunes, C., Sevin, E., Fenart, L., Gosselet, F., Coelho, M.A.N., Pereira, M.C., 2017. Resveratrol and grape extract-loaded solid lipid nanoparticles for the treatment of alzheimer's disease. Molecules 22, 277. doi:10.3390/molecules22020277.

Luo, Y., Wang, Q., 2014. Zein-based micro- and nano-particles for drug and nutrient delivery: a review. J. Appl. Polym. Sci. 131. doi:10.1002/app.40696.

Luo, Y., Wang, Q., Zhang, Y., 2020. Biopolymer-based nanotechnology approaches to deliver bioactive compounds for food applications: a perspective on the past, present, and future. J. Agric. Food Chem.. doi:10.1021/acs.jafc.0c00277.

Magana, J.R., Homs, M., Esquena, J., Freilich, I., Kesselman, E., Danino, D., Rodríguez-Abreu, C., Solans, C., 2019. Formulating stable hexosome dispersions with a technical grade diglycerol-based surfactant. J. Colloid Interface Sci. 550, 73–80. doi:10.1016/j.jcis.2019.04.084.

Manca, M.L., Castangia, I., Zaru, M., Nácher, A., Valenti, D., Fernández-Busquets, X., Fadda, A.M., Manconi, M., 2015. Development of curcumin loaded sodium hyaluronate immobilized vesicles (hyalurosomes) and their potential on skin inflammation and wound restoring. Biomaterials 71, 100–109. doi:10.1016/j.biomaterials.2015.08.034.

Manca, M.L., Peris, J.E., Melis, V., Valenti, D., Cardia, M.C., Lattuada, D., Escribano-Ferrer, E., Fadda, A.M., Manconi, M., 2015. Nanoincorporation of curcumin in polymer-glycerosomes and evaluation of their in vitro/in vivo suitability as pulmonary delivery systems. RSC Adv. 5, 105149–105159. doi:10.1039/C5RA24032H.

Manconi, M., Caddeo, C., Nacher, A., Diez-Sales, O., Peris, J.E., Ferrer, E.E., Fadda, A.M., Manca, M.L., 2019. Eco-scalable baicalin loaded vesicles developed by combining phospholipid with ethanol, glycerol, and propylene glycol to enhance skin permeation and protection. Colloids Surfaces B Biointerfaces 184, 110504. doi:10.1016/j.colsurfb.2019.110504.

Martínez-López, A.L., Pangua, C., Reboredo, C., Campión, R., Morales-Gracia, J., Irache, J.M., 2020. Protein-based nanoparticles for drug delivery purposes. Int. J. Pharm. 581, 119289. doi:10.1016/j.ijpharm.2020.119289.

Martínez-Patiño, J.C., Gullón, B., Romero, I., Ruiz, E., Brnčić, M., Žlabur, J.Š., Castro, E., 2019. Optimization of ultrasound-assisted extraction of biomass from olive trees using response surface methodology. Ultrason. Sonochem. 51, 487–495.

Mello, B.C.B.S., Petrus, J.C.C., Hubinger, M.D., 2010. Concentration of flavonoids and phenolic compounds in aqueous and ethanolic propolis extracts through nanofiltration. J. Food Eng. 96, 533–539. doi:10.1016/j.jfoodeng.2009.08.040.

Meneses, M.A., Caputo, G., Scognamiglio, M., Reverchon, E., Adami, R., 2015. Antioxidant phenolic compounds recovery from Mangifera indica L . by-products by supercritical antisolvent extraction. J. Food Eng. 163, 45–53. doi:10.1016/j.jfoodeng.2015.04.025.

Meng, L., Huang, W., Wang, D., Huang, X., Zhu, X., Yan, D., 2013. Chitosan-based nanocarriers with pH and light dual response for anticancer drug delivery. Biomacromolecules 14, 2601–2610. doi:10.1021/bm400451v.

Meng, D., Wang, B., Zhen, T., Zhang, M., Yang, R., 2018. Pulsed electric fields-modified ferritin realizes loading of rutin by a moderate pH transition. J. Agric. Food Chem. 66, 12404–12411. doi:10.1021/acs.jafc.8b03021.

Miao, T., Wang, J., Zeng, Y., Liu, G., Chen, X., 2018. Polysaccharide-based controlled release systems for therapeutics delivery and tissue engineering: from bench to bedside. Adv. Sci. 5, 1700513. doi:10.1002/advs.201700513.

Mizrahy, S., Peer, D., 2012. Polysaccharides as building blocks for nanotherapeutics. Chem. Soc. Rev. 41, 2623–2640. doi:10.1039/C1CS15239D.

Mkaouar, S., Bahloul, N., Gelicus, A., Allaf, K., Kechaou, N., 2015. Instant controlled pressure drop texturing for intensifying ethanol solvent extraction of olive (Olea europaea) leaf polyphenols. Sep. Purif. Technol. 145, 139–146. doi:10.1016/j.seppur.2015.03.014.

Moghadam, M., Salami, M., Mohammadian, M., Delphi, L., Sepehri, H., Emam-Djomeh, Z., Moosavi-Movahedi, A., 2020. Walnut proteinâ€ curcumin complexes: fabrication, structural characterization, antioxidant properties, and in vitro anticancer activity. J. Food Meas. Charact. 14, 876–885. doi:10.1007/s11694-019-00336-9.

Morán, M.C., Carazo, J., Busquets, M.A., 2018. Dual responsive gelatin-based nanoparticles for enhanced 5-fluorouracil efficiency. Colloids Surfaces B Biointerfaces 172, 646–654. doi:10.1016/j.colsurfb.2018.09.027.

Moreira, S.A., Alexandre, E.M.C., Pintado, M., Saraiva, J.A., 2019. Effect of emergent non-thermal extraction technologies on bioactive individual compounds profile from different plant materials. Food Res. Int. 115, 177–190. doi:10.1016/j.foodres.2018.08.046.

Moreira, S.A., Silva, S., Costa, E.M., Saraiva, J.A., Pintado, M., 2020. Effect of high hydrostatic pressure extraction on biological activities of stinging nettle extracts. Food Funct. 11, 921–931. doi:10.1039/c9fo02442e.

Moreno-Sastre, M., Pastor, M., Esquisabel, A., Sans, E., Viñas, M., Bachiller, D., Pedraz, J.L., 2016. Stability study of sodium colistimethate-loaded lipid nanoparticles. J. Microencapsul. 33, 636–645. doi:10.1080/02652048.2016.1242665.

Morikawa, Y., Tagami, T., Hoshikawa, A., Ozeki, T., 2018. The use of an efficient microfluidic mixing system for generating stabilized polymeric nanoparticles for controlled drug release. Biol. Pharm. Bull. JID - 9311984. doi:10.1248/bpb.b17-01036.

Mosaiab, T., Farr, D.C., Kiefel, M.J., Houston, T.A., 2019. Carbohydrate-based nanocarriers and their application to target macrophages and deliver antimicrobial agents. Adv. Drug Deliv. Rev. Ed. Collect. 151–152, 94–129. doi:10.1016/j.addr.2019.09.002.

Moschakis, T., Biliaderis, C.G., 2017. Biopolymer-based coacervates: Structures, functionality and applications in food products. Curr. Opin. Colloid Interface Sci. 28, 96–109. doi:10.1016/j.cocis.2017.03.006.

Muhammad, A.I., Liao, X., Cullen, P.J., Liu, D., Xiang, Q., Wang, J., Chen, S., Ye, X., Ding, T., 2018. Effects of nonthermal plasma technology on functional food components. Compr. Rev. Food Sci. Food Saf. 17, 1379–1394. doi:10.1111/1541-4337.12379.

Müller, R.H., Mäder, K., Gohla, S., 2000. Solid lipid nanoparticles (SLN) for controlled drug delivery: a review of the state of the art. Eur. J. Pharm. Biopharm. 50, 161–177. doi:10.1016/S0939-6411(00)00087-4.

Müller, R.H., Radtke, M., Wissing, S.A., 2002. Nanostructured lipid matrices for improved microencapsulation of drugs. Int. J. Pharm. 242, 121–128. doi:10.1016/S0378-5173(02)00180-1.

Müller, R.H., Shegokar, R., Keck, C.M., 2011. 20 years of lipid nanoparticles (SLN & NLC): present state of development & industrial applications. Curr. Drug Discov. Technol. 8, 207–227. doi:10.2174/157016311796799062.

Murray, B.S., Phisarnchananan, N., 2016. Whey protein microgel particles as stabilizers of waxy corn starch + locust bean gum water-in-water emulsions. Food Hydrocoll. 56, 161–169. doi:10.1016/j.foodhyd.2015.11.032.

Nastić, N., Švarc-Gajić, J., Delerue-Matos, C., Barroso, M.F., Soares, C., Moreira, M.M., Morais, S., Mašković, P., Gaurina Srček, V., Slivac, I., Radošević, K., Radojković, M., 2018. Subcritical water extraction as an environmentally-friendly technique to recover bioactive compounds from traditional Serbian medicinal plants. Ind. Crops Prod. 111, 579–589.

Negm, N.A., Hefni, H.H.H., Abd-Elaal, A., Badr, E.A., Abou Kana, M.T.H., 2020. Advancement on modification of chitosan biopolymer and its potential applications. Int. J. Biol. Macromol. 152, 681–702. doi:10.1016/j.ijbiomac.2020.02.196.

Obeid, M.A., Khadra, I., Albaloushi, A., Mullin, M., Alyamani, H., Ferro, V.A., 2019. Microfluidic manufacturing of different niosomes nanoparticles for curcumin encapsulation: physical characteristics, encapsulation efficacy, and drug release. Beilstein J. Nanotechnol. 10, 1826–1832. doi:10.3762/bjnano.10.177.

Obeidat, W.M., Schwabe, K., Müller, R.H., Keck, C.M., 2010. Preservation of nanostructured lipid carriers (NLC). Eur. J. Pharm. Biopharm. 76, 56–67. doi:10.1016/j.ejpb.2010.05.001.

Palazzo, I., Campardelli, R., Scognamiglio, M., Reverchon, E., 2019. Zein/luteolin microparticles formation using a supercritical fluids assisted technique. Powder Technol. 356, 899–908. doi:10.1016/j.powtec.2019.09.034.

Pan, K., Zhong, Q., 2016. Low energy, organic solvent-free co-assembly of zein and caseinate to prepare stable dispersions. Food Hydrocoll. 52, 600–606. doi:10.1016/j.foodhyd.2015.08.014.

Pandolfi, L., Bellini, M., Vanna, R., Morasso, C., Zago, A., Carcano, S., Avvakumova, S., Bertolini, J.A., Rizzuto, M.A., Colombo, M., Prosperi, D., 2017. H-Ferritin enriches the curcumin uptake and improves the therapeutic efficacy in triple negative breast cancer cells. Biomacromolecules 18, 3318–3330. doi:10.1021/acs.biomac.7b00974.

Pashazadeh, B., Elhamirad, A.H., Hajnajari, H., Sharayei, P., Armin, M., 2020. Optimization of the pulsed electric field -assisted extraction of functional compounds from cinnamon. Biocatal. Agric. Biotechnol. 23, 101461. doi:10.1016/j.bcab.2019.101461.

Pathak, J., Priyadarshini, E., Rawat, K., Bohidar, H.B., 2017. Complex coacervation in charge complementary biopolymers: electrostatic versus surface patch binding. Adv. Colloid Interface Sci. 250, 40–53. doi:10.1016/j.cis.2017.10.006.

Pedrozo, R.C., Antonio, E., Khalil, N.M., Mainardes, R.M., 2020. Bovine serum albumin-based nanoparticles containing the flavonoid rutin produced by nano spray drying. Braz. J. Pharm. Sci. 56. doi:10.1590/s2175-97902019000317692.

Peiró, S., Luengo, E., Segovia, F., Raso, J., Almajano, M.P., 2019. Improving polyphenol extraction from lemon residues by pulsed electric fields. Waste Biomass Valorization 10, 889–897. doi:10.1007/s12649-017-0116-6.

Peñalva, R., Morales, J., González-Navarro, C.J., Larrañeta, E., Quincoces, G., Peñuelas, I., Irache, J.M., 2018. Increased oral bioavailability of resveratrol by its encapsulation in casein nanoparticles. Int. J. Mol. Sci. 19, 2816. doi:10.3390/ijms19092816.

Peñalva, R., Esparza, I., Morales-Gracia, J., González-Navarro, C.J., Larrañeta, E., Irache, J.M., 2019. Casein nanoparticles in combination with 2-hydroxypropyl-β-cyclodextrin improves the oral bioavailability of quercetin. Int. J. Pharm. 570, 118652. doi:10.1016/j.ijpharm.2019.118652.

Peng, S., Zou, L., Zhou, W., Liu, W., Liu, C., McClements, D.J., 2019. Encapsulation of lipophilic polyphenols into nanoliposomes using pH-driven method: advantages and disadvantages. J. Agric. Food Chem. 67, 7506–7511. doi:10.1021/acs.jafc.9b01602.

Peng, S., Zhou, L., Cai, Q., Zou, L., Liu, C., Liu, W., McClements, D.J., 2020. Utilization of biopolymers to stabilize curcumin nanoparticles prepared by the pH-shift method: caseinate, whey protein, soy protein and gum Arabic. Food Hydrocoll. 107, 105963. doi:10.1016/j.foodhyd.2020.105963.

Piacentini, E., Dragosavac, M., Giorno, L., 2018. Pharmaceutical particles design by membrane emulsification: preparation methods and applications in drug delivery. Curr. Pharm. Des. 23, 302–318. doi:10.2174/1381612823666161117160940.

Piacentini, E., Mazzei, R., Bazzarelli, F., Ranieri, G., Poerio, T., Giorno, L., 2019. Oleuropein aglycone production and formulation by integrated membrane process. Ind. Eng. Chem. Res. 58, 16813–16822. doi:10.1021/acs.iecr.9b03210.

Piacentini, E., Bazzarelli, F., Poerio, T., Albisa, A., Irusta, S., Mendoza, G., Sebastian, V., Giorno, L., 2020. Encapsulation of water-soluble drugs in Poly (vinyl alcohol) (PVA)-microparticles via membrane emulsification: Influence of process and formulation parameters on structural and functional properties. Mater. Today Commun. 24, 100967. doi:10.1016/j.mtcomm.2020.100967.

Piccolella, S., Crescente, G., Candela, L., Pacifico, S., 2019. Nutraceutical polyphenols: new analytical challenges and opportunities. J. Pharm. Biomed. Anal. 175, 112774. doi:10.1016/j.jpba.2019.07.022.

Prabaharan, M., Mano, J.F., 2005. Chitosan-based particles as controlled drug delivery systems. Drug Deliv. JID - 9417471. doi:10.1080/10717540590889781.

Pyo, S.-M., Müller, R.H., Keck, C.M., 2017. 4 - Encapsulation by nanostructured lipid carriers. In: Jafari, S.M. (Ed.), Nanoencapsulation Technologies for the Food and Nutraceutical Industries. Academic Press, pp. 114–137. doi:10.1016/B978-0-12-809436-5.00004-5.

Qin, Y., Wang, J., Qiu, C., Hu, Y., Xu, X., Jin, Z., 2019. Self-assembly of metal-phenolic networks as functional coatings for preparation of antioxidant, antimicrobial, and pH-sensitive-modified starch nanoparticles. ACS Sustain. Chem. Eng. 7, 17379–17389. doi:10.1021/acssuschemeng.9b04332.

Qu, J., Liu, Y., Yu, Y., Li, J., Luo, J., Li, M., 2014. Silk fibroin nanoparticles prepared by electrospray as controlled release carriers of cisplatin. Mater. Sci. Eng. C 44, 166–174. doi:10.1016/j.msec.2014.08.034.

Ranjbar, N., Eikani, M.H., Javanmard, M., Golmohammad, F., 2016. Impact of instant controlled pressure drop on phenolic compounds extraction from pomegranate peel. Innov. Food Sci. Emerg. Technol. 37, 177–183.

Reddy, I.M., Kella, N.K.D., Kinsella, J.E., 1988. Structural and conformational basis of the resistance of .beta.-lactoglobulin to peptic and chymotryptic digestion. J. Agric. Food Chem. 36, 737–741. doi:10.1021/jf00082a015.

Reddy, A.S., Lakshmi, B.A., Kim, S., Kim, J., 2019. Synthesis and characterization of acetyl curcumin-loaded core/shell liposome nanoparticles via an electrospray process for drug delivery, and theranostic applications. Eur. J. Pharm. Biopharm. 142, 518–530. doi:10.1016/j.ejpb.2019.07.024.

Reverchon, E., 2001. (12) Patent Application Publication (10) Pub. No.: US 2004/0178529 A1.

Reverchon, E., 2002. Supercritical-assisted atomization to produce micro- and/or nanoparticles of controlled size and distribution. Ind. Eng. Chem. Res. 41, 2405–2411. doi:10.1021/ie010943k.

Ribas-Agustí, A., Martín-Belloso, O., Soliva-Fortuny, R., Elez-Martínez, P., 2019. Enhancing hydroxycinnamic acids and flavan-3-ol contents by pulsed electric fields without affecting quality attributes of apple. Food Res. Int. 121, 433–440.

Riyajan, S.-A., Nuim, J., 2013. Interaction of green polymer blend of modified sodium alginate and carboxylmethyl cellulose encapsulation of turmeric extract. Int. J. Polym. Sci. 2013. doi:10.1155/2013/364253.

Romani, A., Scardigli, A., Pinelli, P., 2017. An environmentally friendly process for the production of extracts rich in phenolic antioxidants from Olea europaea L. and Cynara scolymus L. matrices. Eur. Food Res. Technol. 243, 1229–1238. doi:10.1007/s00217-016-2835-5.

Rostamabadi, H., Falsafi, S.R., Jafari, S.M., 2019. Nanoencapsulation of carotenoids within lipid-based nanocarriers. J. Control. Release 298, 38–67. doi:10.1016/j.jconrel.2019.02.005.

Ruesgas-Ramón, M., Figueroa-Espinoza, M., Durand, E., 2017. Application of deep eutectic solvents (DES) for phenolic compounds extraction: overview, challenges, and opportunities. J. Agric. Food Chem. 65, 3591–3601. doi:10.1021/acs.jafc.7b01054.

Sahlan Dienayati, D., Hamdi, D., Zahra, S., Hermansyah, H., Chulasiri, M.M., 2017. Encapsulation process of propolis extract by Casein micelle improves sunscreen activity. Makara J. Technol. 21.

Sánchez-Valdepeñas, V., Barrajón, E., Vegara, S., Funes, L., Martí, N., Valero, M., Saura, D., 2015. Effect of instant controlled pressure drop (DIC) pre-treatment on conventional solvent extraction of phenolic compounds from grape stalk powder. Ind. Crops Prod. 76, 545–549. doi:10.1016/j.indcrop.2015.04.033.

Sarmento, B., Ribeiro, A., Veiga, F., Sampaio, P., Neufeld, R., Ferreira, D., 2007. Alginate/Chitosan nanoparticles are effective for oral insulin delivery. Pharm. Res. 24, 2198–2206. doi:10.1007/s11095-007-9367-4.

Singh, B.G., Das, R.P., Kunwar, A., 2019. Protein: a versatile biopolymer for the fabrication of smart materials for drug delivery. J. Chem. Sci. 131, 1–14. doi:10.1007/s12039-019-1671-0.

Sivapragasam, M., Moniruzzaman, M., Goto, M., 2020. An overview on the toxicological properties of ionic liquids toward microorganisms. Biotechnol. J. 15, 1–9. doi:10.1002/biot.201900073.

Sklavos, S., Gatidou, G., Stasinakis, A.S., Haralambopoulos, D., 2015. Use of solar distillation for olive mill wastewater drying and recovery of polyphenolic compounds. J. Environ. Manage. 162, 46–52.

Soleimanifar, M., Jafari, S.M., Assadpour, E., 2020. Encapsulation of olive leaf phenolics within electrosprayed whey protein nanoparticles; production and characterization. Food Hydrocoll. 101, 105572. doi:10.1016/j.foodhyd.2019.105572.

Stefan, L., Rainer, M., 1994. Medication vehicles made of solid lipid particles (solid lipid nanospheres - sln).

Tan, C., Xie, J., Zhang, X., Cai, J., Xia, S., 2016. Polysaccharide-based nanoparticles by chitosan and gum arabic polyelectrolyte complexation as carriers for curcumin. Food Hydrocoll. 57, 236–245. doi:10.1016/j.foodhyd.2016.01.021.

Tan, C., Arshadi, M., Lee, M.C., Godec, M., Azizi, M., Yan, B., Eskandarloo, H., Deisenroth, T.W., Darji, R.H., Van Pho, T., Abbaspourrad, A., 2019. A robust aqueous

core-shell-shell coconut-like nanostructure for stimuli-responsive delivery of hydrophilic cargo. ACS Nano 13, 9016–9027. doi:10.1021/acsnano.9b03049.

Tapia-Salazar, M., Arévalo-Rivera, I.G., Maldonado-Muñiz, M., Garcia-Amezquita, L., Nieto-López, M.G., Ricque-Marie, D., Cruz-Suárez, L.E., Welti-Chanes, J., 2019. The dietary fiber profile, total polyphenol content, functionality of silvetia compressa and ecklonia arborea, and modifications induced by high hydrostatic pressure treatments. Food Bioprocess Technol. 12, 512–523. doi:10.1007/s11947-018-2229-8.

Thomas, D., KurienThomas, K., Latha, M.S., 2020. Preparation and evaluation of alginate nanoparticles prepared by green method for drug delivery applications. Int. J. Biol. Macromol. 154, 888–895. doi:10.1016/j.ijbiomac.2020.03.167.

Tian, B., Wang, Y., Wang, T., Mao, L., Lu, Y., Wang, H., Feng, Z., 2019. Structure and functional properties of antioxidant nanoemulsions prepared with tea polyphenols and soybean protein isolate. J. Oleo Sci. 68, 689–697. doi:10.5650/jos.ess19067.

Tirado, D.F., Latini, A., Calvo, L., 2021. The encapsulation of hydroxytyrosol-rich olive oil in Eudraguard® protect via supercritical fluid extraction of emulsions. J. Food Eng. 290, 110215. doi:10.1016/j.jfoodeng.2020.110215.

Trucillo, P., Campardelli, R., Aliakbarian, B., Perego, P., Reverchon, E., 2018. Supercritical assisted process for the encapsulation of olive pomace extract into liposomes. J. Supercrit. Fluids 135, 152–159.

Ubeyitogullari, A., Ciftci, O.N., 2019. A novel and green nanoparticle formation approach to forming low-crystallinity curcumin nanoparticles to improve curcumin's bioaccessibility. Sci. Rep. 9, 19112. doi:10.1038/s41598-019-55619-4.

Vairo, C., Basas, J., Pastor, M., Palau, M., Gomis, X., Almirante, B., Gainza, E., Hernández, R.M., Igartua, M., Gavaldà, J., Gainza, G., 2020. In vitro and in vivo antimicrobial activity of sodium colistimethate and amikacin-loaded nanostructured lipid carriers (NLC). Nanomed. Nanotechnol. Biol. Med. 102259. doi:10.1016/j.nano.2020.102259.

Van Tran, V., Moon, J.-Y., Lee, Y.-C., 2019. Liposomes for delivery of antioxidants in cosmeceuticals: challenges and development strategies. J. Control. Release 300, 114–140. doi:10.1016/j.jconrel.2019.03.003.

Varshosaz, J., Eskandari, S., Tabbakhian, M., 2012. Freeze-drying of nanostructure lipid carriers by different carbohydrate polymers used as cryoprotectants. Carbohydr. Polym. 88, 1157–1163. doi:10.1016/j.carbpol.2012.01.051.

Vasquez, D., Milusheva, R., Baumann, P., Constantin, D., Chami, M., Palivan, C.G., 2014. The amine content of PEGylated Chitosan bombyx mori nanoparticles acts as a trigger for protein delivery. Langmuir 30, 965–975. doi:10.1021/la404558g.

Vetten, M.A., Yah, C.S., Singh, T., Gulumian, M., 2014. Challenges facing sterilization and depyrogenation of nanoparticles: effects on structural stability and biomedical applications. Nanomed. Nanotechnol. Biol. Med. 10, 1391–1399. doi:10.1016/j.nano.2014.03.017.

Wang, Y.-S., Liu, L.-R., Jiang, Q., Zhang, Q.-Q., 2007. Self-aggregated nanoparticles of cholesterol-modified chitosan conjugate as a novel carrier of epirubicin. Eur. Polym. J. 43, 43–51. doi:10.1016/j.eurpolymj.2006.09.007.

Wang, R., Tian, Z., Chen, L., 2011. Nano-encapsulations liberated from barley protein microparticles for oral delivery of bioactive compounds. Int. J. Pharm. 406, 153–162. doi:10.1016/j.ijpharm.2010.12.039.

Weissig, V., 2017. Liposomes came first: the early history of liposomology. In: D'Souza, G.G.M. (Ed.), Liposomes: Methods and Protocols. Springer New York, New York, NY, pp. 1–15. doi:10.1007/978-1-4939-6591-5_1.

Wijayanto, A., Putri, Y.R.P., Hermansyah, H., Sahlan, M., 2017. Encapsulation of eugenol from clove oil using casein micelle for solid preparation. In: AIP Conference Proceedings. doi:10.1063/1.4976781.

Windbergs, M., Zhao, Y. Fau, Heyman, J., Heyman, J.F.A.U., Weitz, A.D., Weitz, D.A., 2013. Biodegradable core-shell carriers for simultaneous encapsulation of synergistic actives. J. Am. Chem. Soc. JID - 7503056. doi:10.1021/ja401422r.

Wu, K., Ju, T., Deng, Y., Xi, J., 2017. Mechanochemical assisted extraction: a novel, efficient, eco-friendly technology. Trends Food Sci. Technol. 66, 166–175. doi:10.1016/j.tifs.2017.06.011.

Wu, M., Jin, J., Jin, P., Xu, Y., Yin, J., Qin, D., Wang, K., Du, Q., 2017. Epigallocatechin gallate-Î²-lactoglobulin nanoparticles improve the antitumor activity of EGCG for inducing cancer cell apoptosis. J. Funct. Foods 39, 257–263. doi:10.1016/j.jff.2017.10.038.

Xie, Y., Qiao, H., Su, Z., Chen, M., Ping, Q., Sun, M., 2014. PEGylated carboxymethyl chitosan/calcium phosphate hybrid anionic nanoparticles mediated hTERT siRNA delivery for anticancer therapy. Biomaterials 35, 7978–7991. doi:10.1016/j.biomaterials.2014.05.068.

Xie, M.-B., Li, Y., Zhao, Z., Chen, A.-Z., Li, J.-S., Hu, J.-Y., Li, G., Li, Z., 2015. Solubility enhancement of curcumin via supercritical CO2 based silk fibroin carrier. J. Supercrit. Fluids 103, 1–9. doi:10.1016/j.supflu.2015.04.021.

Xie, M., Fan, D., Li, Y., He, X., Chen, X., Chen, Y., Zhu, J., Xu, G., Wu, X., Lan, P., 2017. Supercritical carbon dioxide-developed silk fibroin nanoplatform for smart colon cancer therapy. Int. J. Nanomedicine 12, 7751–7761. doi:10.2147/IJN.S145012.

Xu, P.Y., Fu, C.P., Kankala, R.K., Wang, S.B., Chen, A.Z., 2020. Supercritical carbon dioxide-assisted nanonization of dihydromyricetin for anticancer and bacterial biofilm inhibition efficacies. J. Supercrit. Fluids 161, 104840.

Xue, J., Wang, T., Hu, Q., Zhou, M., Luo, Y., 2017. A novel and organic solvent-free preparation of solid lipid nanoparticles using natural biopolymers as emulsifier and stabilizer. Int. J. Pharm. 531, 59–66.

Xue, J., Wang, T., Hu, Q., Zhou, M., Luo, Y., 2018. Insight into natural biopolymer-emulsified solid lipid nanoparticles for encapsulation of curcumin: Effect of loading methods. Food Hydrocoll. 79, 110–116.

Xue, B., Zhang, Y., Xu, M., Wang, C., Huang, J., Zhang, H., Meng, S., Xie, M., Tao, A., Li, X., 2019. Curcumin-silk fibroin nanoparticles for enhanced anti-candida albicans activity in vitro and in vivo. J. Biomed. Nanotechnol. 15, 769–778. doi:10.1166/jbn.2019.2722.

Yan, Y., Kizilay, E., Seeman, D., Flanagan, S., Dubin, P.L., Bovetto, L., Donato, L., Schmitt, C., 2013. Heteroprotein complex coacervation: bovine β-lactoglobulin and lactoferrin. Langmuir 29, 15614–15623. doi:10.1021/la4027464.

Yang, J., Han, S., Zheng, H., Dong, H., Liu, J., 2015. Preparation and application of micro/nanoparticles based on natural polysaccharides. Carbohydr. Polym. 123, 53–66. doi:10.1016/j.carbpol.2015.01.029.

Yang, R., Liu, Y., Meng, D., Chen, Z., Blanchard, C.L., Zhou, Z., 2017. Urea-Driven Epigallocatechin Gallate (EGCG) Permeation into the Ferritin Cage, an innovative method for fabrication of protein-polyphenol co-assemblies. J. Agric. Food Chem. 65, 1410–1419. doi:10.1021/acs.jafc.6b04671.

Yang, R., Liu, Y., Blanchard, C., Zhou, Z., 2018. Channel directed rutin nano-encapsulation in phytoferritin induced by guanidine hydrochloride. Food Chem. 240, 935–939. doi:10.1016/j.foodchem.2017.07.088.

Yang, R., Liu, Y., Gao, Y., Yang, Z., Zhao, S., Wang, Y., Blanchard, C., Zhou, Z., 2018. Nano-encapsulation of epigallocatechin gallate in the ferritin-chitosan double shells: simulated digestion and absorption evaluation. Food Res. Int. 108, 1–7. doi:10.1016/j.foodres.2018.02.074.

Yang, R., Zuo, P., Zhang, M., Meng, D., Wang, B., Zhen, T., 2019. Transglutaminase induced oligochitosan glycosylation of ferritin as a novel nanocarrier for food bioactive molecules. Food Hydrocoll. 94, 500–509.

Zhan, X., Dai, L., Zhang, L., Gao, Y., 2020. Entrapment of curcumin in whey protein isolate and zein composite nanoparticles using pH-driven method. Food Hydrocoll. 106. doi:10.1016/j.foodhyd.2020.105839.

Zhang, H., Fu, Y., Xu, Y., Niu, F., Li, Z., Ba, C., Jin, B., Chen, G., Li, X., 2019. One-step assembly of zein/caseinate/alginate nanoparticles for encapsulation and improved bioaccessibility of propolis. Food Funct. 10, 635–645. doi:10.1039/c8fo01614c.

Zhao, Y., Jiang, Y., Ding, Y., Wang, D., Deng, Y., 2019. High hydrostatic pressure-assisted extraction of high-molecular-weight melanoidins from black garlic: Composition, structure, and bioactive properties. J. Food Qual. 2019. doi:10.1155/2019/1682749.

Zhao, Yanna, Cai, C., Liu, M., Zhao, Yuping, Pei, W., Chu, X., Zhang, H., Wang, Z., Han, J., 2019. An organic solvent-free technology for the fabrication of albumin-based paclitaxel nanoparticles for effective cancer therapy. Colloids Surfaces B Biointerfaces 183, 110394. doi:10.1016/j.colsurfb.2019.110394.

Zhao, M., Huang, X., Zhang, H., Zhang, Y., Gänzle, M., Yang, N., Nishinari, K., Fang, Y., 2020. Probiotic encapsulation in water-in-water emulsion via heteroprotein complex coacervation of type-A gelatin/sodium caseinate. Food Hydrocoll. 105. doi:10.1016/j.foodhyd.2020.105790.

Zheng, J., Gao, Q., Tang, C. he, Ge, G., Zhao, M., Sun, W., 2020. Heteroprotein complex formation of soy protein isolate and lactoferrin: thermodynamic formation mechanism and morphologic structure. Food Hydrocoll. 100. doi:10.1016/j.foodhyd.2019.105415.

Zhou, R., Wang, F., Guo, Z., Zhao, Y.L., 2012. Preparation and characterization of resveratrol/hydroxypropyl-β-cyclodextrin inclusion complex using supercritical antisolvent technology. J. Food Process Eng. 35, 677–686. doi:10.1111/j.1745-4530.2010.00617.x.

Zou, Y., Zhong, J., Pan, R., Wan, Z., Guo, J., Wang, J., Yin, S., Yang, X., 2017. Zein/tannic acid complex nanoparticles-stabilised emulsion as a novel delivery system for controlled release of curcumin. Int. J. Food Sci. Technol. 52, 1221–1228. doi:10.1111/ijfs.13380.

Žugčić, T., Abdelkebir, R., Alcantara, C., Collado, M.C., García-Pérez, J.V., Meléndez-Martínez, A.J., Režek Jambrak, A., Lorenzo, J.M., Barba, F.J., 2019. From extraction of valuable compounds to health promoting benefits of olive leaves through bioaccessibility, bioavailability and impact on gut microbiota. Trends Food Sci. Technol. 83, 63–77.

Zurob, E., Cabezas, R., Villarroel, E., Rosas, N., Merlet, G., Quijada-Maldonado, E., Romero, J., Plaza, A., 2020. Design of natural deep eutectic solvents for the ultrasound-assisted extraction of hydroxytyrosol from olive leaves supported by COSMO-RS. Sep. Purif. Technol. 248, 117054. doi:10.1016/j.seppur.2020.117054.