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Plant oils: From chemical composition to encapsulated form use

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Abbreviations

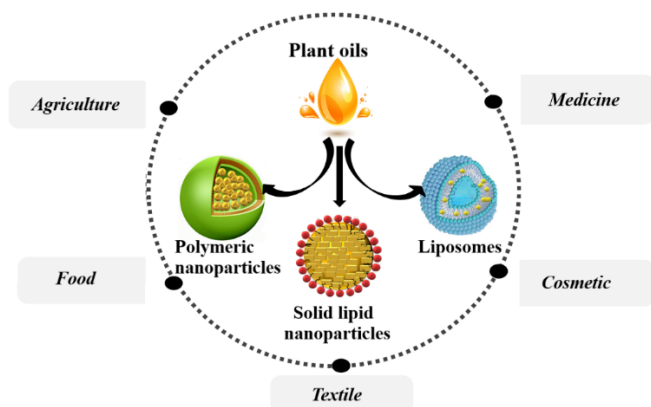
EO: Essential oil; VO: Vegetable oil; pNPs: Polymeric nanoparticles; SLN: Solid lipid nanoparticles; EE%: Encapsulation efficiency; HLB: Hydrophilic lipophilic balance; SUV: Small unilamellar vesicles; LUV: Large unilamellar vesicles; MLV: Multilamellar vesicles; NLC: Nanostructured lipid carriers; MIC: Minimum inhibitory concentration; AUC: Area under the curve.

25 **Abstract**

26 The last decade has witnessed a burgeoning global movement towards essential and
27 vegetable oils in the food, agriculture, pharmaceutical, cosmetic, and textile industries thanks
28 to their natural and safe status, broad acceptance by consumers, and versatile functional
29 properties. However, efforts to develop new therapy or functional agents based on plant oils
30 have met with challenges of limited stability and/or reduced efficacy. As a result, there has been
31 increased research interest in the encapsulation of plant oils, whereby the nanocarriers serve as
32 barrier between plant oils and the environment and control oil release leading to improved
33 efficacy, reduced toxicity and enhanced patient compliance and convenience. In this review,
34 special concern has been addressed to the encapsulation of essential and vegetable oils in three
35 types of nanocarriers: polymeric nanoparticles, liposomes and solid lipid nanoparticles. First,
36 the chemical composition of essential and vegetable oils was handled. Moreover, we gather
37 together the research findings reported by the literature regarding the different techniques used
38 to generate these nanocarriers with their significant findings. Finally, differences and
39 similarities between these nanocarriers are discussed, along with current and future applications
40 that are warranted by their structures and properties.

41 **Key words:** Essential oil, vegetable oil, encapsulation, polymeric nanoparticle, liposome, solid
42 lipid nanoparticle.

43 **Graphical abstract**



44

45 **1. Introduction**

46 The last decade has evidently witnessed a tremendous surge in the use of herbal
47 medicine as a form of complementary or replacement therapy (Mainardi et al., 2009). The
48 global acceptance and public concern in the use of herbal medicines, phytonutrients or
49 nutraceuticals continue to assume exponential increase. It has been estimated that up to 80% of
50 people worldwide relying on them as a primary source of healthcare (Ekor, 2013). This concern
51 in drugs of natural origin is related to numerous reasons, namely, the traditional medicine is
52 more affordable, closer to the patient's ideology and receives greater public access than
53 chemical synthesized treatment. Furthermore, abusive and/or incorrect use of conventional
54 medicines results in some cases in harmful side effects (Wachtel-Galor and Benzie, 2011). The
55 use of aromatic and medicinal plants is incessantly expanding due to increasing consumers
56 demand and concern in these plants for several applications. In fact, consumers are becoming
57 more and more aware of the benefits of inherent practice of medicinal and aromatic plants and
58 their metabolites (Chikezie et al., 2015; Rates, 2001). These plants produce a large variety of
59 secondary metabolites; among them, essential and vegetable oils deserve particular attention
60 (Dhifi et al., 2016; Kumar et al., 2016; Pandey et al., 2016; Yara-Varón et al., 2017).

61 Essential oils (EO) comprised volatile and semi-volatile organic compounds determining the
62 specific aroma, flavor and fragrance of plants. They are volatile and instable at room-
63 temperature. In the other hand, vegetable oils (VO) consist of esters of glycerol and fatty acids
64 and are nonvolatile and stable at room temperature (Moghaddam and Mehdizadeh, 2017; Sagiri
65 et al., 2016). Besides being edible in their refined or virgin form, VO play a crucial role in
66 therapeutic and prophylactic prevention of diseases such as inflammation, diabetes, cancer and
67 atherosclerosis (Ganesan et al., 2018; Kochikuzhyil et al., 2010; Saha and Ghosh, 2011; Yu et
68 al., 2004). Subsequently, EO received significant attention in food, agricultural and
69 pharmaceutical fields due to their antioxidant, antibacterial, antiviral and antifungal properties.

70 The diverse health benefits associated with the consumption of EO constitute an area of intense
71 research (Ali et al., 2015; Dhifi et al., 2016; Elshafie and Ippolito, 2017). Meantime, the benefits
72 linked to these bioactive agents is generally hampered by several obstacles. For instance, the
73 oxidation is the main problem limiting the use of VO in several fields. The unsaturated fatty
74 acids present in VO lead to increase the risk of lipid oxidation which in turn result in producing
75 numerous free radical species, primary oxidation products such as lipid hydroperoxides and
76 secondary oxidation products such as hydrocarbons, epoxides, ketones and aldehydes that
77 negatively impact aroma. Moreover, VO oxidation can generate toxic products that can largely
78 affect biological tissues (Chen et al., 2011; Matthäus, 2010). At the same time, numerous
79 studies have evidenced that EO are unstable and degraded easily if they are not protected from
80 external factors like oxidation, volatilization, heat and light (Turek and Stintzing, 2013).
81 Besides all these, the low water solubility, low permeation and low bioavailability of plant oils
82 in biological fluids and tissues constitute other factors that limit their rational use (Dima et al.,
83 2020; Rein et al., 2013). Therefore, designing suitable carriers by using nanoencapsulation
84 approach is crucial to overcome restrictions outlined (El-Asbahani et al., 2015; Sagiri et al.,
85 2016). Hoyos-leyva et al. (2019) revealed that the encapsulation of almond oil in starch
86 microcapsules conferred more protection against oxidation when compared to unencapsulated
87 oil. Similar results were already reported when investigating the stability of linseed, jasmine
88 and holy basil oils-loaded nanoparticles against heat, oxidation and volatilization as compared
89 to the free oils (Lv et al., 2014; Rubilar et al., 2012; Sutaphanit and Chitprasert, 2014).
90 Moreover, several studies have evidenced the amelioration of plant oils biological performance
91 after being incorporated in nanosystems. Alaarg et al. (2016) depicted that the encapsulation of
92 docosahexaenoic acid in liposomes improve its anticancer activity. Zhavveh et al. (2015) related
93 the superior performance of *Cuminum cyminum* EO nanogels against *Aspergillus flavus* as
94 compared to the free oil to the increased surface area of the nanoparticles.

95 Depending on the preparation method, nanocarriers can be mainly classified into two
96 main groups: polymer-based nanocarriers and lipid-based nanocarriers. Among the several
97 colloidal systems investigated in drug delivery, polymeric nanoparticles (pNPs), liposomes and
98 solid lipid nanoparticles (SLN) gained more interest (Allen and Cullis, 2013; El-say and El-
99 sawy, 2017; Geszke-Moritz and Moritz, 2016; Immordino et al., 2006; Mehnert and Mäder,
100 2012; Rani et al., 2017). In this context, the present review covers literature data summarizing
101 the current development of nanocarrier systems for plant oils delivery with a focus on the main
102 properties and preparation technique of pNPs, liposomes and SLN. In addition, the chemical
103 composition of both essential and vegetable oils along with the emerging and potential
104 applications of plant oils loaded nanocarriers in several fields were explored.

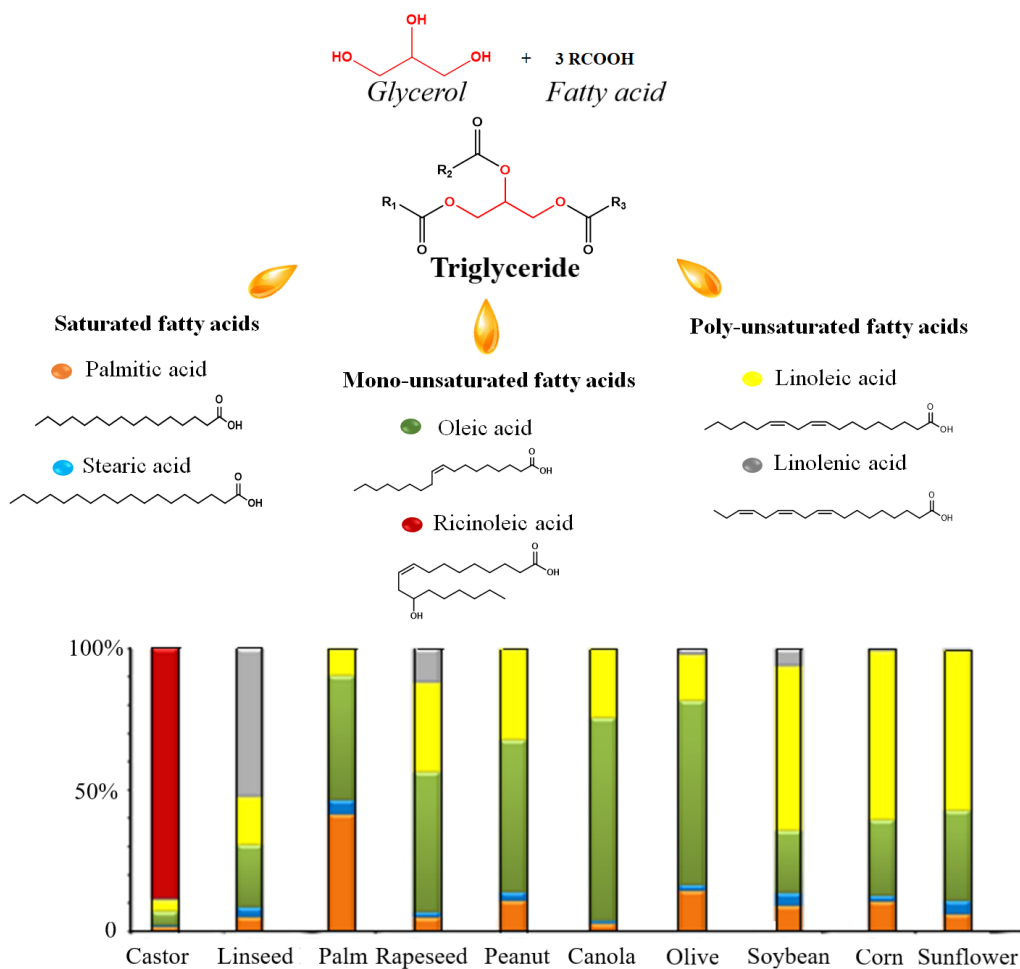
105 **2. Chemical composition of vegetable oils**

106 Vegetable oils, also named non-essential or fixed oils, are fats usually extracted from
107 plant seeds (e.g., soybean oil, rapeseed oil, sesame oil etc.), or less often from other parts of
108 fruits (e.g., olive oil, palm oil etc.), by simple pressing and/or solvent extraction process (Yara-
109 Varón et al., 2017). Depending on the origin, the crop, the season, and the producing methods,
110 their composition is highly variable and complex (Lligadas et al., 2010).

111 **2.1. Triglycerides**

112 The main components of VO are triglycerides; they represent 95 to 98% of the global
113 constituents depending on the source of oil (Yara-Varón et al., 2017). The word ‘oil’ hereby
114 refers to triglycerides that are liquid at room temperature (Guner et al., 2006). Triglycerides are
115 composed of three fatty acid molecules esterified to one glycerol molecule, as demonstrated in
116 **Fig. 1** (Miao et al., 2014). Depending on the saturation degree of fatty acids, triglycerides are
117 classified into saturated, mono- and poly-unsaturated fatty acids. The characteristics of VO
118 depend on several parameters including; i) fatty acid chain length, ii) the degree of unsaturation,
119 and iii) the stereochemistry of the double bonds (Meier et al., 2007). Additionally, varieties in

120 climatic, agronomic and cultivation may engender difference in fatty acid composition of
 121 triglycerides (Yara-Varón et al., 2017).



122
123 **Fig. 1.** Triglycerides composition of different vegetable oils.

124 2.2. Minor Components

125 Apart of triglycerides, VO contain also a diversity of non-triglyceride minor compounds
 126 (less than 5%) which present crucial biological properties and nutritional values for
 127 nutraceutical and pharmaceutical industries (**Fig. 2**) (Yara-Varón et al., 2017). They comprised
 128 two types: glycerolipids including monoglycerides, diglycerides and phospholipids; and non-
 129 glycerolipids such as tocopherols/tocotrienols, sterols, free fatty acids, pigments, vitamins,
 130 phenolic compounds, proteins and water (Xenakis et al., 2010).

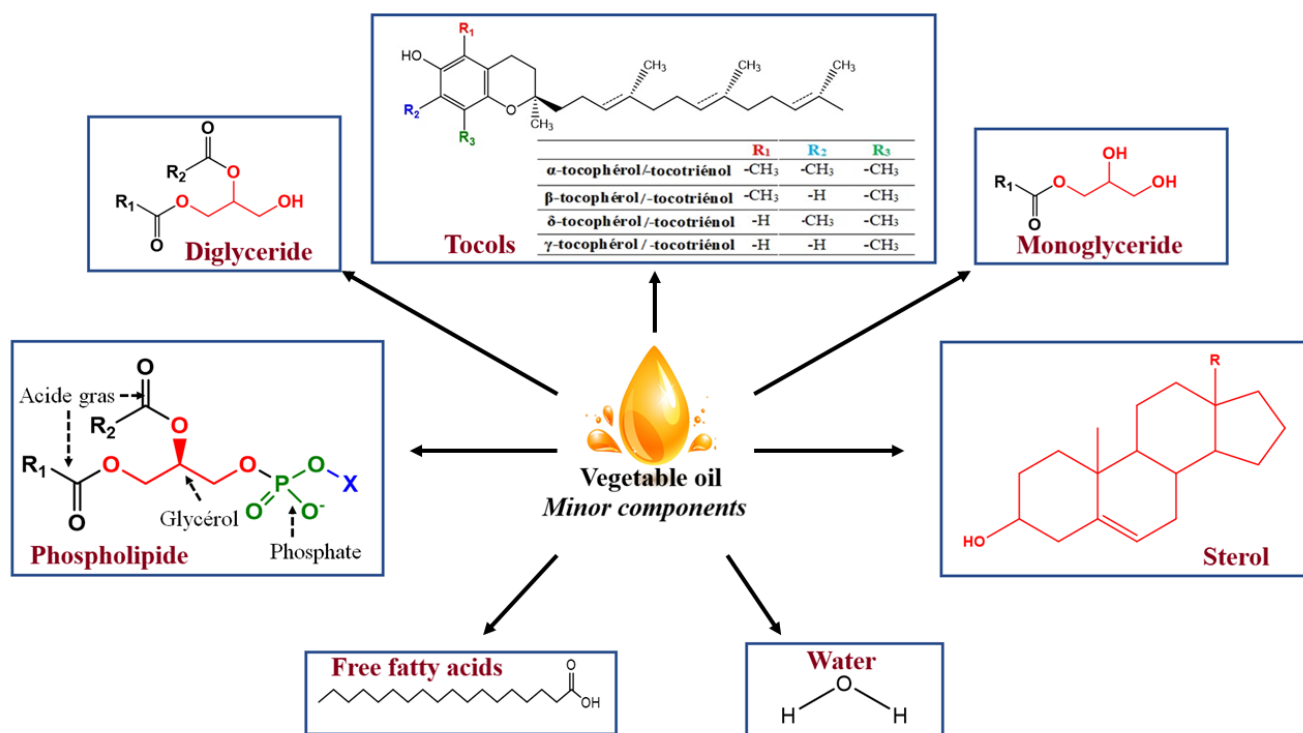


Fig. 2. Minor components of vegetable oils.

3. Chemical composition of essential oils

Essential oils are oily aromatic liquids extracted from different plant organs as secondary metabolites like, leaves (eucalyptus, thym, salvia), zest (citrus), flowers (lavender, rose, jasmine), fruits (citrus), seeds (sesame), roots (ginger) and wood (sandal) (El-Asbahani et al., 2015). The EO are generally complex mixtures of individual aroma compounds. Even they are not strictly oils, they are poorly soluble in water (Calo et al., 2015). In last decades, innovative methods have been emerged to extract EO from plant raw materials (Boukroufa et al., 2015; Gavahian et al., 2015; Sodeifian et al., 2016; Zermane et al., 2016). The constituents of plant EO comprise mainly four main groups: terpenes, phenylpropanoids, straight-chain compounds and miscellaneous groups.

3.1. Terpenes

Terpenes are the most abundant compounds found in plant EO (Chizzola, 2013). They are synthesized via the mevalonic acid pathway in the cytoplasm of plant cells (Morsy, 2017).

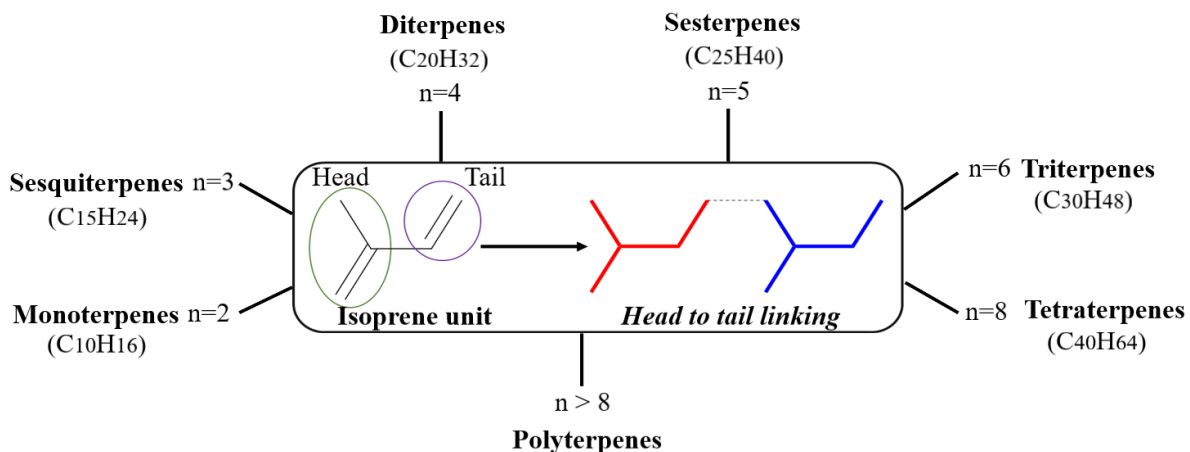
146 Terpene compounds can be divided into two main categories: terpene hydrocarbons and
147 oxygenated compounds (Moghaddam and Mehdizadeh, 2017).

148 **3.1.1. Terpenes hydrocarbon**

149 The essential building block of terpenes is the isoprene unit joined in a head-to-tail
150 manner. Basing on the number of isoprene units, different terpenes can be found in EO, as
151 demonstrated in **Fig. 3** (El-Asbahani et al., 2015; Morsy, 2017). Terpenes hydrocarbons are the
152 first main group of components composed completely of carbon and hydrogen atoms and varied
153 significantly in size and complexity (Moghaddam and Mehdizadeh, 2017). Monoterpenes and
154 sesquiterpenes are the dominant terpenes found in plant EO. They are built up by two and three
155 isoprene units, respectively. These terpenes could present acyclic, cyclic or aromatic structures.
156 Cyclic terpenes can be classified depending on their ring size into monocyclic, bicyclic or
157 tricyclic terpenes (**Table 1**). These compounds oxidize rapidly due to their fast reaction to heat
158 and air sources (George et al., 2015). Diterpenes result by the combination of four isoprene
159 units in a head-to-tail manner; they are essential constituents of plant resins (Langenheim,
160 2003). Commonly, diterpenes, triterpenes and tetraterpenes are present in EOs at a very low
161 concentration. Their content may vary with the extraction method (Morsy, 2017).

162 **3.1.2. Terpenoids**

163 Terpene can be changed by adding functional groups and become terpenoid. When a
164 monoterpene or a sesquiterpene has a functional group added to it, it is known as a
165 monoterpenoid or sesquiterpenoid; respectively. The suffix “oid” means “derived from” or
166 “like” therefore “terpenoid” can refer to all molecules with a terpene-like structure
167 (Moghaddam and Mehdizadeh, 2017). They are classified into carboxylic acids, alcohols,
168 aldehydes, esters, ethers, ketones, phenols, lactones, oxides, etc.



169
170

Fig. 3. Composition of terpenes.

171 3.2. Phenylpropanoid

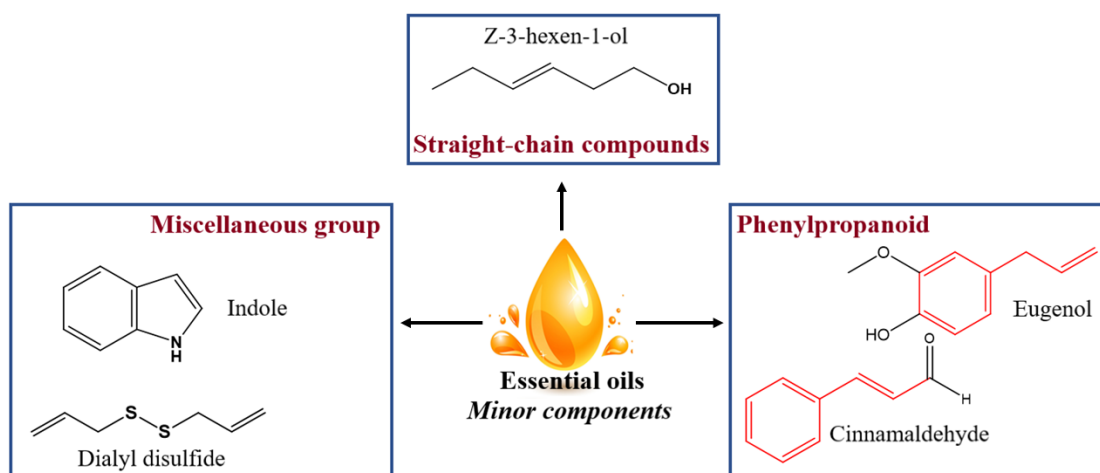
172 This class of compounds, derived from phenylpropene, is synthesized from the amino
173 acid phenylalanine and l-tyrosine via the shikimic acid pathway. Their name is derived from
174 the aromatic phenyl group and the propene tail. The propyl side chain may contain hydroxyl or
175 carboxyl group; while the aromatic ring may carry methoxy, hydroxyl and methylene dioxy
176 groups (Morsy, 2017). Phenylpropanoids give a specific flavor and odor to the plant when they
177 are present (Moghaddam and Mehdizadeh, 2017). Eugenol and cinnamaldehyde are example
178 of this group of constituents (**Fig. 4**).

179 3.3. Straight-chain compounds

180 This group contains only straight-chain compounds, not containing any side branches.
181 They range from n-heptane, to compounds with 35 carbon atoms. The leaf alcohol (3(Z)-hexen-
182 1-ol) (**Fig. 4**) represents an example of this class; it gives an intense grassy-green odor upon
183 cutting green grass and leaves (Morsy, 2017).

184 3.4. Miscellaneous group

185 They issue from the degradation of unsaturated fatty acids, lactones, terpenes,
186 glycosides and represent sulfur- and nitrogen-containing compounds. Diallyl disulfide and
187 indole are example of this class of compounds (**Fig. 4**) (Morsy, 2017).



188

189 **Fig. 4.** Examples of phenylpropanoids, straight chain compounds and miscellaneous groups.

190

191 **4. Limitation in clinical use of plant oils**

192 Since ancient times, EO have been recommended all over the world for a variety of

193 health problems and diseases (Moghaddam and Mehdizadeh, 2017). Enormous studies have

194 investigated the biological properties of EO, including antimicrobial, antifungal (Ceole et al.,

195 2017; Garcia-Rellán et al., 2016), antiviral (Zeghib et al., 2017), insecticidal (Chen et al., 2016;

196 Jassbi et al., 2017), antioxidant (Hassanen et al., 2015; Limaverde et al., 2017), anticancer

197 (Carneiro et al., 2017; Thakre et al., 2016), antidiabetic (Tahir et al., 2016), anti-inflammatory

198 (Chansang et al., 2018; Nonato et al., 2012), antihypertensive (Cherkaoui-Tangi et al., 2016)

199 and immunomodulatory (Orhan et al., 2016; Ozek et al., 2017). In medical field, EO have been

200 used against nosocomial infections, as a cleaning liquid for disinfection of medical equipment

201 and surfaces (Warnke et al., 2009) or as an aerosol in operating blocks and waiting rooms for

202 air cleaning to limit contaminations (De Billerbeck, 2007). The application of EO has emerged

203 to food and agriculture fields. They are used as antioxidants and preservatives in food

204 (Khosravi, 2013; Pandey et al., 2016), as plant and crop protectants (Abdullah et al., 2018) and

205 incorporated into foodstuff packaging (Ribeiro-Santos et al., 2017).

206 In the other side, VO is a source of everlasting components which are responsible of
207 pertinent biological properties. Many of the fatty acids and other compounds present in VO
208 have long been known to benefit our health. Numerous experimental studies approved that a
209 dietary intake of omega-3 polyunsaturated fatty acids can reduce inflammation and may prevent
210 the risk of chronic diseases like heart disease, cancer, and arthritis (Gammone et al., 2019;
211 Hardman and Fakas, 2016; Kris-Etherton et al., 2003). In addition, polyphenols, medium chain
212 fatty acids and tocopherol present in some VO were the reason of their antioxidant and antistress
213 activities (Duthie et al., 2016; Yaep et al., 2015). Current animal studies have indicated that
214 palmitic acid had a potent antiviral property against HIV-1 and HIV-2 (Özçelik et al., 2005).
215 Linoleic and oleic acids were considered as effective antibacterial agents (Dilika et al., 2000).
216 Further experimental studies highlighted other biological benefits of VO such as anti-
217 inflammatory (Hsu and Parthasarathy, 2017), analgesic and antipyretic (Intahphuak et al.,
218 2010), hypolipidemic (Ali and El-Anany, 2017), antibacterial (Tabassum and Vidyasagar,
219 2014), antiviral (Orhan et al., 2011), hepatoprotective and gastroprotective properties (Cheng
220 et al., 2015).

221 In the pharmaceutical field, plant oils entered in the composition of many dosage forms
222 through several pathways, including the cutaneous route (creams, ointments, massage oils,
223 gels), the oral route (tablets, syrup, capsules), the rectal route (suppositories) and the pulmonary
224 route (aerosols, nasal drops, sprays) (El-Asbahani et al., 2015). Despite that, the preparations
225 based on plant oil have some important constraints. The VO oral delivery is always confronted
226 to their low solubility in biological fluids, low permeation and poor bioavailability because of
227 their possible oxidation in the gastrointestinal tract (Márquez-Ruiz et al., 2008). For instance,
228 Kanner and Lapidot (2001) suggested that the adsorbed oxygen and low pH of the human
229 gastric fluid may enhance the oxidation of VO in the presence of catalysts found in foods.
230 Moreover, it was reported that hydroperoxide resulted from the hydrolysis of triacylglycerol

231 contained in VO by pancreatic lipase are not likely to be absorbed in their intact form (Suomela
232 et al., 2004).

233 Additionally, the toxicity and irritation effects of EO on the oesophageal and gastro
234 intestinal mucosa limit also their uses. EO could be the reason of potential allergic reactions of
235 the skin if they are undiluted or insufficiently diluted (Pedro et al., 2013; Warshaw et al., 2015).
236 For instance, applying excessive amounts of cinnamaldehyde rich-EO to a large surface of the
237 skin can result in significant allergic reaction and anaphylactic shock, which in turn may be
238 fatal (Diba and Statham, 2003). Some oils like those extracted from cumin, bergamot, verbena
239 and lemon can cause photosensitization and induce malignant skin changes like redness,
240 itching, burns, hyperpigmentation, pigmentary changes or berloque dermatitis (Zammit, 2010).
241 Moreover, the high volatility and the high risk of deterioration of EO upon their direct exposure
242 to heat, humidity, light, or oxygen discourages their free use, *i.e.* without a pharmaceutical
243 vehicle (Turek and Stintzing, 2013). Therefore, the nanoncapsulation has been considered as a
244 key to overcome the mentioned limitations (El-Asbahani et al., 2015; Sagiri et al., 2016).

245 Encapsulation strategies help in converting oils into several dosage forms including,
246 liquid, solid or semi-solid dosage forms and thus enables retention of their activity for longer
247 periods of time (Sagiri et al., 2016). Nanocarriers protect plant oils from environmental factors
248 such as pH, oxygen, light etc., serving as barrier between the molecule and the environment.
249 They also shield the oils from oxidative degradation, evaporation and photo-degradation (Bilia
250 et al., 2014). Their ability to control oil release confers improved efficacy, reduced toxicity,
251 improved patient compliance and convenience (El-Asbahani et al., 2015; Zhao et al., 2017).

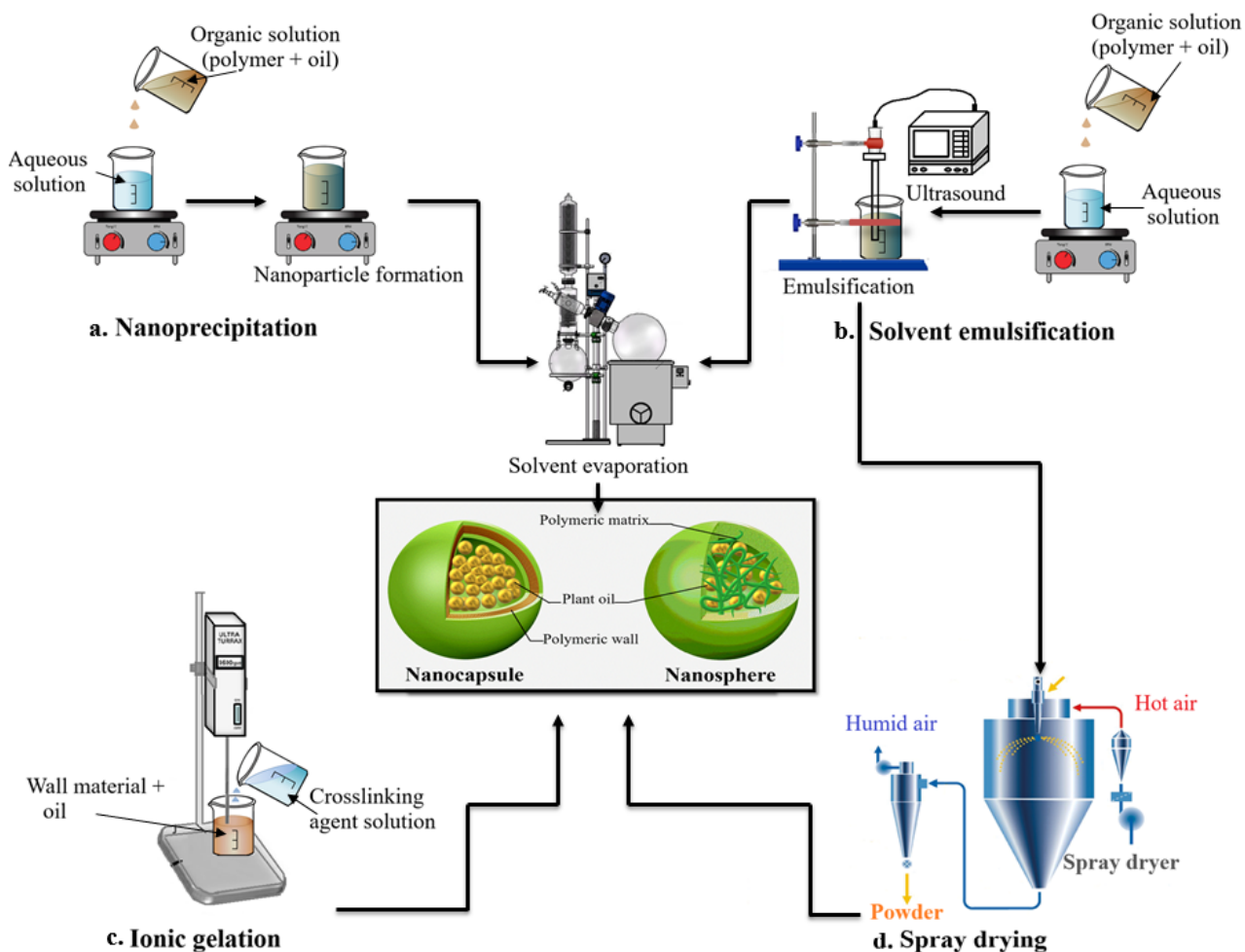
252 **5. Plant oils-loaded nanodelivery systems**

253 Nanodelivery systems is an area of intense research as they provide a number of benefits
254 for therapy, such as (i) high drug efficacy, specificity and tolerability, (ii) sustained and
255 controlled release of drugs (iii) less risk of toxicity (iv) deep tissue diffusion due to the

256 nanometric size, and (iv) protection of drugs at both extracellular and intracellular levels (Bilia
257 et al., 2014; Kumari et al., 2010). In this paper, we highlighted the different experimental
258 strategies designed to encapsulate plants oils into two main groups of organic nanocarriers;
259 polymer based-nanocarriers (including polymeric nanoparticles) and lipid based-nanocarriers
260 (including liposomes and solid lipid nanoparticles).

261 **5.1. Encapsulation in polymer-based nanocarriers**

262 Polymeric nanoparticles (pNP) are submicronic core–shell spherical systems prepared
263 from natural or synthetic polymers (Mattheolabakis et al., 2012). Depending on the nanoparticle
264 preparation process, nanocapsule or nanosphere can be obtained. Nanospheres have a matrix-
265 like form in which the drug is evenly distributed. Nanocapsules are, however, vesicular
266 structures in which the drug is confined in an inner core surrounded by a polymeric membrane
267 (Crucho and Barros, 2017) (**Fig. 5**). Many polymers were used for this purpose, notably,
268 biodegradable polyesters like poly(lactide-co-glycolide), polylactide and poly (ϵ -caprolactone)
269 were widely used (Froiiio et al., 2020). Recently, pNP are extensively studied for plant oil
270 delivery in view of their ability to entrap and protect oils, biodegradability, bioavailability and
271 their high stability. The plant oil may be conjugated with the polymer (matrix or wall) or
272 entrapped in the oily core (Bilia et al., 2014). Several methods have been reported for
273 developing pNP while the nanoprecipitation, the ionic gelation, the emulsification/solvent
274 evaporation and spray drying methods, are extensively used and **Fig. 5** demonstrates the
275 principle of each technique.



277 **Fig. 5.** Schematic illustration of the techniques used to produce polymeric nanoparticles.

278

279 5.1.1. Spray drying

280 Spray-drying technique has been used for decades to encapsulate plant oils in micro-
 281 and nano polymeric particles. It is based on the conversion of an infeed (solution, emulsion or
 282 suspension) into a dry powder in a single and continuous step. With respect to the encapsulation
 283 of plant oil, oil in water emulsion was atomized into fine drops in a drying chamber where hot
 284 air is passed (150-250°C). A fast evaporation of water occurred leading to the instantaneous
 285 formation of powder (**Fig.5.d**) (Encina et al., 2016; Matos et al., 2019). Spray drying technique
 286 is extensively used to encapsulate both essential and vegetable oils in micro and nanoparticles,
 287 as illustrated in **Table 1**.

288 Regarding the particle size and the encapsulation efficiency (EE%) of the particles
289 produced by spray drying technique, high average diameter with moderate oil entrapment
290 amount have been reported by numerous work studies, as depicted in **Table 1**. Hoyos-leyva et
291 al. (2019) reported that almond oil loaded taro starch particles had an average size ranging from
292 1.4 to 31.1 μm with an EE% of 37.5%. In addition, De-Oliveira et al. (2014) found that *Lippia*
293 *sidoides* EO loaded alginate : cashew gum nanoparticles exhibited a spherical shape with size
294 ranging from 223 to 399 nm, zeta potential values in range of -30 to -36 mV and EE% of about
295 50 %. In another work, the same EO was encapsulated in chitosan : cashew gum based
296 nanoparticles owning an EE% of 70% with an average particle sizes in the range 335–558 nm
297 (Abreu et al., 2012). Furthermore, the mixture maltodextrin : soy protein was used to
298 encapsulate walnut oil and the resultant particles showed an average diameter of 4 to 10 μm
299 with an EE% equal to 60% (González et al., 2016).

300 The main feature of spray drying method is the formation of special particles. Indeed,
301 the scanning electron microscopy carried by Tonon et al. (2011) on flaxseed oil loaded
302 microparticles revealed the formation of hollow particles, i.e. particles with concave and
303 shriveled surfaces. Same images were found by Gallardo et al. when visualizing linseed oil-
304 loaded gum arabic microcapsules. They ascribed this form to vacuoles formation inside the
305 particles after the crust development. The magnitude of this process is inversely related to solid
306 concentration in the emulsion (Gallardo et al., 2013). Moreover, Wang et al. (2018) carrying
307 out confocal scanning laser microscopy on peony seed oil microparticles stated that the spray
308 dried particles had a complete core-shell structure with smooth surface and no apparent fissures
309 or cracks.

310 *In vitro* release profile of plant oils from particles prepared by spray drying technique
311 generally exhibit a controlled manner. In a study carried out by De-Oliveira et al. (2014) the
312 nanoparticles have reached a level of maximal release around 30–50 h. In that time, the content

313 of *Lippia sidoides* EO from alginate : cashew gum particles varied from 45 and 95% depending
314 on the ratio of used polymers. Higher and faster release rate was achieved with high amount of
315 cashew gum due to its greater hydrophilic character which allows greater diffusion of EO
316 through the polymeric wall. Conversely, a smaller and more controlled release was assessed
317 when increasing alginate content; after 50h, only 45% of oil was released. This was related to
318 the formation of compact network which in turn slow down the diffusion of EO to the external
319 medium (De-Oliveira et al., 2014).

320 Particles produced by spray drying process provides a high stability for encapsulated
321 oils. In this context, Hoyos-leyva et al. (2019) investigated the oxidative stability of almond oil
322 before and after encapsulation into taro starch microcapsules. They found that these systems
323 conferred more protection against oxidation when compared to unencapsulated almond oil due
324 to the relatively reduced porosity of the material, which in turn limits the exposure of the oil to
325 stress conditions during storage.

326 Several parameters have to be taken into consideration to efficiently entrap plant oils in
327 polymeric micro- and nanoparticles by spray drying technique. The influence of type and
328 amount of wall material on plant oils-loaded particles characteristics has been extensively
329 studied in the literature (Bae and Lee, 2008; Chin et al., 2018; Gallardo et al., 2013;
330 Laohasongkram et al., 2011; Lozano et al., 2012; Rodea-gonzález et al., 2012; Rubilar et al.,
331 2012; Shamaei et al., 2017). Carneiro et al. (2013) investigated the microencapsulation of
332 flaxseed oil by spray drying technique. They studied the potential of maltodextrin mixed with
333 different wall materials: arabic gum, whey protein concentrate and two types of modified starch
334 (Hi-Cap 100TM and Capsul TA) on droplets size. Results showed that the highest viscosity
335 presented by maltodextrin : arabic gum emulsion implies a higher resistance to droplets
336 movement, thus preventing coalescence and leading to smaller droplets size. Shamaei et al.
337 (2017) related the differences in the mean droplet size of the emulsions using different wall

338 material to the surface activity and molecular weight of wall material constituents. They found
339 that as the ratio of tween 80 to skim milk powder increases, the mean droplet size decreases.
340 This in turn was attributed to the fact that tween 80 mitigated droplet coalescence and Ostwald
341 ripening phenomena in the emulsion by reducing the surface tension and interfacial free energy
342 of the emulsion. In another study, emulsion droplet size was found to decrease as the ratio of
343 wall to core material increases due to the fact that at low ratio, there may not be enough coating
344 materials to cover the whole surface of the droplets in order to prevent them from coalescence
345 which in turn increases the droplet size (Rodea-gonzález et al., 2012). Same result was also
346 reported for chia seed oil-loaded microcapsules prepared by spray drying process
347 (Laohasongkram et al., 2011). Moreover, Chew et al. (2018) spotlighted that adding β -
348 cyclodextrin to the wall matrix increases the EE% of refined kenaf seed oil due to its host-guest
349 character. In fact, its interior cavity acts as a host which can fix the guest (hydrophobic oil),
350 while the exterior surface can bind with water or hydrophilic head of other wall materials.
351 Furthermore, Us-medina and coworkers (2018) stated that adding chia mucilage to sodium
352 caseinate : maltodextrin wall matrix increases the EE% of chia seed oil from 71.26 to 86.65%.
353 They attributed this result to the fact that chia mucilage, used as thickener agent, increases the
354 viscosity of the system which in turn promotes a greater physical stability of the emulsion
355 during the spray drying process.

356 With respect to the oil content, Rubilar et al. (2012) revealed that increasing the oil
357 concentration provokes a significant increase in droplet emulsion size and viscosity, which in
358 turn reduces the EE% and increases the surface oil content of the powder leading to potential
359 lipid oxidation. Similar result was already published (Tonon et al., 2012).

360 Air inlet temperature is another factor to take into account for the development of plant
361 oil-loaded particles; and it was widely investigated in the literature (Frascareli et al., 2011;
362 Laohasongkram et al., 2011; Roccia et al., 2014; Shamaei et al., 2017). Frascareli et al. (2011)

363 studied the encapsulation of coffee oil and observed that as the air flow temperature increases
364 the EE% decreases due to the fact that higher temperature leads to faster drying of the external
365 phase which creates cracks in the particle wall, resulting in oil loss. Moisture content is an
366 important variable for the shelf life of powders. It was reported that increasing the inlet
367 temperature reduced the moisture content (Mohammed et al., 2017). However, higher values
368 (more than 175 °C) resulted in an increase in moisture content due to the formation of rapid
369 crust which hampered the water evaporation leading to particles with more moisture content.
370 The particle size is another parameter which vary when modifying the air inlet temperature. In
371 2017, Mohammed and coworkers pointed out that an increased inlet air temperature produced
372 larger-sized *Nigella sativa* EO particles and ascribed this result to the microcapsule structure.
373 Indeed, high temperature enable the particles to form early which in turn prevents the shrinkage
374 of particles during drying (Mohammed et al., 2017).

375 To sum up, despite of the high temperature required, the spray drying method is widely
376 used to encapsulate either essential or vegetable oils. This was related to the fact that short time
377 of contact between hot air and plant oil occurred, and thus the evaporation happens between 15
378 and 30 seconds and takes place at the surface of the particle; hence , the oils never reach the
379 inlet temperature of drying gas (Fang and Bhandari, 2012). According to **Table 1**, natural
380 polymers like maltodextrin, gums and chitosan are the mostly used wall materials. Currently,
381 this technique is widely used in nutraceutical and food industry due to its benefits including i)
382 ease of scaling up, ii) simplicity, iii) low production costs, and iv) ability to produce
383 microparticles facile to the transport and storage. Many drawbacks are associated to the use of
384 this process including the lack of uniformity; high particle size, low oil loading and possibility
385 of oil loss. Moreover, the wall material used must have good water solubility as most
386 formulations used by the food industry are aqueous-based and simultaneously impart a suitable
387 viscosity in order to enable the drying process (Corrêa-Filho et al., 2019).

388 5.1.2. Emulsion evaporation

389 Emulsion evaporation method has been proposed by Vanderhoff and Asser (1979) to
390 develop pNPs. In this process, an organic solution consisting of polymer and oil is emulsified
391 with a non-solvent mixture under a high shear stress (e.g. by high-shear homogenization or
392 ultrasonication). After that, the organic solvent is evaporated either by continuous magnetic
393 stirring at room temperature or under reduced pressure leading to nanoparticles formation
394 (**Fig.5.b**) (Rao and Geckeler, 2011; Rodríguez et al., 2016). This technique has been used to
395 encapsulate both essential and vegetable oils in pNPs, as depicted in **Table 1**.

396 The emulsion evaporation technique produces nanoparticles with higher EE% and
397 smaller average diameter, as compared to the spray drying technique. In this context, Gomes et
398 al. (2011a) reported a particle size of 179.3 and 173.8 nm with an EE% of 98 and 92% for
399 eugenol- and trans-cinnamaldehyde loaded poly (lactide-co-glycolide) nanoparticles,
400 respectively. Similarly, chia seed oil loaded nanoparticles using chia mucilage as wall material
401 exhibited a small particle size (205 nm) with negative zeta potential (-11.58 mv) and high EE%
402 (82.8%) (Campo et al., 2017). Moreover, poly (lactide-co-glycolide) nanoparticles were
403 prepared to encapsulate clove EO, rich in eugenol which has potent antimicrobial activities
404 (Priyadarshini et al., 2018). The average size of the resultant nanoparticles was about 237 nm
405 with negative zeta potential of -40 mv and an EE% equal to 93%.

406 The nanoparticles prepared by emulsion evaporation process exhibited *in vitro* release
407 pattern similar to that of particles produced by spray drying. In 2018, Priyadarshini et al. pointed
408 out that *in vitro* cumulative clove EO release from poly (lactide-co-glycolide) nanoparticles
409 followed a biphasic profile with an initial burst release at the first 4h due to the release of clove
410 EO found near the nanoparticles surface (Priyadarshini et al., 2018). A cumulative amount of
411 75% was progressively released up to ~15 days. Similar *in vitro* release kinetics were governed
412 by eugenol and trans-cinnamaldehyde from poly (lactide-co-glycolide) nanoparticles where 64

413 and 87% of the initial load was released in the medium within 72 h, respectively (Gomes et al.,
414 2011a).

415 The stability of the pNPs formulated by this technique was investigated in the literature.
416 In 2017, Campo et al. studied the oxidation of chia seed oil by gas chromatography with flame
417 ionization detector in both emulsions and chia seed mucilage based-nanoparticles at accelerated
418 conditions ($40\pm 1^\circ\text{C}$) during 28 days of storage (Campo et al., 2017). No significant change was
419 shown in term of particle size, zeta potential or polydispersity index. However, the fatty acid
420 methyl esters content reduction in pNPs was smaller than in emulsions; therefore, the chia seed
421 mucilage provided a high protection against oil oxidation (Campo et al., 2017).

422 With respect to the emulsification evaporation process, several parameters may affect
423 the nanoparticles properties. Freiburger et al. (2015) investigated the effect of polymer type
424 (poly(3-hydroxybutyrate-co-3-hydroxyvalerate)/polylactide); dispersion mechanism
425 (ultrasonication / high shear homogenization) and polymer : oil ratio on the average size and
426 oil recovery of biocompatible nanoparticles containing coffee oil. The statistical analysis
427 showed non-significant effect of the experimental factors on the nanoparticle size within the
428 experimental range. While for the coffee oil recovery, regression analysis produced a significant
429 model. Less oil was lost by volatilization when sonication was used, because the required
430 dispersion time (3min) was smaller when compared to the ultraturrax time (10min). Results
431 showed also that less coffee oil loss was pronounced when using poly(3-hydroxybutyrate-co-
432 3-hydroxyvalerate) combined to the high shear homogenization as well as using polylactide
433 combined with sonication. This was explained by the high viscosity of poly(3-
434 hydroxybutyrate-co-3-hydroxyvalerate)-dichloromethane solution which could avoid oil
435 volatilization even with high shear homogenization (Freiburger et al., 2015). Regarding the
436 polymer:oil ratio, an increase in polymer amount lead to increase the viscosity of the solution
437 resulting in efficient oil protection from the heat generated by the homogenizer.

438 To sum up, the emulsification evaporation method can be used to encapsulate both
439 essential and vegetable oils. Although it provides high EE%, this method is less used to
440 encapsulate plant oils, as compared to the spray drying technique. The possible reason behind
441 this is the possible coalescence of droplets during evaporation which may lead to polydisperse
442 particles and the need for a high shear process.

443 **5.1.3. Nanoprecipitation**

444 Nanoprecipitation is a simple, fast and increasingly trending technique for nanoparticles
445 preparation (Almoustafa et al., 2017). It was firstly reported by Fessi et al. (1989) and it is
446 based on the interfacial deposition of polymers as a result of the displacement of a water
447 miscible solvent from a lipophilic solution (**Fig.5.a**) (Miladi et al., 2016). This method has been
448 widely used to encapsulate plants oils in pNPs and **Table 1** summarizes some work studies
449 using the nanoprecipitation process to encapsulate either essential or vegetable oils during the
450 last decade.

451 According to **Table 1**, the nanoparticles produced by nanoprecipitation process owned
452 small particle size, narrow distribution with high EE%. Iannitelli et al. (2011) developed
453 carvacrol loaded poly (lactide-co-glycolide) based-nanocapsules with a spherical shape, small
454 particle size (209.8 nm) and regular distribution (poly dispersibility index=0.26). Similarly,
455 *Cymbopogon martini* EO was efficiently entrapped in poly (ϵ -caprolactone) based-
456 nanoparticles with an average size of 282.1 nm, zeta potential equal to -27.2 mV and EE% of
457 about 99.54 % (Khoobdel et al., 2017). Furthermore, Babassu tree nut oil loaded- poly (lactide-
458 co-glycolide) nanoparticles exhibited an average diameter about 209.2 nm with a negative zeta
459 potential of -15.8 mV (Sousa et al., 2013).

460 In term of particle size, Esfandyari-Manesh and coworkers (2013) compared the
461 nanoprecipitation to the emulsification solvent evaporation method to design carvone/anethole
462 loaded poly (lactide-co-glycolide) nanoparticles and found that the particles produced by

463 nanoprecipitation had smaller average diameter (158 and 126 nm for anethole and carvone,
464 respectively) and narrower size distribution (0.08). Additionally, the amount of carvone and
465 anethole were determined respectively by HPLC and UV analysis and results showed higher
466 oil loading for the particles produced by nanoprecipitation (14.73 and 12.32% for anethole and
467 carvone, respectively). The authors related the low EO loading for the emulsification method
468 to its loss during the evaporation step which has taken a long time (about 3h). In addition, the
469 high particle diameter of the nanoparticles prepared by this method was attributed to the
470 difficulty for the mutual dispersion of the phase which is viscous due to the presence of high
471 amount of oil and polymer.

472 According to the literature, to develop pNPs with suitable physicochemical properties,
473 numerous factors had to be taken into consideration. The polymer type and amount have a
474 critical effect on nanoparticles average size. In 2017, Khoobdel et al. (2017) developing poly
475 (ϵ -caprolactone) -based nanoparticles loaded with rosemary EO reported that increasing
476 polymer quantity, leads in increasing the thickness of the particles shell and thus increasing
477 their mean diameter, instead of increasing their number. Moreover, low values of EE% were
478 observed when using Eudragit L100 as polymer for the encapsulation of *Siberian cedar* seed
479 oil or free fatty acids due to its porous structure which enabled oil leakage (Averina and
480 Allémann, 2013). Regarding the type of the EO, Liakos et al. (2018) studied the influence of
481 EO chemical composition on the particle size of three types of pNPs: Peppermint, cinnamon
482 and lemongrass EOs loaded-cellulose acetate nanocapsules. The average size was increasing as
483 follow: Cinnamon-pNPs <Peppermint-pNPs <Lemongrass pNPs. The larger pNPs were those
484 containing lemongrass EO, due to the presence of high percentage of geranial and neral which
485 have long carbon chains (≈ 10 C atoms) leading to larger pNPs when attached to cellulose
486 acetate. While, peppermint contains mainly 35% menthol and 27% menthone leading to the
487 creation of less uniform, complex and large nanoparticles. In the other hand, cinnamon EO

488 consists essentially of cinnamaldehyde which reacts with hydroxyl group of cellulose acetate
489 giving hemiacetal bound and hence combats the nanocapsules. Liakos and his coworkers
490 assessed also in their study higher zeta-potential upon increasing lemongrass EO concentration,
491 suggesting that some EO molecules are present onto the outer surface of the particles (Liakos
492 et al., 2018). Similarly, it was reported that the presence of lime EO decreased the zeta potential
493 and the values were 61.1 and 57.0 mV for free- and loaded- chitosan nanocapsules, respectively.
494 They attributed this result to the diminution of free NH_3^+ groups of chitosan following their
495 interaction with lime EO (Sotelo-Boyás et al., 2017b). However, in another work study, the
496 presence of rosemary EO did not affect the zeta potential of poly (ϵ -caprolactone) nanoparticles
497 which confirm its presence in the core of the nanoparticles instead of being adsorbed on their
498 surface (Khoobdel et al., 2017).

499 In term of surfactant type and amount, Badri et al. (2015) pointed out that the amount of
500 polyvinyl alcohol used as surfactant had no significant effect on the average diameter of poly
501 (ϵ -caprolactone) nanoparticles but at higher concentration (more than 0.1mg/mL), a significant
502 increase was assessed due to the deposition of extra polyvinyl alcohol on the nanoparticle
503 surface. Furthermore, it was reported that the use of span 20 instead of tween 20 gave smaller
504 rosemary EO-loaded nanocapsules, lower polydispersity index and limited loss of the oil during
505 the solvent evaporation step. In the presence of span 20, the hydrophilic lipophilic balance
506 (HLB) was between 12 and 15 (14.3), which was in the range of HLB necessary for rosemary
507 EO nanoemulsion stability (Ephrem et al., 2014). Furthermore, the effect of the ratio between
508 organic and aqueous phase may affect the particle size. Indeed, an increase in argan oil loaded
509 nanoparticles was assessed when increasing the organic to aqueous phase ratio due to the slow
510 diffusion of the organic solvent (acetone) to water resulting slow polymer precipitation and
511 thus, larger pNPs were obtained (Badri et al., 2015).

512 Regarding the effect of operating conditions, Badri et al. (2015) investigated the effect of
513 stirring speed and organic phase addition rate consisting of poly (ϵ -caprolactone), acetone,
514 argan oil, indomethacin and span20 on the physicochemical properties of the obtained pNPs.
515 Results revealed a decrease in particle size by increasing the stirring speed. While, it increases
516 when decreasing the organic phase addition speed due to the difficulty to get a homogenous
517 mixture of phases. Furthermore, Ephrem et al. (2014) studied the influence of the evaporation
518 method on the pNPs properties and rosemary EO loss and found that the evaporation of acetone
519 under normal pressure at room temperature was the best since it avoided heat and low pressure,
520 giving negligible loss of the encapsulated EO.

521 Recently, a novel form of pNPs was developed called lipid-core nanocapsules which is
522 composed of a mixture of oil and solid lipid surrounded by a polymeric wall (Ourique et al.,
523 2010). For instance, the oily core of pNP may consist of a liquid lipid, a mixture of liquid lipids,
524 or a mixture of liquid lipid and solid lipid. The latter concerns a specific form of nanocapsules
525 called lipid-core nanocapsules (Frank et al., 2015). Several research works have been already
526 published investigated the feasibility to entrap VO into lipid core NPs (Almeida et al., 2009;
527 Drozdek and Bazyli, 2016; Friedrich et al., 2008; Marchiori et al., 2017; Rigo et al., 2013;
528 Weber et al., 2016). In this context, nanoprecipitation technique was efficiently carried out to
529 develop borage oil : betamethasone co-loaded lipid-core nanocapsules with a mean size around
530 210 nm, negative zeta potential (-16.6mv), low polydispersity index (<0.05) and high EE% (up
531 to 100%) (Weber et al., 2016). Furthermore, Rigo et al. (2013) studied the influence of the type
532 of VO on the release kinetic of clobetasol propionate, selected as model drug, from the lipid
533 core nanoparticles. Results revealed a biphasic drug release profiles for all the formulations.
534 After 168 h, the concentration of clobetasol propionate released from the formulation was in
535 the following order: Sunflower oil-pNPs < Soybean oil-pNPs < Rice ban-pNPs. The authors
536 related these results to the consistency indices of the mixture oil : sorbitan monostearate, used

537 as solid lipid; and a greater control of the drug release was observed with higher consistency
538 index of the VO-sorbitan monostearate.

539 Regarding the nanoparticles stability, Badri et al. (2018) investigated the stability of poly
540 (ϵ -caprolactone) based nanoparticles containing *Nigella sativa* EO coupled with indomethacin
541 during one month under three different conditions (4°C, 25°C and 40°C). The samples were
542 analyzed at predefined times and results demonstrated no significant change in either size or
543 zeta potential for all the tested particles. Similarly, the photodegradation study of the lipid-core
544 nanocapsules containing borage oil and betamethasone was carried out to demonstrate the
545 ability of nanocapsules in the photoprotection of the drug. In brief, nanoparticles suspensions
546 were placed in transparent quartz cell and exposed to UVC radiation and the total concentration
547 of drug was quantified. Results revealed a degradation of 61% from the nanocapsules
548 suspension at the end of the experiment (10 h), while 58% of drug was degraded in 2 h from
549 drug solution. This confirmed the property of polymeric wall to protect the bioactive molecules
550 (Weber et al., 2016).

551 Regarding the scalability and reproducibility of the nanoprecipitation process, it was
552 noticed no significant difference between rosemary EO loaded poly (ϵ -caprolactone)
553 nanocapsules prepared at small and large scales in term of shape, particle size, polydispersity
554 index zeta potential and EE% (Ephrem et al., 2014).

555 Overall, the nanoprecipitation or solvent displacement method is widely used to develop
556 pNPs for plants oils encapsulation. According to the **Table 1**, the polymers commonly used to
557 design the polymeric matrix are synthetic polyesters like poly (lactide-co-glycolide)
558 (Esfandyari-Manesh et al., 2013; Iannitelli et al., 2011; Sousa et al., 2013), poly (ϵ -
559 caprolactone) (Badri et al., 2018; Christofoli et al., 2015; Ephrem et al., 2014; Jummes et al.,
560 2020; Khoobdel et al., 2017), polylactide (Liakos et al., 2016), Eudragit®L100 (Averina and
561 Allémann, 2013), S100 (Averina and Allémann, 2013), L100-55 (Pina-Barrera et al., 2019) and

562 RS100 (El-Asbahani et al., 2015; Froiio et al., 2019). Synthetic polymers are more used than
563 natural ones like chitosan (Luque-Alcaraz et al., 2016; Sotelo-Boyás et al., 2015, 2017a, 2017b)
564 and cellulose derivatives (Liakos et al., 2018; Marchiori et al., 2017) because they have higher
565 purity and better reproducibility. The benefits associated to this encapsulation method are
566 rapidity, simplicity, reproducibility, and scalability. Moreover, NPs with narrow size
567 distribution, high EE% and high stability could be obtained. In addition, the use of surfactant
568 or high production energy is avoided. The main drawback of this method in encapsulating plant
569 oils is the use of organic solvents which may be toxic for health.

570 **5.1.4. Ionic gelation**

571 In order to avoid the use of toxic organic solvent or high shear forces, Calco et al. (1997)
572 proposed a novel approach called ionic gelation or coacervation. Alginate, an anionic
573 polysaccharide, and chitosan, a cationic polyelectrolyte, are extensively used for ionic gelation
574 purpose. These polyelectrolytes can interact with crosslinking agents like tripolyphosphate
575 having an opposite charge via electrostatic interaction and aggregate into nanoparticles (J. Yang
576 et al., 2015). The coacervation consists on the transition from liquid to gel state upon
577 complexation between the oppositely charged molecules at determined pH values leading to
578 the formation of nano-sized particles (Nagavarma et al., 2012) (**Fig.5.c**). A number of studies
579 have been carried out using this technique to encapsulate plant oils, as displayed in **Table 1**.

580 Recently, cinnamon EO-loaded chitosan nanoparticles crosslinked with
581 tripolyphosphate were prepared by using coacervation method and the obtained particles owned
582 small average diameter (80-100 nm) with good zeta potential values (-11.2 to -22.4 mV) (Liu
583 et al., 2017). In addition, cardamom EO was successfully entrapped into chitosan based
584 nanoparticles with an average particle size ranging between 50 and 100 nm, zeta potential more
585 than +50 mV and a high EE% which was more than 90% (Jamil et al., 2016). Furthermore,
586 Woranuch and his coworker (2013) reported that the thermal stability of eugenol was enhanced

587 by encapsulation in chitosan: tripolyphosphate- nanoparticles. According to some research
588 works depicted in Table 2, the ionic gelation technique may produce microparticles with
589 moderate EE% as compared to the nanoprecipitation process (Feyzioglu and Tornuk, 2016;
590 López-meneses et al., 2018; Sutaphanit and Chitprasert, 2014; Yang et al., 2014; K. Zhang et
591 al., 2012).

592 Currently, several research works have been reported to investigate the effect of pNPs
593 composition and operating conditions on physicochemical properties of particles prepared by
594 ionic gelation method. The optimization of the type and amount of polymer and crosslinking
595 agent is crucial to develop pNPs with suitable characteristics. In this approach, *Carum copticum*
596 EO-loaded chitosan nanoparticles were prepared by ionic gelation method using two types of
597 crosslinking agents: tripolyphosphate and hexametaphosphate (Esmaeili and Asgari, 2015). The
598 efficacy of crosslinking agent type and tripolyphosphate concentration on the EE% were
599 evaluated. The particles prepared using hexametaphosphate (0.5% (w/v)) had significantly
600 lower loading capacity and EE% than those prepared using tripolyphosphate (0.5% (w/v)). This
601 was attributed to the ring structure and bigger size of hexametaphosphate which in turn lead to
602 decrease the crosslinking phenomenon. In the same work, different nanoparticles were prepared
603 using different tripolyphosphate concentrations (0.25, 0.5, 0.75 and 1% (w/v)) and results
604 indicated that maximum EE% was obtained with the concentration of 0.5% (w/v). The low
605 value of EE% obtained with the concentration of 0.25% (w/v) was explained by the shortage of
606 tripolyphosphate concentration to crosslink the nanoparticles; while the low values shown with
607 0.75 and 1% (w/v) tripolyphosphate concentrations were related to the particle shrinkage
608 (Esmaeili and Asgari, 2015).

609 With respect to the polymer effect, the viscosity of chitosan was optimized for
610 fabrication of vanilla oil loaded microcapsules using the coacervation method (Yang et al.,
611 2014). Results showed that at low chitosan viscosity, no microcapsules were formed because

612 chitosan at low viscosity could not form hard membrane wall. On the other hand, when using
613 high viscosity chitosan, aggregation problem was observed (Yang et al., 2014).

614 Regarding the EO concentration, Hasheminejad et al. (2019) stated that both particle
615 size and zeta potential decreased significantly when increasing clove EO concentration. The
616 reduction in particle size was explained by the great packing of polymer chains, due to the high
617 number of amino groups in chitosan responsible for the interaction with the oil. Additionally,
618 the thermogravimetric analysis performed by Hosseini et al. (2013) on oregano EO loaded-
619 chitosan nanoparticles demonstrated that as the initial EO content increases from 0.1 to 0.8 g/g
620 chitosan, loading capacity increases too from 3 to 8%, but the EE% decreases from 47 to 21%.
621 This was explained by the saturation of oregano EO loaded into chitosan nanoparticles. The EO
622 concentration was found to affect also the *in vitro* release profile. Indeed, Hosseini and his
623 coworkers reported that low concentration of oregano EO (0.1 g/g chitosan) leads to burst
624 release (82% of encapsulated EO was released from the nanoparticles within 3 h). While, as
625 oregano EO amount increased, the burst effect was dramatically alleviated and the cumulative
626 release was reduced from 82 to 12% after 3h. This phenomenon was attributed to the fact that
627 chitosan nanoparticles with smaller particle size would have bigger surface-to-volume ratio
628 which may result in fast release of oregano EO adsorbed on their surfaces (Hosseini et al.,
629 2013). Another factor affecting the release profile was found to be the composition of the
630 encapsulated material. In 2014, Dima et al. investigating the release of *Pimenta dioica* EO
631 found that chitosan microspheres covered with k-carrageenan are more fragile and exhibit
632 higher swelling degree with zero order release kinetics, as compared to the chitosan : k-
633 carrageenan microspheres hardened by glutaraldehyde crosslinking which show non-Fickian
634 release mechanism (Dima et al., 2014).

635 Numerous research works noticed the stability of pNPs produced by ionic gelation
636 method. In 2014, Sutaphanit et al. reported that the encapsulation of holy basil EO into gelatin

637 by simple coacervation method could prevent its volatility and oxidation (Sutaphanit and
638 Chitprasert, 2014). Indeed, the particles stored under accelerated conditions at 60 °C for 49 days
639 exhibited small decreases in the holy basil EO retention rate and antioxidant activity (Sutaphanit
640 and Chitprasert, 2014). Moreover, the stability studies performed on peppermint oil loaded
641 capsules showed that only 7% of the oil was released during the storage of 40 days in cold water
642 (Dong et al., 2011). In another work study, jasmine EO nanoparticles exhibited high heat-
643 stability against humid heat (80°C for 7h) (Lv et al., 2014).

644 On the whole, ionic gelation method is broadly used to encapsulate plants oils when
645 compared to simple emulsion evaporation method. Gelatin (Devi et al., 2012; Dong et al., 2011;
646 Sutaphanit and Chitprasert, 2014; K. Zhang et al., 2012), arabic gum (Dong et al., 2011; Lv et
647 al., 2014; X. Yang et al., 2015; K. Zhang et al., 2012), alginate (Devi et al., 2012; Natrajan et
648 al., 2015) and chitosan (Feyzioglu and Tornuk, 2016; Hosseini et al., 2013; Jamil et al., 2016;
649 Liu et al., 2017; López-meneses et al., 2018) are the most commonly used wall materials. In
650 addition, tripolyphosphate (Hasheminejad et al., 2019; Hosseini et al., 2013; Hu et al., 2015;
651 Liu et al., 2017; Woranuch and Yoksan, 2013) and glutaraldehyde (Devi et al., 2012; Dima et
652 al., 2014; Natrajan et al., 2015; Sutaphanit and Chitprasert, 2014) are widely used as
653 crosslinking agents. The main advantages of ionic gelation method are, in particular; the
654 avoidance of high shear forces and the use of aqueous solvents instead of organic ones.
655 Moreover, ionic gelation is simple, economic and reproducible. However, moderate EE% and
656 larger particle size were assessed using this method as compared to the nanoprecipitation
657 technique.

658 **Table 1.** Preparation methods for plant oils encapsulation in polymeric nanoparticles and fine applications.

Encapsulated oil	Plant (origin)	Wall material	Physicochemical properties			Biological properties	Application	Ref.
			Size (nm)	Z.pot (mv)	EE (%)			
<i>Nanoprecipitation method</i>								
Costus	<i>Saussurea lappa</i>	Eudragit RS 100	145	+45	/	Anticholinesterase, anti-inflammatory	Medicine	(Lammari et al., 2021)
Baccharis dracunculifolia	<i>Baccharis dracunculifolia</i> DC	Eudragit RS 100	151.6	+51.7	99.4	Antibacterial	Food	(Timbe et al., 2020)
Oregano	<i>Origanum vulgare</i> L.	PCL	158-300	-13.8 to -28.5		Antibacterial	Food	(Souza et al., 2020)
Palmorasa	<i>Cymbopogon martini</i> Roxb.	PCL	282.1	-27.2	99.54	Antioxidant, antimicrobial	Cosmetic	(Jummes et al., 2020)
Geraniol	/	PCL	289.3	-26.6	99.88	Antioxidant, antimicrobial	Cosmetics	(Jummes et al., 2020)
Zataria	<i>Zataria multiflora</i> Boiss.	PCL	192-398	+13.9 to +29.2	75-79	Insecticide	Agriculture	(Ahsaei et al., 2020)
Thyme	<i>Thymus vulgaris</i> L.	Eudragit L 100-55	153.9	-4.11	52.81	Antioxidant	Food	(Pina-Barrera et al., 2019)
	<i>Thymus leptobotrys</i> L.	Eudragit RS 100	144	+80.9	/	Bacteriostatic, fungistatic	Medicine	(El-Asbahani et al., 2015)
	<i>Thymus satureoides</i> L.	Eudragit RS 100	132	81.6	/	Bacteriostatic, fungistatic	Medicine	(El-Asbahani et al., 2015)
	<i>Thymus serpyllum</i> L.	Chitosan	117-226	+27	/	Antimicrobial	Agriculture	(Sotelo-Boyás et al., 2015)
		Chitosan	/	/	68	Antimicrobial	Agriculture	(Sotelo-Boyás et al., 2017a)
Sweet orange	<i>Citrus sinensis</i> L.	Eudragit RS100	57- 208	+39 to +74	56-96	Antimicrobial	Food	(Froiio et al., 2019)
Bergamot	<i>Citrus bergamia</i> Risso.	Eudragit RS100	57- 208	+39 to +74	28-84	Antimicrobial	Food	(Froiio et al., 2019)
Rosemary	<i>Rosmarinus officinalis</i> L.	PCL	181-407	+11.6 to +28.3	82.9-84.3	Insecticide	Agriculture	(Ahsaei et al., 2020)
		Eudragit EPO	200	/	59	Antioxidant	Cosmetics	(Silva-Flores et al., 2019)
		PCL	145	-11.0	78.2	Insecticide	Agriculture	(Khoobdel et al., 2017)
		PCL	220	-19.9	99	Antioxidant, antimicrobial	Medicine	(Ephrem et al., 2014)
Lavender	<i>Lavandula dentate</i> L.	Eudragit EPO	200	/	41	Antioxidant	Cosmetics	(Silva-Flores et al., 2019)
		PEO-b-PLA	10-75	/	70-75	Antimicrobial	Textile	(Popiolski et al., 2016)
Peppermint	<i>Mentha piperita</i> L.	Cellulose acetate	180	-38	/	Antimicrobial	Medicine	(Liakos et al., 2018)
Cinnamon	<i>Cinnamomum cassia</i> persl.	Cellulose acetate	150	-40	/	Antimicrobial	Medicine	(Liakos et al., 2018)
Lemongrass	<i>Cymbopogon citratus</i> DC.	PLA	96.4	/	99	Antifungal	Medicine	(Antonioli et al., 2020)
		Cellulose acetate	200	-36	/	Antimicrobial	Medicine	(Liakos et al., 2018)
		PLA	300	-6	/	Antimicrobial	Medicine	(Liakos et al., 2016)
Black seed oil + Indometacin	<i>Nigella sativa</i> L.	PCL	230–260	–20 to–30	Oil=84 Drug=70	Anti-inflammatory	Cosmetics	(Badri et al., 2018)

Lime	<i>Citrus aurantiifolia</i> Christm.	Chitosan	100-300	+57	/	Antimicrobial	Food	(Sotelo-Boyás et al., 2017b)
		Chitosan	250-1000	+20.2	/	Antimicrobial	Agriculture	(Sotelo-Boyás et al., 2015)
Pepper tree	<i>Schinus molle</i> L.	Chitosan	754	+9.1	/	Antifungal	Food	(Luque-Alcaraz et al., 2016)
<i>Zanthoxylum rhoifolium</i>	<i>Zanthoxylum rhoifolium</i> L.	PCL	500	-20	96	Insecticide	Agriculture	(Christofoli et al., 2015)
Argan oil +Indometacin	<i>Argania spinosa</i> L.	PCL	290 - 350	-40 to-50	65 - 75	Anti-inflammatory	Cosmetics	(Badri et al., 2015)
<i>Pelargonium graveolens</i>	<i>Pelargonium graveolens</i> L.	Eudragit RS 100	113	+80.6	/	Bacteriostatic, fungistatic	Medicine	(El-Asbahani et al., 2015)
<i>Eugenia caryophyllata</i>	<i>Eugenia caryophyllata</i> C.	Eudragit RS 100	131	+80.7	/	Bacteriostatic, fungistatic	Medicine	(El-Asbahani et al., 2015)
Carvacrol	/	PLA	114.7	+54.7	53.9	Antimicrobial	Food	(Niza et al., 2020)
		PHB	146	-26	21	Antimicrobial	/	(Shakeri et al., 2014)
		PLGA	209.8	/	26	Antimicrobial	Medicine	(Iannitelli et al., 2011)
Carvone	/	PLGA	126	/	/	Antimicrobial	Food	(Esfandiyari-Manesh et al., 2013)
Anethole	/	PLGA	158	/	/	Antimicrobial	Food	(Esfandiyari-Manesh et al., 2013)
Date seed	<i>Phoenix dactylifera</i> L.	Eudragit RS 100	207	+59	97	Antidiabetic	Medicine	(Lammari et al., 2020)
Pomegranate oil+ Silibinin	<i>Punica granatum</i> L.	Ethylcellulose	/	/	/	Anti-inflammatory for skin damage UVB	Cosmetics	(Marchiori et al., 2017)
Rosehip	<i>Rosa rugosa</i> Thunb.	Eudragit RS100	158	+9.8	/	Accelerate the skin regenerating process	Cosmetics	(Contri et al., 2016)
Castor	<i>Ricin commun</i> L.	TAD	260-150	/	/	Source of PUFA	/	(Chattopadhyay and Prez, 2016)
Olive	<i>Olea europaea</i> L.	TAD	185	-30	/	Source of PUFA	/	(Chattopadhyay and Prez, 2016)
Pumpkin	<i>Cucurbita pepo</i> L.	TAD	172	-35	/	Source of PUFA	/	(Chattopadhyay and Prez, 2016)
Sunflower	<i>Helianthus annuus</i> L.	TAD	178	-33	/	Source of PUFA	/	(Chattopadhyay and Prez, 2016)
Hazelnut	<i>Corylus avellana</i> L.	TAD	175	-35	/	Source of PUFA	/	(Chattopadhyay and Prez, 2016)

Borage oil+ Betamethason e dipropionate	<i>Borago officinalis</i> L.	PCL	210	-16.6	100	Treatment of atopic dermatitis	Cosmetics	(Weber et al., 2016)
Rice bran	<i>Oryza sativa</i> L.	PCL	200	-9	/	Sunscreen (treatment of inflammatory disorders of skin)	Cosmetics	(Rigo et al., 2015)
Pine seed Free fatty acid	<i>Pinus pinea</i> L. /	Eudragit L 100-55 / Eudragit L100 / Eudragit S100	236-296 260-319	/ /	85-91 83-99	Source of PUFA	Medicine	(Averina and Allémann, 2013)
Babassu	<i>Attalea speciosa</i> Mart.	PLGA	209.2	-15.8	/	Treatment of benign prostatic hyperplasia	Medicine	(Sousa et al., 2013)
Emulsion evaporation method								
Mastic tree of Chios	<i>Pistacia lentiscus</i> L. var. chia	PLA	239-286	-29.1 to -34.5	9-37	Antimicrobial	Cosmetic	(Vrouvaki et al., 2020)
Clove	<i>Syzygium aromaticum</i> L.	PLGA	237.6	-40	93.95	Antimicrobial	Medicine	(Priyadarshini et al., 2018)
Eugenol	/	PLGA	179.3	/	98	Antimicrobial	Food	(Gomes et al., 2011a)
Trans- cinnamaldehy de	/	PLGA	173.8	/	92	Antimicrobial	Food	(Gomes et al., 2011a)
Chia seed	<i>Salvia hispanica</i> L.	Chia seed mucilage	205	-11.58	82.8	Source of PUFA	/	(Campo et al., 2017)
Coffee	<i>Coffea arabica</i> L.	PLA	263	/	112.7	Flavoring agent	Food	(Freiberger et al., 2015)
		PHBV	271		94.5	Flavoring agent	Food	(Freiberger et al., 2015)
Ionic gelation method								
Homalomena pineodora	<i>Homalomena pineodora</i> L.	Chitosan	70	+24.1		Wound healing	Medicine	(Rozman et al., 2020)
Piper nigrum	<i>Piper nigrum</i> L.	Chitosan	527.5	-5.3	35-40	Pesticide	Agriculture	(Rajkumar et al., 2020)
Nettle	<i>Urtica dioica</i> L.	Chitosan	208.3– 369.4	/	59.5-68.2	Antimicrobial	Food; Medicine	(Bagheri et al., 2020)
Tarragon	<i>Artemisia dracunculus</i> L.	Gelatin+Chitosan	246–505	27.1–37.1	9.8–35.6	Preservative	Food	(Zhang et al., 2020)
Camelthorn	<i>Alhagi maurorum</i> L.	Chitosan	172	+28.6	/	Antimicrobial	Medicine	(Hassanshahian et al., 2020)
Great morinda	<i>Morinda citrifolia</i> L.	Chitosan	1006	+43.5	/	Anticancer	Medicine	(Rajivgandhi et al., 2020)
Clove	<i>Syzygium aromaticum</i> L.	Chitosan	268.5	+22.4	/	Antifungal	Agriculture; Food	(Hasheminejad et al., 2019)
Pepper tree	<i>Schinus molle</i> L.	Chitosan	516.9	+40.2	26.6	Antifungal, anti- aflatoxicogenic	Medicine	(López-meneses et al., 2018)

Cinnamon	<i>Cinnamomum cassia</i> persl.	Chitosan	80–100	-11.2 to -22.4	47.67 - 55.64	Antimicrobial	Food	(Liu et al., 2017)
		Chitosan	215	/	/	Antimicrobial	Food	(Hu et al., 2015)
Cardamon	<i>Elettaria cardamomum</i> L. <i>Summer savory</i>	Chitosan	50–100	>+50	>90	Antimicrobial	Medicine	(Jamil et al., 2016)
		Chitosan	135.5-237.4	-9.68 to -21.12	35.1 –40.7	Antioxidant, antimicrobial	Food	(Feyzioglu and Tornuk, 2016)
	<i>Carum copticum</i>	Chitosan	/	/	36.2	Antioxidant, antimicrobial	Cosmetics; Medicine	(Esmacili and Asgari, 2015)
Tumeric	<i>Curcuma longa</i> L.	Alginate+Chitosan	<300	/	71	Anticancer	Medicine	(Natrajan et al., 2015)
Lemongrass	<i>Cymbopogon citratus</i> DC.	Chitosan	58	/	/	Antimicrobial	Food	(Sameen et al., 2020)
		Alginate+Chitosan	<300	/	86.9	Anticancer	Medicine	(Natrajan et al., 2015)
Jasmine	<i>Jasminum polyanthum</i> L.	Gelatin+Gum arabic		/	/	Flavor agent	Food; Textile	(Lv et al., 2014)
Holy basil	<i>Ocimum tenuiflorum</i> L.	Gelatin	392.30 .10 ³	/	95.41	Antioxidant	Medicine	(Sutaphanit and Chitprasert, 2014)
Pimenta	<i>Pimenta dioica</i> L.	Chitosan + k-carrageenan	/	/	/	Antioxidant, antifungal	Food	(Dima et al., 2014)
Eugenol	/	Chitosan	80–100	+16.2 to +33.5	1.1–20.2	Antioxidant	Food	(Woranuch and Yoksan, 2013)
Oregano	<i>Origanum vulgare</i> L.	Chitosan	40 - 80	/	/	Antioxidant, antimicrobial	/	(Hosseini et al., 2013)
Poppy seed	<i>Papaver somniferum</i> L.	Gelatin+arabic gum	<5000	/	76.8	Anti-cancer, anti-tumor, anti-diabetic	Medicine	(X. Yang et al., 2015)
Vanilla	<i>Vanilla planifolia</i> L.	Chitosan+arabic gum	7500	/	94.2	Flavor agent	Food	(Yang et al., 2014)
Olive	<i>Olea europaea</i> L.	Gelatin + Sodium alginate	/	/	/	Source of vitamins and fatty acids	Medicine	(Devi et al., 2012)
Peppermint	<i>Mentha piperita</i> L.	Gelatin+Arabic gum	/	/	/	/	/	(Dong et al., 2011)
Spray drying method								
Carvacrol	/	Pectin+sodium alginate	2580-5300	/	/	Antioxidant, antimicrobial	/	(Sun et al., 2020)
Black seed	<i>Nigella sativa</i> L.	Sodium caseinate + maltodextrin DE10	18500	/	95.4	Antioxidant	Medicine	(Mohammed et al., 2017)
Eucalyptus	<i>Eucalyptus staigeriana</i> L.	Cashew gum	27.7-432.6	+24.5 to +10.4	24.89 - 26.80	Antimicrobial	Food	(Herculano et al., 2015)
<i>Lippia sidoides</i>	<i>Lippia sidoides</i> L.	Alginate:cashew gum	223- 399	-30 to -36	50	Larvicide	Agriculture	(De-Oliveira et al., 2014)
		Chitosan+cashew gum	335–558	/	70	Larvicide	Agriculture	(Abreu et al., 2012)
		Chitosan	25	-17.3	77.8	Larvicide	Agriculture	(Paula et al., 2010)

Oregano	<i>Origanum vulgare</i> L.	Inulin	3000 - 4500	/	/	Antioxidant	Food	(Beirão da costa et al., 2013)
		Rice starch	3000 – 4500	/	/	Antioxidant, antimicrobial	Food	(Beirão da costa et al., 2012)
		Gelatine/sucrose	3000 – 4500	/	/	Antioxidant, antimicrobial	Food	(Beirão da costa et al., 2012)
Soybean	<i>Glycine max</i> L.	Kafirin + sodium caseinate	10450	/	/	Source of PUFA	Food	(X. Bai et al., 2019)
Almond	<i>Prunus dulcis</i> L.	Taro starch	1600–31.1.10 ³	/	37.5	Prevention of colon cancer and cardiovascular diseases	Medicine	(Hoyos-leyva et al., 2019)
Peony	<i>Paeonia lactiflora</i> L.	Whey protein+Corn syrup + Lecithin	/	/	93.6	Source of PUFA	Food	(Wang et al., 2018)
Refined kenaf seed	<i>Hibiscus cannabinus</i> L.	β-cyclodextrin + gum arabic + sodium caseinate	/	/	/	Source of MUFA and PUFA	/	(Chew et al., 2020)
		β-cyclodextrin + Arabic gum	(25.4–37.3). 10 ³	/	90.0-95.3	Source of MUFA and PUFA	/	(Chew et al., 2018)
		β-cyclodextrin +sodium caseinate						
Chia seed	<i>Salvia hispanica</i> L.	β-cyclodextrin + gum arabic + sodium caseinate						
		Sodium caseinate + maltodextrin + chia protein rich fraction + chia mucilage	/	/	53.4- 96.2	Source of omega 3	Food	(Us-medina et al., 2018)
		Maltodextrin + soy protein	4000-10000	/	≈ 60	Source of omega 3	Food	(González et al., 2016)
Walnut	<i>Juglans cinerea</i> L.	Skim milk powder + Tween 80	/	/	/	Source of PUFA, tocopherols and phytosterols.	Food; Medicine	(Shamaei et al., 2017)
Sunflower	<i>Helianthus annuus</i> L.	Maltodextrin + HPMC	/	/	79.43	Source of PUFA	/	(Roccia et al., 2014)
Linseed	<i>Linum usitatissimum</i> L.	Alginate+ whey protein	/	-44	84	Source of omega 3	Food	(Fioramonti et al., 2019)
		Maltodextrin +	600 -26000		62.3-95.7	Source of omega 3	Food	(Carneiro et al., 2013)

		Gum arabic					
		Gum arabic	/	/	≈ 90	Source of omega 3	Food (Gallardo et al., 2013)
		Gum arabic + Maltodextrin + whey protein	/	/	≈ 90	Source of omega 3	Food (Gallardo et al., 2013)
		Maltodextrin + methylcellulose	/	/	≈ 90	Source of omega 3	Food (Gallardo et al., 2013)
		Gum arabic	/	/	54.9 - 90.7	Source of omega 3	Food (Rubilar et al., 2012)
		Gum arabic + Maltodextrin	/	/	54.9 – 90.7	Source of omega 3	Food (Rubilar et al., 2012)
	<i>Macadamia integrifolia</i>	Sodium caseinate + maltodextrin	9750	/	88.75	Source of MUFA	Medicine (Laohasongkram et al., 2011)
Coffee	<i>Coffea arabica</i> L.	Arabic gum	4000-11.10 ³	/	10-30	Antioxidant	Cosmetic (Nosari et al., 2015)
		Arabic gum	7880-13.10 ³	/	48-88	Flavoring agent	Food (Frascareli et al., 2011)

659 PLGA: Polylactic glycolic acid; PCL: Polycaprolactone; PLA: Poly lactic acid; PHB: Poly(3-hydroxybutyrate); PEO: poly (ethylene oxide); TAD: 1,2,4-Triazoline-3,5-dione; PHBV: Poly(3-hydroxybutyrate-co-3-hydroxyvalerate);

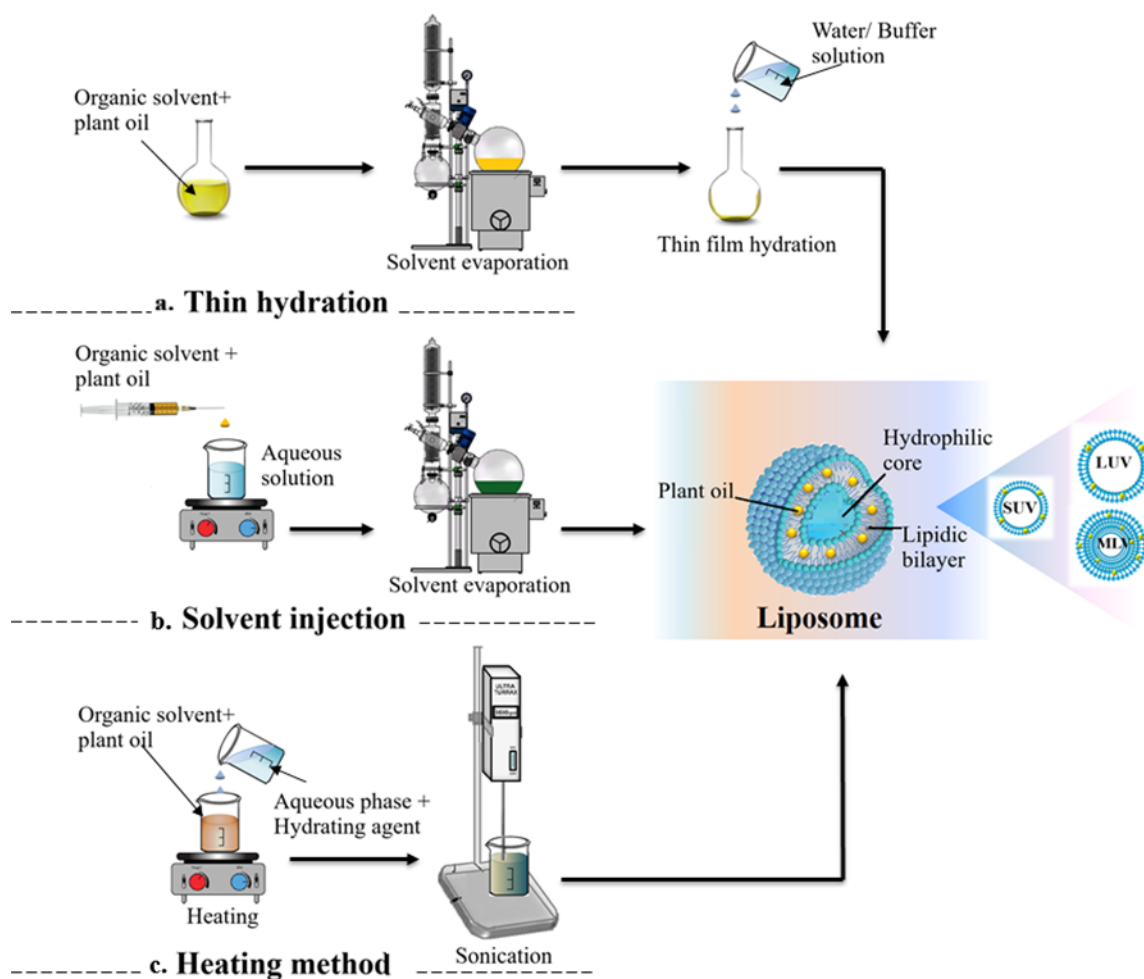
660 HPC: Hydroxypropylcellulose; HPMC: Hydroxypropylmethylcellulose; PVA: Poly vinyl alcohol; PUFA: Poly unsaturated fatty acids; MUFA: Mono unsaturated fatty acids.

661

662 **5.2. Encapsulation in lipid based nanocarriers**

663 **5.2.1. Liposomes**

664 Liposomes were first developed for drug delivery purposes by Bangham et al. in 1965
665 (1965). Liposomes are vesicles formed by one or more lipid bilayers defining one or several
666 aqueous compartments. They can be classified depending on their size and lamellarity to: i)
667 small unilamellar vesicles (SUV) with a size between 20nm and 100 nm, ii) large unilamellar
668 vesicles (LUV) with a size greater than 100 nm and iii) multilamellar vesicles (MLV) with a
669 size greater than 0.5 μ m, as demonstrated in **Fig. 6** (El-Asbahani et al., 2015). Generally, the
670 liposome bilayer consists of natural and/or synthetic phospholipids like phosphatidylcholine,
671 phosphatidylethanolamine, phosphatidylserine, phosphatidylglycerol and phosphatidylinositol.
672 Cholesterol may also be incorporated to the lipidic bilayer to reduce the permeability of water-
673 soluble molecules through the membrane and improve its fluidity, and stability (Laouini et al.,
674 2012). Due to the lipophilic character of the liposome bilayer, plant oils like essential or
675 vegetable oils are highly entrapped to enhance their bioavailability and hurdle their
676 physicochemical instability upon exposure to light, oxygen and temperature (El-Asbahani et
677 al., 2015). Several methods have been used to develop liposomes containing plants oils, while
678 the thin film hydration, solvent injection and heating methods were widely used in the last
679 decade.



680

681

Fig. 6. Schematic illustration of the techniques used to produce liposomes.

682

5.2.1.1. Thin lipid film hydration

683

Thin lipid film hydration or thin membrane hydration is the first process which was initially used for liposomes production (Bangham et al., 1965). A mixture of lipid ingredients was dispersed in organic solvent in a round-bottom flask. Subsequent evaporation of the organic solvent was performed using a rotary evaporator at reduced pressure. Finally, the hydration of the formed lipid film by water or buffer solution under agitation at temperature above the lipid transition temperature allows the formation of MLVs dispersion (**Fig.6.a**) (Laouini et al., 2012).

689

Liposome size reduction techniques, such as sonication or extrusion were applied to ensure size reduction and particles uniformity (Patil and Jadhav, 2014). Thin hydration method was extensively used to develop plant oils-loaded liposomes, as illustrated in **Table 2**.

691

692 Regarding the size of liposomes prepared by this method, several work studies reported
693 a small average diameter with a spherical shape. Cui et al. (2015) revealed that clove EO loaded-
694 liposomes had small size of 149.2 nm, a high zeta potential (-24.5 mV) with an entrapment
695 efficiency of 20.41%, for 5.0 mg/mL clove oil concentration. Accordingly, Cui et al. (2016)
696 used the same method to limit the volatility of salvia EO by encapsulation in soy
697 lecithin/cholesterol based liposomes. Atomic force microscopy images showed that the
698 obtained liposomes were spherical in shape, uniformly dispersed without any aggregation with
699 an average size ranging from 100 to 700 nm. Furthermore, bergamot EO and its fraction
700 (bergapten) were entrapped in phospholipids based-liposomes using thin lipid hydration
701 process (Celia et al., 2013). The prepared liposomes had an average size of 188.25 and 185.14
702 nm, a zeta potential of -2.95 and -2.57 mV and a high EE% of 75.0 and 77.0% for bergamot
703 EO and its fraction, respectively (Celia et al., 2013).

704 Several authors have compared the size of empty liposomes to EO-loaded liposomes
705 prepared by thin hydration method. Ge and his coworker (2016) revealed a significant
706 difference in the average size between empty- and *Melaleuca alternifolia* EO loaded-liposomes.
707 Empty liposomes had an average size of 142 nm, while loaded liposomes were smaller with
708 size around 75 nm. Similar results were found by Yoshida et al. (Yoshida et al., 2010). Risaliti
709 et al. (2019) attributed this to the high cohesion package of oil components to the bilayer
710 constituents. On the other hand, Detoni et al. (2012) reported no difference in liposomes size
711 between empty and *Zanthoxylum tingoassuiba* EO-loading MLVs and SUVs, respectively.
712 Moreover, nerolidol- and cyclodextrin/nerolidol-loaded liposomes prepared by thin lipid
713 hydration method showed larger mean particle size than blank liposomes (Azzi et al., 2018).
714 Cui et al. studying the encapsulation of curry EO in liposomes, revealed that the oil
715 concentration had a positive effect on vesicles size (Cui et al., 2017a). For instance, the vesicles
716 size was increased from 103.86 to 257.36 nm as a consequence of an increase in the oil

717 concentration from 2.0 to 6.0 mg/ml. Similar behavior was pointed for the encapsulation of
718 cinnamon EO in soy lecithin/cholesterol based liposomes prepared by thin hydration method
719 (Cui et al., 2016a). Accompanying the increase of cinnamon oil concentration from 3.0 to 6.0
720 mg/mL, the vesicles size was progressively increased from 133 to 157 nm. Similar results were
721 also reported when increasing cardamom EO (Nahr et al., 2019), thyme EO (Cui et al., 2017b)
722 and chrysanthemum EO (Lin et al., 2019b).

723 The liposome size was not only affected by the EO concentration. In fact, Nazari et al.,
724 (2019) developing garlic EO nanophytosomes by thin hydration method, investigated the effect
725 of the preparation method. For instance, nanophytosomes were a novel lipid based vesicular
726 delivery systems where stable hydrogen bonds are formed between the phosphatidylcholine
727 molecules and nutraceuticals leading to the formation of stable complex (Ghanbarzadeh et al.,
728 2016). In this study, MLVs reduction size was performed using three different types of methods:
729 sonication, homogenization and the combination of sonication and homogenization. Results
730 showed that the combination of two methods produced the smallest liposomes (115 nm) with
731 transparent suspension view. Homogenization produced larger particles than probe sonication
732 method and the average size was around 161 and 135 nm, respectively. Considering the zeta
733 potential, all the prepared phytosomes had lower values (-12.36 to -3.86 mV) than the expected
734 and reported values for soy bean phosphatidylcholine made nanovesicular systems (around -26
735 mV). This was linked to the interaction between the positively charged allicin (the main
736 component of garlic EO) and the negatively charged phosphate group of phosphatidylcholine
737 (Nazari et al., 2019). In another work study, Salari and his colleague (2019) developing
738 rosemary EO loaded- L- α -phosphatidylethanolamine dioleoyl : cholesteryl hemisuccinate
739 liposomes found that sonication method produced smaller liposome than filtration method. The
740 average sizes were 142.5 and 437.2 nm, respectively. Results showed also that increasing the

741 lipid ratio of L- α -phosphatidylethanolamine dioleoyl to cholesteryl hemisuccinate from 3:2 to
742 7:3 resulted in much larger liposomes with more negative zeta potential.

743 As there are several types of phospholipids, it is reliable to alter the size, charge and
744 EE%, upon variation of type or addition of new ingredients to the lipid mixture. In this
745 approach, the effect of lipid composition on the EE% of *Anethum graveolens* EO-loaded
746 liposomes was investigated by Ortan et. al (2009). Liposomes with different lipids; fresh egg
747 yolk, dimiristroylphosphatidyl choline, dipalmitoylphosphatidyl choline,
748 dimiristroylphosphatidyl glycerol and dioleoylphosphatidyl choline, were prepared by thin
749 hydration method. Results showed that oil entrapment varied in this way:
750 dimiristroylphosphatidyl glycerol (55.2%) < dimiristroylphosphatidyl choline (58.9%) <
751 dioleoylphosphatidyl choline (77%) < dipalmitoylphosphatidyl choline (97%) < fresh egg yolk
752 (98%). Although dipalmitoylphosphatidyl choline showed good entrapment efficiency, its use
753 was difficult as it required high temperature due to its high transition temperature. The authors
754 related the low values of EE% of dioleoylphosphatidyl choline, dimiristroylphosphatidyl
755 glycerol and dimiristroylphosphatidyl choline to their unsaturation.

756 In addition to the factors mentioned above, other parameters may affect the
757 physicochemical properties of liposomes prepared by thin hydration process. In this context,
758 Plackett–Burman design was applied in order to investigate the effect of the mass ratio of
759 phosphatidylcholine and cholesterol, tree tea EO concentration, tween 80 concentration,
760 hydration medium pH, temperature, sonication time and power on physicochemical properties
761 of tree tea EO-loaded liposomes (Ge & Ge, 2015). Results revealed that only three factors (the
762 ratio of phosphatidylcholine and cholesterol, EO concentration and tween 80) exhibited a
763 significant impact on the entrapment efficiency of tree tea EO. Increasing the lipid ratio with
764 EO amount and decreasing tween 80 had a positive effect on EO encapsulation efficiency. Good
765 EE% (97.18%) was obtained with the following parameters: the mass ratio of fresh egg yolk

766 and cholesterol (5:51); EO concentration (1.21%); tween 80 concentration (0.79%); pH 7.4;
767 temperature (55 °C); sonication time (15 min) and sonication power (300w) (Ge & Ge, 2015).

768 Regarding the stability of EO loaded in liposomes, Liolios et al. (2009) investigated the
769 oxidative stability of carvacrol and thymol isolated from *Origanum dictamnus* L. EO and their
770 mixtures, before and after their encapsulation in egg L- α phosphatidylcholine/cholesterol-based
771 liposomes by differential scanning calorimetry analysis. Results showed the appearance of
772 exothermic peaks related to the auto-oxidation process of the samples. The onset temperatures
773 at which the auto-oxidation process starts were in the following order: Carvacrol
774 (258°C)<Thymol (273°C)<Carvacrol : Thymol (302°C) <Empty liposomes (362°C) <
775 Liposomes +Carvacrol : Thymol (392°C). One can conclude that carvacrol and thymol
776 presented better antioxidant action when encapsulated than when in pure form. The antioxidant
777 activity of empty liposomes is lower than that of oil loaded- liposome, suggesting that the
778 liposome membranes were stabilized by the link of the lipophilic compounds with lipid bilayers
779 (Liolios et al., 2009).

780 Beyond EO, liposomes can potentially enable the encapsulation of VO and their
781 derivatives, as illustrated in **Table 3**. Recently, numerous studies have been investigated to
782 encapsulate fatty acids in liposomes. Among the several polyunsaturated fatty acids (PUFAs),
783 dietary ω 3 like eicosapentaenoic and docosahexaenoic acids have been extensively investigated
784 for their beneficial effects (Hadian, 2016). Alaarg et al. (2016) developed docosahexaenoic
785 acid- loaded liposomes by thin hydration method. The obtained liposomes exhibited small
786 average diameter around 100 nm, narrow size distributions, negative zeta potential ($15.7 \pm$
787 2.5mv) and high EE% of 81.35 %. Moreover, eicosapentaenoic and docosahexaenoic acids
788 were entrapped in nanoliposomes (i.e. nanoscale lipid vesicles) developed by thin hydration
789 followed by either extrusion ultrasonic irradiation; bath sonication; probe sonication; or
790 combined probe and bath sonication (Hadian et al., 2014). Results showed that probe sonication

791 produced liposomes with higher EE% for both investigated fatty acids. Results displayed also
792 that EE% differs from a VO to another for liposomes prepared in the same experimental
793 conditions. Indeed, the EE% value was higher for docosahexaenoic acid than for
794 eicosapentaenoic acid. This was ascribed to the fact that docosahexaenoic acid may change the
795 physical properties of 1, 2-dipalmitoyl-sn-glycero-3-phosphocholine bilayer, as it would
796 provide a tightly pack conformation because of the coiled configuration (Hadian et al., 2014).

797 In overall, thin hydration method is widely employed to develop plant oils loaded
798 liposomes due to its simplicity. Several phospholipids are used in the literature including
799 soybean phosphatidylcholine (Ge & Ge, 2016; Ge & Ge, 2015; Khatibi et al., 2017; Nazari et
800 al., 2019; Rasti et al., 2012; Q. Wang et al., 2015), dipalmitoyl phosphatidylcholine (Detoni et
801 al., 2012), egg phosphatidylcholine (Saffari et al., 2016), phospholipon[®]90G (Risaliti et al.,
802 2019). Cholesterol is the most used fluidifying agent (Alikhani-Koupaei, 2015; H. Cui, Yuan,
803 et al., 2017; Y. Cui et al., 2010; Y. Ge & Ge, 2016; Ge & Ge, 2015; Khatibi et al., 2017; Lin et
804 al., 2018; Lin, Chen, et al., 2019; Q. Wang et al., 2015); in other cases, tween 80 (Y. Ge et al.,
805 2019; Y. Ge & Ge, 2016; Ge & Ge, 2015; Lin, Chen, et al., 2019) and poly vinyl pyrrolidone
806 (Cui et al., 2017a, 2017b, 2016a, 2016b, 2015; Lin et al., 2019b, 2018) were incorporated as
807 surfactants.

808 Using this method, heterogeneous vesicles of large sizes may be produced which
809 requires additional steps like sonication and extrusion to reduce and homogenize the vesicle
810 size and thus, the process consumes more time. Besides, thin hydration method is difficult to
811 scale up and requires organic solvents which in turn represent the major drawback. In fact, their
812 residues may remain in the final liposome preparation resulting in potential toxicity and reduced
813 stability of the lipid vesicles (Cortesi et al., 1999; Vemuri and Rhodes, 1995).

814 **5.2.1.2 Solvent injection**

815 The solvent injection method, firstly described in 1973 (Batzri and Korn, 1973), implies
816 the dissolution of the lipid into an organic phase such as ethanol or ether, followed by the
817 injection of the lipid solution into aqueous solution resulting in liposomes dispersion (Laouini
818 et al., 2012). After that, the organic solvent was evaporated under reduced pressure (**Fig. 6.b**).
819 This technique is widely used for plant oil encapsulation, as demonstrated in **Table 2**. The
820 solvent injection' main feature is that narrow size distribution of submicron liposomes (under
821 100 nm) could be produced without extrusion or sonication (Stano et al., 2004). Moreover,
822 compared with thin hydration method, the ethanol injection technique was found to be scalable.
823 In fact, clove EO-liposomes were successfully scaled-up using a membrane contactor (600ml)
824 and a pilot plant (3L) (Sebaaly et al., 2015a). Furthermore, various eugenol- and clove EO-
825 liposomes were prepared at laboratory (ethanol injection) and large scale (membrane
826 contactor): free hydroxypropyl- β -cyclodextrin loaded liposomes; drug in hydroxypropyl- β -
827 cyclodextrin in liposomes (DCL) and DCL₂ obtained by double loading technique, where the
828 drug is added in the organic phase and the inclusion complex in the aqueous phase (Sebaaly et
829 al., 2016a). Results showed that eugenol and clove EO loaded DCL and DCL₂ developed at
830 large scale had a mean size similar to those obtained by laboratory scale. Besides, Eugenol and
831 clove EO loaded DCL and DCL₂ had a mean particle size significantly smaller than that of free
832 hydroxypropyl- β -cyclodextrin liposomes containing either eugenol or clove EO at both
833 laboratory and large scales. This was explained by the complete incorporation of the aromatic
834 cycle of eugenol inside the hydrophobic cavity of hydroxypropyl- β -cyclodextrin, resulting in
835 limit interaction between eugenol and lipidic bilayers. Regarding the polydispersity index and
836 zeta potential, no difference was assessed between all the tested liposomes.

837 Currently, several studies have been reported to investigate the effect of liposome
838 composition and operating conditions on physicochemical properties of liposomes prepared by
839 ethanol injection method (Hammoud et al., 2019; Rushmi et al., 2017; Sebaaly et al., 2016b).

840 The effect of oil concentration, injection rate, stirring speed on the average diameter of black
841 seed oil-liposomes was studied (Rushmi et al., 2017). Results showed that liposomes decrease
842 in size from 520.70 to 51.48 nm after oil incorporation. As the concentration of oil increases
843 from 0.17 to 0.67% v/v, liposomes size reduced significantly due to the antioxidant activity of
844 the oil which could decrease phospholipid bilayer oxidation, preventing liposomes growth;
845 while, no change in average size of liposomes was noticed upon further increase in oil (0.67%
846 v/v). Thus, the oil concentration of 0.67% v/v was found to be optimum for its antioxidant
847 activity. Results showed also that small sized liposomes were formed under 1mL/min injection
848 rate and 2200 rpm stirring speed. Low injection rates result in faster lipids oxidation while high
849 rates may cause a variable distribution of particle size. Similar results were already reported
850 (Sebaaly et al., 2016b). In regards of the phospholipid:cholesterol ratio effect, the EE% was
851 improved from 39.8 to 49.9 % after increasing the ratio of egg extract to cholesterol from 3:1
852 to 3:2 (Rushmi et al., 2017). This was related to the fact that cholesterol may reduce the
853 flexibility and mobility of lipidic layer which in turn lead to enhance liposomes stability.
854 Moreover, another study performed by Hammoud et al. (2019) spotlighted that the type of
855 encapsulated EO affects significantly the phospholipid and cholesterol incorporation rates into
856 the lipid layer. Lower phospholipids incorporation rates were observed when encapsulating
857 isoeugenol, pulegone or thymol. While, high cholesterol incorporation rates were measured in
858 presence of estragole or terpineole. Additionally, the oil entrapment efficiency was found to be
859 affected by the chemical structure of encapsulated EO. In fact, EO bearing hydroxyl groups in
860 their structure are more greatly to fluidize the lipid layer than those without a hydroxyl group
861 leading to higher EE%. The authors concluded that EO bearing hydroxyl groups had low
862 aqueous solubility with low Henry constant value and higher liposomal EE% (Hammoud et al.,
863 2019).

864 Regarding the stability of liposomes prepared by ethanol injection process, Liu et al.
865 (2016) investigated the stability of galanga EO-loaded liposomes at low temperature (4°C) and
866 dark conditions and results revealed minor change in mean particle size and polydispersity
867 index. Furthermore, the photostability of eugenol in aqueous solution and in liposome
868 formulations (Phospholipon 80H, Phospholipon 90H and Lipoid S100) was investigated under
869 UV light irradiation for 96hours (Sebaaly et al., 2015b). Results revealed that liposomes
870 formulations protect eugenol more than aqueous solutions. The percentages of remaining
871 eugenol were 58, 82, 91 and 95% for aqueous solution, Phospholipon 80H-, 90H- and S100-
872 liposomes, respectively. The highest value of remaining eugenol for lipoid S100 was related to
873 the flexibility of the membrane resulting in a deep insertion of eugenol into the lipid bilayer
874 leading to better protection from any UV light effect (Sebaaly et al., 2015b).

875 Despite using ethanol injection for EO encapsulation in liposomes, a few reports have
876 been published during the last decade regarding the encapsulation of VO. Recently, Huang et
877 al. (2020) developed co-loaded linseed oil with quercetin in liposomes with the aim of
878 enhancing their solubility and stability. The produced liposomes owned a spherical shape with
879 a small average size (262.2 nm). In 2019, Bai and his coworkers investigated the effect of
880 different coix seed oil: β -carotene ratios on the physiochemical properties, stability and
881 antioxidant activity of coix seed oil : β -carotene co-loaded-liposomes (C. Bai et al., 2019).
882 Results showed that by increasing coix seed oil, the EE% of β -carotene in the liposomes
883 decreased. The values of EE% for 1:1, 1:5, and 1:10, β -carotene:coix seed oil liposomes were
884 83.8, 81.3, and 80.8 %, respectively, which were slightly lower than that of liposomes
885 containing β -carotene alone (86.0%). This was ascribed to the ability of coix seed oil to compete
886 for the available hydrophobic domains within the phospholipid bilayers.

887 To sum up, ethanol injection method is widely employed for plant oils encapsulation as
888 it is simple, easy to scalable and it does not require any additional process for vesicle size

889 reduction. According to the previous work studies, phospholipon[®]90H (Sebaaly et al., 2016a,
890 2016b), phospholipon[®]80H (Sebaaly et al., 2016b), lipoid[®] S100 (Hammoud et al., 2019;
891 Sebaaly et al., 2016b) and egg phospholipids (C. Bai et al., 2019; Rushmi et al., 2017) are
892 widely used as bilayer forming lipids. Ethanol injection method suffers from several drawbacks
893 including continuous exposure of plant oils to high temperature and organic solvents which
894 may affect both the safety and stability of the liposomes (Nkanga et al., 2019).

895 **5.2.1.3. Heating method**

896 The heating method, called also Mozafari method, was first developed in 2005. It is
897 known to be the most attractive method for liposomes preparation due to its organic
898 solvent/detergents free characteristics (Mozafari & Mortazavi, 2005). In this technique, lipids
899 are hydrated in the presence of hydrating agent (glycerin or propylene glycol) and heated at 40–
900 120°C (at the temperature which is above the transition temperature of the phospholipids)
901 depending on the properties of the ingredients, the presence or absence of cholesterol, and the
902 type of material to be entrapped (**Fig.6.c**) (Mozafari et al., 2008).

903 Currently, Mozafari method is widely used to encapsulate VO and polyunsaturated fatty
904 acids (**Table 2**). When compared to thin hydration process, Mozafari method produce
905 liposomes with higher stability. Rsati et al. (2012) investigated the difference between the
906 oxidative stability of liposomes (before sonication) and nanoliposomes (after sonication)
907 produced by Mozafari and conventional thin hydration techniques. For both methods,
908 polyunsaturated fatty acids entrapment efficiency values of nanoliposomes were higher than
909 those of liposomes. Authors related this result to the fact that size reduction increases the surface
910 area of the liposomes resulting in increasing the contact and bond between the fatty acids and
911 phospholipids in the bilayers. Moreover, liposomes prepared by Mozafari process showed
912 higher physical stability than those prepared by conventional method (Rasti et al., 2012). In

913 another work study, the effect of formulation strategies on phytosterol, extracted from canola
914 oil, loaded-liposomes was investigated (Poudel et al., 2019). The results showed that Mozafari
915 method produce liposomes with high average size (260 nm) as compared to those obtained by
916 thin film hydration homogenization (186 nm) and thin film hydration ultrasonication (196 nm).
917 This result was attributed to the high shear force and cavitation involved in size reduction during
918 the ultrasonication and homogenization process; while in Mozafari method, less intense
919 magnetic stirring will probably yield to larger particles. In term of polydispersity index and zeta
920 potential, no difference was found for all the formulations (Poudel et al., 2019).

921 Like the methods discussed above, Mozafari method was affected by several operating
922 conditions. In 2013, Rasti et al. investigated the effect of shear rate, mixing and sonication times
923 on colloidal properties of polyunsaturated fatty acids (docosahexaenoic acid and
924 eicosapentaenoic acid) nanoliposomes (Rasti et al., 2013). In their study, response surface
925 methodology was applied to predict the optimum levels of liposome preparation condition
926 producing maximum EE% and minimum average size. According to ANOVA analysis, all the
927 independent variables and their interactions were found significant; while, the main significant
928 effect on liposome size and EE% was found to be the shear rate. After optimizing the operating
929 parameters; shear rate (795 rpm), mixing time (60 min) and sonication time (10 min), the
930 nanoliposome exhibited an average diameter of 81.4nm with an EE% of 100% (Rasti et al.,
931 2013).

932 Besides using heating method to encapsulate VO in liposomes, no report was found
933 regarding the encapsulation of EO maybe due to their high sensitivity and volatility upon
934 exposure at high temperature. Thus, this technique is not suitable for thermosensitive bioactive
935 agents. In closing, Mozafari method showed to be a fast, simple, scalable, and non-toxic
936 technique for liposome preparation with high EE%. In addition, the obtained liposomes can be
937 freely used without any further sterilization treatments as they were prepared under heating

938 conditions which in turn could minimize both formulation timing and complexity (Nkanga et
939 al., 2019).

940 **Table 2.** Preparation methods for plant oils encapsulation in liposomes with their fine applications.

Encapsulated oil	Plant (origin)	Phospholipid used	Physicochemical properties			Biological properties	Application	Ref.
			Size (nm)	Z.pot (mV)	EE (%)			
<i>Thin hydration method</i>								
Myristica	<i>Myristica fragrans</i> Houtt.	Soybean phospholipid	/	/	/	Antimicrobial, antioxidant	Food	(Zhu et al., 2020)
<i>Ferula gummosa</i> Boiss.	<i>Ferula gummosa</i> Boiss.	Phospholipid	74.3 -99.9	/	/	Antibacterial		(Najafi et al., 2020)
Laurel	<i>Laurelia sempervirens</i> Tul.	L- α -PCH	200	/	/	Antibacterial, antioxidant	Food	(Wu et al., 2020)
Cardamon	<i>Elettaria cardamomum</i> L.	Phospholipid	71.8–147.9	-17.4 to -10.7	< 60	Antimicrobial, antioxidant	Food	(Nahr et al., 2019)
Chrysanthemum	<i>Chrysanthemum pacificum</i> L.	Soybean phospholipid	132.4	-37.6	42.7	Antibacterial	Food	(Lin et al., 2019b)
Sage	<i>Salvia triloba</i> L.	Phospholipon 90G	≈200	-20 to -35	57	Antioxidant, antibacterial Anti-inflammatory	Medicine	(Risaliti et al., 2019)
		Soybean phospholipid	188.5	-48.38	46.5	Antibacterial	Food	(Cui et al., 2016b)
Rosemary	<i>Rosmarinus officinalis</i> L.	L- α -PEA dioleoyl	79	-2.77	45	Anticancer	Medicine	(Salari and Salari, 2019)
		Phospholipon 90G	≈200	-20 to -35	65	Antioxidant; antibacterial Anti-inflammatory	Medicine	(Risaliti et al., 2019)
		PCH	/	/	/	Preservative	Food	(Alikhani-Koupaei, 2015)
Garlic	<i>Allium sativum</i> L.	Soybean PCH	115	-12.36	86.00	Antibacterial, antioxidant	Food	(Nazari et al., 2019)
Tea tree	<i>Melaleuca alternifolia</i> Cheel.	Soybean PCH	50-100	/	98.49	Antimicrobial	/	(Ge et al., 2019)
		Soybean PCH	58	/	97.18	Antimicrobial	/	(Ge & Ge, 2015)
		Soybean PCH	75	-7.45	96.08	Antimicrobial	/	(Ge and Ge, 2016)
Ajwain	<i>Trachyspermum copticum</i> L.	Soybean PCH	170.8	/	85.9	Antimicrobial	Cosmetics	(Tabatabai et al., 2018)
Thyme	<i>Thymus vulgaris</i> L.	Soybean phospholipid	182.60	-40.90	35.35	Antibacterial	Food	(Lin et al., 2018)
		Soybean phospholipid	208.1	-52.2	38.16	Antibacterial	Food	(Cui et al., 2017b)
Eucalyptus	<i>Eucalyptus globulus</i> L'Hér.	Soybean phospholipid	/	/	97.35	Antimicrobial	Medicine	(Tang and Ge, 2017)
	<i>Eucalyptus citriodora</i> L.	Soybean phospholipid	266.56	-33.73	22.47	Antimicrobial	/	(Lin et al., 2019a)

Cineole	/	Egg yolk PCH	128	6.8	67.7	Permeation enhancers	Medicine	(Saffari et al., 2016)
Thymol	+	Soybean PCH	270.20	+39.99	/	Antibacterial	Food	(Engel et al., 2017)
Carvacrol		L- α -PCH	/	/	/	Antimicrobial	Food	(Liolios et al., 2009)
<i>Zataria multiflora</i>	<i>Zataria multiflora</i> Boiss.	Soybean PCH	99.9	/	18.4	Antimicrobial	Food	(Khatibi et al., 2017)
							Cosmetics	
							Medicine	
Curry	<i>Helichrysum italicum</i> G.	Soybean phospholipid	196.6	-31.1	56.3	Antibacterial	Food	(Cui et al., 2017a)
Limonene	/	Egg yolk PCH	102	6.1	71.0	Permeation enhancers	Medicine	(Saffari et al., 2016)
Cinnamon	<i>Cinnamomum cassia</i> persl.	Soybean phospholipid	144.3	-54.7	29.2	Antibacterial	Medicine	(Cui et al., 2016a)
Clove	<i>Syzygium aromaticum</i> L.	Soybean phospholipid	149	-24.5	20.4	Antibacterial	Food	(Cui et al., 2015)
<i>Bergamot</i>	<i>Monarda didyma</i> L.	Phospholipid	185.1	-2.95	75.0	Anticancer	Medicine	(Celia et al., 2013)
Bergapten	/	Phospholipid	185.1	-2.95	75.0	Anticancer	Medicine	(Celia et al., 2013)
Macassar kernels	<i>Brucea javanica</i> L.	Phospholipid	108.2	-57.0	92.4	Anticancer	Medicine	(Cui et al., 2010)
Dill	<i>Anethum graveolens</i> L.	PCH	/	/	98	Antimicrobial	/	(Ortan et al., 2009)
<i>Zanthoxylum tingoassuiba</i>	<i>Zanthoxylum tingoassuiba</i> L.	1,2-Dipalmitoyl PCH	210-3630	/	68.5-79.2	Anticancer	Medicine	(Detoni et al., 2012)
Sterol	/	PCH	< 200	-9 to -14	>89	Antioxidant	Food	(Poudel et al., 2019)
DHA	/	1,2-Dipalmitoyl PCH	99	-15.7	81.4	Anticancer; anti-inflammatory	Medicine	(Alaarg et al., 2016)
		PCH	/	/	38.6	Anticancer; anti-inflammatory	Medicine	(Hadian et al., 2014)
EPA	/	1,2-Dipalmitoyl PCH	/	/	56.9	Anticancer; anti-inflammatory	Medicine	(Hadian et al., 2014)
EPA+DHA	/	Soybean phospholipid	<100	-48.4	/	Anticancer; anti-inflammatory	Medicine	(Rasti et al., 2012)

Solvent injection method

Anethole	/	Lipoid S100	/	/	/	Antibacterial	/	(Auezova et al., 2020)
Cinnamaldehyde	/	Egg yolk phospholipid	1000-2500	/	/	Antimicrobial	/	(Wang et al., 2019)
Isoeugenol	/	Lipoid S100	/	/	96.4	/	/	(Hammoud et al., 2019)
Pulegone	/	Lipoid S100	/	/	90.5	/	/	(Hammoud et al., 2019)
Terpineol	/	Lipoid S100	/	/	73.7	/	/	(Hammoud et al., 2019)
Thymol	/	Lipoid S100	/	/	79.1	/	/	(Hammoud et al., 2019)
Estragole	/	Lipoid S100	/	/	90.9	/	/	(Hammoud et al., 2019)
Eucalyptol	/	Lipoid S100	/	/	61.9	/	/	(Hammoud et al., 2019)
Black seed	<i>Nigella sativa</i> L.	Egg yolk PCH	50-900	/	34-87	Analgesic	Medicine	(Rushmi et al., 2017)

Garlic	<i>Allium sativum</i> L.	Phospholipid	131.7	/	64.3	Antimicrobial	Food	(Zabihi et al., 2017)
Galangal	<i>Alpinia officinarum</i> L.	Phospholipid	61.9	-16	/	Antimicrobial; antioxidant	Medicine	(Liu et al., 2016)
Clove	<i>Syzygium aromaticum</i> L.	Phospholipid	125.6	-35.5	35.6	Antimicrobial; antioxidant	Medicine	(Cao et al., 2016)
		Phospholipon 90H	/	/	54.2 - 59.7	Anti-inflammatory	Medicine	(Sebaaly et al., 2016a)
Eugenol	/	Phospholipid	/	/	/	Anti-inflammatory	Medicine	(Sebaaly et al., 2015b)
		Lipoid S100	74.6	/	24.2	Anti-cancer	Medicine	(Mishra et al., 2019)
		Phospholipon 90H	/	/	63.1 - 63.5	Anti-inflammatory	Medicine	(Sebaaly et al., 2016a)
		Phospholipid S75	58.6	/	59.2	Antibacterial	Food	(Peng et al., 2015)
Linseed oil + quercetin	<i>Linum usitatissimum</i> L.	Phospholipid	/	/	/	Anti-inflammatory	Medicine	(Sebaaly et al., 2015b)
		Soybean phospholipid	262.2	/	/	Source of PUFA	Food	(Huang et al., 2020)
Coix seed oil + B-carotene	<i>Coix lacryma-jobi</i> L.	Egg yolk PCH	156.7- 193.1	-47.8 to -32.4	80.8 – 83.8	Anticancer	Medicine	(C. Bai et al., 2019)
Linoleic acid	/	Soybean PCH	266	/	83.3	/	Food	(Vélez et al., 2019)
Heating method								
Sterol	/	Soybean phospholipid	> 200	-9 to -14	>89	Antioxidant	Food	(Poudel et al., 2019)
EPA + DHA	/	Soybean phospholipid	<200	-48.3	/	/	/	(Rasti et al., 2012)

941 EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid; PUFA: Polyunsaturated fatty acids; PCH: phosphatidylcholine; PEA: phosphatidylethanolamine.

942

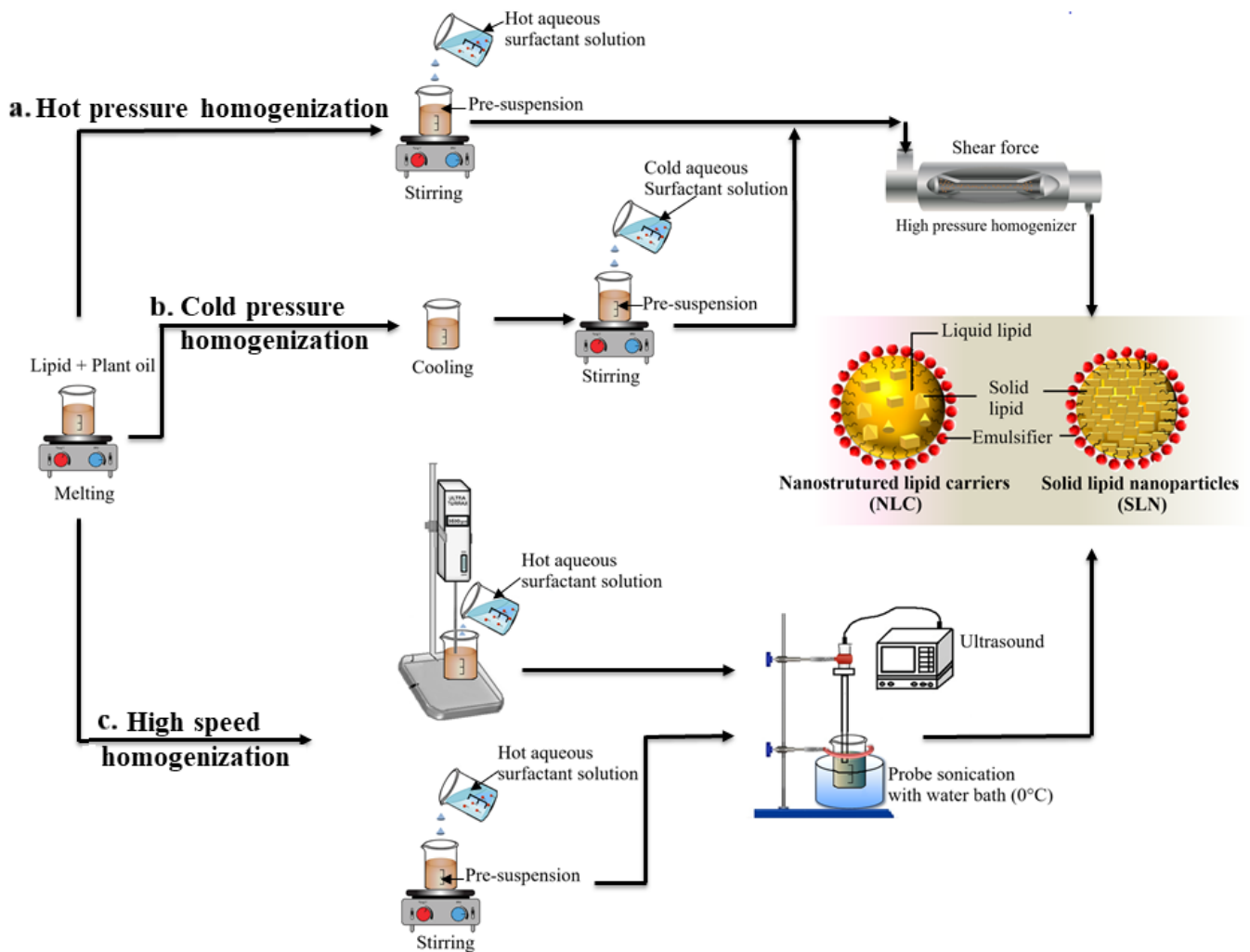
943 **5.2.2. Solid lipid nanoparticles and nanostructured lipid carriers**

944 Solid lipid nanoparticles (SLN) are other lipid-based carriers that have emerged as they
945 combine the benefits of liposomes and polymeric nanoparticles (Sarangi and Padhi, 2016).
946 Solid lipid nanoparticles, developed since 1990, are suspensions of nanosized solid lipid
947 particles dispersed in an aqueous media (Patel, 2013). They are composed of surfactants and a
948 lipid matrix that acquires a solid-state lipid at ambient temperature (Bayón-Cordero et al.,
949 2019). The commonly used materials to structure the lipid core are fatty acids (stearic acid,
950 palmitic acid, decanoic acid and benzoic acid), triacylglycerols (trimyristin, trilaurin, tristearin
951 and tripalmitin) and acyl glycerols (glycerol monostearate, glycerol palmitostearate and
952 glycerol benzoate). These lipids are characterized by their purity, low price, safety and
953 biodegradability. In the other hand, phospholipids (phosphatidylcholine, soy and egg lecithins),
954 poloxamer, pluronic[®]F127, bile salts, tween 80 and polyvinyl alcohol are example of commonly
955 used surfactants (Kaliampurthi and Selvaraj, 2016).

956 In the aim of enhancing the loading capacity of SLN, a second generation of lipid
957 nanoparticles was developed in 1999; so called nanostructured lipid carriers (NLC) in which
958 the matrix is composed not only of a solid lipid, but of a blend of a solid and a liquid lipid oil,
959 as illustrated in **Fig. 7**. These carriers may provide an additional space for the loading of
960 bioactive agents, improving in this way the amount of the active compounds entrapped and
961 minimizing the probability of expulsion from the lipid phase (Patel, 2013).

962 Considering the delivery of plant oil, the main reason to use SLN or NLC as nanocarriers is the
963 improvement of entrapment efficiency. Since the oils are mostly lipophilic, they present a good
964 miscibility with the lipid matrix, resulting high amount of oil could be entrapped (Falcao et al.,
965 2015). In addition, these lipid-based carriers protect the labile and sensitive oil components
966 from chemical, photochemical or oxidative degradation, due to the immobilization by solid
967 lipids. Different methods are employed to produce SLN, however, high pressure

968 homogenization and high-speed homogenization (ultrasonication) are commonly used due to
 969 their simplicity and facility of scaling up.



970
 971 **Fig. 7.** Schematic illustration of solid lipid nanoparticles and nanostructured lipid carriers'
 972 preparation methods.

973 **5.2.2.1. High pressure homogenization**

974 The high-pressure homogenization method was extensively used to encapsulate plant
 975 oils in SLN since it produces particles with small size and higher homogeneity. Using a high-
 976 pressure homogenizer, liquids were pushed with high pressure (100-2000 bar) through a narrow
 977 gap (micron size) creating fluid acceleration over a very short distance at very high viscosity of

978 over 1000 km/h which in turn result in disrupting the particles down to submicron range (Garud
979 et al., 2012).

980 Using the high-pressure homogenization to encapsulate plants oils, the lipid is heated at
981 5 to 10°C above its melting point, and the oil is dissolved within (**Fig.7.a**). After that two
982 approaches are involved: hot or cold homogenization. In hot homogenization, hot aqueous
983 surfactant solution is dispersed with the plant oil-lipid melt under stirring at the same
984 temperature creating the pre-emulsion. The resultant pre-emulsion was pushed through a
985 piston-gap homogenizer creating a hot oil-in-water (O/W) nanoemulsion which is cooled after
986 at room temperature allowing the crystallization of the lipid and the formation of SLN.

987 Using the cold homogenization approach the oil-lipid melt was cooled down creating
988 solid lipid microparticles that are dispersed after in a cold aqueous surfactant solution forming
989 a pre-suspension. The subsequent homogenization of this pre-suspension creates SLN
990 (**Fig.7.b**). Several studies have been already published investigating the use of high-pressure
991 homogenization process to encapsulate plant oils (see **Table 3**).

992 Regarding the size of SLN prepared by this technique, numerous research works
993 reported a small average diameter with good stability and high EE%. For example, SLN
994 containing frankincense and myhrr EO in a ratio 1:1 were developed using hot homogenization
995 process by Wang et al. (Wang, 2012). An average mean size of 113.3 nm, a zeta potential of -
996 16.8 mV and an EE% of 80.60% were assessed for the obtained SLN. The same process was
997 used to prepare SLN encapsulating the VO: copaiba oil with and without allantoin which is
998 widely used in cosmetology for its keratolytic, moisturizing, soothing and wound healing
999 properties (Svetlichny et al., 2015). The dynamic light scattering analysis revealed an average
1000 particle size of 126.06 nm and 118.63 nm for the copaiba oil-loaded SLN and copaiba oil:
1001 allantoin-co-loaded SLN, respectively.

1002 Concerning the stability of SLN, previous works highlighted their efficiency in
1003 preserving the quality of encapsulated oil during long-term storage as compared to un-
1004 encapsulated-form (Tian et al., 2018; Zielinska et al., 2019). Tian et al. (2018) reported that
1005 SLN can enhance the stability of citral in acidic surroundings. Gas-chromatography analysis
1006 showed that after 12 days storage, 67% of citral remained in the citral loaded-SLN formulations,
1007 while only 8% remained in the control. In addition, the overall flavour of the degradation
1008 products generated from citral-SLN were assessed and results demonstrated that the off-
1009 flavours had little effect on the whole flavour of citral-SLN in the system sample as compared
1010 with the control (Tian et al., 2018).

1011 Several factors such as the kind of lipid, surfactant and the operating process conditions
1012 could influence the physicochemical properties of the particles obtained by high-pressure
1013 homogenization. In this context, Mai et al. (2018) investigated the influence of homogenization
1014 conditions on gac fruit EO-loaded SLN prepared by hot and cold homogenization. Results
1015 showed that increasing hot homogenization speed from 5000 to 10000 rpm was accompanied
1016 with a decrease in particle size from 3297 to 201 nm. However, further increase in speed leads
1017 to increase the particle size due to the fact that the oil particles are more likely to collide and
1018 aggregate with others. Concerning hot homogenization time, short time was found not enough
1019 for active ingredient encapsulation while more homogenization time result in small particles
1020 which in turn lead to reduce the volume containing active ingredients (Mai et al., 2018).

1021 In another work study, the impact of the surfactant content, the ratio of citral to lipid,
1022 and their total content on the physicochemical characteristics of citral-loaded SLN has been
1023 explored (Tian et al., 2018). As the surfactant amount increases the EE% decreases due to the
1024 fact that the surface of the formed SLN was not large enough to absorb the excess of surfactant
1025 which in turn form micelles, resulting a partitioning phenomenon of citral between micelles and
1026 SLN; therefore, a decrease in entrapment efficiency was noticed. Results revealed also an

1027 increase in particle size and a decrease in EE% when increasing the content of the mixture citral
1028 : glyceryl monostearate, used as lipid matrix, from 1 to 5%. The increase in the content of citral
1029 : lipid leads to increase the viscosity of the system which in turn reduce the efficiency of the
1030 high-pressure homogenization process to decrease the particle size. Additionally, too much
1031 citral and lipid cannot be emulsified when the surfactant content is kept constant this is why the
1032 EE% decreased. The same behavior of EE% was observed when increasing the ratio of citral to
1033 glycerol monostearate. In fact, the excess of citral cannot be entrapped when the content of the
1034 mixture citral : lipid was kept constant (Tian et al., 2018).

1035 In recent years, NLC were introduced to bypass the potential problems associated with
1036 the use of SLN. They were widely used for plant oils encapsulation, as depicted in **Table 3**.
1037 The main feature of these nanocarriers is to enhance the drug loading and prevent drug
1038 expulsion during long term storage (Sailaja et al., 2011) and this was confirmed by several
1039 research works. In 2019, using the high-pressure homogenization technique, Miranda and his
1040 colleagues developed *Ridolfia segetum* EO loaded-NLC with a small particle size (148.1 nm),
1041 a high zeta potential (16.3 mV) with excellent loading capacity (EE%=100%) (Miranda et al.,
1042 2019). In another research work, NLC containing sucupira EO produced by hot homogenization
1043 process owning an average diameter of 143 nm with an EE% of 99.98% (Vieira et al., 2020).

1044 Another characteristic intended by using either SLN or NLC as plant oils carrier is
1045 providing a controlled released pattern. For this context, *in vitro* release profile of sucupira oil
1046 from NLC was assessed by means of Franz glass diffusion cells and the recorded release profile
1047 was fitted into four mathematical models i.e., zero order, first order, Higuchi and Korsmeyer-
1048 Peppas (Vieira et al., 2020). Results showed that the release profile of sucupira oil followed a
1049 sustained manner over the course of 8 h. About 17.5% was released within the first hour, while
1050 the cumulative amount reached 30% at the end of the 8 h (Vieira et al., 2020). Results showed
1051 also that the best model describing the release of sucupira oil from NLC was the first order with

1052 a regression coefficient close to 1. In contrary to SLN, the release profile of plant oils from
1053 NLC does not follow Higuchi or Korsmeyers–Peppas model. Indeed, the release was governed
1054 by sucupira oil concentration inside the particles rather than the physicochemical properties of
1055 the carriers and this was expected as NLC are made of blend of solid and liquid lipids. Higuchi
1056 and Korsmeyers–Peppas are typically followed in the case of SLN formulations as these have
1057 a higher degree of crystallinity which controls better the release profile.

1058 With respect to vegetable oils, NLC were employed for co-delivery of VO with another
1059 bioactive molecule (Badea et al., 2015; Lacatusu et al., 2015; Rahman et al., 2013, 2014;
1060 Sidding et al., 2013). The benefit of these nanocarriers is that the VO can complement or even
1061 enhance the biological activity of the synthetic drug (Lacatusu et al., 2015). For this context,
1062 diethylamino hydroxybenzoyl hexyl benzoate used as UVA filter was co-encapsulated with
1063 various vegetable oils and their combinations (pomegranate seed oil, wheat germ oil,
1064 blackcurrant seed oil, sesame seed oil, carrot root oil, raspberry seed oil and rice bran oil) in
1065 NLC by high pressure homogenization method in order to enhance its antioxidant activity and
1066 UV protection performance (Badea et al., 2015). All the prepared NLC owned a mean particle
1067 size in the range of 108 to 145 nm with narrow size distribution, high zeta potential ranging
1068 from –34.4 to –44.3 mV and an entrapment efficiency between 51 and 70% (Badea et al., 2015).
1069 In another work study, in the aim of enhancing the anti-inflammatory properties, olive oil was
1070 co entrapped with thymoquinone in NLC and the resultant particles owned an average diameter
1071 around 75 nm with negative zeta potential of -31 mV (Sidding et al., 2013). Olive oil was further
1072 encapsulated in hydrogenated palm oil-NLC for co-delivery with synthetic drug purpose. The
1073 resultant particles had a mean diameter, polydispersity index, zeta potential, specific surface
1074 area, and crystallinity index of 61.14 nm, 0.461, -25.4 mV, 49.07 m² and 27.12% respectively
1075 (How et al., 2013).

1076 Besides the synthesized drugs, VO may be co-encapsulated with EO in NLC. For
1077 instance, Lacatusu et al. (2015) highlighted the possible blend of plant and animal oils – grape
1078 seed oil or fish oil with laurel leaf EO in NLC. The mean average diameter of obtained NLC
1079 reduces after increase of grape seed oil or fish oil content. This was ascribed to the role of the
1080 long fatty chains of these oils which lead to a more confined lipid core.

1081 On the whole the high-pressure homogenization technique is largely employed thanks
1082 to its benefits including low cost, good scalability and high stability of particles. While, with
1083 respect to the encapsulation of plant oils hot homogenization is more used as compared to the
1084 cold homogenization method. Lipids like tristearin (Salminen et al., 2017), n-hexadecyl
1085 palmitate (Lacatusu et al., 2015), myritol[®]318 (caprylic/capric triglyceride) (Lacatusu et al.,
1086 2015), compritol[®]888 ATO (Wang, 2012), glyceryl monolinoleate (Shi et al., 2013; Tian et al.,
1087 2018), oleoyl macroglycerides (Shi et al., 2013), lipoid[®]S100 (Sidding et al., 2013), cetyl
1088 palmitate (Svetlichny et al., 2015) and glycerol monostearate (Shi et al., 2013) are usually used
1089 to structure either SLN or NLC. Soybean lecithin (Salminen et al., 2017; Wang, 2012), tween
1090 80 (Shi et al., 2013; Sidding et al., 2013; Svetlichny et al., 2015; Wang, 2012), tween 20 (Badea
1091 et al., 2015; Lacatusu et al., 2015), span 80 (Mai et al., 2018; Tian et al., 2018) poloxamer
1092 (Badea et al., 2015) and sodium taurodeoxycholate hydrate (Salminen et al., 2017) are example
1093 of used emulsifiers.

1094 The use of high-speed homogenization process is often limited by the need of high
1095 energy input and the high temperature which cause oil loss.

1096 **5.2.2.2. Ultrasonication / high speed homogenization**

1097 Solid lipid nanoparticles may also be prepared by ultrasonication or high-speed
1098 homogenization technique. In brief, the heated aqueous phase was added to the melted lipid
1099 phase and emulsified by high speed stirrer, probe sonication or by adding the aqueous phase
1100 drop by drop to the lipid phase under magnetic stirring. The obtained pre-emulsion was

1101 ultrasonicated using probe sonicator with water bath (**Fig.7.c**). In order to prevent re-
1102 crystallization during the process, the production temperature was kept at least 5°C above the
1103 lipid melting point (Ramteke et al., 2012; Yadav et al., 2013).

1104 With respect to the encapsulation of plant oils, the ultrasonication technique is widely used,
1105 as described in **Table 3**. *Zataria multiflora* EO-loaded SLN were developed using Precirol[®]
1106 ATO 5 (Glyceryl monostearate) as lipidic matrix and tween 80 with poloxamer 188 as
1107 surfactants (Nasseri et al., 2016). The obtained SLN owned a particle size around 255.5 nm
1108 with zeta potential of -37.8 mV and high EE% of 84 %. The same technique was used to develop
1109 cardamom EO loaded-NLC using cocoa butter (as solid lipid), olive oil (as liquid lipid) and
1110 tween 80 (as surfactant); and the resultant particles had round shape, smooth surface with
1111 particle size less than 100 nm (Nahr et al., 2018). Similarly, NLC were developed using palm
1112 stearin as solid lipid and lecithin as emulsifier and the resultant particles were physically and
1113 chemically stable during 70-day storage at room temperature and 4°C (Zhu et al., 2015).
1114 Furthermore, Noor et al. (2013) successfully loaded coconut VO into SLN by the same process
1115 and reported high EE% (99.97%).

1116 Like all the colloidal formulations discussed above, both SLN and NLC prepared by
1117 high-speed homogenization provide a controlled release profile of plant oils (Pivetta et al.,
1118 2018; Zhao et al., 2017). The release profile of EO from these nanocarriers may be affected by
1119 several factors such as the particle size and the composition of lipidic matrix. In 2011, Garg and
1120 his coworkers compared the release profile of eugenol from SLN and NLC formulations made
1121 from stearic acid and the mixture stearic acid: caprylic triglyceride, respectively (Garg and
1122 Singh, 2011). Results revealed a biphasic release pattern from both nanocarriers. After initial
1123 burst release, the cumulative amounts of eugenol released within 12 h were 65 and 78% from
1124 SLN and NLC, respectively. This was related to the structure of the nanocarrier's matrix. The
1125 addition of liquid lipid in the case of NLC provides fewer barriers to partitioning of eugenol to

1126 the dissolution media. The authors ascribed also this result to the small particle size of NLC
1127 (87.7 nm) as compared to that of SLN (332 nm). Indeed, the addition of liquid lipid decreases
1128 the viscosity of the organic phase (lipid solution) to be dispersed in the aqueous one resulting
1129 in smaller particles. Moreover, liquid lipid may inhibit the crystallization of solid lipid leading
1130 to smaller particle size (Garg and Singh, 2011). One may conclude that the incorporation of
1131 liquid lipid improves the EE% but decreases the barrier provided by lipid matrix for the
1132 diffusion of bioactive molecule in the dissolution medium.

1133 The particle size and zeta potential of NLC were influenced by several parameters
1134 including solid lipid composition, oil and surfactant (type and concentration), lipid:surfactant
1135 ratio, etc. The impact of these factors was extensively studied in the literature (Krasodomska et
1136 al., 2016; Lacatusu et al., 2013; Soleimanian et al., 2018). It was found that increasing stearic
1137 acid concentration results in increasing the size of *Eugenia caryophyllata* EO-loaded SLN
1138 prepared by ultrasonication method (Bazzaz et al., 2018). Moreover, Soleimanian et al. (2018)
1139 developing pomegranate seed oil-loaded NLC using two types of natural waxes: beeswax and
1140 propolis wax, investigated the influence of solid lipid composition, surfactant blend
1141 concentration and oil content on NLC physicochemical properties. Results demonstrated that
1142 increasing oil amount resulted in a decrease in particle size of beeswax NLC. This was related
1143 to the reduction of core viscosity and enhancement of fluidity which results in a decrease in
1144 particle size. The opposite behavior was observed in the case of propolis wax NLC. The particle
1145 size increases by increasing the oil content. The authors ascribed that to enhanced interfacial
1146 tension or swelling rate of the core as result of greater oil concentration. Concerning the impact
1147 of solid lipid type, Soleimanian et al. (2018) reported that small differences in the lipid
1148 composition (particularly, the melting point) might have considerable impact on size and
1149 quality of nano lipid carriers. Beeswax consisting of a longer series of carboxylic acid
1150 homologues, alcohols and hydrocarbons exhibits higher melting point, leading to higher

1151 viscosity of the dispersed phase which in turn results in increasing particle size (203 nm). On
1152 the other hand, propolis wax having lower proportion of components produced smaller NLC
1153 (143 nm). Regarding the zeta potential, the same authors reported that increasing the
1154 concentration of surfactant mixture (Lecithin:Tween 80) results in decreasing the zeta potential
1155 of NLC. They related this result to the differences in mobility and redistribution of used
1156 surfactants. In fact, high amounts of surfactant decrease the surface tension and enhance the
1157 particle partition during homogenization, resulting to a decrease in particle size and thus new
1158 NLC appear. The time required for the redistribution of surfactant molecules to cover the new
1159 surfaces differ. Indeed, low molecular weight surfactants such as tween 80 adsorb rapidly at the
1160 interface, while lecithin, as high molecular weight surfactant, needs more time to be adsorbed.
1161 Therefore, tween 80, external hydrophilic non-ionic surfactant, will cover the internal lipophilic
1162 surfactant (i.e. lecithin), and thus the zeta potential decreases (Soleimanian et al., 2018).

1163 In summary, the ultrasonication is chosen by scientists to design both SLN and NLC
1164 systems to entrap plant oils. The commonly used lipid are glyceryl behenate (Zhao et al., 2017),
1165 stearic acid (Bazzaz et al., 2018; Garg and Singh, 2013, 2011), carnauba wax (Lacatusu et al.,
1166 2013), whey protein isolate (Azizi et al., 2019), glycerol stearate (Lacatusu et al., 2013),
1167 palmitic acid (Azizi et al., 2019), propolis (Soleimanian et al., 2018), palm stearin (Zhu et al.,
1168 2015), beeswax (Shakeri et al., 2019; Soleimanian et al., 2018), illipe butter (Pivetta et al.,
1169 2018), cocoa butter (Nahr et al., 2018), Precirol® ATO 5 (glyceryl palmitostearate) (Ghodrati
1170 et al., 2019), miglyol®812 (caprylic/capric triglycerides) (Ghodrati et al., 2019) and myverol®
1171 RX GMS 95P (mixture of glycerol palmitic (57,8%) stearic (37.3%) and myristic (1.3%) acid)
1172 (Krasodomska et al., 2016). Lecithin (Soleimanian et al., 2018; Zhu et al., 2015), poly vinyl
1173 alcohol (Zhao et al., 2017), tween 80 (Lacatusu et al., 2013; Nahr et al., 2018; Noor et al., 2013),
1174 poloxamer (Ghodrati et al., 2019; Lacatusu et al., 2013) and pluronic® F68 (Pivetta et al., 2018)
1175 are example of used emulsifiers. The main features of the ultrasonication process including

1176 facility, simplicity and reduced high shear. However, it is limited by the high metal
1177 contamination potential, unproven scalability and high energy requirement.

1178 **Table 3.** Preparation methods for plant oils encapsulation in solid lipid nanoparticles and nanostructured lipid carriers with their fine applications.

Encapsulated oil	Plant (origin)	Lipid used	Physicochemical properties			Biological properties	Application	Ref.
			Size (nm)	Z.pot (mV)	EE (%)			
<i>Solid lipid nanoparticles</i>								
<i>High pressure homogenization</i>								
Carvacrol	/	Cocoa butter	/	/	/	Antioxidant	Medicine	(Carvalho et al., 2020)
Geranial	/	Monoterpene	120.1	0	/	/	/	(Zielińska et al., 2020)
Ziziphora	<i>Ziziphora clinopodioides</i>	Imwitor® 900K Percinol ATO5	241.1	-22.6	93	Insecticide	Agriculture	(Jajarm et al., 2020)
Eugenol	/	Campritol 888 Caprylic triglyceride	332	-18.7	91.8	Anticancer	Medicine	(Garg and Singh, 2011)
	/	Stearic acid Hydrogenated palm oil	164.5-172.9	/	/	Antifungal	Food	(McDaniel et al., 2019)
Thymol	/	Coconut oil Hydrogenated palm oil	166.4-170.5 198.0-202.1	/	/	Antifungal	Food	(McDaniel et al., 2019)
Cinnamaldehyde	/	Coconut oil						
Sclareol	/	Compritol	128	-29.3	/	Treatment of metabolic disorder	Medicine	(Cerri et al., 2019)
Chamomile	<i>Matricaria chamomilla</i> L.	Stearic acid	542	-35.9	/	Wound healing	Cosmetics	(Gad et al., 2019)
α -pinene	/	Imwitor® 900K Monoterpene	136.7 89.7	/ 0	/ /	Antimicrobial, antioxidant	/	(Zielinska et al., 2019) (Zielińska et al., 2020)
Citral	/	Imwitor® 900K Glyceryl monostearate	215.4	/	/	Flavoring agent	Food	(Tian et al., 2018)
		Monoterpene Imwitor® 900K	125.4	0	/	/	/	(Zielińska et al., 2020)
Gac fruit EO	<i>Momordica cochinchinensis</i> L.	Emulgade	200	/	90	Antioxidant; Anti-aging Skin tanning, skin care and skin protection	Cosmetics	(Mai et al., 2018)
Frankincense + Myhrr oil	<i>Commiphora myrrha</i> L.	Compritol888 ATO	113.3	-16.8	80-60	Antitumor	Medicine	(Wang, 2012)
Copaiba oil	<i>Copaifera officinalis</i> L.	Cetyl palmitate	126.06	/	/	Antifungal	Cosmetics	(Svetlichny et al., 2015)

Copaiba oil+ Allantoin	<i>Copaifera officinalis</i> L.	Cetyl palmitate	118.63	/	/	Antifungal	Cosmetics	(Svetlichny et al., 2015)
Ultrasonication method								
<i>Zataria multiflora</i>	<i>Zataria multiflora</i> Boiss.	Precirol ATO 5	220-486	-37.8 to -27.2	85.3-95.2	Fungicide Pesticide	Food Medicine Agriculture	(Nasseri et al., 2020)
		Stearic acid Glyceryl monostearate	255.5	-37.8	84	Antifungal	Medicine	(Nasseri et al., 2016)
β -elemene	/	Precirol® ATO 5 Glyceryl monostearate	128.4	-3.07	/	Antitumor	Medicine	(He et al., 2019)
		Glyceryl tristearate						
Clove	<i>Syzygium aromaticum</i> L.	Precirol® ATO 5 Stearic acid Glyceryl monostearate	397.2	-20.9	/	Antimicrobial	Medicine	(Bazzaz et al., 2018)
Linalool	/	Myristyl myristate Cetyl esters	90-130	-4	>80	Anticancer	Medicine	(Rodenak-Kladniew et al., 2017)
Eugenol	/	Cetyl palmitate Stearic acid/Compritol	363– 423	/	/	Antifungal	Medicine	(Garg and Singh, 2013)
		Stearic acid Caprylic triglyceride	87.7	-19.2	98.5	Antifungal	Medicine	(Garg and Singh, 2011)
Coconut	<i>Cocos nucifera</i> L.	Stearic acid	608	-47.5	99.9	Moisturizing lotion	Cosmetics	(Noor et al., 2013)
Nanostructured lipid carriers								
High pressure homogenization								
Cinnamon	<i>Cinnamomum cassia</i> persl.	Cocoa butter Almond oil	100-120	-14.9 to -17.5	>82.1	Antimicrobial, antioxidant	Food	(Bashiri et al., 2020b)
Sucupira	<i>Pterodon emarginatus</i> L.	Imwitor® 900 K Tripalmitin	148.1	/	99.9	Antidiabetic	Medicine	(Vieira et al., 2020)
Squaw mint	<i>Mentha pulegium</i> L.	Precirol® ATO 5 Miglyol®812	40-250	-10 to -15	/	Wound healing	Cosmetics	(Khezri et al., 2020)

Rosemary	<i>Rosmarinus officinalis</i> L.	Precirol [®] ATO 5 Miglyol [®] 812	100-250	-15.7	92.1	Wound healing	Cosmetics	(Khezri et al., 2019)
Peppermint	<i>Mentha piperita</i> L.	Precirol [®] ATO 5 Miglyol [®] 812	40-250	-10 to -15	/	Wound healing	Cosmetics	(Ghodrati et al., 2019)
Clove	<i>Syzygium aromaticum</i> L.	Beeswax Coconut oil	121-367	/	≈60	Cholinesterase enzyme inhibition	Medicine	(de Meneses et al., 2019)
<i>Ridolfia segetum</i>	<i>Ridolfia segetum</i> L.	Precirol [®] ATO 5	143	16.3	100	Antioxidant; anti-inflammatory	Medicine	(Miranda et al., 2019)
B-elemene	/	Glycerol monostearate Glyceryl monolinoleate Oleoyl macrogolglycerides	138.9	-20.2	82.11	Antitumor	Medicine	(Shi et al., 2013)
Thymoquinone	/	Hydrogenated palm oil Olive oil Lipoid [®] S100	75	-31	/	Antiulcer	Medicine	(Sidding et al., 2013)
Sunflower	<i>Helianthus annuus</i> L.	Sunflower oil	48.23 - 342.10	-22.3 to -29.7	/	Source of phytosterols	Food	(Santos et al., 2019)
Crambe	<i>Crambe maritima</i> L.	Crambe oil						
Canola	<i>Brassica napus</i> L.	Canola oil						
Pomegranate seed	<i>Punica granatum</i> L.	Glycerol monostearate	108 -145	34.4 to -44.3	51 – 70	Antioxidant UVA protector	Cosmetics	(Badea et al., 2015)
Wheat germ	<i>Triticum aestivum</i> L.	Emulgade						
Blackcurrant seed	<i>Ribes nigrum</i> L.							
Sesame	<i>Sesamum indicum</i> L.							
Carrot root	<i>Daucus carota</i> subsp. <i>Sativus</i>							
Raspberry seed	<i>Rubus idaeus</i> L.							
Rice bran	<i>Oryza sativa</i> L.							
Olive	<i>Olea europaea</i> L.	Hydrogenated palm oil	61.14	-25.4	/	Source of PUFA	Medicine	(How et al., 2013)
Grape seed + Laurel	<i>Vitis vinifera</i> L.	n-Hexadecyl palmitate	< 150	/	/	Antitumor; antioxidant	Medicine	(Lacatusu et al., 2015)

Glycerol
monostearate
Myritol®318

Ultrasonication method

Cinnamon	<i>Cinnamomum cassia</i> persl.	Cocoa butter	119.4	+21.4	84.6	Antioxidant	Food	(Bashiri et al., 2020a)
<i>Lippia sidoides</i>	<i>Lippia sidoides</i> L.	Gelucire® Labrasol®	214.4-423.2	-40.6 to -23.0	/	Antifungal	/	(Baldim et al., 2019)
Carvacrol + Astaxanthin	/	Lecithin Beeswax	58.8	-36	Asta=95 Car=88	Antioxidant Antibiofilm	Medicine	(Shakeri et al., 2019)
Eucalyptus	<i>Eucalyptus globulus</i> L.	Olive oil	50 – 60	-22.07	101.7	Wound healing	Cosmetics	(Saporito et al., 2018)
Peppermint	<i>Mentha piperita</i> L.	Miglyol-812 Precirol-ATO 5	40-250	-10 to -15	93.2	Wound healing	Cosmetics	(Ghodrati et al., 2019)
Cardamon	<i>Elettaria cardamomum</i> L.	Cocoa butter Olive oil	<150	/	>90	Antimicrobial	Food	(Nahr et al., 2018)
Thymol	/	Illipe butter Calendula oil	107.7	-11.6	89.1	Anti-inflammatory Antipsoriatic	Cosmetics	(Pivetta et al., 2018)
Houttuynia cordata	<i>Houttuynia cordata</i> Thunb.	Glyceryl behenate	171	-19.3	90.20	Treatment of pneumonia, respiratory and urinary tract infections	Medicine	(Zhao et al., 2017)
Pomegranate seed	<i>Punica granatum</i> L.	Propolis Beeswax	71.4 - 366.3	-18.3 to -27.2	96-99	Antioxidant	Food	(Soleimani et al., 2018)
Blackcurrant	<i>Ribes nigrum</i> L.	Myverol RX	/	/	/	Source of PUFA	Medicine	(Krasodomska et al., 2016)
Blackberry	<i>Rubus fruticosus</i> L.	GMS 95P						
Raspberry	<i>Rubus idaeus</i> L.	Chemal EO-20						
Strawberry	<i>Fragaria ananassa</i>							
Plum	Duchesne. <i>Prunus domestica</i> L.							

1180 **6. Application**

1181 **6.1. Agriculture field**

1182 The indiscriminate use of chemicals in field as well as during postharvest poses serious
1183 problems for the environment and the human health. The excessive application of synthetic
1184 fungicides can also have other negative side effects. The appearance of resistance in the
1185 pathogen populations has been notified for many fungi (Saharan et al., 2013). In addition, over
1186 the last few years increasing consumers concern regarding contamination of crops with
1187 fungicidal residues has been reported (Shukla, 2018). Therefore, low toxicity and more
1188 environmentally friendly compounds as an alternative to chemical fungicides was brought to
1189 the forefront. Among them, GRAS (generally regarded as safe) antifungal compounds such as
1190 EO have been reported (Shukla, 2018; Sotelo-Boyás et al., 2015). Due to their broad spectrum
1191 of activity against plant pathogenic fungi and insects-pests, EO have been used as antifungal,
1192 insecticidal, repellent, antifeedant and oviposition deterrent (De Souza et al., 2005; Shukla,
1193 2018). However, the replacement of synthetic compounds is not easy due to the poor stability
1194 shown by EOs during the processing steps. Therefore, nanoencapsulation has been proposed
1195 for this purpose (Maryam et al., 2015). According to the literature, pNPs are widely used for
1196 EO encapsulation in agriculture industry.

1197 Recently, Khoobdel et al. (2017) investigated the insecticidal activity of *Rosmarinus*
1198 *officinalis* EO-loaded pNPs against the red flour beetle, *Tribolium castaneum*. Fumigant and
1199 contact toxicity assays revealed that the developed particles had significant increase in fumigant
1200 and contact toxicity as compared to the pure EO. At the 72 h exposure for fumigant toxicity,
1201 the mortality of *Tribolium castaneum* adults was 83.3 % for free EO at a concentration of 27.76
1202 $\mu\text{L/L}$ air and 100 % for EO-loaded nanoparticles at concentration of 19.12 $\mu\text{L/L}$ air (Khoobdel
1203 et al., 2017). Moreover, Zhavah et al. (2015) related the superior performance of *Cuminum*
1204 *cuminum EO* nanogels against *Aspergillus flavus* as compared to the free oil to the encapsulation

1205 in chitosan : caffeic acid nanoparticles. Similar results were already reported when investigating
1206 insecticidal activity against *Bemisia tabaci* for *Zanthoxylum rhoifolium* EO-loaded
1207 nanoparticles as compared to the free oil (Christofoli et al., 2015). Therefore, the
1208 nanoencapsulation can enhance the insecticidal potential of EO due to the controlled and slow
1209 release of EO and increased surface area of the nanoparticles.

1210 Sotelo-Boyas and his coworkers (2015) combined the bacterial efficiency of chitosan
1211 with those of lime and thyme EO in pNPs to eradicate *Pectobacterium carotovorum*, plant
1212 phytopathogenic bacteria, involved in the decay of fresh vegetables and fruits like radishes,
1213 onions, potatoes, cucumbers, carrots, eggplant, squash, peppers, tomato and cabbage. For
1214 instance, chitosan was highly used for its potential effect in the control of phytopathogenic
1215 fungi Gram-negative and Gram positive bacteria (Benhabiles et al., 2012; Kaur et al., 2012;
1216 Zhu et al., 2016). The antibacterial study demonstrated that thyme based-nanoparticles showed
1217 the highest inhibitory effect on the growth of *Pectobacterium carotovorum* than free chitosan
1218 nanoparticles and lime based- nanoparticles. The inhibition halo diameters were found 15, 13
1219 and 24 mm for chitosan free nanoparticles, lime-chitosan nanoparticles and Thyme-chitosan
1220 nanoparticles, respectively. Moreover, the number of colonies forming units (CFU) could not
1221 be determined (countless colonies) for chitosan free nanoparticles. While for lime- and thyme-
1222 chitosan nanoparticles, CFU were found 450 and 240, respectively (Sotelo-Boyás et al., 2015).
1223 Furthermore, the results of antifungal assay carried out on chitosan:pepper tree EO
1224 nanoparticles revealed that higher activity was assessed for the nanoparticles on the viability of
1225 *Aspergillus parasiticus* spores as compared to that of chitosan and pepper tree oil present
1226 individually. One may conclude that the antifungal effect of chitosan nanoparticles was
1227 attributed to two reasons: 1) the small size of nanoparticles will increase the contact area with
1228 fungus; 2) The cationic nature of chitosan allows electrostatic interaction with proteins and

1229 phospholipids of the plasmatic membrane of the microorganism which in turn cause membrane
1230 destabilization and death.

1231 With respect to the use of lipid based-nanocarriers in agriculture industry, few reports
1232 have been investigated in the last decade. Liposomes were used for the first time for rosemary
1233 EO encapsulation to inhibit the seed germination of invasive alien species (*Acacia saligna*)
1234 (Maccioni et al., 2019). The incorporation of rosemary EO in liposomes limited the loss of EO
1235 volatile components and delivering them into the seed resulting in enhancing EO efficacy.
1236 Similarly, Adel et al. (2015) pointed out that *Pelargonium graveolens* EO loaded-SLN were
1237 stable under field conditions and exhibit higher larvicidal activity against *Phthorimaea*
1238 *operaculella* as compared to the free oil.

1239 **6.2. Food field**

1240 In recent years, consumer demands in eating healthy and less processed foods have
1241 boosted remarkably. Functional foods play a pivotal role in promoting health and preventing
1242 degenerative diseases such as heart disease, cancer and diabetes, which account for almost two
1243 thirds of deaths in the world (Conto et al., 2012; Rubilar et al., 2012). Foods enriched with long
1244 chain omega-3 polyunsaturated fatty acids are classified as functional foods by acting on human
1245 health. The ingestion of omega-3 fatty acids is accompanied with a prevention of cardiovascular
1246 diseases, a decreased risk of cancer, autoimmune and inflammatory diseases (Azizi et al., 2019;
1247 Conto et al., 2012; Gallardo et al., 2013). However, polyunsaturated fatty acids are very
1248 susceptible to oxidation during processing and storage resulting in decreased nutritional value
1249 and sensory quality. Thus, micro and nanoencapsulation of lipids have been used in this concern
1250 (Gökmen et al., 2011).

1251 Currently, several nanocarriers have been designed in the literature to encapsulate
1252 several healthful oils like chia seed oil (Campo et al., 2017), walnut oil (Shamaei et al., 2017),

1253 flaxseed oil (Carneiro et al., 2013; Gallardo et al., 2013; Pu et al., 2010), pomegranate oil
1254 (Soleimanian et al., 2018), roasted coffee oil (Freiberger et al., 2015) and fruit seed oil
1255 (blackcurrant, blackberry, raspberry, strawberry and plum) (Krasodomska et al., 2016). In 2012,
1256 Rubilar et al. developed a soup fortified with linseed oil microcapsules and depicted that
1257 microencapsulation protected linseed oil from oxidation with respect to free oil (Rubilar et al.,
1258 2012). Similarly, Gökmen et al. (2011) demonstrated the feasibility to include flaxseed oil
1259 nanoparticles in bread without affecting the sensorial properties.

1260 At the same time, foods are paramount carriers of many damaging agents like virus,
1261 bacteria, parasites, and toxins which can cause food-borne diseases (Dussault et al., 2014).
1262 Every year, around 30% of people suffer from foodborne diseases in developed countries (Lee
1263 et al., 2014). Meanwhile, due to the increased consumer awareness to the use of synthetic food
1264 preservatives or aromatic agents, the tendency toward natural ones is gaining more and more
1265 attention (Alikhani-Koupaei, 2015). In light of that, using EO with antioxidant, antibacterial
1266 and antifungal properties and applying nanoparticulate systems are effective approaches in this
1267 regard (Bazzaz et al., 2018; Khatibi et al., 2017). In 2017, Cui and his coworkers developed
1268 thyme EO-loaded liposomes to treat salmonellosis, an important food-borne disease, usually
1269 associated with direct consumption or cross contamination of animal origin foods, especially
1270 poultry, and poultry related products (Cui et al., 2017b). They investigated in their study the
1271 time-kill analysis of liposome-encapsulated thyme oil on fresh chicken contaminated with
1272 *Salmonella enteritidis*. Results demonstrated that *Salmonella enteritidis* colonies reduced by
1273 71.16, 90.45, 83.02, 89.53 and 97.71% after exposure to 300 mg/mL liposomes for 3, 4, 5, 6,
1274 and 7 days, respectively (Cui et al., 2017b). In another work study, the antimicrobial activity of
1275 curry plant EO loaded-liposomes against *Bacillus cereus* in rice flour was investigated (Cui et
1276 al., 2017a). Results showed that the antibacterial activity and active time of curry plant EO
1277 loaded-liposomes were significantly boosted when compared to the free EO. For instance, the

1278 population of *Bacillus cereus* in rice flour was almost unchanged or even increased after EO
1279 treatment. However, it reduced significantly after 4 days liposomes treatment (Cui et al.,
1280 2017a). Gomes et al. (2011b) related the boosting in trans cinnamaldehyde or –eugenol against
1281 both *Salmonella* and *Listeria Spp* activity to three reasons: the improved hydrophilicity, the
1282 sustained release, and the small size of pNPs. In 2018, Lin et al. investigated the antimicrobial
1283 activity of thyme EO-loaded liposomes against *Escherichia coli* O157:H7 in four vegetable
1284 juices: tomato, carrot, cucumber and lettuce juices (Lin et al., 2018). Indeed,
1285 Enterohaemorrhagic *Escherichia coli* serotype O157:H7 as a main human pathogen may cause
1286 food borne outbreaks, bloody diarrhea, hemorrhagic colitis and hemolytic uremic syndrome
1287 and even death (Khatibi et al., 2017). Results showed that solid liposomes exhibited significant
1288 reduction in *Escherichia coli* O157:H7 when compared to group control. For instance, no
1289 bacterial growth was observed on nutrient agar plate in the case of cucumber juice and lettuce
1290 juice treated with 5 mg/mL liposomes. While, treating tomato juice and carrot juice with the
1291 same concentration of liposomes lead to 99.99 and 99.80% reduction of *Escherichia coli*
1292 O157:H7 (Lin et al., 2018). Moreover, Khatibi et al. (2017) found that the relative
1293 transcriptional level of Stx2A gene of *Escherichia coli* O157:H7 was decreased from 0.721 to
1294 0.646 when using 75% minimum inhibitory concentration (MIC) of *Zataria multiflora* EO
1295 loaded-nanoliposomes.

1296 The antibacterial mechanism of EOs loaded-nanocarriers has been investigated. In 2015,
1297 Cui et al. investigated the antibacterial mechanism of liposomes containing clove EO against
1298 *Staphylococcus aureus* in Tofu (Cui et al., 2015). A selective antimicrobial activity for
1299 *Staphylococcus aureus* by means of pore-forming toxins to activate clove oil release from
1300 liposomes was noticed. In fact, the liposomes did not fuse with biological membranes but
1301 release clove oil after toxins secretion by the bacteria. About 99.87% reduction in population
1302 was observed in *Staphylococcus aureus* after 24 h of liposome treatment. However, no

1303 reduction was observed in *Escherichia coli* population after liposome treatment due to the fact
1304 that these bacteria did not secrete toxins and therefore clove oil could not reach them (Cui et
1305 al., 2015).

1306 The antioxidant and antimicrobial activities of EO-loaded nanocarriers were found to
1307 be conserved for long period. In this context, the physicochemical qualities of fresh-cut bananas
1308 in contact with free rosemary EO, rosemary oil plus mucilage and rosemary oil liposomes were
1309 evaluated during 9 days storage at 5°C (Alikhani-Koupaei, 2015). Sensory analysis revealed
1310 that liposomal formulations was more efficient in enhancing the quality of fresh-cut bananas
1311 and extending their shelf life (Alikhani-Koupaei, 2015). Likewise, the conversion of cardamom
1312 EO to NLC (Nahr et al., 2018) and nanoliposomes (Nahr et al., 2019) greatly conserves its
1313 antioxidant and antimicrobial activities for long period. The NLC showed MIC values around
1314 1100 µg/ml for both bacteria after 30 days compared to that of cardamom oil emulsion. The
1315 MIC values were around 4400 and 2200 µg/ml for *Staphylococcus aureus* and *Escherichia coli*,
1316 respectively (Nahr et al., 2018).

1317 The biological activity of nanocarriers encapsulated plant oils was affected by operating
1318 parameters and particles ingredients. In 2017, Mohammed and his coworkers depicted that a
1319 high antioxidant efficiency of *Nigella sativa* EO-loaded microparticles prepared by spray
1320 drying process was associated with high ratio of wall material (30%), medium of oil
1321 concentration (10%) and low inlet temperature (160°C) (Mohammed et al., 2017).
1322 Furthermore, Bazzaz et al. (2018) investigated the antimicrobial activity of SLN encapsulated
1323 *Eugenia caryophyllata* EO against *Salmonella typhi*, *Pseudomonas aeruginosa*,
1324 *Staphylococcus aureus* and *Candida albicans* using time-kill methods. Results demonstrated
1325 that the SLN formulations were effective in Gram negative bacteria and fungi killing, especially
1326 those containing stearic acid compared to glycerol monostearate (Bazzaz et al., 2018).

1327 In recent years, the use of EO has emerged to the food packaging industry as reported
1328 by several work studies (Cui et al., 2016a, 2016b; Engel et al., 2017; Liu et al., 2017). Cinnamon
1329 EO, known for its antimicrobial properties, has been formulated in chitosan/poly lactic acid
1330 fibers for food packaging application as an alternative for synthetic chemicals due to consumer
1331 concerns over food safety (Liu et al., 2017). Results showed high long-term inactivation rates
1332 against *Escherichia coli* and *Staphylococcus aureus* (Liu et al., 2017). Cinnamon EO was
1333 further formulated in liposomes and tested for its Methicillin-resistant *Staphylococcus aureus*
1334 antibiofilm properties on the surfaces of different materials like stainless steel, gauze, nylon
1335 membrane, and non-woven fabrics (Cui et al., 2016a). Results revealed a significant
1336 enhancement of the anti-biofilm activities and active time for liposome-encapsulated cinnamon
1337 EO when compared to the free oil. For instance, the counts of viable *Staphylococcus aureus* in
1338 biofilms formed were reduced by 2.08 and 2.82 logs on gauze and 4.55 and 5.42 logs on non-
1339 woven fabrics after five days treatment with free cinnamon oil and liposome containing
1340 cinnamon oil, respectively (Cui et al., 2016a). Additionally, the antibacterial effect of salvia EO
1341 nanoliposomes against *Staphylococcus aureus* biofilms attached on milk container was
1342 explored by scanning electron microscopy and confocal laser scanning microscopy and results
1343 revealed that salvia EO nanoliposomes have high anti-biofilm activity against *Staphylococcus*
1344 *aureus* biofilms on milk container (Cui et al., 2016b). Furthermore, Engel et al. (2017) noticed
1345 the antimicrobial potential of liposome-encapsulated thymol and carvacrol against pools of
1346 *Staphylococcus aureus* and *Salmonella* adhered to stainless steel.

1347 **6.3. Medicinal field**

1348 **6.3.1. Antimicrobial activity**

1349 The management of bacterial infection is raising serious concern across the globe. The
1350 emergence of multi-drug-resistant bacterial pathogens and the ability of microorganisms to
1351 form biofilms result high tolerance to high amounts of antibiotics and to all host defense

1352 mechanisms (Mandal et al., 2014). Faced with this challenge, the scientists throughout the
1353 world search for new antimicrobial agents, such as plant oils based formulations which are
1354 economic and ecologic antimicrobial agents; and combine them with nanotechnology (Liakos
1355 et al., 2018). In this context, Iannitelli et al. (2011) investigated the effects of carvacrol-loaded
1356 poly (lactide-co-glycolide)-nanocapsules on the viscoelastic features of *Staphylococcus*
1357 *epidermidis* biofilms by rheological measurements. Results revealed the ability of carvacrol
1358 loaded nanoparticles to reduce the elasticity and mechanical stability of preformed biofilms
1359 which in turn enable the penetration of antimicrobial agents into the deep core of biofilms
1360 (Iannitelli et al., 2011). Liakos et al. (2016) tested the antibiofilm activity of poly lactide
1361 nanoparticles encapsulating lemongrass EO against *Candida albicans*, *Escherichia coli*,
1362 *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Results showed higher anti-biofilm
1363 effect for *Candida albicans* and *Escherichia coli* tested strains. The cytotoxicity of the prepared
1364 nanoparticles was further analyzed and results revealed a high cell viability and good growth
1365 of human cells (Liakos et al., 2016). Subsequently, in 2018, the same research team tested the
1366 antibiofilm activity of cellulose acetate pNPs containing either lemongrass, peppermint or
1367 cinnamon EO and the results showed high antibiofilm activity against *Candida albicans* and
1368 *Staphylococcus aureus* (Liakos et al., 2018). Manconi et al. (2018) proposed the use of
1369 liposomes containing *Thymus capitatus* EO as antibacterial-antioxidant mouthwash for the
1370 treatment of oral cavity diseases. The liposomes were biocompatible, able to prevent oxidative
1371 stress and favor wound repair in keratinocytes. Their antibacterial activity was evidenced
1372 against commensal *Streptococcus sanguinis* and cariogenic *Streptococcus mutans* and
1373 *Lactobacillus acidophilus* (Manconi et al., 2018). Similarly, Priyadarshini et al. (2018)
1374 proposed the use of poly (lactide-co-glycolide)-nanoparticles containing clove EO as
1375 antibacterial systems for dental purposes by removing bacterial plaque and reducing dental
1376 diseases. Confocal microscopy demonstrated successful delivery and position of clove oil

1377 loaded-nanoparticles inside dentinal tubules. In another work study, the antiviral activity of
1378 *Santolina insularis* EO loaded-liposomes against Herpes simplex virus-type 1 was investigated
1379 (Valenti et al., 2001). Although the *in vitro* activity of free oil was higher than liposomal oil,
1380 the high stability of liposomes make them an interesting delivery system for antiviral treatment;
1381 they could be administered in drops for ocular herpetic infection, parenterally for diffused
1382 systemic infections or topically on lips and mucosae from gel or cream formulations (Valenti
1383 et al., 2001). Furthermore, Zhao et al. (2017) highlighted the use of SLN as a carrier for the
1384 encapsulation and sustained inhalation delivery of yuxingcago EO for the treatment of
1385 respiratory infectious diseases. Besides prolonging pulmonary retention up to 24h after
1386 intratracheal administration to rats, yuxingcago EO loaded-SLN enhance the area under the
1387 curve (AUC) values by 4.5-7.7 folds compared to the intratracheally dosed EO solution and by
1388 257–438 folds to the intravenously dosed EO solution (Zhao et al., 2017).

1389 **6.3.2. Antifungal activity**

1390 Considering the antifungal properties of *Zataria multiflora* EO, Nasser et al. developed
1391 *Zataria multiflora* EO loaded-SLN to enhance its activity against *Aspergillus ochraceus*,
1392 *Aspergillus niger*, *Aspergillus flavus*, *Alternaria solani*, *Rhizoctonia solani*, and *Rhizopus*
1393 *stolonifera* (Nasser et al., 2016). Results showed that the encapsulated oil was more efficient
1394 than the free one. For instance, the MIC for the encapsulated oil on the fungal pathogens of
1395 *Aspergillus ochraceus*, *Aspergillus niger*, *Aspergillus flavus*, *Alternaria solani*, *Rhizoctonia*
1396 *solani*, and *Rhizopus stolonifer* was 200, 200, 200, 100, 50 and 50 ppm, respectively; while for
1397 un-encapsulated oil, it was 300, 200, 300, 200, 200 and 200 ppm (Nasser et al., 2016).
1398 Furthermore, the nanoencapsulation enhanced the antifungal properties of copaiba oil against
1399 *Candida krusei*, *Microsporium canis*, *Candida parapsilosis* and *Trichophyton rubrum* with
1400 MIC₉₀ values of 250, 1.95, 7.8 and 1.95µg/mL, respectively. In another work study,
1401 microparticles encapsulating *Lippia sidoides* EO were found more efficient than ketaconazole,

1402 used as positive control, in eradicating *Candida albicans*, *Candida glabrata*, *Candida krusei*
1403 and *Candida parapsilosis* (Fernandes et al., 2008).

1404 Recently, many studies related the occurrence of some diseases like teratogenesis,
1405 mutation and hepatocellular carcinoma to the high exposure to aflatoxin which is secondary
1406 metabolites synthesized by toxigenic fungi: *Aspergillus flavus*, *Aspergillus parasiticus* and
1407 *Aspergillus nomius*. López-meneses et al. (2018) investigated the antifungal and
1408 antiaflatoxic activities against *Aspergillus parasiticus* of *Shinus molle* EO-loaded chitosan
1409 nanoparticles. Results showed that the prepared nanoparticles affected the spore's germination
1410 and viability, delayed mycelial growth and reduced aflatoxin production.

1411 **6.3.3. Larvicidal activity**

1412 Currently, several reports has demonstrated the larvicidal activity of *Lippia sidoides* EO
1413 against larvae of *Aedes (Stegomyia aegypti)*, the dengue vector which is responsible for many
1414 diseases, and even deaths, in tropical countries like Brazil (Carvalho et al., 2003). In order to
1415 boost its larvicidal effect, Paula et al. (2010) developed angico gum : chitosan nanoparticles
1416 containing *Lippia Sidoides* EO and investigated the *in vivo* activity on 20 third instar *Stegomyia*
1417 *aegypti* larvae. Results demonstrated that the larval mortality was proportional to the oil
1418 loading. For instance, the sample oil: angico gum-chitosan 1:20 showed the lowest loading
1419 (3.3%) and consequently the lowest mortality, with 52 % after 24 h and 60 % after 48 h. Sample
1420 oil: angico gum-chitosan 1:10 showed 85 and 92 % mortality after 24 and 48 h, respectively
1421 (Paula et al., 2010). Similar results were found by Abreu et al. when studying the larvicidal
1422 activity of *Lippia Sidoides* EO loaded-cashew gum : chitosan nanoparticles (Abreu et al., 2012).

1423 **6.3.4. Antitumor activity**

1424 The antitumor activity of frankincense and myrrh oil loaded-SLN was assessed on H22
1425 tumor-bearing mice and results revealed an enhancement in antitumor efficiency of SLN when
1426 compared to that of suspension and cyclodextrine inclusion (Wang, 2012). The inhibition rates

1427 were 31.23, 34.81 and 43.66% for oil suspension, oil- β -cyclodextrin and oil-SLN, respectively.
1428 Similarly, Celia et al. (2013) found that liposomal formulations encapsulating bergamot EO
1429 showed a greater reduction in human SH-SY5Y neuroblastoma cells viability and a greater
1430 increase in cell mortality at various concentrations and time points as compared to their free
1431 drug counterparts. Same results were also reported by Detoni et al. (2012) where MLVs and
1432 SUVs containing *Zanthoxylum tingoassuiba* EO were more efficient in reducing the viability
1433 of glioma cells than free EO. In another work study, docosahexaenoic acid was encapsulated in
1434 liposomes and investigated for its anticancer activity and results showed a strong inhibition of
1435 FaDu head, neck squamous carcinoma and 4T1 breast cancer cells in *in vitro* cultures (Alaarg
1436 et al., 2016). In 2013, Shi and his coworkers developed NLC containing β -elemene and
1437 investigated their pharmacokinetics, anti-tumor effects, and venous irritation (Shi et al., 2013).
1438 In this study, β -elemene-NLC suspensions were injected in an ear vein test, and compared with
1439 elemene injection and saline solution used as positive and negative controls, respectively.
1440 Results demonstrated no obvious discoloration or damage at the injection site in either β -
1441 elemene-NLC groups or saline solution group, two days after the injection. However, un-
1442 encapsulated β -elemene caused macroscopic edema and erythema at the injection site.
1443 Additionally, the pharmacokinetic study revealed that the availability of the β -elemene was
1444 increased by formulation into NLC since they showed higher AUC and slower clearance as
1445 compared to elemene injection. Furthermore, the anti-tumor efficacy of β -elemene-NLC was
1446 significantly higher than that of elemene injections with inhibition rates of 34.36 and 24.11%,
1447 respectively (Shi et al., 2013).

1448 **6.4. Cosmetic field**

1449 Wound healing is one of the most complicated physiological processes. Indeed, tissue
1450 regeneration enhancement and infection prevention are key factors to reduce pain, discomfort,
1451 and scar formation (Jahromi et al., 2018). Several chemical products have been proposed for

1452 wound repair; however, their uses are limited due to the complications and side effects (Purohit
1453 et al., 2012). Recently, researchers have paid great attention to the effectiveness of plant oils
1454 thanks to their antioxidant, antimicrobial, and anti-inflammatory properties (Raut and
1455 Karuppayil, 2014). In this context, Ghodrati et al. (2019) investigated the therapeutic effect of
1456 NLC containing peppermint EO on infected wound. For *in vivo* study, two full-thickness
1457 wounds with the size of 5mm were created in each mouse and inoculated with *Pseudomonas*
1458 *aeruginosa* and *Staphylococcus aureus*. Results showed that peppermint EO-NLC could
1459 accelerate wound healing in the infected wound model by reducing the total bacterial count,
1460 and increasing neovascularization, fibroblast infiltration, collagen deposition, re-epithelization,
1461 and levels of FGF-2 and EGF mRNA expressions when compared to control group. Similarly,
1462 Zhang et al. reported a decrease in TGF-*b*1, MMP-1, collagen I and collagen III levels and an
1463 increase in apoptosis cells, caspase -3 and -9 levels after application of *Ligusticum chuanxiong*
1464 EO-loaded liposomes on formed hypertrophic scars in the rabbit ear model (H. Zhang et al.,
1465 2012). Furthermore, NLC based on olive oil and loaded with eucalyptus oil promote wound
1466 healing in rat burn model by cell proliferation enhancement, good bioadhesion, cell
1467 biocompatibility and antimicrobial properties (Saporito et al., 2018). In 2018, Pivetta et al.
1468 prepared carbopol-gels containing thymol loaded-NLC as promising approach for treating skin
1469 inflammatory disorders (Pivetta et al., 2018). In their study, they investigated the anti-
1470 inflammatory effects of thymol-NLC gel on two mouse models: the cutaneous acute
1471 inflammation model induced by croton oil and ear edema model induced by anthralin. Results
1472 showed that thymol encapsulated in NLC provided better anti-inflammatory effect than free
1473 thymol (Pivetta et al., 2018).

1474 Chronic skin infections in immunocompromised patients has become an important
1475 public health issue because they can become serious, resulting in invasive infections
1476 (Svetlichny et al., 2015). In this context, Ortan et al. (2013) developed hydrogels containing

1477 *Anethum graveolens* oil entrapped in liposomes to treat fungal infections in skin. The *in vitro*
1478 release kinetics study using Franz diffusion cell showed that the designed hydrogels follow a
1479 zero order kinetic model after a period of three hours from the beginning of the experiment
1480 (Ortan et al., 2013). Moreover, hydrogel containing eugenol entrapped in either stearic acid- or
1481 Compritol-SLN were designed for epidermal targeting to treat fungal infections in skin (Garg
1482 and Singh, 2013). *Ex vivo* permeation and retention studies for almond oil solution of eugenol
1483 and three types of hydrogels containing: eugenol-stearic acid-SLN, eugenol-compritol-SLN or
1484 eugenol-hydroxypropyl- β -cyclodextrin complex; were established with full thickness human
1485 cadaver skin using Franz diffusion cell. Results revealed higher accumulation of eugenol in the
1486 epidermis (62.65 and 52.86 $\mu\text{g}/\text{cm}^2$ for eugenol-stearic acid-SLN and eugenol-compritol-SLN,
1487 respectively) when compared to that of almond oil solution of eugenol (3.45 $\mu\text{g}/\text{cm}^2$) and
1488 eugenol-hydroxypropyl- β -cyclodextrine complex (9.77 $\mu\text{g}/\text{cm}^2$) (Garg and Singh, 2013).

1489 Currently, VO exhibit a great concern as raw materials in the development of natural
1490 and eco-friendly cosmetics due to their benefits including antioxidant, moisturizers and
1491 emollients properties. In addition, they provide skin protection against reactive oxygen species
1492 and prevent oxidative stress (Dhavamani et al., 2014; Saraf et al., 2010). In order to obtain
1493 efficient formulations with UV protection performance and antioxidant activity, Badea et al.
1494 (2015) formulated creams containing NLC entrapping various VO and their combinations
1495 (pomegranate seed oil, wheat germ oil, blackcurrant seed oil, sesame seed oil, carrot root oil,
1496 raspberry seed oil and rice bran oil) with a synthetic UVA filter (diethylamino hydroxy benzoyl
1497 hexyl benzoate). The UV protection factors were evaluated on the individual VO and on cream
1498 formulations based on NLC and results showed that the best UV protection was assured by
1499 pomegranate seed oil combined with wheat germ-loaded NLC based cream resulting in a SPF
1500 of 5.1 and an UVAPF of 9.5 (Badea et al., 2015).

1501 **6.5. Textiles**

1502 Nowadays, functional textiles fascinated consumers interest due to their crucial benefits
1503 as they enhance the native properties and promote new functions in the textile products like
1504 flame retardency, UV resistance, photo-catalytic, antimicrobial, antibiotic and wrinkle recovery
1505 to the fabrics (Javid et al., 2014). In medical field, textile consumers are becoming more aware
1506 and conscious of the deleterious effect that microorganisms may have upon textile materials
1507 like drapes, bed sheets, pillow cases, gowns and masks which are frequently used in hospitals
1508 (Thelagavath and Kannaian, 2008). In this context, Li et al. (2013) grafted moxa oil
1509 microcapsules made with gelatin and arabic gum on cotton fabric and investigated their
1510 antibacterial activity against *Staphylococcus aureus* and the results showed strong antibacterial
1511 effect. Similarly, ozonated red pepper seed oil antimicrobial microcapsules were applied on
1512 100% polypropylene non-woven fabric and showed good antimicrobial activity against
1513 *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans* (Ozyıldız et al., 2012).
1514 Furthermore, Rajendran et al. (2013) reported that *Ocimum sanctum* oil loaded alginate-
1515 nanoparticles possessed remarkable antibacterial activities with excellent wash durability. After
1516 20 washes, the inhibition percentage was 100% for *Bacillus cereus*, *Pseudomonas aeruginosa*
1517 and *Staphylococcus aureus* except for *Escherichia coli* (90%). After 30 washes, the bacterial
1518 inhibition was reduced to 95, 87, 98 and 98% for *Bacillus cereus*, *Escherichia coli*,
1519 *Pseudomonas aeruginosa* and *Staphylococcus aureus*, respectively (Rajendran et al., 2013). In
1520 2013, Javid et al. reported that antibacterial activity of cotton fabric grafted with chitosan
1521 capsules containing eucalyptus and sandal wood oils increased with the increase in chitosan
1522 and EO concentrations (Javid et al., 2014).

1523 Recent developments in textile industry were conducted to perfumed textiles in jackets,
1524 sweaters, T-shirts and undershirts to meet consumers' needs for comfort and wellbeing. During
1525 wearing, the mechanical forces on the capsules result in opening of the capsules and releasing
1526 of the designed aroma and deodorant (Ghayempour and Montazer, 2016). In this context, Liu

1527 et al. (2015) treated methyl methacrylate–styrene nanoparticles containing cologne EO on the
1528 cotton fabric through immersion and the release study revealed that 6.8% cologne EO remained
1529 in fabrics after being washed 15 times. In another work, Wang et al. reported that ethyl cellulose
1530 microcapsule can retain 50% of the lavender oil after 2 months, while almost no EO persisted
1531 on the direct sprayed fabric after 7 days (Wang et al., 2009). Additionally, Li et al. (2013) found
1532 that orange oil retention of microcapsules on the cotton and polyester fabrics was 8 days longer
1533 than free oil.

1534 **7. Conclusion and perspectives**

1535 In the last two decades, the growing demand for natural bioactive products especially
1536 essential and vegetable oils with the same efficiency or even more than chemical synthesized
1537 drugs has urged researchers to focalize most of their efforts on developing new approaches of
1538 extending the shelf life of these bioactive agents. In fact, plant oils are very sensitive to external
1539 factors when used as such. The encapsulation of these bioactive agents represents a relevant
1540 alternative to extend their physical stabilities, protecting them from oxidation and other
1541 deleterious environmental factors like light, heat, oxygen and humidity, besides improving their
1542 efficacy mainly owing to their nanometer size range. In this bibliographic paper, we emphasize
1543 recent advances of both polymer and lipid based-nanocarriers including polymeric
1544 nanoparticles, liposomes and solid lipid nanoparticles in the emergence of new concepts for the
1545 effective use of plant oils. A number of benefits and drawbacks are linked to each carrier. For
1546 instance, both solid lipid nanoparticles and polymeric nanoparticles have more oil stability and
1547 prolonged release than liposomes; while liposomes offer wide application spectrum especially
1548 to the skin delivery thanks to their chemical nature which is very close to that of the skin layers.
1549 Although solid lipid nanoparticles are safer than polymeric nanoparticles since the avoidance
1550 of organic solvents, they were less used to encapsulate both essential and vegetable oils,
1551 according to the investigations discussed above. This may be related to the high

1552 temperature requirements which in turn cause oil loss and thus decrease the encapsulation
1553 efficiency. Several preparation methods have been reported for each nanocarrier; they are
1554 differentiated by the complexity of their execution and the characteristic of their final product;
1555 nonetheless, the right selection of the suitable carrier with the appropriate preparation method
1556 is the crucial key to determine the carrier features responsible for the best attainment of the final
1557 goal. The discussed nanostructured systems provide pertinent perspectives for applications in
1558 several fields like medicinal, cosmetic, culinary, agriculture and textiles. Nowadays, the
1559 association of plants oils and active molecules is attracting special attention. Lipid core
1560 nanocapsules and nanostructured lipid carriers represent promising carriers to entrap both plant
1561 oil and synthetic drugs. The appropriate selection of plant oil is very important for achieving
1562 the high loading capacity and physical stability of the hydrophobic drugs. In addition, the oil
1563 may complement or even enhance the biological activities of these drugs. Hence, the research
1564 in the field of plants oils encapsulation can make an important contribution to the development
1565 of new methodologies in the treatment and diagnosis of major chronic diseases.

1566 Experimental advances are necessary in engineering plant oils loaded nanocarriers with
1567 broader applications and functionalities. Some techniques discussed in this review provide poor
1568 control over the final structure and stability of the obtained colloidal systems. Others lack from
1569 scalability and reproducibility; therefore, new techniques with improved control and
1570 reproducibility are crucial to design nanocarriers with predictable properties.

1571 Even if several advances have been already reported in the literature regarding the
1572 application of plants oils nanocarriers for pharmaceutical and cosmetics purposes, more *in vivo*
1573 studies are required to provide reliable results. Additionally, plant oils mechanism of action,
1574 toxic effects, pharmacokinetic parameters, biodistribution in biological systems and removal
1575 mechanisms must be investigated. Moreover, with the aim of improving the biodistribution of
1576 colloidal systems, scientists throughout the world are currently focalizing their efforts on the

1577 functionalization of the particle surface with special ligands to target specific organs and tissues.
1578 However, to our knowledge, there are no reports in the literature that deal with targeting
1579 delivery of plant oils loaded nanocarriers. Such demonstrations would provide a blueprint for
1580 the development of new concepts and products in large-scale for broader application.

1581 **CRedit authorship contribution statement**

1582 **Narimane Lammari:** Conceptualization, Writing - original draft, Investigation, Visualization.

1583 **Ouahida Louaer:** Supervision, Writing - review & editing. **Abdeslam Hassen Meniai:**

1584 Writing - review & editing. **Hatem Fessi:** Conceptualization. **Abdelhamid Elaissari:**

1585 Supervision, Writing - review & editing, Conceptualization.

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1587 The authors declare that they have no known competing financial interests or personal
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