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1 **Oral delivery strategies for nutraceuticals: delivery vehicles and absorption** 2 **enhancers**

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6 ***Background***

7 Lifestyle issues contribute to the development of obesity, type 2 diabetes, and cardiovascular
8 disease. Together with appropriate diet and exercise, **nutraceuticals** may contribute to
9 managing prevention at an early stage prior to therapeutic intervention. However, many
10 useful **food-derived bioactive compounds** will not sufficiently permeate the small intestine
11 to yield efficacy without appropriate oral delivery technology. The pharmaceutical industry
12 uses commercialised approaches for **oral delivery** including solubilizing technologies for
13 small molecules, which could be applied to selected nutraceuticals with solubility issues.
14 Systems currently being studied for labile and poorly permeable hydrophilic peptides and
15 macromolecules include **nanoparticles, intestinal permeation enhancers (PE)** and
16 mucolytics. These may also have potential for application to nutraceuticals with similar sub-
17 optimal physicochemical characteristics.

18 ***Scope and Approach***

19 We introduce factors which effect oral delivery of four types of nutraceuticals, namely fatty
20 acids, bioactive peptides, micronutrients, and phytochemicals. Factors preventing oral
21 absorption can arise from molecule physicochemical characteristics, which influence
22 solubility, stability, and epithelial permeability in the gastrointestinal tract (GIT). We
23 highlight the potential of selected delivery strategies to improve oral bioavailability of
24 different types of nutraceuticals.

25 ***Key Findings and Conclusions***

26 There is an opportunity for the nutraceutical industry to leverage the pharmaceutical
27 industry's progress in oral drug delivery. The use of delivery approaches using formulation
28 with excipients or substances with a history of use in man has potential to improve solubility,
29 stability, or permeability of nutraceuticals, leading to improved **oral bioavailability**.

30 Leveraging oral delivery formulation approaches across nutraceutical and pharmaceutical
31 molecules will lead to synergies for both fields.

32 **Key words:** Nutraceuticals; food-derived bioactives; oral delivery; nanoparticles; intestinal
33 permeation enhancers; oral bioavailability.

34

35 **Introduction**

36 With growing prevalence of lifestyle-associated diseases, including obesity, Type II diabetes
37 and cardiovascular disease, there is a need to reduce risks of onset of these diseases (Menotti
38 & Puddu, 2015). Nutraceuticals are defined as isolated food-derived bioactive molecules,
39 which provide physiological benefits beyond basic nutrition (Pan, Lai, Dushenkov, & Ho,
40 2009). Recently, research has focused on such bioactives with anti-oxidative, anti-
41 inflammatory, anti-hyperlipidemic and anti-hypertensive activities. However, there are many
42 hurdles to overcome for the oral delivery of nutraceuticals depending on the bioactive's
43 physicochemical properties. The molecule may be prone to sub-optimal release and
44 dispersion from the delivery dosage form and/or low solubility in small intestinal fluids
45 (bioaccessibility), pH- and enzymatic degradation, biotransformation during gastrointestinal
46 transit, poor diffusion across mucus and low intestinal epithelial permeability; all of which
47 must be overcome prior to absorption into the bloodstream (Braithwaite, et al., 2014;
48 McClements, Decker, Park, & Weiss, 2009). Without appropriate delivery systems, current
49 nutraceuticals with such characteristics are unlikely to provide the intended physiological
50 effect, despite marketing claims to the contrary.

51 The pharmaceutical industry has examined microbes and plants as sources of drug discovery
52 molecules, examples being penicillin (*Penicillium* species), colchicine (autumn crocus),
53 acetyl salicylic acid (willow tree bark), and paclitaxel (pacific yew tree) (Dias, Urban, &
54 Roessner, 2012). There is now additional focus on food as a new source of bioactives. With
55 the growing consumer market for nutraceuticals, there is scope for the nutraceutical industry
56 to leverage innovative research from the pharmaceutical industry in delivering poorly soluble
57 and poorly absorbed molecules. These particular nutraceuticals may assist with reducing the
58 risks of certain diseases before pharmaceutical intervention is required, but without
59 appropriate oral formulation they will have limited efficacy.

60 Innovative strategies are being attempted by the pharmaceutical industry for oral delivery of
61 peptides including insulin, octreotide, salmon calcitonin (sCT) and parathyroid hormone
62 (PTH). Approaches include entrapment in protective delivery vehicles, strategies for
63 enhanced mucus penetration and epithelial permeation, as well as incorporation of excipients
64 as protease enzyme inhibitors (Maher, Duffy, Ryan, & Brayden, 2014). Chemical
65 modification by a prodrug approach has been successful in improving small molecule oral
66 bioavailability. For example, the anti-viral prodrug, valacyclovir is converted to acyclovir *in*

67 *vivo* and improves oral bioavailability (Huttunen, Raunio, & Rautio, 2011). Pro-vitamins are
68 similar to synthetically- designed prodrugs and can yield improved oral bioavailability of
69 supplements: pantothenic acid (vitamin B₅) is unstable, so a stable alcohol, panthenol (pro-
70 vitamin B₅), is the parent molecule that is subsequently oxidised to the bioactive form *in vivo*.

71 Here, we discuss factors which affect the oral delivery of different classes of *isolated*
72 bioactive components (nutraceuticals) including fatty acids, bioactive peptides,
73 micronutrients and phytochemicals, and we highlight strategies to improve their oral
74 bioavailability (**Fig. 1**). **Another class of nutraceuticals, bioactive carbohydrates have shown**
75 **beneficial effects *in vitro* and *in vivo*, which are discussed in detail elsewhere (Brown, et al.,**
76 **2014; Liu, Willför, & Xu, 2015).** Discussion of factors impacting the delivery of bioactive
77 components within functional food and whole food matrices has been discussed extensively
78 in previous reviews with highly on bioaccessibility, absorption and transformation
79 (McClements, 2013b; McClements, et al., 2009; McClements, Li, & Xiao, 2015;
80 McClements & Xiao, 2014). We review the potential of approaches used in pharmaceutical
81 oral delivery (use of mucolytic agents and intestinal permeation enhancers), as well as new
82 strategies based on nanotechnology and assess whether these might be applied to food-
83 derived bioactive compounds in order to overcome the hurdles in orally delivering
84 nutraceuticals.

85 **Factors affecting oral delivery of nutraceuticals**

86 Physicochemical and physiological factors affect oral delivery of nutraceuticals. However,
87 solubility, stability and intestinal permeability are the major factors which impede effective
88 delivery of compounds including fatty acids (e.g. omega-3 fatty acids), bioactive peptides
89 (e.g. Ile-Pro-Pro), micronutrients (e.g. α -tocopherol) and phytochemicals (e.g. resveratrol)
90 (**Fig. 1**). Delivery systems should be designed based on overcoming specific factors which
91 can affect the particular loaded nutraceutical.

92 ***Nutraceutical compounds:***

93 ***Fatty acids***

94 Long chain polyunsaturated fatty acids (LC-PUFA) are recognised for their role in brain
95 development and potential to decrease risk of cardiovascular disease. Two fatty acids are
96 essential for human health, α -linolenic acid (ALA, an omega-3 fatty acid) and linoleic acid
97 (LA, an omega-6 fatty acid). However, the process involved in converting ALA to

98 eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in the body is inefficient and
99 supplementation is often required (Deckelbaum & Torrejon, 2012). Although cod liver oil has
100 been an established source of EPA and DHA, there is interest in sustainable alternatives
101 including krill oil, flax-seed and walnut oil (Adarme-Vega, Thomas-Hall, & Schenk, 2014).
102 EPA and DHA enhance production of anti-inflammatory lipid mediators, decrease production
103 of pro-inflammatory cytokines and decrease serum C-reactive protein, a clinical marker of
104 inflammation (Skulas-Ray, 2015). Supplementation with omega-3 fatty acids has anti-
105 hyperlipidemic activity, reducing LDL-cholesterol and triglycerides (Maki, Yurko-Mauro,
106 Dicklin, Schild, & Geohas, 2014). Furthermore, Amarin Corporation's (Dublin, Ireland)
107 Vascepa® icosapent ethyl (eicosapentaenoic acid ethyl ester) is an FDA-approved
108 prescription medication for hypertriglyceridemia and there are plans to achieve a wider label
109 for use in patients with moderately elevated triglyceride levels (Braeckman, Stirtan, & Soni,
110 2015).

111 Delivery of omega-3 fatty acids is difficult due to low aqueous solubility in the small
112 intestine and oxidative instability. Unsaturated fatty acids are prone to lipid oxidation, which
113 is accelerated by exposure to air, light and heat, resulting in a loss in functionality and leading
114 to off-flavour (Arab-Tehrany, et al., 2012). Upon reaching the small intestine, the fatty acids
115 need to be liberated from the delivery matrix, often an oil capsule, to allow incorporation into
116 mixed micelles, which seem to permeate the mucus layer and intestinal epithelia (Walker,
117 Decker, & McClements, 2015). Delivery platforms are required to reduce lipid oxidation,
118 improve solubility and overcome poor mucus penetration.

119 ***Bioactive peptides***

120 Proteins from food undergo enzymatic hydrolysis by digestive enzymes thereby releasing
121 smaller peptides, which have bioactive properties if they can be absorbed. Some peptides
122 inhibit angiotensin-converting enzyme (ACE), which can help maintain normal blood
123 pressure and prevent escalation of hypertension by subverting the renin-angiotensin-
124 aldosterone system (Turpeinen, Jarvenpaa, Kautiainen, Korpela, & Vapaatalo, 2013). Two
125 such tripeptides have been focussed on: Ile-Pro-Pro (IPP) and Val-Pro-Pro (VPP), both
126 isolated from milk β -casein (**Fig. 1**) following fermentation by *Lactobacillus helveticus*
127 (Nakamura, et al., 1995). Other derived antihypertensive peptides include Val-Tyr-Pro (VYP,
128 rice protein) (Chen, et al., 2013), Gly-Leu-Pro (GLP, chum salmon skin) (Lee, Jeon, &
129 Byun, 2014) and His-Leu-Phe-Gly-Pro-Pro-Gly-Lys-Lys-Asp-Pro-Val (HLFGPPGKKDPV,

130 fertilised hen egg) (Duan, et al., 2014). These peptides can reduce systolic blood pressure
131 following oral gavage to the spontaneously hypertensive rat (SHR). VPY is present in soy
132 protein hydrolysate, inhibits pro-inflammatory cytokine production and reduces histological
133 scoring of lesions in a rodent colitis model (Kovacs-Nolan, et al., 2012). Food-derived
134 proteins such as α -lactalbumin may also have anti-inflammatory action, and this is also of
135 interest for potential treatment of inflammatory bowel disease (IBD) (Chatterton, Nguyen,
136 Bering, & Sangild, 2013).

137 Peptides are prone to pancreatic serine protease digestion by chymotrypsin, trypsin and
138 elastase into small fragments and then further digestion to single amino acids by intracellular
139 carboxypeptidases. Presence of Pro residues confers resistance to such enzymes (Gleeson,
140 Heade, Ryan, & Brayden, 2015). Due to their hydrophilic nature and high molecular weight
141 however, peptides more than three residues long typically have low mucus penetration and
142 intestinal permeability, resulting in variable oral bioavailability (Renukuntla, Vadlapudi,
143 Patel, Boddu, & Mitra, 2013). Delivery strategies therefore need to protect bioactive peptides
144 from enzyme degradation and to enhance both mucus and intestinal permeability.

145 ***Micronutrients***

146 Essential vitamins and minerals are required in small doses, with deficiencies leading to
147 rickets (vitamin D), scurvy (vitamin C), neural tube defects (vitamin B₉), hypothyroidism
148 (iodine), hypokalaemia (potassium), and Keshan's disease (selenium). A nutritionally-
149 balanced diet will provide the required micronutrients to a healthy individual, however, there
150 are many conditions that can still benefit from micronutrient supplementation including
151 calcium for osteoporosis and iron for iron-deficient anaemia (Wallace, et al., 2015). The
152 physiological role of micronutrients includes roles as co-enzymes for metabolic processes,
153 antioxidants to remove reactive oxygen species (ROS), modulation of gene transcription and
154 structural components.

155 Delivery of micronutrients are also limited by individual physicochemical characteristics, as
156 they may be susceptible to bioaccessibility, stability, solubility, and bioavailability issues.
157 Vitamins C and E are prone to oxidation during processing and delivery, while fat soluble
158 vitamins (A, D, E and K) may not be liberated from the delivery matrix due to excessive
159 lipophilicity. Micronutrient bioavailability is effected by multiple processes, for example,
160 vitamin E is easily oxidised and has poor solubility. Anti-nutrients are compounds that

161 interfere with the absorption of nutrients and limit their bioavailability. Calcium, iron and
162 zinc can be chelated and cleared by dietary anti-nutrient phytate, hence the benefit of adding
163 phytase to a micronutrient delivery system. Orally-delivered phytase can therefore improve
164 oral calcium absorption in a pig model (Vigors, Sweeney, O'Shea, Browne, & O'Doherty,
165 2014). Other dietary components act similarly by reducing mineral bioavailability, oxalic
166 acid (spinach) binds calcium while glucosinolates (cruciferous vegetables) bind iodine.
167 Therefore, oral delivery of minerals, somewhat ironically, may benefit from being taken in
168 the *absence* of food.

169 ***Phytochemicals***

170 “Phytochemicals” are a large group of plant-derived compounds (**Fig. 1**), which have been
171 studied for their potent antioxidant activity and potential anti-inflammatory and anti-
172 hyperlipidemic activity. They include phytosterols (e.g. plant stanol esters); organosulfers
173 (e.g. allicin from garlic); terpenoids (e.g. lycopene carotenoid from tomatoes) and
174 sesquiterpenes. Polyphenols are the largest class containing stilbenes (e.g. resveratrol from
175 grapes), isoflavones (e.g. genistein from soybean) and flavonoids-based agents (e.g.
176 kaempferol and naringenin from spinach and grapefruit respectively) (Gonzalez-Castejon &
177 Rodriguez-Casado, 2011). The anti-inflammatory mechanism of action of polyphenols
178 involves modulation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-
179 κ B), inhibition of Mitogen-activated protein kinases (MAPK) cascade, activation of nuclear
180 factor erythroid 2-related factor 2 (Nrf2), and reduction in pro-inflammatory cytokines, all of
181 which are relevant in treatment of IBD (Martin & Bolling, 2015). Resveratrol improved
182 expression of the cytoprotective NAD(P)H dehydrogenase, quinone 1 (NQO1), in cancer
183 patients dosed with [¹⁴C]-resveratrol (Cai, et al., 2015).

184 There are a multitude of factors affecting oral bioavailability of phytochemicals due to their
185 unique physicochemical properties. For example, kaempferol has poor water solubility and
186 favours alkaline pH conditions, resulting in low oral bioavailability (2%) in a rat model
187 (Barve, et al., 2009). It is also prone to biotransformation by Phase I oxidative metabolism
188 and Phase II glucuronidation in intestinal epithelia (Barve, et al., 2009). Resveratrol is readily
189 soluble in ethanol, however, it has poor water solubility and is easily photo-isomerised and
190 metabolised by glucuronidation (Patel, et al., 2011). Oral delivery approaches for
191 phytochemicals need to overcome solubility issues, provide a dose sufficient to overcome
192 partial metabolism, and boost epithelial permeability. It is important to note however, that

193 assumptions of straight-forward pharmacological dose-response concepts being applied to
194 phytochemicals has been challenged by Cai *et al.*, who demonstrated a non-linear dose
195 response for the chemoprotective effects of resveratrol in humans and mice (Cai, et al., 2015),
196 with efficacy seen at the low doses found in food, but not at high doses.

197 ***Bioaccessibility and solubility in GIT***

198 Solubility is one of the first hurdles which must be overcome in oral delivery of bioactive
199 molecules. The Food and Drug Administration (FDA) adopted the Biopharmaceutics
200 Classification System (BCS) in 1995. It aims to predict *in vivo* performance of small drug
201 molecules from immediate release solid oral dosage form based on *in vitro* measurements of
202 solubility and permeability (Larregieu & Benet, 2014). Permeability is typically determined
203 across Caco-2 human *in vitro* intestinal epithelial monolayers grown on filters and solubility
204 is determined in 250 ml of aqueous media of simulated gastric fluid and simulated intestinal
205 fluid over pH ranges 1.0-6.8 over the course of 24 hours. The BCS is also used as a guide for
206 oral drug delivery formulation strategy, for example BCS Class III drugs are often formulated
207 to improve intestinal permeability, while Class II drugs are formulated to improve solubility
208 and cater for food effects (Buckley, Frank, Fricker, & Brandl, 2013). Recently, McClements
209 *et al* developed the Nutraceutical Bioavailability Classification System (NuBACS) (**Fig. 2**),
210 factoring in major issues affecting the oral bioavailability of nutraceuticals (McClements, et
211 al., 2015).

212 NuBACS introduces the concept of “bioaccessibility”, the ability of the bioactive compound
213 to be accessible to the body for absorption from the delivery matrix. Bioaccessibility,
214 absorption and transformation of nutraceuticals are features of the NuBACS, and this is
215 relevant for functional foods. In contrast, oral delivery of pharmaceutical agents is achieved
216 by capsules, tablets or suspensions and is governed by the BCS specifically in terms of
217 solubility and permeability. Although some nutraceuticals may require liberation from a
218 functional food or whole food, the focus here is on delivery strategies for isolated
219 nutraceutical bioactives, therefore, liberation refers to release from a delivery vehicle or
220 formulation prior to solubilisation. Solubility is however, a major hurdle for certain
221 nutraceuticals, particularly fatty acids and phytochemicals.

222 ***Degradation and Metabolism***

223 Degradation and metabolism are hurdles which an oral delivery system needs to overcome
224 after solubilisation has been achieved. The recently developed biopharmaceutics drug
225 disposition classification system (BDDCS) factors in drug metabolism by Phase I and II
226 processes and is useful in predicting drug-drug interactions that may occur in the intestine
227 and liver (Larregieu & Benet, 2014). Enzymatic metabolism is particularly relevant to fatty
228 acids and peptides which are targeted by lipases and peptidases respectively. Lingual and
229 gastric lipases account for a small amount of lipid hydrolysis, whereas pancreatic lipases act
230 on bile-derived emulsified lipids resulting in 90% lipid digestion (Aarak, et al., 2013).
231 However, EPA and DHA are resistant to pancreatic lipase hydrolysis due to the location of
232 bond conjugation in the carbon chain (Akanbi, Sinclair, & Barrow, 2014). Bioactive peptides
233 are prone to peptidases which access specific labile amino acids, although certain peptides are
234 stable due to a lack of target amino acids for peptidases.

235 On the other hand, metabolism can assist in absorption of some phytochemicals: the
236 flavonoid quercetin, is commonly found as a glycoside of either glucose or rutinose, but the
237 capacity to metabolise the sugar moiety effects quercetin's bioavailability. Quercetin-4'-*O*-
238 glucoside is absorbed intact in the small intestinal lumen by sodium-glucose transporter 1
239 (SGLT1) and then hydrolysed by intracellular β -glucosidases, thereby cleaving the sugar
240 moiety, which then passively diffuses across the basolateral membrane (Lotito, Zhang, Yang,
241 Crozier, & Frei, 2011). On the other hand quercetin-3'-*O*-rutinoside does not permeate the
242 small intestine, instead caecally-located bacterial α -rhamnosidases convert it to the quercetin,
243 aglycone, which in turn is absorbed from the colon.

244 ***Intestinal permeation***

245 Nutraceuticals may have limited capacity to permeate the gut wall. Prior to reaching the
246 epithelia, bioactives must traverse intestinal mucus. Mucus is a complex hydrogel consisting
247 of a mixture of glycoproteins, lipids, and sloughed epithelial cells. Interaction with mucus
248 reduces permeability of mucoadhesive lipophilic molecules or large molecules due to steric
249 blocking (Sigurdsson, Kirch, & Lehr, 2013). Lipophilic bioactives can be transported through
250 the mucus layer by mixed micelles formed from bile salts, phospholipids and free fatty acids.
251 Therefore, the lipophilic molecules, EPA, DHA, resveratrol, and kaempferol may pass
252 through mucus in association with luminal-derived moieties. Nanoparticles coated with small

253 hydrophilic polymers including low molecular weight high density polyethylene glycol
254 (PEG) and polysialic acid, can slip through the mesh of mucus potentially allowing for
255 release of nutraceutical at intestinal epithelia or uptake of nutraceutical-entrapped
256 nanoparticles (Ensign, et al., 2013).

257 Upon diffusion through the mucus, there are several routes which a bioactive agent may
258 permeate the intestinal epithelia. Transport via the paracellular route requires movement
259 through tight junctions. A molecular radius between 10-50 Å and molecular weight <500 Da
260 is required and the bioactive must be hydrophilic in nature (Larregieu & Benet, 2014).

261 Paracellular transport reduces risk of intracellular metabolism, which is relevant for
262 phytochemicals and bioactive peptides. Transcellular transport involves molecules passing
263 across the apical membrane by passive diffusion, receptor mediation or endocytosis.

264 Hydrophobic molecules can pass across the phospholipid bilayer by passive diffusion.

265 According to Fick's law of diffusion molecules with a relatively high oil-water partition
266 coefficient (K_{ow}) or greater hydrophobicity ($\log P$) can pass the cell membrane more
267 efficiently (e.g. β -carotene, $\log P=15.2$) compared to molecules with lower values (e.g. IPP,
268 $\log P= 1.07$; vitamin C, $\log P= 2.77$) (McClements, et al., 2015). There is a balance required,
269 as the greater the $\log P$ the less the solubility: a $\log P$ of < 2.5 may be optimal, however, this
270 depends on the formulation or presence of bile salts and surfactants, which may assist in
271 solubilising lipophilic nutraceuticals and presenting them as components of mixed micelles.

272 The epithelium of the small and large intestine has a multitude of transporters localised on the
273 apical membrane which have roles in uptake of nutrients and absorption of drugs. These
274 membrane bound proteins are relevant to the uptake of many nutraceuticals. Fatty acids are
275 transported by intestinal fatty acid-binding proteins (I-FABP), and bioactive di- and
276 tripeptides are carried by the proton coupled peptide transporter (PEPT1). Calcium uptake is
277 mediated by the vitamin D receptor, while vitamin C is carried on the sodium-vitamin C co-
278 transporter (SVCT) (Lin, Yee, Kim, & Giacomini, 2015). In the case of IPP at least two
279 uptake pathways are likely to play a role: the paracellular route due to its low molecular
280 weight (MW) and the transcellular route due to its interaction with the PEPT1 carrier.
281 Appropriate exploitation of one or both of these intestinal permeation routes may enhance
282 absorption of these types of molecules.

283 **Food-based strategies for improving oral delivery of nutraceuticals**

284 ***Delivery vehicles***

285 A delivery vehicle can control delivery and release of the nutraceutical. The use of delivery
286 vehicles in the pharmaceutical industry has been investigated for oral delivery of antibiotics,
287 vaccines, cancer therapeutics and biopharmaceuticals (Choonara, et al., 2014; Ryan, et al.,
288 2013). Due to the hurdles which must be overcome to orally deliver a therapeutically effect
289 dose of a nutraceutical, delivery vehicles are of increasing interest. In particular the utilisation
290 of food grade ingredients with GRAS (generally regarded as safe) status to create the delivery
291 vehicle is a promising area of current research. Furthermore, nutraceutical loaded in
292 pharmaceutical grade delivery vehicle formulations has also emerged in recent years.

293 ***Lipid and surfactant based systems***

294 *Liposomes* or *nanoliposomes* are formed when phospholipids self-assemble into a lipid
295 bilayer due to hydrophobic interactions with the fatty acid chain. *Niosomes* are formed when
296 non-ionic surfactants assemble into similar structures (**Fig. 3**). Cholesterol is often added to
297 the formulation as it increases rigidity strength of the membrane and confers steric stability.
298 Egg yolk- and soy-derived phosphatidylcholines are commonly used to form liposomes,
299 whereas Tween® 80, Span® 80 and sucrose laurate have been used to form niosomes (Nui, et
300 al., 2012; Pando, Gutiérrez, Coca, & Pazos, 2013; Shin, Chung, Kim, Joung, & Park, 2013).
301 There are some characteristic differences between liposomes and niosomes, particularly the
302 oxidative stability of the particles due to phospholipid oxidative degradation. They are both
303 suitable for loading of lipophilic nutraceuticals in the inner core of the bilayer membrane, as
304 well as hydrophilic compounds in the aqueous core.

305 The carotenoid class of phytochemicals show strong anti-oxidative potential, however, they
306 are highly hydrophobic ($\log P > 13$), which makes them suitable candidates for liposome
307 formulation. Lutein was found to be most easily incorporated from a series of carotenoids
308 with the rank order lutein > β -carotene > lycopene > canthaxanthin (Xia, et al., 2015). *In vitro*
309 release showed lycopene and canthaxanthin exhibited a burst release from liposomes whereas
310 lutein and β -carotene displayed a sustained release (Tan, et al., 2014). Curcumin is another
311 lipophilic phytochemical with anticancer and antimalarial activity, which can be incorporated
312 into liposomes (Shin, et al., 2013). Curcumin was soluble upon *in vitro* lipolysis, and
313 permeation across Caco-2 monolayers was enhanced compared to free curcumin (Memvanga,

314 Coco, & Pr at, 2013). When delivered in combination with β -arteether (an antimalarial drug),
315 curcumin loaded liposomes increased survival rate in rodents compared to β -arteether or
316 curcumin alone, thereby showing potential of the liposome formulation.

317 Due to their structure, liposomes and niosomes have the potential for co-encapsulation. One
318 example is to have curcumin-loaded cyclodextrin in the core along with a curcumin-loaded
319 bilayer membrane, a formulation which induced apoptosis in the osteosarcoma xenograft
320 mouse model (Dhule, et al., 2012). Niosomes have co-encapsulated antioxidant
321 nutraceuticals, two examples of which are gallic acid (hydrophilic core) with curcumin, and
322 ascorbic acid (hydrophilic core) with quercetin. Co-encapsulation of two antioxidants
323 resulted in an improved antioxidant scavenging effect *in vitro* compared to individual
324 molecules (Tavano, Muzzalupa, Picci, & de Cindo, 2014).

325 *Nanoemulsions* are colloidal dispersions formed from emulsified oils in water (O/W) with a
326 core-shell structure (**Fig. 3**). Emulsions are commonly found in food and examples are
327 mayonnaise (O/W) emulsion stabilised by egg yolk lecithin, or butter (W/O) emulsion
328 stabilised by milk proteins. Nanoemulsions differ from traditional emulsions in a number of
329 ways: <100 nm in droplet size, high optical clarity and increased stability against flocculation
330 and coalescence. Nanoemulsions can be fabricated by low-energy (spontaneous formation
331 due to high concentrations of surfactants) or high-energy (mechanical disruption of oil phase
332 resulting in nano-sized droplets). They are suitable for loading of lipophilic nutraceuticals,
333 which are solubilised in the oil phase prior to addition of surfactant and/or mechanical
334 disruption, resulting in an entrapped bioactive (McClements, 2013a).

335 The loading of phytochemicals into nanoemulsions such as curcumin, genistein, and the
336 citrus flavonoid, 5-demethyltangeretin (5DT), greatly improved solubility in simulated
337 intestinal fluid from ~10% to 80% (Aditya, et al., 2013). Formation of emulsions from
338 essential oils is of particular interest, as it only requires addition of an emulsifier to a
339 bioactive oil. Many of these oils exhibit antimicrobial and antioxidant activity and have been
340 investigated to prevent food spoilage (Xue & Zhong, 2014). Lipid oxidation may be a
341 limitation of nanoemulsions, although addition of an antioxidant like ascorbic acid was found
342 to reduce lipid hydroperoxide production of soybean oil emulsions (Uluata, McClements, &
343 Decker, 2015). The size of the lipid droplet effects epithelial cellular uptake of flavonoid
344 loaded nanoemulsions in HCT116 cells, with 67 nm and 125 nm showing 4-fold higher
345 uptake compared to 203 nm (Zheng, et al., 2014). Coenzyme Q₁₀ (CoQ₁₀) is a powerful

346 antioxidant which is highly hydrophobic and is also required for healthy mitochondrial
347 function. CoQ₁₀ formulated into a salmon oil-salmon lecithin nanoemulsion had a 10-fold
348 increase in plasma concentration compared to water vehicle after oral gavage in Wistar rat
349 (**Fig. 4**) (Belhaj, et al., 2012). Tangeretin, a citrus flavone, has shown potential as an
350 anticancer agent when formulated into a nanoemulsion it improved *in vitro* tumour
351 suppression and reduced incidence of colonic adenomas compared to control in the
352 azoxymethan/dextran sodium sulphate (AOM/DSS)-induced colitis mouse model (Ting,
353 Chiou, Pan, Ho, & Huang, 2015).

354 *Solid lipid nanoparticles (SLNs)* are O/W emulsions in which the internal lipid core has been
355 fully or semi-solidified (**Fig. 3**). SLNs are prepared as a 'hot' nanoemulsions at a temperature
356 above the melting point of the particular lipid, and temperature is rapidly decreased inducing
357 lipid crystallisation. SLNs have shown promise as a pharmaceutical oral delivery system
358 since the early 90's as they combine the advantages of polymeric particles, liposomes, and
359 emulsions. β -carotene is prone to oxidation and degradation over time and during GIT transit.
360 When formulated into a SLN (stearic acid emulsified with lecithin), degradation was
361 prevented for up to 20 days incubation at room temperature (Helgason, et al., 2009).
362 Curcumin formulated into a SLN showed improved permeability across co-cultured
363 monolayers of HT29-MTX and Caco-2 cells compared to curcumin formulated in a
364 nanoemulsion *in vitro*, although only 1% of loaded curcumin permeated (Guri, Gulseren, &
365 Corredig, 2013). The serum area under the curve (AUC) concentration of a 50mg/kg of either
366 free curcumin or curcumin-loaded SLNs in a rat model showed that the latter increased the
367 AUC to 41 $\mu\text{g/mL}$ compared to 1 $\mu\text{g/mL}$ (Kakkar, Singh, Singla, & Kaur, 2011). Resveratrol
368 is sensitive to light, however, resveratrol-loaded SLNs improved the photostability of the
369 bioactive and improved its oral bioavailability 8-fold compared to resveratrol solution in a rat
370 model (Pandita, Kumar, Poonia, & Lather, 2014). SLN also improved oral bioavailability
371 with other bioactives in rat studies: candesartan cilexetil (a treatment for hypertension) and β -
372 arteether (second line treatment for malaria) (Dwivedi, et al., 2014; Zhang, Gao, Bu, Xiao, &
373 Li, 2012).

374 ***Biopolymer based systems***

375 *Polyelectrolyte complexes (PECs)* are formed by electrostatic interaction between oppositely
376 charged biopolymers e.g. iota carrageenan and protamine (**Fig. 3**). Entrapped PECs are
377 formed by solubilising nutraceuticals in either the positively or negatively charged

378 biopolymer, and then the opposite charged biopolymer is mixed in. PECs formed between
379 cationic gelatin and gum Arabic swelled and aggregated at pH 4.5, whereas they were stable
380 between pH 5.5 – 7.5 and had diameters of 110 – 160 nm (Sarika, Pavithran, & James, 2015).
381 These PECs may be promising carriers for nutraceuticals, however the swelling at lower pH
382 poses issues at gastric pH values.

383 GRAS food biopolymers are an abundant source for polyelectrolyte complexation e.g.
384 amylose, starch, pectin, carrageenan and chitosan. Resveratrol complexed in a gelatin PEC
385 showed improved anti-proliferative efficacy than free resveratrol and improved
386 bioavailability in mice compared to free resveratrol solution after intravenous injection
387 (Karthikeyan, Rajendra Prasad, Ganamani, & Balamurugan, 2013). PECs are a class of
388 nanoparticles which are not well exploited for nutraceuticals to date with limited *in vivo* data;
389 on the other hand they have shown promise for therapeutic peptides. For example, insulin and
390 sCT display improved stability when complexed in PECs (Lu, et al., 2012; Ryan, et al.,
391 2013).

392 *Hydrogels* are a 3D polymer network with an extremely high abundance of water, which
393 when appropriately cross-linked can form hydrogel particles in the nano-sized range (**Fig. 3**).
394 These can be formed from protein gelation via physical, chemical or biochemical methods
395 which self-crosslink between denatured proteins, whereas, carbohydrate based hydrogels
396 generally require addition of an ionic cross-linker. They may be composed of GRAS
397 biopolymers including pectin, alginate, carrageenans, agar, chitosan, gelatin, whey protein,
398 caseins, soy protein. Hydrogel particles can also contain dispersed oil droplets for carrying
399 lipophilic molecules. When β -carotene was formulated into each of a conventional emulsion,
400 a hydrogel, and an oil dispersion-“filled” hydrogel, the latter had an improved release of the
401 bioactive compared to both formulations due to solubilising effect and increased lipid surface
402 area (Mun, Kim, & McClements, 2015).

403 Comprehensive preclinical *in vivo* studies of oral delivery of hydrogel particles with
404 nutraceutical bioactives are lacking similar to PECs, providing an area of under-exploited
405 delivery vehicles. However, one rodent study suggested that Nile Red-loaded conventional
406 emulsions had superior oral bioavailability compared to lipid-entrapped hydrogels (Li, Kim,
407 Park, & McClements, 2012). Caveats were that the diameters of particles were not
408 comparable (0.36 μm vs. 510 μm respectively) and the loading of a nutraceutical may yield
409 different results compared to Nile Red. Insulin has been delivered orally *in vivo* in hydrogels

410 in rodents, but there are major issue in how to translate such formulations from rodent models
411 to clinical trials (Déat-Lainé, et al., 2013). Hydrogel particles formulated from whey protein
412 and alginate were loaded with insulin and yielded ~2.4% relative bioavailability after intra-
413 duodenal instillation in a rat model. Polyacrylic acid-derived hydrogels were cross-linked
414 with poly(L-glutamic acid) and then loaded with insulin (60 IU/kg); this formulation resulted
415 in a 33% reduction of plasma glucose levels in the streptozotocin (STZ)-induced rat Type 1
416 diabetes model (Gao, He, Xiao, Zhuang, & Chen, 2013). Finally, insulin was also loaded into
417 lectin-functionalized and ionically-gelated carboxymethylated *kappa*-carrageenan particulates
418 and induced 14% relative bioavailability by the oral route compared to subcutaneous
419 injection in rats (Leong, et al., 2011).

420 *Protein-carbohydrates (self-assembly structures)* are formed from interaction between
421 anionic polysaccharides and cationic protein surface groups, similar to PECs. Alternatively,
422 they may be formed by thermal denaturation or aggregation of a globular protein followed by
423 addition of an ionic polysaccharide, while still relying in part on electrostatic charge (**Fig. 3**).
424 Vitamin D₂ was bound to β-lactoglobulin and complexed with anionic pectin, resulting in
425 stable nanoparticles 50-70 nm, which improved the shelf-life stability of the bioactive
426 compared to storage in water and uncomplexed β-lactoglobulin (Ron, Zimet, Bargarum, &
427 Livney, 2010). Nanoencapsulation of anthocyanins in a complexation of whey protein and
428 pectin also resulted in improved protection against thermal degradation (Arroyo-Maya &
429 McClements, 2015). Due to the amphiphilic nature of proteins, it is possible to load
430 hydrophilic or lipophilic nutraceuticals inside the self-assembly structured particulates.

431 Curcumin was complexed into chitosan-zein particulates, improved thermal and UV stability
432 and anti-oxidative scavenging capacity was retained (Liang, et al., 2015). Similarly, when
433 curcumin was complexed in a carboxymethyl chitosan- kafirin (a prolamin protein from
434 sorghum) particulates, it again improved UV stability and improved cellular uptake in Caco-2
435 (Xiao, Nian, & Huang, 2015). EGCG is an abundant polyphenol from green tea and a potent
436 antioxidant; it had a burst release profile and retained cytotoxicity against cancer cell lines *in*
437 *vitro* when complexed in a chitosan-caseinophosphopeptide particulate (Hu, Xie, Zhang, &
438 Zeng, 2014). Furthermore, EGCG complexed in ovalbumin-dextran, saw a small increase in
439 permeability across Caco-2 monolayers compared to free EGCG (Li & Gu, 2014).
440 Resveratrol complexed in a zein-based nanoparticle improved oral bioavailability 19-fold

441 compared to resveratrol solution (**Error! Reference source not found.**) and reduced serum
442 TNF- α (15%) against control in a mouse model of endotoxic shock (Penalva, et al., 2015).

443 *Intestinal Absorption Improvements*

444 Although delivery vehicles increase permeability *in vitro* and *in vivo* animal models, there is
445 still potential to further increase the intestinal permeability. Intestinal permeation enhancers
446 (PEs) have been researched for oral delivery of hydrophilic peptide drugs in the last two
447 decades (Choonara, et al., 2014). Improving nutraceutical absorption can be achieved in two
448 ways (**Fig. 6**); improve mucodiffusion of lipophilic agents (e.g. omega-3 fatty acids and
449 phytochemicals) using mucolytics; improve paracellular and transcellular permeability of
450 bioactive peptides, micronutrients and hydrophilic phytochemicals using PEs.

451 *Mucolytics*

452 Mucus diffusion enhancers such as *N*-acetylcysteine (NAC), bromelain, and papain hold
453 potential for nutraceuticals affected by inability to penetrate the small intestinal mucus layer.
454 Papain is a mucolytic protease found in papaya; when decorated on nanoparticles, it
455 improved permeation and reduced mucus viscosity *in vitro* (Müller, et al., 2012). Bromelain,
456 a pineapple stem mucolytic enzyme, was formulated on the surface of nanoparticles and
457 compared against papain for *in vitro* mucus permeation resulting in enhanced penetration:
458 bromelain > papain > conventional nanoparticles (Pereira de Sousa, et al., 2015). Papain
459 decorated nanoparticles were also shown to penetrate into deeper mucus layers, when
460 delivered by oral gavage in a rat model, with higher retention within the jejunum (Müller,
461 Perera, König, & Bernkop-Schnürch, 2014). This is of particular interest, as the jejunum is
462 the main target for nutraceutical bioactive absorption.

463 NAC is an antioxidant nutritional supplement and it is also used as a mucolytic agent by
464 breaking disulphide bonds (Yuan, et al., 2015). When an intestinal PE, tetradecyl maltoside
465 (TDM) was tested on Caco-2- and mucus-producing HT29-MTX-E12 monolayers, it was
466 shown that NAC-pre-treatment on E12 monolayers resulted in comparable apparent
467 permeability (P_{app}) values of salmon calcitonin across Caco-2 and E12 (Petersen, Nielsen,
468 Rahbek, Guldbandt, & Brayden, 2013). The blood serum levels of fluorescein
469 isothiocyanate-dextran MW 4000 (FD-4, a fluorescent marker molecule for the paracellular
470 route) was improved 2.8-fold upon intra-jejunal administration of NAC (5% w/v) in rats, and

471 showed a mucolytic effect up to 60 minutes (Takatsuka, Kitazawa, Morita, Horikiri, &
472 Yoshino, 2006).

473 The application of mucolytic agents also holds promise for lipophilic nutraceuticals, which
474 interact with glycoproteins and lipids in mucus (Sigurdsson, et al., 2013). This interaction
475 reduces the likelihood of epithelial permeation as mucus is continuously turned over and
476 would result in the bioactive being washed away. Whereas mucolytics reduce this risk of this
477 occurring by enhancing mucus penetration. Mucolytics are most often investigated in the
478 context of airway mucus in cystic fibrosis, where NAC is used at high concentrations.
479 Recently a synthetic thiol-carbohydrate (methyl 6-thio-6deoxy- α -D-galactopyranoside) was
480 found to be a more potent mucolytic (Yuan, et al., 2015). Co-administration of lipophilic
481 nutraceuticals and mucolytics in the context of an enteric coated oral dosage form may
482 therefore control release in the small intestine, improve mucus penetration and improve
483 absorption.

484 ***Intestinal Permeation Enhancers (PEs)***

485 PEs can increase oral bioavailability assuming that the nutraceutical can also survive liver
486 first pass metabolism. Of these, the medium chain fatty acid (MCFS) sodium caprate (C₁₀) is
487 well established as a food additive and was a component of an antibiotic suppository once
488 marketed in Sweden and Japan (Maher, et al., 2014). Ideally, PEs should be
489 pharmacologically inert, have excipient or Generally-Regarded-As-Safe (GRAS) status, and
490 have a history of use in man. PEs are often used for peptide oral delivery with candidates
491 including sCT, insulin, glucagon-like Peptide 1 (GLP-1) analogues, and octreotide. For
492 example, The technology of Enteris Biopharma (New Jersey, USA) is currently in Phase II
493 with a PE (an acyl carnitine), a peptidase inhibitor (citric acid) and parathyroid hormone
494 (Stern, Mehta, & Carl, 2013). The technology of Chiasma (Jerusalem, Israel) recently
495 completed Phase III for oral octreotide and it comprises a PE (caprylic acid) in a water-in-oil
496 suspension (Tuvia, et al., 2012). Merrion Pharmaceuticals (Dublin, Ireland) uses a
497 gastrointestinal permeation enhancement technology (GIPET™) built around the PE (C₁₀) in
498 matrix tablets and it completed an oral Phase I study with GLP-1 (Karsdal, et al., 2015).
499 Finally, the technology of Oramed (Jerusalem, Israel) is has reached Phase IIb for oral insulin
500 and it comprises a PE (EDTA) and soy-bean trypsin inhibitor (Lewis & Richard, 2015).

501 MCFA-based PEs act by re-organising proteins at the epithelial tight junction (**Fig. 6**), (e.g.
502 tricellulin and claudin 5), and by mild detergent fluidizing effect on the plasma membrane
503 (Brayden, Gleeson, & Walsh, 2014; Krug, et al., 2013). This allows for poorly permeable
504 molecules to either transiently permeate across tight junctions, or possibly to be entrapped in
505 mixed micelles with capacity to cross lipid bilayers. PEs generally cause a reduction of
506 transepithelial electrical resistance (TEER) using *in vitro* and *ex vivo* intestinal epithelial
507 models. This reduction suggests an opening of tight junctions or perturbation of the epithelia.
508 They have shown significant increase in apparent permeability of [¹⁴C]-mannitol (a marker
509 for paracellular transport) and FD-4 across isolated intestinal mucosa on the Ussing chamber
510 model. For example, C₁₀ showed an increase in FD-4 permeability in Caco-2 monolayers, an
511 8-fold increase across isolated colonic mucosa and a 2-fold increase in colonic instillations *in*
512 *vivo* (Brayden & Walsh, 2014). This effect is also associated with a temporary perturbation of
513 the intestinal epithelia. However this mild damage induced by MCFA such as C₁₀ is quickly
514 repaired, which was shown after *in situ* intestinal injections in rats (Wang, Maher, &
515 Brayden, 2010). The continuing progress of C₁₀ and other PEs in clinical trials for oral
516 peptides is also addressing safety aspects that may be associated with increased oral
517 bioavailability.

518 Many of these PEs are commonly used in food processing with GRAS status or are of food
519 origin. Candidates PEs include coco-glucosides (CG), chitosan derivatives, bromelain,
520 EDTA, oleic acid, alkyl maltosides, medium chain fatty acids (MCFA) and sucrose esters
521 (Aguirre, et al., 2014; Szűts & Szabó-Révész, 2012). Furthermore, many isolated food
522 components can modulate tight junction integrity *in vitro* by enhancing permeability by
523 opening tight junctions. Although many of these PEs work especially well in the colon, the
524 target site for absorption of nutraceuticals is predominantly the jejunum. The capacity for
525 enhancement was tested in different regions of the rat intestine with C₁₀ and insulin using an
526 *in situ* loop model, which showed a rank order of plasma glucose reduction: colon > ileum >
527 jejunum > duodenum (Morishita, Morishita, Takayama, Machida, & Nagai, 1993). The apical
528 membrane of the small intestine is often exposed to bile salts and fatty acids resulting in
529 resistance to surfactant perturbation compared to colon. TEER decreased in isolated rat
530 jejunum and ileum using TDM and CG, however, there was no increase in the permeability
531 of FD-4. This lack of effect from these PEs may be due to the marker MW of 4kDa, because
532 when HT-29/B6 monolayers were treated with C₁₀, a 3-fold increase in fluorescein (330Da)
533 was detected (Krug, et al., 2013). Isolated rat jejunum was treated with C₁₀ and sodium salt of

534 10-undecylenic acid (uC₁₁, an antifungal agent), a 1.4-3.6-fold increase was shown for FITC-
535 labelled IPP (714 Da) and LKP (745 Da) (Brayden & Walsh, 2014; Gleeson, et al., 2015).
536 Therefore, using the appropriate PE in the jejunum holds the potential to improve the
537 permeability of nutraceuticals and potentially improve oral bioavailability. On the other hand,
538 kaempferol, curcumin and daidzein may have potential for useful application in inflammatory
539 bowel disease (Kosińska & Andlauer, 2013), where they can repair membranes and reduce
540 abnormally high epithelial permeability.

541 **Conclusions**

542 Nutraceuticals offer the opportunity to prevent onset and escalation of lifestyle-associated
543 diseases due to their range anti-oxidative, anti-inflammatory, anti-hyperlipidemic and
544 antihypertensive activities. Progress has been made in adopting Pharma oral delivery
545 strategies to improve solubility, stability and permeability of nutraceutical bioactives. In
546 particular, solubilisation technologies can overcome issues associated with the delivery of
547 hydrophobic compounds (e.g. resveratrol and curcumin) using lipid-based systems. There has
548 often been too much emphasis put on the *in vitro* assays suggesting anti-oxidative, anti-
549 inflammatory and anti-hypertensive actions of nutraceuticals. One of the main issues is that
550 many nutraceuticals are not tested in *in vivo* preclinical studies, it is therefore impossible to
551 assess whether they are predictive of efficacy. However, at least some nutraceuticals can be
552 efficiently formulated and show promising data in rodent models (Dhule, et al., 2012;
553 Kakkar, et al., 2011; Karthikeyan, et al., 2013; Memvanga, et al., 2013; Pandita, et al., 2014;
554 Penalva, et al., 2015). In relation to clinical trials of nutraceuticals, these are costly and rare,
555 difficult to design, and display conflicting results. For example, opposing effects have been
556 detected in man for antihypertensive tripeptide, IPP, although a meta-analysis concluded that
557 it has a hypotensive effect in pre-hypertensive subjects (Xu, Qin, Wang, Li, & Chang, 2008).
558 A renewed emphasis on clinical data is required to establish a relationship between
559 nutraceuticals in delivery systems and possible health benefits. **However, to obtain a health
560 claim, different countries have different regulations. For example, the US Food and Drug
561 Administration (FDA) has granted category ‘A’ status to soy with the health claim “reduction
562 of the risk of heart disease”. Yet in Europe, the European Food and Safety Authority (EFSA)
563 rejected a similar application due to lack of confirmatory data establishing a reduction in
564 blood LDL-cholesterol due to the intake of isolated soy protein (Girgih, Myrie, Aluko, &
565 Jones, 2013; Mannarino, Ministrini, & Pirro, 2014).**

566 Absorption enhancement is an area yet to be used for improving oral nutraceutical delivery.
567 Mucolytics and PEs hold potential to improve absorption of both lipophilic and hydrophilic
568 nutraceuticals, particularly as many of these are food-grade and/or food additives. However,
569 there is a question regarding the safety of PEs due to perturbation of the intestinal epithelia
570 through mild detergent-based surfactant effects, even for agents with GRAS status or with a
571 history of use in man (Chassaing, et al., 2015). Although toxicity of various PEs under acute
572 dosing regimens has not been found in clinical trials for oral peptides to date (Melmed, et al.,
573 2015; Tuvia, et al., 2014), PEs would not be suitable for administration to patients with
574 inflammatory bowel- or coeliac disease (Laukoetter, Nava, & Nusrat, 2008) and chronic
575 dosing studies are yet to be investigated for most PE examples (McCartney, Gleeson, &
576 Brayden, 2016). There is therefore potential to harness strategies in oral drug delivery to
577 nutraceutical delivery using established excipient and GRAS-listed reagents. This will result
578 in an overall improved knowledge of delivery systems allowing for development of oral
579 nutraceutical systems for important candidate molecules.

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937 **Figure Captions**

938 **Fig. 1** – Overview of food-derived bioactive compounds being investigated as nutraceuticals;
939 Fatty acids (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)), bioactive
940 peptides (Ile-Pro-Pro (IPP), and Leu-Lys-Pro, (LKP)), micronutrients (Vitamins B6, C and
941 D3) and phytochemicals (the remainder). Adapted with permission (Pan, et al., 2009).

942 **Fig. 1** - Comparison of the Biopharmaceutics Classification System (BCS) and the recently
943 proposed Nutraceutical Bioavailability Classification System (NuBACS) (Larregieu & Benet,
944 2014; McClements, et al., 2015).

945 **Fig. 2** – Examples of food-based delivery systems currently being investigated for delivery of
946 nutraceuticals. Lipid and surfactant-based vehicles including liposomes, niosomes,
947 nanoemulsions and solid lipid nanoparticles (**Error! Reference source not found.**) are
948 suitable for loading lipophilic bioactives (curcumin and resveratrol). Biopolymer-based
949 vehicles including polyelectrolyte complexes, hydrogel particles and protein-polysaccharide
950 structures are suitable for loading hydrophilic bioactives such (EGCG and ascorbic acid).

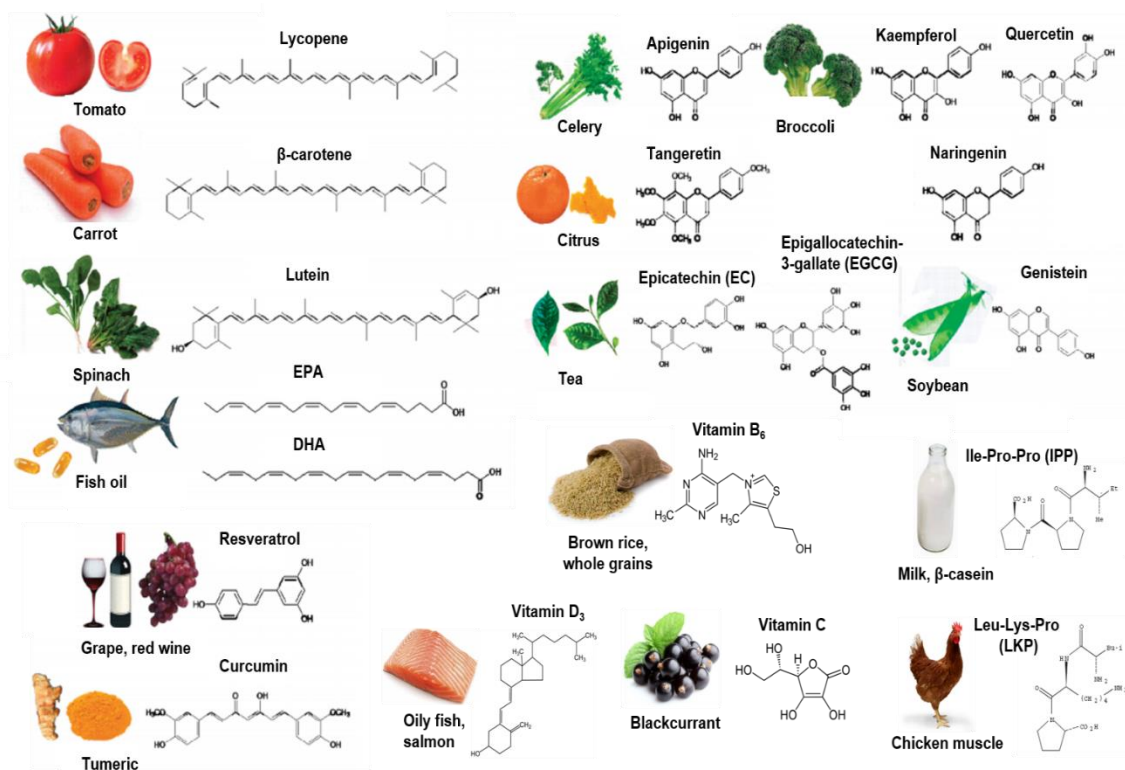
951 **Fig. 3.** – CoQ₁₀ plasma concentration after oral delivery in a nanoemulsion in rats. CoQ₁₀
952 plasma AUC 26.14 (CoQ₁₀ nanoemulsion) > 15.38 (commercial oil mixture) > 12.79 (oily
953 mixture + CoQ₁₀) > 2.32 (water and oily mixture). The commercial oil mixture consisted of

954 soybean oil and 6% CoQ₁₀. Oily mixture consisted of same constituents of nanoemulsion
 955 without water sonication. Reproduced with permission (Belhaj, et al., 2012).

956 **Fig. 4.** – Resveratrol plasma concentration significantly improved after oral delivery of
 957 resveratrol loaded zein-based nanoparticle (■) compared to resveratrol solution (●) and
 958 resveratrol suspension (▲) in an endotoxic shock mouse model. The dose was 15 mg/kg and
 959 resveratrol plasma AUC was 5.17 > 0.60 > ND respectively. Adapted with permission
 960 (Penalva, et al., 2015).

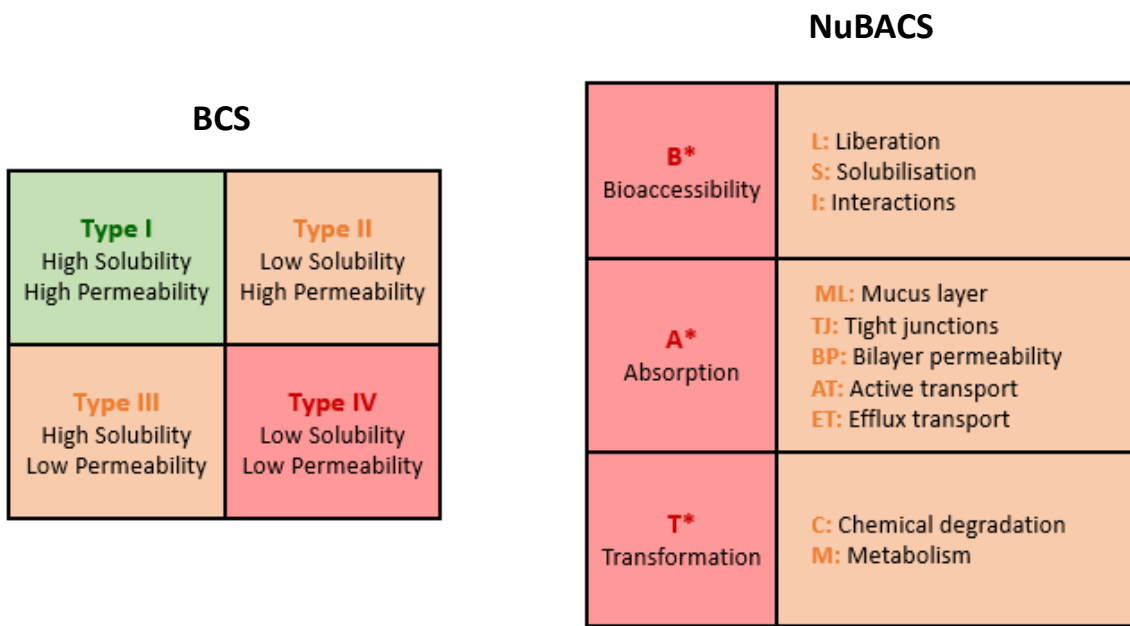
961 **Fig. 5** – The effect of PEs on nutraceutical compounds by improving mucodiffusion by
 962 mucolytic agents and improving permeability. Adapted with permission (Gleeson, et al.,
 963 2015).

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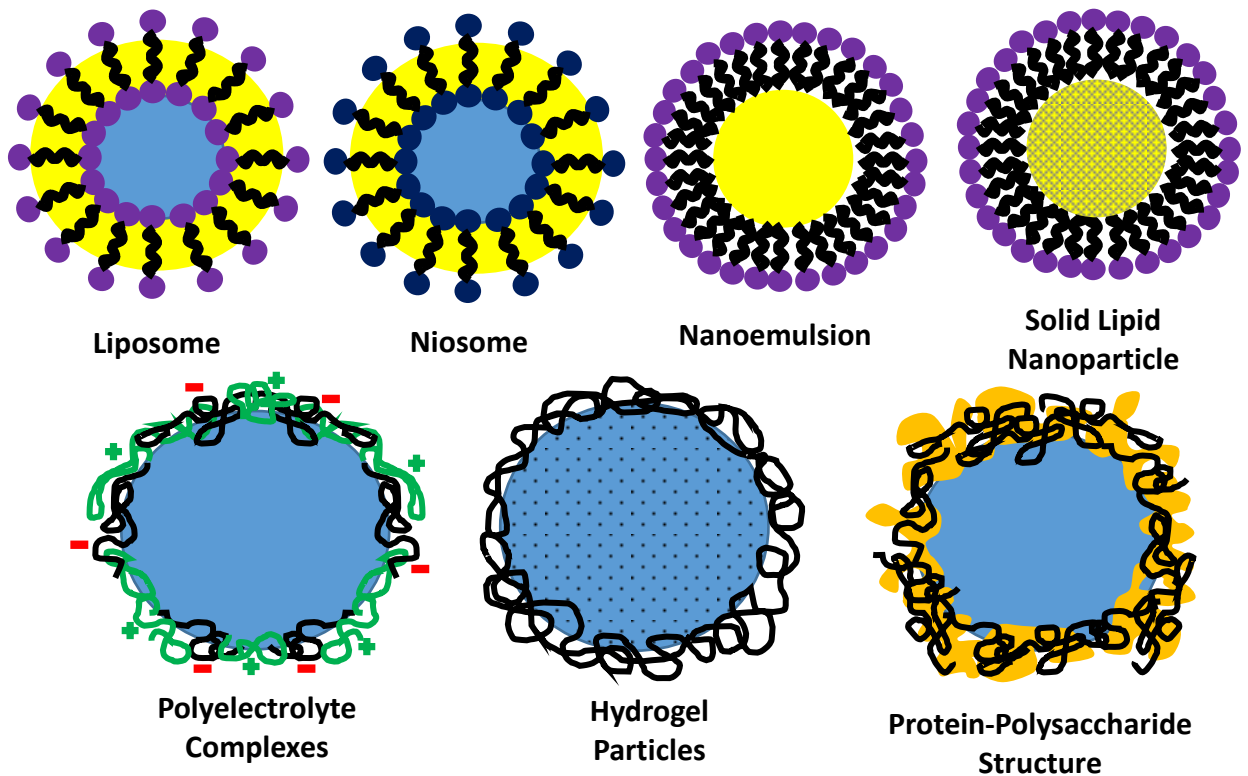
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966 **Fig 1**



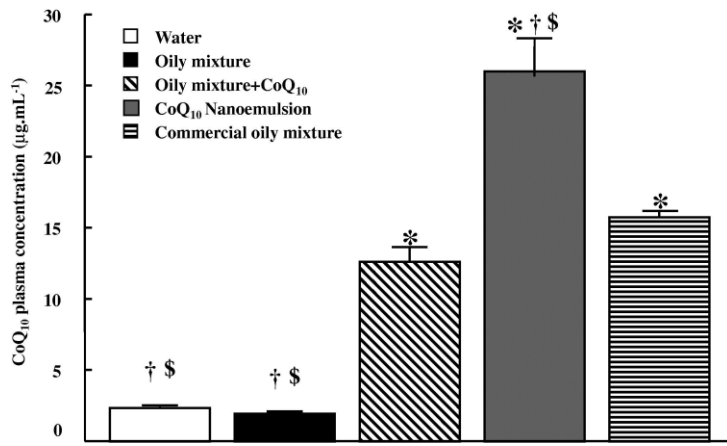
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968 **Fig 2**



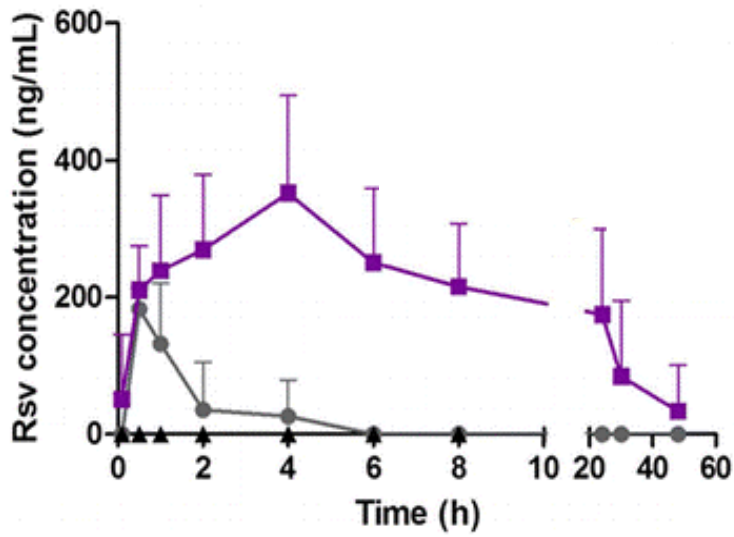
969

970 **Fig 3**



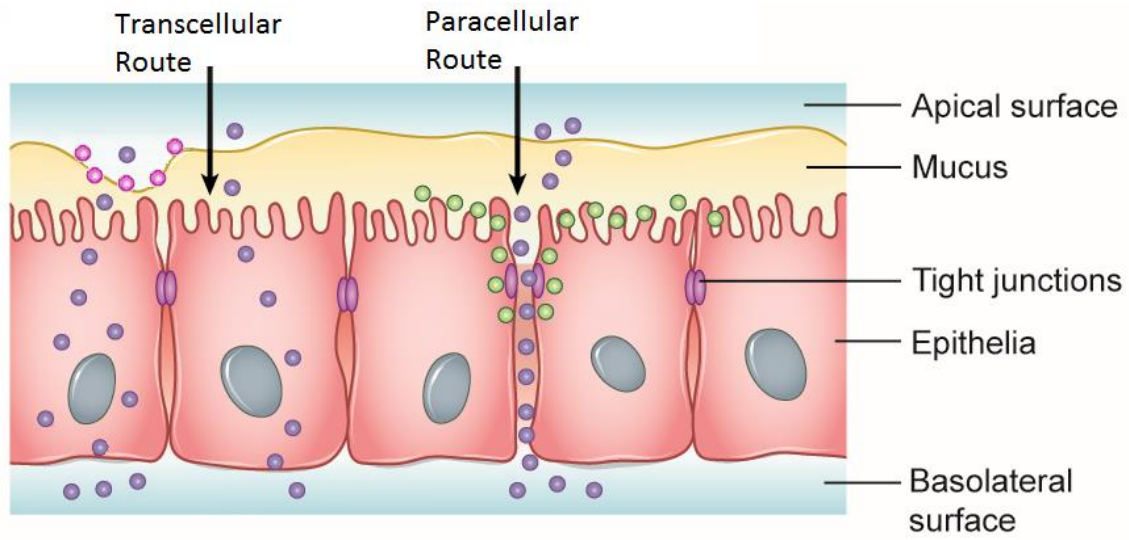
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972 **Fig 4**



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974 **Fig 5**



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976 **Fig 6**

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981 **Table 1** – Overview of nano-sized delivery vehicles created from food-based ingredients
 982 which have been formulated containing nutraceutical bioactives.

Type	Primary constituent	Food-based vehicle (nanoparticle material)	Nutraceutical (loaded in nanoparticle)
Liposomes and Niosomes	Phospholipid or Non-ionic surfactant	Egg yolk phosphatidylcholine (Memvanga, et al., 2013; Tan, et al., 2014; Xia, et al., 2015); Sucrose laurate (Pando, et al., 2013; Tavano, et al., 2014)	Carotenoids (Tan, et al., 2014); Curcumin (Dhule, et al., 2012; Memvanga, et al., 2013; Nui, et al., 2012; Shin, et al., 2013);
Nanoemulsions	Surfactant and oil	Essential oils (Gulotta, Saberi,	Essential oils (Gulotta, et al.,

		Nicoli, & McClements, 2014; Xue & Zhong, 2014); Medium chain tryglyceride (Gulotta, et al., 2014; Zheng, et al., 2014); Soybean lecithin (Aditya, et al., 2013); β - Lactoglobulin (Zheng, et al., 2014)	2014; Xue & Zhong, 2014); 5-DT (Zheng, et al., 2014); Curcumin (Aditya, et al., 2013); Genistein (Aditya, et al., 2013); omega-3 FAs (Gulotta, et al., 2014);
Solid Lipid Nanoparticles (SLN)	Semi- or fully solidified lipid	Soy lecithin (Guri, et al., 2013; Kakkar, et al., 2011; Pandita, et al., 2014); palmitic acid (Kakkar, et al., 2011); stearic acid (Pandita, et al., 2014);	Curcumin (Guri, et al., 2013); β - Carotene (Helgason, et al., 2009); Resveratrol (Pandita, et al., 2014)
Polyelectrolyte complexes (PEC)	Oppositely charged biopolymers	β - Lactoglobulin (Hosseini, Emam-Djomeh, Sabatino, & Van der Meeren, 2015); sodium alginate (Hosseini, et al., 2015); gelatin (Karthikeyan, et al., 2013; Sarika, et al., 2015); Arabic gum (Sarika, et al., 2015)	Curcumin (Hosseini, et al., 2015); β - carotene (Hosseini, et al., 2015); Resveratrol (Karthikeyan, et al., 2013)
Hydrogels	Denatured proteins or ionically crosslinked polysaccharides	Rice starch (Mun, et al., 2015); caseinophosphopeptide (Hu, et al., 2014); chitosan (Hu, et al., 2014); Whey protein isolate (Sung, Xiao, Decker, & McClements, 2015); β - Lactoglobulin (Li, et al., 2012)	β - Carotene (Mun, et al., 2015); Epigallocatechin gallate (EGCG) (Hu, et al., 2014);
Protein-carbohydrate (self-assembly structures)	Globular proteins and ionic polysaccharides	β - Lactoglobulin (Ron, et al., 2010); pectin (Ron, et al., 2010); zein (Liang, et al., 2015); kafirin (Xiao, et al., 2015); ovalbumin (Li & Gu, 2014)	Vitamin D₂ (Ron, et al., 2010); Curcumin (Liang, et al., 2015; Xiao, et al., 2015); EGCG (Hu, et al., 2014; Li & Gu, 2014)