Trends in Food Science & Technology 53 (2016) 90–101

Contents lists available at ScienceDirect

Trends in Food Science & Technology

journal homepage: http://www.journals.elsevier.com/trends-in-food-science-and-technology

Oral delivery strategies for nutraceuticals: Delivery vehicles and absorption enhancers

John P. Gleeson, Sinéad M. Ryan, David J. Brayden*

UCD School of Veterinary Medicine and UCD Conway Institute, University College Dublin, Belfield, Dublin 4, Ireland

ARTICLE INFO

Article history:
Received 21 September 2015
Received in revised form
6 May 2016
Accepted 10 May 2016
Available online 14 May 2016

Keywords:
Nutraceuticals
Food-derived bioactives
Oral delivery
Nanoparticles
Intestinal permeation enhancers
Oral bioavailability

ABSTRACT

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

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

Key findings and conclusions: There is an opportunity for the nutraceutical industry to leverage the pharmaceutical industry's progress in oral drug delivery. The use of delivery approaches using formulation with excipients or substances with a history of use in man has potential to improve solubility, stability, or permeability of nutraceuticals, leading to improved oral bioavailability. Leveraging oral delivery formulation approaches across nutraceutical and pharmaceutical molecules will lead to synergies for both fields.

1. Introduction

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

The pharmaceutical industry has examined microbes and plants as sources of drug discovery molecules, examples being penicillin (*Penicillium* species), colchicine (autumn crocus), acetyl salicylic acid (willow tree bark), and paclitaxel (pacific yew tree) (Dias, Urban, & Roessner, 2012). There is now additional focus on food

* Corresponding author.
E-mail address: david.brayden@ucd.ie (D.J. Brayden).

http://dx.doi.org/10.1016/j.tifs.2016.05.007
0924-2244/

as a new source of bioactives. With the growing consumer market for nutraceuticals, there is scope for the nutraceutical industry to leverage innovative research from the pharmaceutical industry in delivering poorly soluble and poorly absorbed molecules. These particular nutraceuticals may assist with reducing the risks of certain diseases before pharmaceutical intervention is required, but without appropriate oral formulation they will have limited efficacy.

Innovative strategies are being attempted by the pharmaceutical industry for oral delivery of peptides including insulin, octreotide, salmon calcitonin (sCT) and parathyroid hormone (PTH). Approaches include entrapment in protective delivery vehicles, strategies for enhanced mucus penetration and epithelial permeation, as well as incorporation of excipients as protease enzyme inhibitors (Maher, Duffy, Ryan, & Brayden, 2014). Chemical modification by a prodrug approach has been successful in improving small molecule oral bioavailability. For example, the anti-viral prodrug, valacyclovir is converted to acyclovir *in vivo* and improves oral bioavailability (Huttunen, Raunio, & Rautio, 2011). Pro-vitamins are similar to synthetically-designed prodrugs and can yield improved oral bioavailability of supplements: pantothenic acid (vitamin B_5) is unstable, so a stable alcohol, panthenol (pro-vitamin B_5), is the parent molecule that is subsequently oxidised to the bioactive form *in vivo*.

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

2. Factors affecting oral delivery of nutraceuticals

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

2.1. Nutraceutical compounds

2.1.1. Fatty acids

Long chain polyunsaturated fatty acids (LC-PUFA) are recognised

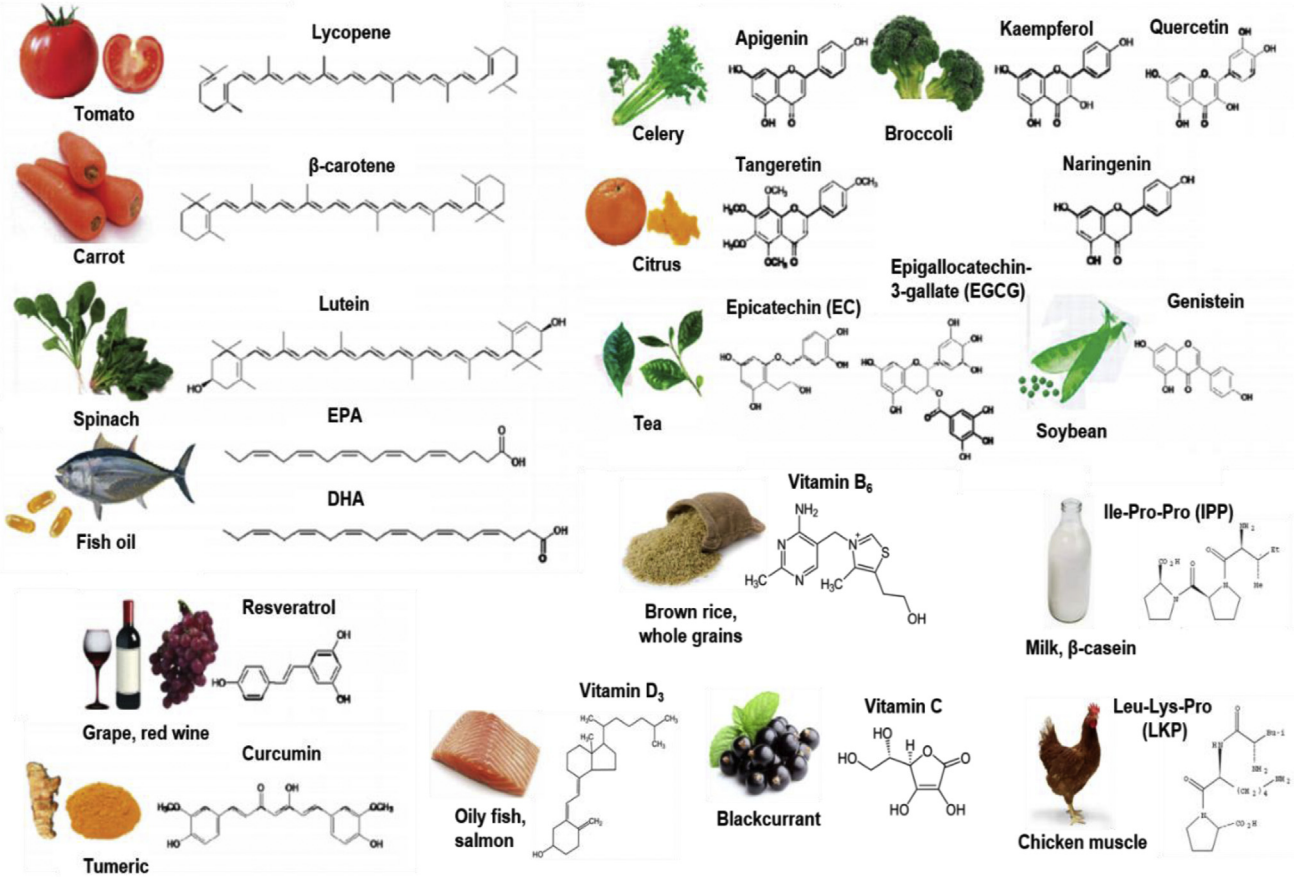

Fig. 1. Overview of food-derived bioactive compounds being investigated as nutraceuticals; Fatty acids (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)), bioactive peptides (Ile-Pro-Pro (IPP), and Leu-Lys-Pro, (LKP)), micronutrients (Vitamins B6, C and D3) and phytochemicals (the remainder).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