Trends in Food Science & Technology 54 (2016) 114–126

Contents lists available at ScienceDirect

Trends in Food Science & Technology

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

Nanocarriers based delivery of nutraceuticals for cancer prevention and treatment: A review of recent research developments

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ARTICLE INFO

Article history:
Received 8 April 2016
Received in revised form
13 May 2016
Accepted 4 June 2016
Available online 7 June 2016

Keywords:
Nutraceuticals
Delivery systems
Nanoparticles
Micelles
Cancer

ABSTRACT

Background: In recent years scientific community has drawn a great deal of attention on the phrase "Let food be thy medicine and medicine be thy food" coined by Hippocrates. Nutraceuticals are any food containing additives that have some medicinal benefits. They prevent the progression of cancer by downregulating the signal transduction pathways which are vital for the development of cancer. However, their clinical efficacy is limited due to poor aqueous solubility which ultimately leads to poor oral bioavailability. Therefore, to tackle these challenges, the scientific community has shifted its considerable interests towards nanocarriers based delivery of nutraceuticals due to its potential for enhancing bioavailability and efficacy.

Scope and approach: Different kinds of polymeric, lipid based and inorganic nanocarriers have been explored to enhance the bioavailability and clinical efficacy of nutraceuticals. In recent years, combination of chemotherapeutic drugs along with nutraceutical in a single nanocarrier have emerged due to its potential towards the concept of 'magic bullet' *i.e.* killing the cancer cells while preventing the toxicity towards normal cells.

Key findings and conclusions: Despite an effective production process of nano-nutraceutical products, the quality, stability, efficacy and adverse effects should work out and address on priority. To exploit the full potential of nanocarriers further preclinical and clinical investigations are required with nano-formulated nutraceuticals.

1. Introduction

Cancer is regarded as one of the most fatal diseases and characterized by the uncontrolled growth of abnormal cells (Pérez-Herrero & Fernández-Medarde, 2015). The International Agency for Research on Cancer GLOBOCAN project estimates that about 14 million new cancer cases were diagnosed worldwide in 2012 and approximately 8 million cancer deaths occurred. Among these, approximately 1 million new cases and nearly 700,000 of the deaths occurred in India, which constitutes around 17% of the world population. The agency also predicts cancer burden in India will double in the year 2035 and there will be more than 1.7 million new cases (Ferlay et al. 2015; Mallath et al. 2014). According to estimates of American Cancer Society, cancer is the second most general cause of mortality in the US, exceeded only by heart disease (Siegel, Miller, & Jemal, 2016). It is also estimated that about one-third of incident cancers that occur in the US are related to life style factors such as poor nutrition, excess alcohol consumption, physical inactivity and excess weight and, therefore, can be prevented (Gonzalez-Vallinas, Gonzalez-Castejon, RodrÃguez-Casado, & de Molina, 2013; Makarem, Lin, Bandera, Jacques, & Parekh, 2015). Besides modifying lifestyle factors as a primary cancer prevention method, another approach is to decrease of the progress of cancer through the administration of nutraceuticals.

Nutraceutical, a hybrid term from 'nutrition' and 'pharmaceutical' was coined by Stephen L. DeFelice, founder, and chairman of the Foundation for Innovation in Medicine (FIM), Cranford in 1989. He defined nutraceuticals as 'any substance that is a food or a part of the food and provides medical or health benefits, including the prevention and treatment of disease' (Brower, 1998; DeFelice, 1995; Li, Ahmad, Kong, Bao, & Sarkar, 2014). Recently, nutraceuticals have gained much attention in the area of cancer research because of their pleiotropic effects and relatively non-toxic behavior (Nair

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http://dx.doi.org/10.1016/j.tifs.2016.06.003
0924-2244/

et al. 2010). These are structurally and functionally diverse bioactive compounds and include numerous agents such as carotenoids, vitamins, dietary fiber, probiotics, prebiotics, fatty acids and phenolics (Fig. 1) (Kalra, 2003; Wang, Guleria, et al., 2016; Wang, Wang, et al., 2016). Nutraceuticals prevent cancer through several mechanisms such as inhibiting cell proliferation and differentiation, inhibiting efflux transporters such as Breast Cancer Resistance Protein (BCRP), P-glycoprotein (P-gp), Multidrug Resistance Protein (MRP) or by reducing the toxicity of chemotherapeutic drugs (Saneja, Khare, et al., 2014; Trottier, Boström, Lawrentschuk, & Fleshner, 2010). For example, a study was conducted in order to investigate the relationship between pancreatic cancer risk and dietary carotenoids. The study revealed that consumption of lycopene (a major component of tomatoes) decreases 31% reduction in pancreatic cancer risk among men and indicated that tomato-based products with high levels of lycopene could reduce pancreatic cancer risk (Nkondjock, Ghadirian, Johnson, Krewski, & Canadian Cancer Registries Epidemiology Research G, 2005).

A large number of nutraceuticals have been investigated for cancer prevention worldwide but most of them suffer from poor aqueous solubility, poor permeability which ultimately leads to poor bioavailability in humans (Bethune, Schultheiss, & Henck, 2011; McClements, Li, & Xiao, 2015). Several other physicochemical and/or physiological processes may also contribute for poor bioavailability of nutraceuticals such as (i) restricted release from the food matrix (Moelants et al. 2012), (ii) formation of insoluble complexes with other components in the gastrointestinal tract (GIT) and/or (iii) biotransformations in the GIT (D'Ambrosio, Clugston, & Blaner, 2011; Fernandez-Garcia et al., 2012; Hurst, Loi, Brodfuehrer, & El-Kattan, 2007). For example, a study conducted on healthy human volunteers demonstrated that after administration of 12,000 mg dose of curcumin only 51.2 ng/ml was detected in serum after 4 h due to its rapid degradation (Lao et al., 2006). Recently, in order to characterize the main factors limiting the oral availability of nutraceutical, a new classification system called nutraceutical biopharmaceutical classification scheme (NuBACS) has been introduced which is analogous to biopharmaceutical classification system (BCS) (McClements et al. 2015). A detailed discussion in this area is beyond the scope of this article.

To overcome these challenges nanocarriers based drug delivery platforms have emerged as suitable vehicles owing to their high surface-to-volume ratio, nanoscale size, and favorable physicochemical characteristics. Nanoscale drug delivery enhances aqueous solubility, extends shelf life, protects the food components against moisture, enables controlled release, influence texture, and flavor. Further, nanocarriers have the ability to modulate pharmacodynamic as well as pharmacokinetic profiles of nutraceuticals (Fig. 2) (Díaz & Vivas-Mejia, 2013). Various kinds of nanocarriers such as polymeric nanoparticles, micelles, liposomes *etc.* have been employed in order to enhance the bioavailability and efficacy of nutraceuticals in recent years. In this manuscript, we present the application of various nanocarriers based approaches for nutraceutical delivery with emphasis on phytochemicals in cancer chemotherapy and their pharmacokinetics as well as pharmacodynamics outcomes.

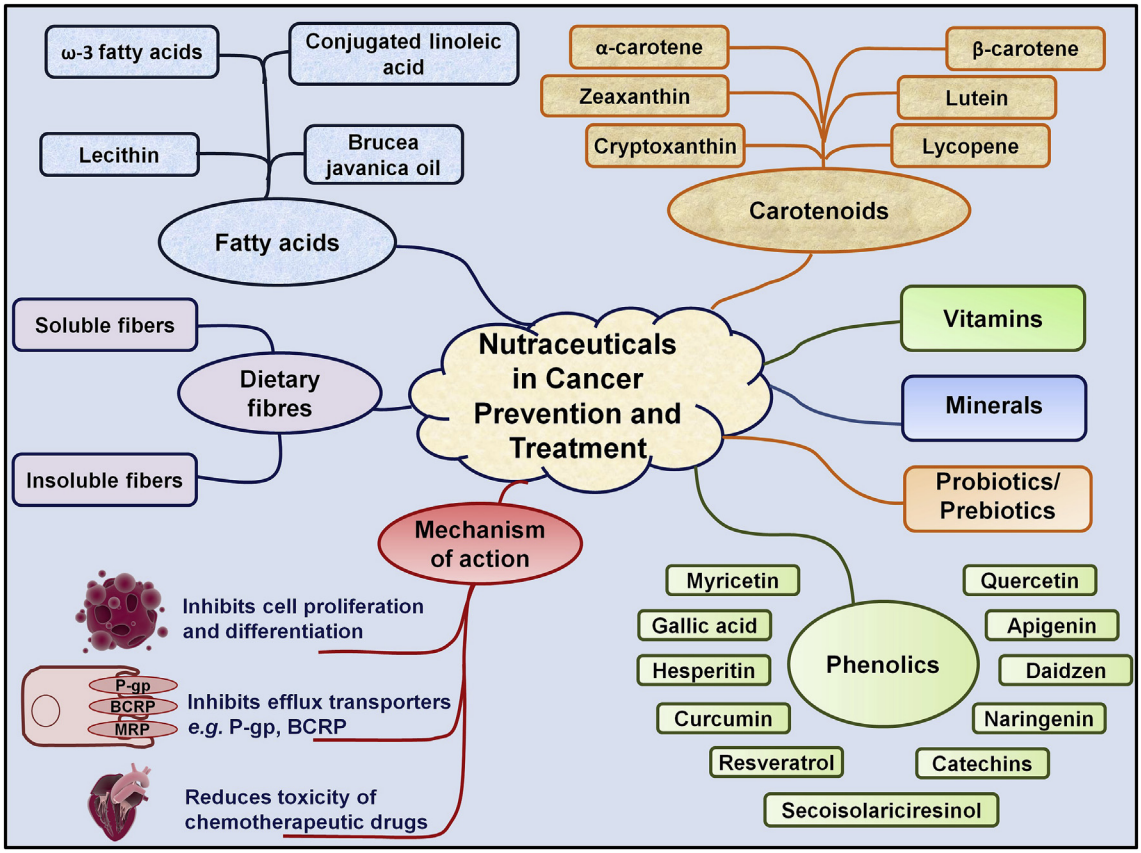

Fig. 1. Schematic illustration of various kinds of nutraceuticals used in cancer prevention and treatment. Nutraceutical acts by inhibiting cell proliferation and differentiation of cancer cells, inhibiting efflux transporters such as P-gp or by reducing the toxicity of chemotherapeutic drugs such as cardiotoxicity, hepatotoxicity etc. Drawing was performed with the website http://www.somersault1824.com.