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Review

Designing food structure and composition to enhance nutraceutical bioactivity to support cancer inhibition

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ABSTRACT

Many types of bioactive molecules found in foods ("nutraceuticals") have been shown to exert anticancer activities, including curcumin, resveratrol, polyphenols, sulforaphane, anthocyanins, genistein, quercetin and lycopene. The potential health benefits of nutraceuticals are often not realized because of their poor water solubility, chemical instability, adverse taste profile, and low oral bioavailability. Carefully designed food matrices are being developed to overcome these problems. Nutraceuticals can be isolated from their natural environment, and then incorporated into functional foods, often with the help of delivery systems (such as emulsions, nanoemulsions, liposomes, biopolymer nanoparticles, and microgels). Alternatively, the stability and bioavailability of nutraceuticals can be improved by leaving them in their natural environment, but ingesting them with a specially designed "excipient food". The structure and composition of an excipient food is controlled so as to enhance the bioaccessibilty, stability, and absorption of the nutraceuticals in the gastrointestinal tract. This review article provides an overview of some of the most important anticancer nutraceuticals found in foods, then highlights the main factors impacting their bioaccessibility, absorption and transformation. Finally, it describes different types of delivery systems and excipient systems that can be used to improve the overall bioavailability of anticancer nutraceuticals.

1. Introduction

Nutraceuticals are biologically active molecules found in foods that may not be essential for maintaining normal human functions, but may enhance human health and wellbeing by inhibiting certain diseases or improving human performance [1,2]. Numerous different classes of nutraceuticals are found in both natural and processed foods including carotenoids, flavonoids, curcuminoids, phytosterols, and certain fatty acids [1]. Many of these nutraceuticals have the potential to act as anticancer agents, and may therefore be suitable for incorporation into functional or medical foods as a means of preventing or treating certain types of cancer.

Nutraceuticals vary considerably in their chemical structures, physiochemical properties, and biological effects [1,3]. For example, nutraceuticals vary in their molar mass, structure, polarity, charge and functional groups, which influences their chemical reactivity, physical state, solubility characteristics, and biological fate and functions [4]. Some nutraceuticals are naturally present in whole foods, such as fruits, vegetables, and cereals, and are therefore often consumed in this form. Conversely, other nutraceuticals are isolated from their natural states and converted into additives that can be incorporated into functional foods, dietary supplements, or pharmaceuticals. In this article, we will mainly focus on the delivery of nutraceuticals using foods, as it has been proposed that increased consumption of foods rich in nutraceuticals may decrease the risk of certain types of chronic diseases, including cancer. However, if consumers are going to benefit from consuming foods containing nutraceuticals, it is important that they have certain characteristics:

- The nutraceuticals should initially be present in functional foods at a sufficiently high level to have a beneficial physiological effect.
- The nutraceuticals should remain stable within the functional foods during manufacturing, storage, and utilization, otherwise they may lose their beneficial health effects.
- The nutraceuticals should not have an adverse effect on the color, taste, or shelf-life of a food product.
- After ingestion, the nutraceuticals should be released from the functional foods and delivered to the appropriate site-of-action within the human body.

There are a number of factors that currently limit the utilization of many types of anticancer nutraceuticals in functional foods [5–7].

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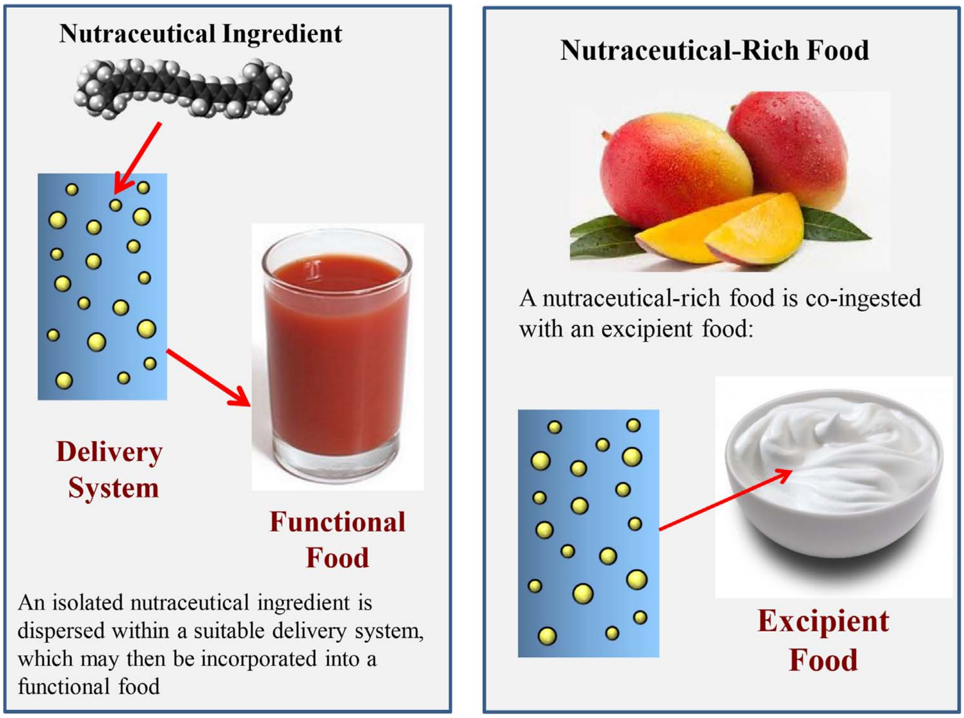

Fig. 1. Nutraceuticals may be ingested as part of functional foods or excipient foods.

Firstly, many nutraceuticals cannot easily be incorporated into foods because they have poor-solubility characteristics, or they cause undesirable changes in appearance, texture, or flavor of foods. Second, many nutraceuticals are chemically or biochemically unstable and therefore lose their bioactivity because they are degraded within food products or the human body. Third, many nutraceuticals have a low bioavailability and therefore only a small fraction of them are actually absorbed and utilized by the body. Fourth, for some nutraceuticals the optimum dose has not been established, and therefore it is unclear how much to deliver in a bioactive form, *e.g.,* the anticancer efficacy of resveratrol actually decreases as the dose increases [8]

The purpose of this review article is to highlight how food matrices can be designed to enhance the biological activity of anticancer nutraceuticals. In particular, we focus on two different approaches that can be utilized for this purpose (Fig. 1):

- Delivery systems: In this approach, nutraceuticals isolated from their original environment are encapsulated within a delivery system that is specifically designed to enhance their bioavailability [5,9–11]. An example of this approach would be a carotenoid ingredient isolated from carrots that is encapsulated within an oil-in-water emulsion that could then be added to foods such as soft drinks, yogurts, dressings, or sauces [12].
- Excipient systems: In this approach, a nutraceutical-rich food is co-ingested with an excipient food, which is again specially designed to improve the bioavailability of the nutraceuticals [13]. An example of this approach would be an oil-in-water excipient emulsion consumed at the same time as carotenoid-rich carrots [14].

Initially, a brief overview of some of the most important anticancer nutraceuticals that have been identified in foods is given. Some of the major factors limiting the bioavailability of nutraceuticals is then discussed, and potential approaches to overcome these limitations are highlighted. The design of delivery and excipient systems to enhance the bioavailability of anticancer nutraceuticals is then described.

2. Anticancer nutraceuticals

Accumulating evidence suggests that many nutraceuticals, such as curcumin, resveratrol, tea polyphenols, sulforaphane, anthocyanins, genistein, quercetin and lycopene, exhibit anticancer activities against various forms of cancer [15,16]. One of the important advantages of utilizing nutraceuticals to prevent and treat cancer is that they generally exhibit little or no adverse effects frequently associated with pharmaceutical agents after long-term administration. Nutraceuticals have been found to exert a wide range of cellular effects. The possible mechanisms of action of anticancer nutraceuticals include induction of cell cycle arrest and apoptosis in cancerous cells, detoxification of highly reactive molecules, activation of the host immune system, and sensitization of malignant cells to cytotoxic agents [17,18]. In this section, we focus on several important anticancer nutraceuticals that have been intensively investigated with particular emphasis on the clinical evidence supporting the safety and efficacy of these compounds in cancer prevention and treatment.

- *Curcumin*: Curcumin is a polyphenol found in turmeric (*Curcuma longa*), a member of the ginger family (Zingiberaceae) [19]. A large number of *in vitro* and *in vivo* studies have shown that curcumin inhibits the development of various cancers by inducing cell cycle arrest and cellular apoptosis, through pleiotropic modulation on several key cancer targets such as Wnt/β-catenin, nuclear factor kappa B (NF- κ B), cyclooxygenase-2 (COX-2), tumor necrosis factor alpha (TNF- α), STAT-3 and cyclin D1 [20]. Several phase I and phase II clinical trials have been conducted and demonstrated the safety and anticancer effects of curcumin in patients with different malignancies including myeloma, pancreatic and colorectal cancer [17]. Since curcumin is preferentially distributed in the colonic mucosa, in comparison to other tissues, many clinical trials have been focused on its chemo-preventive efficacy on colorectal cancer [21]. In a phase IIa clinical trial, patients taking 4 g of curcumin daily were found to have a 40% decrease in the number of aberrant crypt foci (ACF) lesions, which are one of the early histologic signs seen in the colon that may lead to cancer [22]. One of the most important factors limiting the bioefficacy of curcumin is its poor