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Research review paper

Nanotechnology for the delivery of phytochemicals in cancer therapy

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ABSTRACT

The aim of this review is to summarize advances that have been made in the delivery of phytochemicals for cancer therapy by the use of nanotechnology. Over recent decades, much research effort has been invested in developing phytochemicals as cancer therapeutic agents. However, several impediments to their wide spread use as drugs still have to be overcome. Among these are low solubility, poor penetration into cells, high hepatic disposition, and narrow therapeutic index. Rapid clearance or uptake by normal tissues and wide tissue distribution result in low drug accumulation in the target tumor sites can result in undesired drug exposure in normal tissues. Association with or encapsulation in nanoscale drug carriers is a potential strategy to address these problems. This review discussed lessons learned on the use of nanotechnology for delivery of phytochemicals that been tested in clinical trials or are moving towards the clinic.

Contents

1. Introduction

According to World Cancer Report 2014 edited by the International Agency for Research on Cancer (IARC), the incidence of cancer is predicted to increase from 14.1 million in 2012 to 25 million by 2035. Identifying novel therapeutics with greater anti-cancer activity and better safety is urgently needed. Natural phytochemicals derived from plants make up a large portion of potential therapeutic agents used to combat cancer (Al-Farsi and Ellis, 2014; Overby et al., 2014). Some of them, such as paclitaxel (Legha et al., 1986; Riondel et al., 1986; Wiernik et al., 1987), vinblastine (Costa et al., 1963; Frei et al., 1961) and topotecan (Cheson and Arbuck, 1993; Wall et al., 1992), have

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shown potent bioactivity and have been successfully developed into clinical drugs. However, several impediments to their wide spread use as drugs still have to be overcome. These issues include low solubility, poor penetration into cells, high hepatic disposition, and narrow therapeutic window (Lipinski, 2000; Mastropaolo et al., 1995). Additionally, unfavorable pharmacokinetic parameters and drug resistance are also major obstacles to application of phytochemicals in the clinic (Lin et al., 2003). Nanoparticles have shown promise for improving the delivery of phytochemicals. Nanoparticle delivery of phytochemicals has been shown to increase their solubility, change unfavorable pharmacokinetic parameters and overcome multidrug resistance (MDR) in tumor cells (Davis et al., 2008; Duncan, 2003; Patel et al., 2013). In this review, we discuss lessons learned from using nanotechnology for the delivery of phytochemicals, and potential strategies to make them more effective in cancer treatment.

2. Phytochemicals in cancer therapy

Potential antineoplastic phytochemicals are often extracted from edible plants, including medicinal plants, vegetables and fruits. The abundance and easy-availability of plants make phytochemicals diverse and economical to study. Moreover, phytochemicals derived from these edible sources are usually safe for human consumption, even beneficial for normal physiological functions. This means they exhibit low or no toxicity on normal human organs and cells when used at a physiologically relevant concentration. Further studies on pharmacological mechanisms of natural anti-cancer components showed that they usually not only show bioactivities such as anti-inflammation, antioxidation, and immuno-modulation, but also target multiple cancer-related processes and signaling pathways (Wang et al., 2012). Their anti-cancer bioactivities, including apoptosis promoting, anti-proliferative and anti-metastatic activities, work alone or in combination to kill cancer cells. Briefly, phytochemicals can act with multiple anti-cancer mechanisms. Once bioactive phytochemicals are identified, they are usually used as a foundation for structural modification or as lead chemicals to synthesize new compounds based on structure–function relationships, physicochemical and pharmacodynamics characteristics, in order to improve their bioavailability and minimize their toxicity for further development (Tan et al., 2014).

A variety of novel phytochemicals with antineoplastic function have been discovered. Some examples of interesting natural phytogenic compounds are introduced below. They are currently in the clinical trial or in clinic use for cancer therapy, and have shown promising clinical activity. Genistein, 5,7-dihydroxy-3-(4-hydroxyphenyl)chromen-4-one, belongs to the group of chemicals called isoflavones. It is present mainly in Leguminous plants, including soybeans, lupine and fava beans (Fig. 1). Studies reveal that genistein exhibits various beneficial biological effects on cardiovascular disease, diabetes, neuropathy, osteoporosis, inflammatory diseases, and cancer. In recent decade, several cancer treatment-related clinical trials on genistein, including colorectal, prostate, pancreatic, breast and kidney cancers, have been carried out worldwide. Meanwhile, the inhibition effects of genistein on different types of cancers and underlying mechanisms are under investigation. As a phytoestrogen, genistein can competitively bind to estrogen receptors (ERs) and affect estrogen dependent cancers. Hwang et al reported that genistein inhibited growth of ovarian cancer cells (BG-1) via both ER and insulin-like growth factor-1 receptor (IGF-1R) signaling pathways both in vitro and in vivo (Hwang et al., 2013). Genistein also suppresses the proliferation and differentiation of MCF-7 and 3T3-L1 breast cancer cells by down-regulating the expression of ERα (Choi et al., 2014). Moreover, genistein induces apoptosis by inhibiting the nuclear factor-kappa B (NF-κB) pathway in LoVo and HT-29 human colon cancer cells (Luo et al., 2014) and T-cell leukemia cells (Yamasaki et al., 2013). In addition, genistein activates ATM/P53 dependent pathways in colon cancer cells (HCT-116 and SW-480) (Zhang et al., 2013). Genistein has been identified as a tyrosine kinase inhibitor and antiangiogenic agent, as well as a DNA topoisomerase II inhibitor, all of which contribute to its antineoplastic function. Recently, there are reports on regulatory effect of genistein on microRNAs in cancer cells. The expressions of onco-miR miR-1260b in prostate cancer cells (Hirata et al., 2014) and renal cancer cells (Hirata et al., 2013) are decreased by genistein. On the other hand, genistein upregulates the expression of tumor-suppressors miR-34a (Chiyomaru et al., 2013a, 2013b) and miR-574-3p (Chiyomaru et al., 2013a, 2013b) in prostate cancer. Collectively, these bioactivities of genistein result in inhibition of cancer cells growth.

Lycopene is a carotenoid derived from red-color fruits and vegetables, like red carrot, watermelon, grapefruit, papaya and particularly tomato. Due to its structure, a polyunsaturated hydrocarbon chain with 13 double bonds, 11 of which are conjugated, lycopene is highly lipophilic

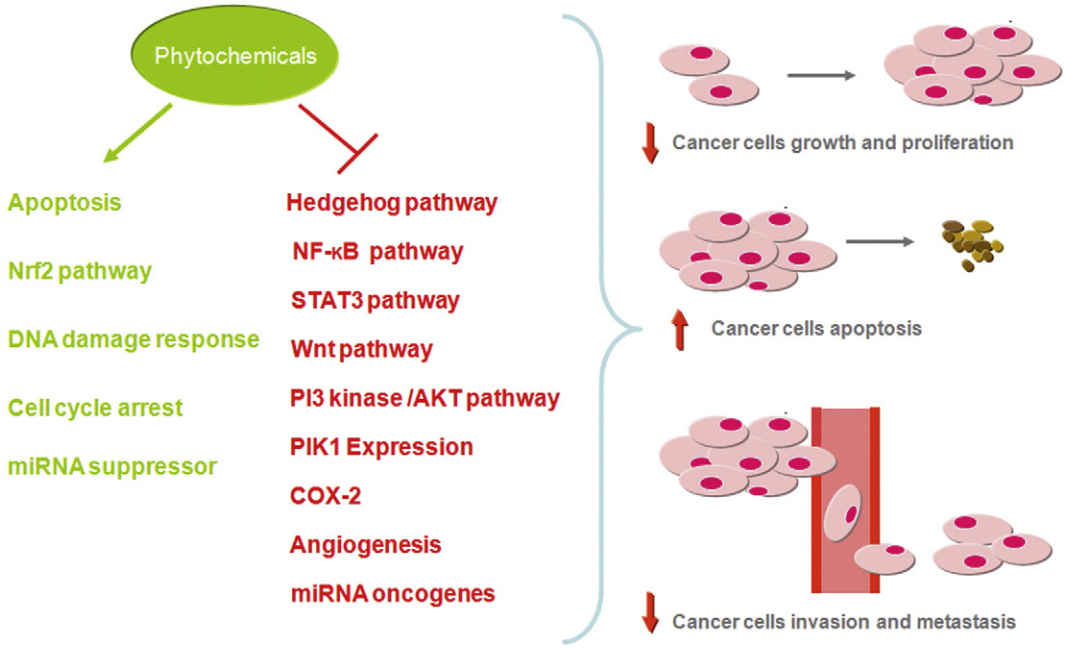

Fig. 1. Anticancer mechanisms of phytochemicals.