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Review

Natural molecules as tumour inhibitors: Promises and prospects

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ABSTRACT

Numerous natural substances derived from plants have demonstrated promising roles in providing substantial benefit in the prevention, treatment and management of various forms of cancer. Of the myriad of natural constituents found in plants, only a limited number have been screened for their potential role in cancer prevention or their cancer inhibition efficiency using *in vitro* or *in silico* models. Of those constituents that have been screened, an even smaller number are ultimately the subject of further studies in animal models or full scale double blind placebo controlled clinical studies in humans.

This paper comprises a review of the available literature with regard to the potential benefits of natural substances in the prevention, treatment and management of cancer and aims to provide readers with an insight on the potential benefits of the same. The paper will look at the mechanisms of action through altering multiple pathways and the benefits of some of the more comprehensively researched plant derived molecules like resveratrol, damnacanthal and morindone, anthocyanins and garcinol. Details on natural molecules derived from microbial and marine sources, namely didemnins, plitidepsin, dolastatins and bryostatin-1, are also discussed. Furthermore, information on pharmacological and toxicological advantages of natural molecules over synthetic molecules in the treatment of cancer is explored. Finally, the authors consider the means by which to achieve optimum benefits from natural compounds in cancer therapy, along with discussion regarding future approaches to cancer drug discovery.

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1. Introduction

Cancer treatment modalities have been constantly improving year on year, but a comprehensive and uniformly reliable cure for this ailment is still a long way off. Cancer chemotherapeutics can often provide temporary relief of symptoms, increase life expectancy, and occasionally provide prolonged relief or minimize risk factors. In recent years, efforts have been made to identify and synthesize possible potential anticancer molecules/drugs. However, extensive synthetic chemistry research has led to relatively small improvements in the existing prototype drugs. So, with the availability of fewer novel molecules for therapeutic application, modification of existing drugs continues to be an important aspect of cancer therapeutics research. There is a continued need for development of new prototypes, *i.e.*, new templates to use in the design of potential chemotherapeutic agents. Natural products are constantly providing such templates for prophylactic and therapeutic purposes in cancer and other chronic diseases. Recent studies into tumour-inhibiting compounds of natural origin have yielded an impressive array of novel structures and these are capable of acting through multiple pathways to ensure selective killing of cancer cells alone. Many of these natural products are extremely complex in structure, and it is most unlikely that such compounds would have been synthesized in empirical approaches to new drugs. Some of the major challenges with synthetic molecules include, *inter alia*, the complexity of the molecules, stereochemistry of natural products, together with the balancing between toxicity and induction of programmed cell death. In their natural form, bioactive molecules occur in a specific stereochemical formation that is pharmacologically active. These molecules will be either inactive or less efficient when extracted or separated from the plant cellular organization; mainly due to changes in structural conformation. It is also difficult synthetically to produce these molecules in the same manner as they exist in nature. For example, bioavailability of β-carotene from a natural source (which contains both *cis* and *trans* stereoisomers) will be more biologically active than synthetic β-carotene, which only contains the *trans* isomer (Ben-Amotz and Levy, 1996). Similarly many alkaloids are known to be either less potent or have a different pharmacological effect with changes in optical isomerism.

A plethora of natural compounds has been tested for their cytotoxic potential. One of them is from cucurbitaceous plants containing steroid nucleus phytochemicals, commonly known as Cucurbitacins, which could induce differentiation and arrest cell cycle growth *in vitro* (Haritunians et al., 2008). Unfortunately, their high toxicity *in vivo* resulted in a narrow therapeutic index, making them relatively unpromising therapeutic agents. In addition to this, other molecules have demonstrated their multimodal benefits in cancer prevention and progression. These include resveratrol, anthocyanin, damnacanthal, morindone, garcinol, didemnins, plitidepsin bryostatins and dolastatins. Table 1 summarizes some natural molecules that have made significant contributions towards cancer management. Structures for these highly promising molecules are depicted in Fig. 1. The advantage of considering molecules derived from dietary sources is their relatively low toxicity to normal tissue. This review provides details of some of the promising natural compounds that are effective in both *in vitro* and *in vivo*. Additionally, information on ingredients that are part of various formulations available for cancer management is also provided.

2. Resveratrol

Resveratrol (3,5,4′-trihydroxystilbene) is a naturally occurring dietary polyphenol and phytoalexin mainly found in plants such as grapes (*Vitis vinifera*), peanuts (*Arachis hypogea*) and mulberries. Resveratrol has been demonstrated to have an interesting spectrum of pharmacological properties. It is indicated in various ailments, such as cardiovascular disorders (Leifert and Abeywardena, 2008), diabetes mellitus, lipid metabolism disorders (Wu et al., 2013), inflammation, cancer (Wu et al., 2013), HIV and bacterial infections (Aggarwal et al., 2004a,b).