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Review

Fruit-derived phenolic compounds and pancreatic cancer: Perspectives from Australian native fruits

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ABSTRACT

Ethnopharmacological relevance: Pancreatic cancer is a devastating cancer that presents late, is rapidly progressive and has current therapeutics with only limited efficacy. Bioactive compounds are ubiquitously present in fruits and numerous studies *in vitro* are addressing the activity of these compounds against pancreatic cancer, thus studies of specific bioactive compounds could lead to new anti-pancreatic cancer strategies. Australian native fruits have been used as foods and medicines by Australian Aboriginals for thousands of years, and preliminary studies have found these fruits to contain rich and diversified bioactive components with high antioxidant activity. Thus, Australian native fruits may possess key components for preventing or delaying the onset of tumorigenesis, or for the treatment of existing cancers, including pancreatic cancer.

Materials and methods: Numerous databases including PubMed, SciFinder, Web of Knowledge, Scopus, and Sciencedirect were analysed for correlations between bioactive components from fruits and pancreatic cancer, as well as studies concerning Australian native fruits.

Results: In this review, we comprehensively highlight the proposed mechanisms of action of fruit bioactives as anti-cancer agents, update the potential anti-pancreatic cancer activity of various major classes of bioactive compounds derived from fruits, and discuss the existence of bioactive compounds identified from a selection Australian native fruits for future studies.

Conclusion: Bioactive compounds derived from fruits possess the potential for the discovery of new anti-pancreatic cancer strategies. Further, Australian native fruits are rich in polyphenols including some flora that contain unique phenolic compounds, thereby warranting further investigations into their anti-cancer properties.

Contents

1. Introduction . . . 228
2. Fruit-derived bioactive compounds and their plausible anti-cancer mechanisms . . . 229
3. Fruit-derived bioactive compounds and pancreatic cancer . . . 229
   3.1. Flavonols . . . 230
   3.2. Flavones . . . 230
   3.3. Flavanones . . . 231
   3.4. Isoflavones . . . 231
   3.5. Anthocyanins . . . 233
   3.6. Flavanols . . . 233
   3.7. Phenolic acids . . . 234

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3.8. Stilbenes . . . 234
3.9. Lignans . . . 236
4. Potential for the discovery of novel anti-cancer phytochemicals from Australian native fruits . . . 236
5. Conclusions and future considerations . . . 239
Acknowledgements . . . 239
References . . . 239

1. Introduction

For many years, plants have been used as *traditional indigenous* remedies for a variety of ailments in many parts of the world, especially Asia (Pierson et al., 2012). It is thought that 75–90% of the rural population worldwide still rely on plant medicine (Aju and Ezeibekwe, 2010).

Since the first attempts in the 1950s to search for anti-cancer agents from plants with the discovery of vinca alkaloids, such as vinblastine and vincristine (Cragg and Newman, 2005), numerous plant-derived agents have been developed and clinically used for the treatment of a variety of cancers (Table 1), and a number of agents are currently in preclinical development (Cragg and Newman, 2005). For example, triptolide from the *Tripterygium wilfordii* Hook. f. vine, has shown to be a potent inhibitor of pancreatic tumour growth and spread, and improved survival in an orthotopic xenograft mouse model of pancreatic cancer (Phillips et al., 2007). Recent studies by the same group modified triptolide to make a second generation water soluble version called Minnelide, which was also found to inhibit several different clinically relevant models of pancreatic cancer (Chugh et al., 2012). As such, Phase I clinical trials are expected to commence imminently (Chugh et al., 2012).

Over the last 30 years, approximately 45% of all anticancer drugs have been derived directly or indirectly from plant compounds, of which 12% are natural products and 32% are semi-synthetic derivatives of such natural products (Newman and Cragg, 2012). A significant percentage of anti-cancer drugs are entirely dependent on natural products, their structures and bioactivity (Newman and Cragg, 2007), however only 10% of the estimated 250,000 species worldwide have been screened for evidence of bioactivity and elucidation of their bioactive components (Mohanty and Cock, 2012). As such, there is great potential for using bioactives unique to fruits as anti-cancer therapies, and continued research into this field is warranted.

Presently many cancers are still incurable, especially at advanced stages when cancer cells metastasise throughout the body. Pancreatic cancer is considered as one of the most devastating cancers as it presents late and is rapidly progressive (Scarlett et al., 2006). Having a dismal 5-year survival rate of less than 5%, it remains as the third most common gastrointestinal cancer and the fourth most common cause of cancer death (Chang et al., 2008; Siegel et al., 2012; Vuong et al., 2012). Pancreatic cancer has been found to be largely resistant to conventional therapeutic strategies, thus it is essential to control and manage its development (Biankin et al., 2012). The use of natural bioactive components may additionally serve as a useful strategy to prolong or block the process of carcinogenesis (Vuong et al., 2012).

As an island continent and the world's sixth largest country, located between the Indian and Pacific Oceans, Australia experiences diversified weather throughout the country (White, 1994). Consequently, fruit bearing plants have developed their unique survival characteristics to adapt to such conditions (Mohanty and Cock, 2012). For example, there are over 2400 species of fruiting rainforest plants found in the tropical region alone providing great opportunity to identify novel medicinal agents. This immense diversity requires an appropriate selection rationale, via ethnobotanical analyses, to determine which fruits should be investigated further (Tan et al., 2010; Tan et al., 2011); such as those with high phenolic content and enhanced antioxidant activity. Clearly, native Australian fruits offer enormous opportunities for the discovery of preventive and/or therapeutic phytochemicals, in particular novel anti-cancer agents, including those for pancreatic cancer.

In this review, the anti-cancer activities of phytochemicals will be discussed based on their effect on cancer chemoprevention, as described by Johnson and Gonzalez de Mejia (2011). In this context, cancer chemoprevention is defined as the use of natural, synthetic or biologic chemical agents for pharmacologic intervention to *prevent, inhibit (prevention), or reverse (treatment) carcinogenesis*. As such, the mechanisms of action of selected bioactive

Table 1
Anti-cancer agents that are semi-synthetic derivatives of plant products.

Semi-synthetic derivative	Oncological use	Natural source	References
Vinorelbine	Breast and lung cancers	*Catharanthus roseus* G. Don. (Madagasca periwinkle)	Cragg and Newman, (2005) and Barni et al. (2007)
Etoposide	Lymphomas, bronchial and testicular cancers	*Podophyllum peltatum* Linnaeus (Mayapple) and *Podophyllum emodii* Wallich	Kong et al. (2003)
Paclitaxel	Ovarian, lymphomas, testicular, breast and small cell lung cancers	*Taxus brevifolia* Nutt. (Pacific Yew)	Kong et al. (2003) and Cragg and Newman (2005)
Vindesine	Leukaemias, lymphomas, testicular, breast and small cell lung cancers	*Catharanthus roseus* G. Don. (Madagasca periwinkle)	Kong et al. (2003) and Cragg and Newman (2005)
Teniposide	Lymphomas, bronchial and testicular cancers	*Podophyllum peltatum* Linnaeus (Mayapple) and *Podophyllum emodii* Wallich	Kong et al. (2003) and Cragg and Newman (2005)
Topotecan	Ovarian and small cell lung cancers	*Camptotheca acuminata* Decne (Chinese ornamental tree)	Kong et al. (2003), Guarneri et al. (2010) and Spigel (2012)
Irinotecan	Colorectal cancer	*Camptotheca acuminata* Decne	Kong et al. (2003)
Elliptinium	Breast cancer	*Bleekeria vitensis* A.C.Sm. (Fijian medicinal plant)	Kong et al. (2003)
Minnelide	Pancreatic cancer	*Tripterygium wilfordii* Hook F. (Chinese medicinal vine)	Chugh et al. (2012)