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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.

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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)

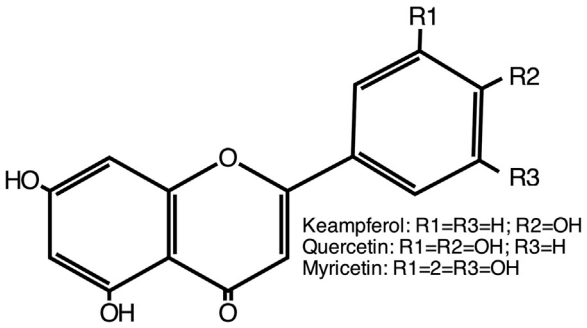

Fig. 1. Chemical structures of flavonols.

compounds derived from fruits will be discussed in terms of their therapeutic efficacy against pancreatic cancer, as well as the potential use of bioactive compounds from Australian native fruits as anti-cancer agents.

2. Fruit-derived bioactive compounds and their plausible anti-cancer mechanisms

Most fruits are generally consumed for their nutritional value; however, they have also been used for their enhancing health properties. For example, the *Psidium guajava* L. (common name: guava) is used as food but has been traditionally used in many parts of the world for the treatment of inflammation, diabetes, hypertension, caries, wounds, pain relief and reducing fever (Gutiérrez et al., 2008). Similarly, the *Passiflora foetida* L. (common name: bush passion fruit) has been used as food (fruit) and medicine (fruit and leaf) by the Aboriginal people in Australia for the treatment of skin disease (Barr et al., 1993). Clearly, it is important to identify and characterise the bioactive compounds present in fruits and further elucidate their association with health benefits.

The majority of bioactive compounds derived from fruits are phenolic compounds. Several suggestions have been proposed to explain the mechanism of action of phenolic compounds as anti-cancer agents. One proposed preventive mechanism driving the inhibition of cancer cell proliferation could be explained through the action of polyphenols on either scavenging the constitutive H_2O_2 or paradoxically generating additional amount of H_2O_2 to inhibit the proliferation of cancer cells (Loo, 2003). Cancer cells are thought to need a certain level of oxidative stress for maintaining a balance between undergoing either proliferation or apoptosis. A large but tolerated amount of H_2O_2 is generated and that activates signalling molecules in the mitogen-activated protein kinase pathway to constantly activate redox sensitive transcription factors and responsive genes which are involved in the survival and proliferation of cancer cells. Therefore, scavenging the excess H_2O_2 can suppress the oxidative stress-responsive genes, thus inhibit cancer cell proliferation. In addition, polyphenols can induce the generation of intolerable amounts of H_2O_2 that initiates apoptosis (Loo, 2003).

Another preventive mechanism proposed is through cytoprotection via Nrf2 in normal cells while eliciting cytotoxicity via modulation of transcription factors NF-κB and AP-1 in cancer cells (Gopalakrishnan and Tony Kong, 2008). Nrf2 is a redox sensitive transcription factor that plays an important role in gene expression. Under unstimulated conditions it remains sequestered in the cytosol by Keap1. Phenolic compounds can break the Nrf2-Keap1 association to release Nrf2, which then translocates to the nucleus and drives the gene expression of detoxifying enzymes (Gopalakrishnan and Tony Kong, 2008). In addition, NF-κB and AP-1 are transcription factors, which also play important role in carcinogenesis as they can bind to the *cis*-acting elements in the promoter of COX-2. COX-2 is known to be upregulated in a number of malignancies. Phenolic compounds can modulate the activities of NF-κB and AP-1 and their upstream signalling molecules, thus causing apoptosis in abnormal cells that over-express these factors and consequently inhibiting their promotion and progression (Gopalakrishnan and Tony Kong, 2008).

Phenolic compounds are also thought to have preventive effects via modulation of epigenetic alterations. Phenolic compounds can change the DNA methylation pattern, regulate histone modifications, and change the expression of some non-coding miRNAs, thus they can inhibit the inactivation of tumour suppressor genes and activation of oncogenes that occurs during carcinogenesis (Link et al., 2010). The mechanism of the anti-carcinogenic actions of phenolic compounds is also proposed as their relation to the modulation of cytochrome p450 expression. The chemical carcinogens can be activated metabolically by cytochrome p450 mixed function oxidases. However, the phenolic compounds are postulated to stimulate the cytochrome p450-conjugating enzymes, such as glutathione transferase, glucurosyl transferase and methyltransferase, which can metabolically inactivate the chemical carcinogens produced by the mixed function oxidases (Vuong et al., 2012).

Further, through their inherent redox properties, phenolic compounds can neutralise free radicals and scavenge reactive oxygen species (ROS) that contribute to oxidative stress within the cells, thereby preventing the growth of cancer cells. This is dependent on the efficiency of scavenging ROS, which are described as being pro-survival, anti-apoptotic factors in pancreatic cancer cells (Donadelli et al., 2006; Acharya et al., 2010). Furthermore, attenuation of ROS by antioxidants was found to suppress hypoxia-induced epithelial to mesenchymal transition (EMT) and metastasis in pancreatic cancer, and thus the use of antioxidants to inhibit EMT and metastasis may be of therapeutic benefit in patients with pancreatic cancers (Shimojo et al., 2012).

Recent evidence has described the great potential of phytochemicals extracted from natural sources due to their inherent antioxidant activity, in targeting the altered redox status apparent in cancer cells. Phenolic compounds work as radical scavengers of lipid peroxidation chain reactions. They donate an electron to reactive free radical species in the body, which neutralise their potentially damaging chain reactions in cell chemistry and form stable phenolic radical products in the process. Furthermore, they are also known as metal chelators that reduce the rate of the Fenton reaction, preventing oxidation caused by highly reactive hydroxyl radicals (Tsao, 2010; Visioli et al., 2011).

Although several studies attempt to elucidate the potential preventive activities of bioactive compounds, mainly using *in vitro* studies, the understanding of these mechanisms of action that alter key pathways driving carcinogenesis is still very limited. As such, further *in vitro, in vivo* and pre-clinical studies are warranted.

3. Fruit-derived bioactive compounds and pancreatic cancer

Despite decades of continuous effort, there has been no reduction in the incidence, nor improvements in the mortality rates of pancreatic cancer (Saif et al., 2009; Siegel et al., 2012). The major treatment modality for pancreatic cancer is limited to surgical removal of the pancreas and/or treatment with gemcitabine, the current standard of care and first-line treatment (Saif et al., 2009). However, the outcomes of surgical resection and gemcitabine for treatment of pancreatic cancer are modest (Bachmann et al., 2006). Therefore, it is necessary to investigate novel preventative and therapeutic agents, which have the potential to improve the survival rate and quality of life for pancreatic cancer patients.

Table 2
Content of flavonoids derived from selected fruits (Bhagwat et al., 2011).

Flavanoid content of selected fruits (mg/100 g)											
		Apple (*Malus domestica* Borkh.)	Apricots (*Prunus armeniaca* L.)	Blackberries (*Rubus spp.*)	Blueberries (*Vaccinium spp.*)	Cherries (*Prunus avium* (L.) L.)	Fig (*Ficus carica* L.)	Grape fruit (*Citrus paradisi* Macfad.)	Red grape (*Vitis vinifera* L.)	Orange (*Citrus sinensis* (L.) Osbeck)	Plum (*Prunus domestica* L.)
Flavonols	Keamferol	0.14	0.63	0.27	2.36	0.24	0.00	0.01	0.00	0.13	0.10
	Myricetin	0.00	0.00	0.67	4.70	0.05	0.00	0.01	0.01	0.15	0.10
	Quercetin	4.01	1.63	3.58	3.43	2.29	5.47	0.33	1.04	0.45	0.70
Flavones	Apigenin	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Luteolin	0.12	0.00	0.00	0.00	0.00	0.00	0.60	1.30	0.19	0.00
Flavanones	Hesperetin	0.00	0.00	0.00	0.00	0.00	0.00	0.35	0.00	27.25	0.00
	Naringenin	0.00	0.00	0.00	0.00	0.00	0.00	32.64	0.00	15.32	0.00
Anthocyanins	Cyanidin	1.27	0.00	90.49	21.60	27.45	0.50	0.00	0.95	0.00	0.28
	Delphinidin	0.00	0.00	0.00	24.28	0.00	0.00	0.00	2.10	0.00	0.00
	Malvidin	0.00	0.00	0.00	0.00	0.00	0.00	0.00	36.20	0.00	0.00
	Pelargonidin	0.00	0.00	0.15	56.77	0.27	0.01	0.00	0.02	0.00	0.00
	Peonidin	0.01	0.00	0.00	15.90	1.33	0.00	0.00	2.90	0.00	0.02
	Petunidin	0.00	0.00	0.00	21.43	0.00	0.00	0.00	1.80	0.00	0.00
Flavanols	Epicatechin	7.53	4.47	4.66	25.66	5.00	0.50	0.00	0.96	0.00	0.00
	Epicatechingallate	0.01	0.00	0.00	0.00	0.05	0.00	0.00	0.17	0.00	0.00
	Epigallocatechin	0.26	0.00	0.10	0.00	0.34	0.00	0.00	0.08	0.00	0.00
	Epigallocatechin-Gallate	0.19	0.00	0.68	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Catechin	1.3	3.67	37.06	98.47	4.36	1.59	0.00	0.82	0.00	0.00
	Gallocatechin	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

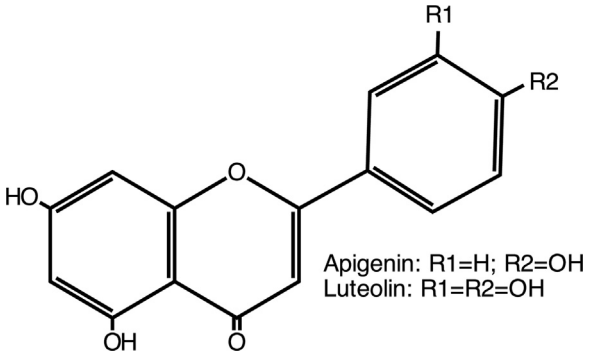

Fig. 2. Chemical structures of flavones.

Fruit derived bioactive compounds have received increasing interest in recent decades due to their potential health benefits in general, and for their anti-cancer activity. The biodiversity of bioactive compounds in fruits provides great potential for inclusion and use for numerous health purposes, while specific compounds unique to certain fruits are also proposed to possess efficacious anti-pancreatic cancer activity. With the advanced development in laboratory technology, identification and isolation of bioactive compounds are becoming less problematic, therefore many bioactive compounds have been identified and tested for their antioxidant and biological activities (Pierson et al., 2012). Based on their source of origin, biological function, and chemical structure, fruit bioactive compounds can be classified into a number of different chemical classes (D'Archivio et al., 2007; Tsao, 2010). This section will comprehensively discuss the putative links between each chemical class and pancreatic cancer.

3.1. Flavonols

Flavonols are a class of flavonoids that have the two benzene rings joined by a linear three-carbon chain (C2, C3, C4), represented as the C6–C3–C6 system (Fig. 1). Their antioxidant and biological properties are thought to be attributed to the presence of phenolic hydroxyl (–OH) moieties on the structure (Kim et al., 2006). Flavonols are ubiquitous flavonoids in fruits with quercetin, keamferol and myricetin as the representative compounds (D'Archivio et al., 2007; Boots et al., 2008) (Table 2). Within the flavonoid group derived from fruits, quercetin accounts for the highest quantity, followed by keamferol and myricetin. Quercetin has shown excellent antioxidant activity and is known as the most potent scavenger of reactive oxygen species, including superoxide and reactive nitrogen species like nitric oxide and peroxynitrite (Boots et al., 2008). Quercetin is also found to possess strong anti-inflammatory capacities and anti-proliferative properties (Oršolić et al., 2004; *Angst* et al., 2013). Quercetin was shown to inhibit pancreatic tumour growth *in vitro* and *in vivo* via an increase in apoptosis (Mouria et al., 2002; Aghdassi et al., 2007; Borska et al., 2010). More recently, using *in vitro* and *in vivo* models of pancreatic cancer, a recent study found that quercetin targeted pancreatic cancer stem cell-like characteristics (Zhou et al., 2010). Quercetin alone or in combination with sulforaphane, could affect self-renewal potential, ALDH1 activity, induction of apoptosis, inhibition of angiogenesis, nuclear factor κB (NF-κB) and epithelial to mesenchymal transition (EMT) processes (Zhou et al., 2010).

More recently, the flavonol myricetin was demonstrated to induce pancreatic cancer cell death both *in vitro* and *in vivo* via induction of apoptosis through inhibition of the phosphatidylinositol 3-kinase (PI3K) signalling pathway (Phillips et al., 2011). Another study *in vitro* also found that kaempferol effectively inhibits pancreatic cancer cell proliferation and induces cancer cell apoptosis, which may sensitise pancreatic tumour cells to chemotherapy (Zhang et al., 2008). Additionally, in a multiethnic cohort study, Nöthlings et al. (2007, 2008) provided evidence for a pancreatic cancer preventive effect of dietary flavonols, particularly among current smokers. Although flavanols have been positively linked with the prevention of pancreatic cancer, further studies *in vivo* and at the pre-clinical level are required to validate these correlations.

3.2. Flavones

Flavones present higher in the skins of fruit with apigenin and luteolin as the representative compounds (Fig. 2). Apigenin and

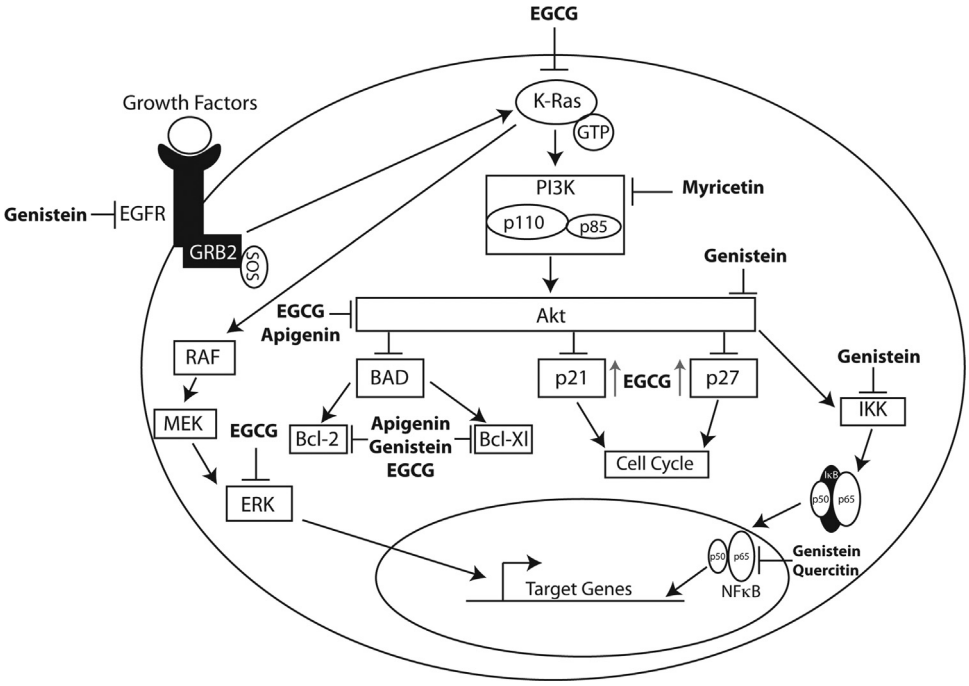

Fig. 3. Cellular signalling pathways affected in pancreatic cancer cells by apigenin, genistein, myricetin, quercitin and EGCG. Modified from (Johnson and Gonzalez de Mejia, 2011).

luteolin vary in different fruits (Table 2). In the skin of the mandarin, their content may account for up to 6.5 g/L of the skin's essential oil (D'Archivio et al., 2007). A study on 22 citrus compounds found that luteolin and apigenin had the highest inhibitory effects on glycogen synthase kinase-3β, which is known to lead to decreased cancer cell proliferation by abrogating NF-κB activity (Fig. 3) (Johnson et al., 2011). In addition, apigenin was found to inhibit HIF-1α, GLUT-1, and VEGF mRNA and protein expression in pancreatic cancer cells in both normoxic and hypoxic conditions, indicating the mechanism of apigenin's anti-proliferative and anti-angiogenic effects and further supports the potential of apigenin as a future chemopreventive agent for pancreatic cancer (Table 3) (Melstrom et al., 2011).

Apigenin and luteolin have improved the anti-proliferative and pro-apoptotic effect of chemotherapeutic drugs such as gemcitabine, cisplatin, 5-fluorouracil and oxaliplatin on human pancreatic cancer cells (Johnson and Gonzalez de Mejia, 2013). *In vitro*, the combination treatment resulted in more growth inhibition and apoptosis through the down-regulation of NF-κB activity with suppression of Akt activation in pancreatic cancer cell lines. Whereas, *in vivo* the combination therapy augmented tumour growth inhibition through the down-regulation of NF-κB activity with the suppression of Akt in tumour tissue (Lee et al., 2008). Thus, the combination of flavones with chemotherapeutic drugs tentatively enhanced anti-tumour efficacy through Akt and NF-κB activity suppression and apoptosis induction. Although, positive evidence has shown the potential of flavones for the combined treatment of pancreatic cancer *in vitro* and *in vivo*, further studies are necessary to elucidate the exact mechanisms of actions driving their effect.

3.3. Flavanones

Flavanones (Fig. 4) are rich within citrus fruits, tomatoes and other fruits with naringenin, hesperetin and alpinetin as representative compounds. In the orange (*Citrus sinensis* (L.) Osbeck), aringenin and hesperetin levels accounted for 15 and 27 mg per 100 g, respectively (Table 2). Naringenin has been shown to down-regulate EMT markers expression in both mRNA and protein levels by inhibiting TGF-β1/Smad3 signal pathway in pancreatic cancer cells. Consequently, it could suppress cellular migration and invasion and reverse their resistance to gemcitabine (Lou et al., 2012). Naringenin also demonstrated anti-proliferative activity on pancreatic cancer cells (EPP85-181); however, the activity is moderate in comparison with other flavonoids (Duarte et al., 2010).

Hesperetin is also rich in citrus fruits and has been found to inhibit the growth of different cancers *in vitro* such as colon cancer (Aranganathan and Nalini, 2013), cervical cancer (Alshatwi et al., 2013), and breast cancer (Choi, 2007). However, there remains limited information on the link between hesperetin and pancreatic cancer. Hesperetin was found to inhibit the phosphorylation of Smad3, a down-stream target of the TGF-β pathway and it hinders TGF-β1-induced cancer cell migration and invasion (Yang et al., 2012).

Alpinetin, one of the main constituents of the seeds of *Alpinia katsumadae* Hayata, was also found to possess strong anti-cancer effects. Alpinetin was shown to induce apoptosis of pancreatic cancer cells in a dose- and time-dependent manner, and thus may serve as a potential agent for the development of pancreatic cancer cell therapies (Du et al., 2012). In general, flavanones have shown a positive association with anti-pancreatic cancer activity; however, most studies have been limited to being performed at the *in vitro* level

3.4. Isoflavones

Isoflavones (Fig. 5) have been found in high levels within leguminous fruits, with daidzein and genistein as representative compounds (Table 2) (D'Archivio et al., 2007). Daidzein has been shown to inhibit pancreatic cancer cell growth in a dose- and time-dependent manner (Guo et al., 2004), while studies *in vitro* have also linked genistein with the treatment of pancreatic cancer via multiple mechanisms of action; including being pro-apoptotic, a potent chemo-sensitization agent, and displaying a synergistic relationship with gemcitabine. It was shown to inhibit TGF-β1-induced invasion and metastasis in Panc-1 cells (Han et al., 2012), as well as inhibiting cell growth and induction of apoptotic

Table 3
Anti-pancreatic cancer activity of selected fruit bioactive compounds.

Bioactive compound	Anti-pancreatic cancer mechanism of action	References
Flavones		
Apigenin	*In vitro:* Inhibits cell proliferation; induces apoptosis via downregulation of NFκB, suppression of Akt and Bcl-2 expression; increases activity of chemotherapeutic agent gemcitabine *In vivo:* Increases the inhibitory effect of gemcitabine	Ujiki et al. (2006), Lee et al. (2008), Melstrom et al. (2008), Salabat et al. (2008), Strouch et al. (2009) and Johnson and Gonzalez de Mejia (2011)
Isoflavones		
Genistein	*In vitro:* Induces apoptosis via downregulation of Notch-1, pAKT, IKK and therefore NFκB – inhibits p65 expression and NFκB DNA-binding activity; chemosensitises cells to multiple agents (gemcitabine, cisplatin, erlotinib); synergistic relationship with gemcitabine; inhibits TGF-β1- induced invasion and metastasis. *In vivo:* Increases activity of gemcitabine; induces apoptosis via downregulation of NFκB; reduces tumour growth.	Banerjee et al. (2005), Li et al. (2005); Mohammad et al. (2005; 2006), Wang et al. (2006a, 2006b), Banerjee et al. (2007) and Han et al. (2012)
Flavanols		
EGCG	*In vitro:* Induces apoptosis by ROS-mediated caspase-3 and -9activation and inhibits Bcl-2; inhibits cell growth by binding Hsp90 preventing the association with its co-chaperones. *In vivo:* Reduces tumour growth by inhibition of cell proliferation by reduced Ki-67 expression, and upregulation of $p21^{/CIP1/WAF}$ expression resulting in growth arrest.	Qanungo et al. (2005), Shankar et al. (2007) (2008), Basu and Haldar (2009) and Li et al. (2009)
Phenolic acids		
Gallic Acid	*In vitro:*	Liu et al. (2012)
Protocatechuic Acid (PCA)	Inhibited proliferation of CFPAC-1 and MiaPaCa-2 cells and induced apoptosis via the mitochondria-mediated pathways. *In vivo:* Inhibited the late post-initiation or progression phase of chemical-induced pancreatic carcinogenesis.	Nakamura et al. (2000)
Caffeic Acid Phenethyl Ester (CAPE)	*In vitro:* CAPE (10 mg/ml) resulted in marked inhibition of viability of BxPC-3 (80.4%) and PANC-1 (74.3%) cells. *In vivo:* Inhibited the growth and EMT of pancreatic cancer cells with down-regulation of vimentin and Twist 2 expression	Chen et al. (2008) Chen et al. (in press)
Stilbenes		
Resveratrol	*In vitro:* Inhibition of pancreatic cancer cell viability and inhibition of BCL-2 expression in PANC-1, CFPAC-1 and MiaPaca-2 cells; Enhancement of growth inhibition and inter-nucleosomal DNA fragmentation induced apoptosis in Capan-2 and Panc-28 pancreatic cancer cell lines (but not in normal HPDE cells); Inhibited pancreatic cancer cell survival via the Hedgehog signalling pathway. *In vivo:* Resveratrol induced cell cycle arrest by up-regulating the expression of $p21^{/CIP1/WAF}$, $p27^{/KIP1}$ and inhibiting the expression of cyclin D1. Induction of apoptosis by up-regulating Bim and activating caspase-3. Inhibited phosphorylation of FOXOs, and enhanced their nuclear translocation, FOXO-DNA binding and transcriptional activities. Inhibition of the self-renewal capacity of pancreatic cancer stem cells (CSCs) and induced apoptosis by activating capase-3/7 and inhibiting the expression of Bcl-2 and XIAP in human CSCs. Inhibited pluripotency maintaining factors (Nanog, Sox-2, c-Myc and Oct-4) and the drug resistance gene ABCG2 in CSCs. Inhibited CSC's migration and invasion and markers of epithelial-mesenchymal transition (Zeb-1, Slug and Snail); Up-regulated MIC-1 gene expression at the transcriptional level in pancreatic cancer cells. MIC-1 plays a key role in resveratrol-induced growth inhibition.	Mo et al. (2011 and Shamim et al. (2012), Liu et al. (2013) Golkar et al. (2007), Roy et al. (2011) and Shankar et al. (2011)

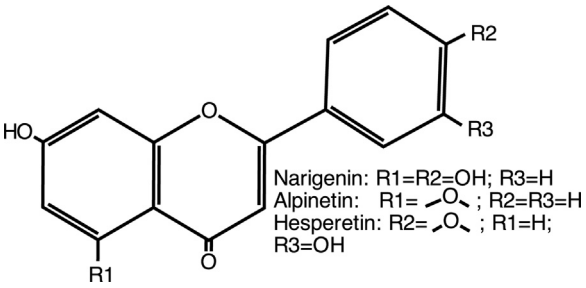

Fig. 4. Chemical structures of flavanones.

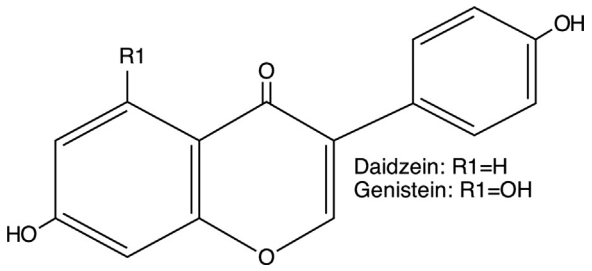

Fig. 5. Chemical structures of isoflavones.

processes in BxPC-3 pancreatic cancer cells partly due to inhibition of Notch-1 activity (Wang et al., 2006a), which can occur via up-regulation of the miR34a by genistein (Xia et al., 2012). Further, genistein has been demonstrated *in vitro* to inhibit p65 expression and also the DNA-binding activity of NF-κB, as well as inhibiting the activity of AKT upstream of IKK. This reduces the capacity of IKK to phosphorylate IκB (NF-κB inhibitory protein) and subsequent proteosomal degradation thereby inhibiting translocation to the nucleus of free NF-κB, resulting in increased growth inhibition and apoptosis (Table 3; Fig. 3) (Bremner and Heinrich, 2002; Banerjee et al., 2005; Li et al., 2005).

In vivo, genistein was found to be much more effective as an anti-tumour agent when combined with gemcitabine, as compared with either agent alone. NF-κB was inactivated in genistein-treated tumours, while gemcitabine-induced activation of NF-κB was completely inhibited in tumours treated with genistein and gemcitabine (Banerjee et al., 2005). Inactivation of the NF-κB signalling pathway by genistein also resulted in the chemo-sensitization of pancreatic tumours to cisplatin and erlotinib, which is widely used against solid tumours, and thus is likely to be an important and novel combination strategy for the treatment of pancreatic cancer (Table 3; Fig. 3) (El-Rayes et al., 2006; Banerjee et al., 2007).

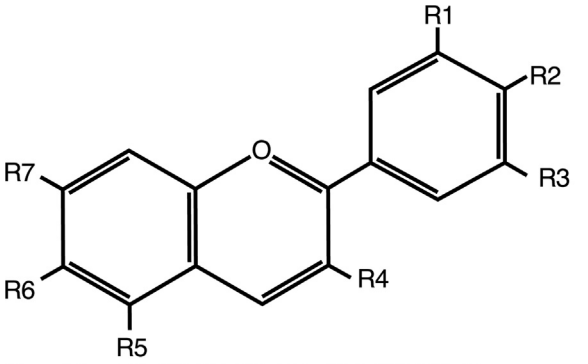

Fig. 6. Chemical structures of anthocyanins.

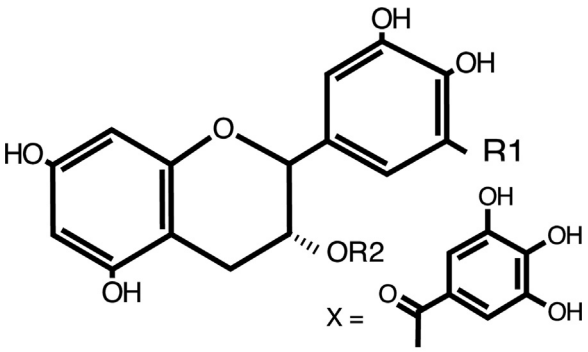

Fig. 7. Chemical structures of flavanols.

3.5. Anthocyanins

Anthocyanins are known as water-soluble pigments responsible for most of the fruit colours with than 635 anthocyanins identified in nature (He and Giusti, 2010). However, six different anthocyanins comprising cyanidin, delphinidin, malvidin, pelargonidin, peonidin and petunidin (Fig. 6) are commonly found in fruits. Fruits which are rich in colour, such as black berries, blueberries and cherries, contain high levels of anthocyanins (Table 2). Anthocyanins have been linked with the anti-cancer activity of cancers such as oral, colon and gastric cancers (Konczak and Zhang, 2004; Thomasset et al., 2009; He and Giusti, 2010). There is limited published data reporting the link between anthocyanins and pancreatic cancer; however, a recent study tested the role of anthocyanins extracted from Chinese bayberry extract for the protection of pancreatic β cells (INS-1) against hydrogen peroxide (H_2O_2)-induced necrosis and apoptosis. Results showed that anthocyanins could protect pancreatic β cells from H_2O_2-induced cell injury via ERK1/2- and PI3K/Akt-mediated HO-1 upregulation (Zhang et al., 2011).

3.6. Flavanols

Flavanols have been found in many fruits such as grape, apricots and cherries with catechins as their representative compounds (Table 2). Catechins are known to possess high antioxidant activity, which is much higher than that of vitamin C or vitamin E (Vuong et al., 2011). Recent reviews have linked catechins with both the prevention and treatment of various cancers (Fujiki and

Table 4
Content of phenolic acids derived from selected fruits (Russell et al., 2009).

	Raspberry (*Rubus idaeus* L.)	**Gooseberry** (*Ribes uvacrispa* L.)	**Blackcurrant** (*Ribes nigrum* L.)	**Strawberry** (*Fragaria ananassa* L.)	**Banana** (*Musa acuminata* L.)	**Apple** (*Malus domestica* L.)	**Pear** (*Pyrus communis* L.)	**Grapes** (*Vitis vinifera* L.)	**Oranges** (*Citrus sinensis* L.)
Gallic	5.73	1.27	5.63	1.67	0.02	0.11	0.00	0.17	0.00
Protocatechuic	3.83	27.22	10.45	39.09	0.16	3.37	0.45	1.67	2.53
p-Hydroxybenzoic	33.31	0.00	4.33	193.91	0.00	34.09	0.48	1.20	17.41
Gentisic	0.00	2.01	0.00	30.85	0.00	0.00	0.00	0.00	0.20
Caffeic	2.33	13.23	3.73	0.00	0.00	0.00	0.00	7.03	1.00
Vanillic	24.58	0.00	15.01	98.46	0.30	0.00	0.00	0.00	4.86
Syringic	107.51	0.00	0.00	0.00	0.21	1.10	0.00	0.00	2.53
p-Coumaric	0.00	0.00	19.83	0.00	0.00	11.65	0.00	0.00	6.65
Ferulic	74.33	0.00	0.00	567.89	0.00	0.00	0.00	0.00	30.06
Sinapic	36.89	0.00	0.00	450.30	0.00	13.42	0.96	0.00	17.28
Salicylic	7.64	0.00	62.09	0.00	0.00	0.00	0.37	0.00	2.37

Suganuma, 2012; Vuong, 2014). Catechins are comprised of eight individual catechins (Fig. 7) and have demonstrated efficacy against pancreatic cancer in the context of both prevention and treatment (Vuong, 2014).

Epigallocatechin-3-gallate (EGCG), a major component of catechins, was shown to inhibit pancreatic cancer growth, invasion, metastasis and angiogenesis (Shankar et al., 2008). It was found to inhibit the growth of the pancreatic cancer cells via blockage of focal adhesion kinase (FAK) and the insulin-like growth factor-1 receptor (IGF-1R) (Takada et al., 2002; Vu et al., 2010). EGCG was also shown to induce stress signals by damaging mitochondria and ROS-mediated JNK activation in MiaPaCa-2 cells (Qanungo et al., 2005) and decreased the expression of the K-ras gene, thus modulating the expression of downstream genes involved in carcinogenesis (Lyn-Cook et al., 1999). EGCG has also been shown to bind to heat shock protein 90 (Hsp90) and impair the association of Hsp90 with its co-chaperones, thereby inducing degradation of Hsp90 client proteins resulting in anti-proliferative effects in pancreatic cancer cells (Table 3; Fig. 3) (Li et al., 2009).

Two other catechins, epicatechin gallate (ECG) and catechin gallate (CG) were also found to inhibit pancreatic cancer cell proliferation in a dose- and time-dependent manner (Kürbitz et al., 2011). These two catechins demonstrated stronger anti-proliferative effects than EGCG. ECG and CG were found to inhibit the TNFα-induced activation of NF-κB and consequently secretion of pro-inflammatory and invasion promoting proteins like IL-8 and uPA, indicating their potential for the treatment of pancreatic cancer (Kürbitz et al., 2011). Of note, the link between flavanols and pancreatic cancer has mainly been limited to the three catechins (EGCG, ECG, CG) and *in vitro*. Further studies on the remaining catechins and their combination with other bioactive compounds are necessary to validate the anti-cancer potential of flavonols. Interestingly, our group has recently demonstrated a synergistic relationship between the catechin EGCG and the chemotherapeutic agent gemcitabine. The combination of EGCG and gemcitabine significantly reduces pancreatic cancer cell viability, when compared to the single agents alone demonstrating powerful anti-proliferative and pro-apoptotic effects. Further, treatment with CG reduces pancreatic cancer cell viability to levels comparable to gemcitabine, however proves to be cytoprotective in normal HPDE cells (*unpublished*).

3.7. Phenolic acids

Phenolic compounds account for a large group of secondary plant products with an aromatic ring bearing one or more hydroxyl substituents. Phenolic acids are one major class of phenolic compounds, found widely in fruits (Mattila et al., 2006). Gallic acid, protocatechuic acid, p-hydroxybenzoic acid, gentistic acid, caffeic acid, syringic acid, p-coumaric acid, ferulic acid, sinapic acid and salicilic acid are the most common phenolic acids present in the fruits (Table 4) (Russell et al., 2009).

Recent studies have demonstrated preventive activity of phenolic acids against pancreatic cancer cells (Table 3). For instance, Chen and colleagues (2008) demonstrated that its derivative caffeic acid phenethyl ester (CAPE) inhibited pancreatic cancer cell viability by increased hypo-diploid percentage and significantly decreased mitochondrial transmembrane potential. Gallic acid has also been found to inhibit the proliferation of pancreatic cancer cells in a time- and dose-dependent manner (Liu et al., 2012). In addition, protocatechuic acid has been found to inhibit the late post-initiation phase of BOP-induced pancreatic carcinogenesis (Nakamura et al., 2000).

The initial findings indicate the potential of phenolic acids for the prevention of pancreatic cancer. However, the link between pancreatic cancer and many other phenolic acids such as p-hydroxybenzoic acid, gentistic acid, syringic acid, p-coumaric acid, ferulic acid, sinapic acid and salicilic acid has yet to be studied. Therefore, further studies on the effect of these phenolic compounds alone or in combination with other bioactive compounds on pancreatic cancer should be conducted.

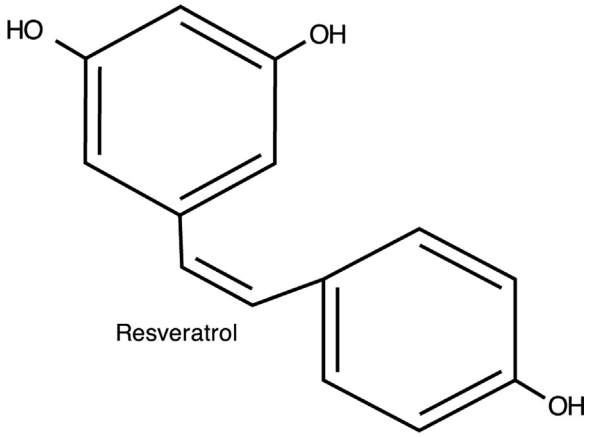

Fig. 8. Chemical structures of resveratrol.

3.8. Stilbenes

Stilbenes are a minor class of polyphenols that are found in many tropical and non-tropical fruits (Pierson et al., 2012). Resveratrol (trans -3,4′,5-trihydroxystilbene) (Fig. 8) is the representative compound of stilbenes. Resveratrol is found largely in grapes and is produced in plants when responding to pathogens or stress conditions (D'Archivio et al., 2007; Pandey and Rizvi, 2009). Recent studies have demonstrated anti-proliferative and pro-apoptotic effects of resveratrol *in vitro* and *in vivo* (Table 3). For example, resveratrol was found to be non-toxic to normal pancreatic cells, but induced apoptosis and inhibited proliferation of pancreatic cancer cells (Cui et al., 2010; Mo et al., 2011; Zhou et al., 2011). The mechanisms might be partly via the Hedgehog signalling pathway as resveratrol can decrease the expression of the Hedgehog pathway members including Gli1, Ptc1 and Smo and it can also down-regulate the expression of Gli1, Ptc1, CCND1 and BCL-2 in Gli1-overexpressed pancreatic cancer cells, but does not act on the Gli1 promoter directly (Mo et al., 2011). Resveratrol was also reported to inhibit growth of orthotopic pancreatic tumours in mice (Roy et al., 2011), as well as pancreatic cancer stem cell characteristics in human and Kras (G12D) transgenic mice by inhibiting pluripotency maintenance factors and epithelial–mesenchymal transition (Shankar et al., 2011).

It is interesting to note that resveratrol was found to potentiate the effects of gemcitabine through suppression of markers of proliferation, invasion, angiogenesis and metastasis (Harikumar et al., 2010). Resveratrol was also shown to inhibit glycogen synthesis and turnover in pancreatic cancer cells, an underlying mechanism of controlling tumour cell proliferation (Harris et al., 2012). A naturally occurring analogue of resveratrol, pterostilbene, is found in blueberries and has antioxidant activity as well as demonstrated efficacy against certain cancers (gastric, colon, breast) *in vitro* and *in vivo* (Mannal et al., 2010). Treatment of pancreatic cancer cells *in vitro* with pterostilbene has been shown to inhibit cell proliferation (Mannal et al., 2010), induce up-regulation of pro-apoptosis genes and reduce tumour volume *in vivo* (McCormack et al., 2012). Interestingly, the combination of pterostilbene with the polyphenol (-)-epigallocatechin-3-gallate (EGCG) has an additive anti-proliferative effect on pancreatic cancer cell lines and can alter their apoptotic mechanisms (Kostin et al., 2012).

Table 5
Botanical name of selected plants and their parts traditionally used as remedies for aliments by Indigenous communities in Australia.

Latin name/Family	Aboriginal name	Parts used	Preparation and traditional use	Reported anti-cancer activity	Source of ethnomedicinal data
Acacia Estrophiolata F.Muell./ Mimosaceae	Athenge	Bark, root, gum	Brewing with water and solution is applied on affected areas to treat infected skin lesions, scabies burns and wounds.	ND	Lister et al. (1996)
Adansonia Gregorii F.Muell./ Bombacaceae	Jamulang	Fruit pulp	Raw fruit powdery pulp is eaten to reduce gastric disturbance.	ND	Lowe (1998)
Avicennia Marina (Forsskal) Vierh./Verbanaceae	Maanyarr	Leaves	Young shoots are chewed and mixed with saliva applied to site of puncture to relive pain caused by the sting of stone-fish/sting-rays.	Inhibition of breast cancer cells	Bandaranayake (1998) and Tsai et al. (2014)
Brachychiton Diversifolius R. Br./Sterculiaceae	Nanungguwa	Leaves	Leaves are crushed and infused. Liquid is used for washing over the body to reduce fevers of unknown origin.	ND	Brand and Cherikoff, (1985)
Buchanania Obovata Engl./ Anacardiaceae	Mangkarrba	Petioles, mid-vein of leaves	Scraping to remove outer layer, heating then inserting into tooth cavity for toothache.	ND	(Barr et al., 1993)
Callitris Intratropica R. Baker & H.G. Smith/Cupressaceae	Gangi	Bark	Bark is boiled with water and used to wash over the whole body to relieve abdominal pain from diarrhoea.	ND	Barr et al. (1993)
Calytrix Brownii (Schauer) Craven/Myrtacea	Alunkwaluwa	Leaves	Young leaves are crushed and boiled in water. Steam is inhaled to relieve congestion of the nasal and bronchial passages.	Inhibition of malignant melanoma and colon carcinoma	Smith (1991) and Rasoanaivo et al. (2013)
Capparis Umbonata Lindley/ Capparaceae	Burnayingmi	Bark	Bark is chopped or pounded and then boiled in water until red in colour. The solution is then applied on affected area such as chicken pox, boils, scabies, muscle and joint pain.	ND	Smith (1991)
Carissa Lanceolata R. Br./ Apocynaceae	Manigudja	Root	Young roots without the bark are chopped, crushed and boiled with water. Solution is used to rub onto the chest as part of treatment.	ND	Smith (1991)
Cassia Notabilis F. Muell./ Caesalpiniaceae	Kampijung	Leaves and twigs	Leaves and twigs are crushed and boiled with water. The liquid is used to wash the body to reduce fever associated with colds and flu.	ND	Barr et al. (1993)
Citrullus Colocynthis (L.) Schrader/Cucurbitaceae	–	Fruit	The pulp of the ripe fruit is directly applied to scabies or tinea.	Inhibit hepatoma cell line, breast cancer cells. In *vivo*: prolong life of mice-bearing tumour of Ehrlich's ascites carcinoma	Habs et al. (1984) , Tannin-Spitz et al. (2007) and Ayyad et al. (2012)
Cochlospermum Fraseri Planchon ssp. Heteronemum (F. Muell.) Poppendieck/ Bixaceae	Kalijpa	Fruit	Unripe fruit is broken and directly applied to localised skin infections.	ND	Barr et al. (1993)
Croton Arnhemicus Muell. Arg./ Euphorbiaceae	Ngarrik	Inner bark	Inner bark is boiled with water and the decoction is used to wash affected areas to relieve headache and joint swelling.	ND	Smith (1991)
Cymbopgon Obtectus S. T. Blake/Poaceae	Linytji	Leaves	Leaves are chopped and boiled with water and the liquid is taken to treat colds and coughs.	ND	Barr et al. (1993)
Diospyros Maritima Blume/ Ebenaceae	Glumunyu	Fruit	Fruit is placed on hot ashes and heated gently until soft and black, then mashed with water and applied on tinea-form lesions.	Cytotoxicity against hepatoma, nasopharynx, colon and cervical carcinomas.	Kuo et al. (1997) and Palombo and Semple (2001)
Eremophila Alternifolia R. Br./ Myoporaceae	Irmangka irmangka	Leaves	Leaves are sun-dried and then infused in boiling water to treat colds, fever, internal pain and severe illness.	ND	Goddard and Kalotas (2002)
Eucalyptus Tetrodonta F. Muell./Myrtaceae	Gadayka	Inner bark, leaves	Inner bark or leaves are brewed with water then used to treat sores and scabies.	ND	Locher and Currie (2010)
Eucalyptus Kino/Myrtaceae	Mijilypa	Gum	Kino is dissolved in water and then used to wash on cuts or sores.	ND	Locher and Currie, (2010)
Flueggea Virosa (Roxb. Ex Wild.) Voigt ssp. Melanyhesoides (F. Muell.) Webster/Euphorbiaceae	Kudjung	Seeds	Seeds are boiled with water and liquid is applied to pruritic skin conditions.	Inhibition of breast and lung carcinoma cell lines	(Isaacs (2002), Gan et al. (2006), Zhao et al. (2011)
Morinda Citrifolia L./Rubiaceae	Gununyi	Fruit	Soft ripe fruit is eaten raw as a remedy for coughs, colds and sore throat.	Prevention of lung and cervical cancers	Isaacs (2002) and Brown (2012)
Nymphaea Macrosperma Merr. & Perry/Nymphaeaceae	Kanyngurniny	Fruiting capsule	After peeling off the fleshy layer, the fruiting capsule is eaten raw to stop diarrhoea.	ND	Barr et al. (1993)
Scaevola Sericea Vahl/ Goodeniaceae	Yilyarra	Fruit, stem	Ripe fruit is squeezed and the juice dropped directly into eyes to relieve redness and soreness. Fruit can be mashed and applied to bites and stings. Stem is extracted in water and used as an anti-cancer agent.	ND	Lassak and McCarthy (1983)
Strychnos Lucida R. Br./ Loganiaceae	Yerrweyi	Fruit	Fruit is mashed and brewed with water. Liquid is used to wash localised skin infections.	ND	Isaacs (2002)
Syzygium Suborbiculare (Benth.) Hartley & Perry/ Myrtaceae	Narrani	Fruit	Fruit is boiled and mashed into liquid, which is then taken to relieve bronchial congestion and colds. Fruit and seed are chewed to relieve the toothache.	ND	Lim (2012)

ND: No data available.

Table 6
Phytochemicals and antioxidant capacity of selected Australian native fruits (Konczak et al., 2009).

Australian native fruits	Total phenolic compounds*	FRAP antioxidant power**	Major phenolic compounds identified	Reported anti-cancer effect *in vitro*	References
Kakadu plum (*Terminalia ferdinandiana* Exell)	158.57	4032.50	Quercetin, hesperitin glucoside, Kaempferol, luteolin glycoside	Activity against human promyelocytic leukaemia; Anti-proliferative & pro-apoptotic activity against colon cancer cells	Tan et al. (2011)
Quandong (*Santalum acuminatum* (R.Br.) A.DC).	90.10	454.90	Cyanidin-3-glucoside, pelargonidin-3-glucoside, quercetin, rutinoside, kaempferol	Anti-proliferative & pro-apoptotic activity against colorectal and gastric adenocarcinoma cells	Konczak et al. (2012)
Davidson's plum (*Davidsonia pruriens* F.Meull.)	50.25	599.80	Delphinidin sambubioside, cyanidin sambubioside, petunidin sambubioside, peonidin sambubioside	Anti-proliferative activity against pancreatic cancer cells	Chuen et al., unpublished
Illawarra plum (*Podocarpus elatus* Endl.)	68.00	864.20	Cyanidin-3-glucoside, pelargonidin	Anti-proliferative & pro-apoptotic activity against colon cancer cells; Inhibits telomerase, increases HDAC activity in colon cancer cells.	Tan et al. (2011) and Symonds et al. (2012)
Lemon aspen (*Acronychia acidula* F. Muell)	10.49	90.20	Kaempferol, luteolin hexoside, quercetin hexoside, rutin, chlorogenic acid, caffeic acid, coumaric acid, ferulic acid	ND	
Riberry (*Syzygium leuhmannii* (F. Muell.) L.A.S. Johnson)	23.62	376.90	Rutin, quercetin hexoside, cyanidin 3-galactoside, Cyanidin-3-glucoside, myricetin hexoside, kaempferol, luteolin rutinoside, quercetin rhamnoside, cyanidin 3,5 - diglucoside	ND	
Australian desert lime (*Citrus glauca* (Lindl.) Burkill)	9.36	177.8	Lutein	ND	

ND: No data on their specific anti-cancer effects.

* mg GA Eq/g DW.
** μmol Fe^{+2}/g DW.

3.9. Lignans

Lignans are present naturally in cereals, soybeans, cruciferous vegetables, and fruits such as apricots and strawberries. Epidemiological studies have reported a potential preventive link for lignans against various types of cancers, such as colorectal (Zamora-Ros et al., 2012), breast (Zaineddin et al., 2012) and gastric cancer (Lin et al., 2012), however there is limited published data reporting the link between lignans and pancreatic cancer. A recent epidemiological study indicated that regular consumption of wholegrain cereals and derived products, which contain fibre, lignans and other bioactive components associated with a reduced risk of pancreatic cancer (Gil et al., 2011).

The lignin Honokiol, isolated from the *Magnolia officinalis* var. *officinalis,* demonstrated growth inhibitory effects, as well as augmenting apoptotic mechanisms and potentiated the cytotoxic effects of gemcitabine in pancreatic cancer cell lines (Arora et al., 2011). Arctigenin is a phenylpropanoid dibenzylbutyrolactone lignan isolated from the *Arctium lappa* L., which shows preferential cytotoxicity against pancreatic cancer cells in nutrient-deprived conditions (Awale et al., 2006). These findings are important as a hallmark of cancer cells is their inherent ability to tolerate extreme conditions such as that characterised by low nutrient and oxygen supply (Awale et al., 2006). Therefore, lignans also show preventive potential for against pancreatic carcinogenesis, with further studies required to validate this link.

4. Potential for the discovery of novel anti-cancer phytochemicals from Australian native fruits

Australia has a great advantage due to its unique botanical diversity, as many plants are only found within Australian shores (Tan et al., 2010). Furthermore, Aborigines have gained experience and knowledge over thousands of years on the cultivation of these Australian floras, and their medicinal use and health benefits (Tan et al., 2010). Numerous indigenous floras have been used as *traditiona*l medicine to treat various ailments such as cold, flu, fever, toothache, internal pain, asthma, and chronic internal illness (Table 5) (Barr et al., 1993), however in the context of cancer, few plants have been traditionally used.

Historically, Australian Aboriginals have used *Scaevola spinescens* R.Br. (Maroon bush) as a medicinal plant to treat cancers of varying types, in addition to various conditions including stomach pain, urinary and skin disorders (Ghisalberti, 2004; Cock and Kukkonen, 2011). The ethnopharmacological knowledge of the traditional uses of *S. spinescens* R.Br. has been handed down through the generations by word of mouth with minimal detail written down. As such, a deeper understanding of Aboriginal medicine is very difficult to ascertain, particularly as the Aboriginal society continues to merge into mainstream Australian society (Tan et al., 2010; Cock and Kukkonen, 2011). Recent investigations by Cock and Kukkonen (2011) have demonstrated that extracts of *S. spinescens* R.Br. contain high levels of flavonoids and terpenes; some of which are known for their anti-cancer potential. Indirect evidence via several reports by the public and medical professionals has attested to the anti-cancer activities of *S. spinescens* R.Br. extract (Ghisalberti, 2004). To date, very few Australian native plants have been investigated for either their preventive or therapeutic activity (Tables 5 and 6). Clearly, more rigorous investigations into the bioactivity of Australian native plants are warranted, particularly those with high polyphenolic and flavonoid levels.

Australian native fruits are often used in cooking, however they have also been known as the source of *indigenous* medicine as well. For example, the quandong (*Santalum acuminatum* (R. Br.) A.DC.) has been traditionally used to prepare sweet or savoury dishes, and its kernel has been used by Aborigines to relieve the pain of swelling, bruises, sprains and backache (Barr et al., 1993; Ahmed and Johnson, 2000). The kernel is ground into paste, then mixed with water or saliva and finally the liniment is rubbed into the affected region to relieve pain (Barr et al., 1993).

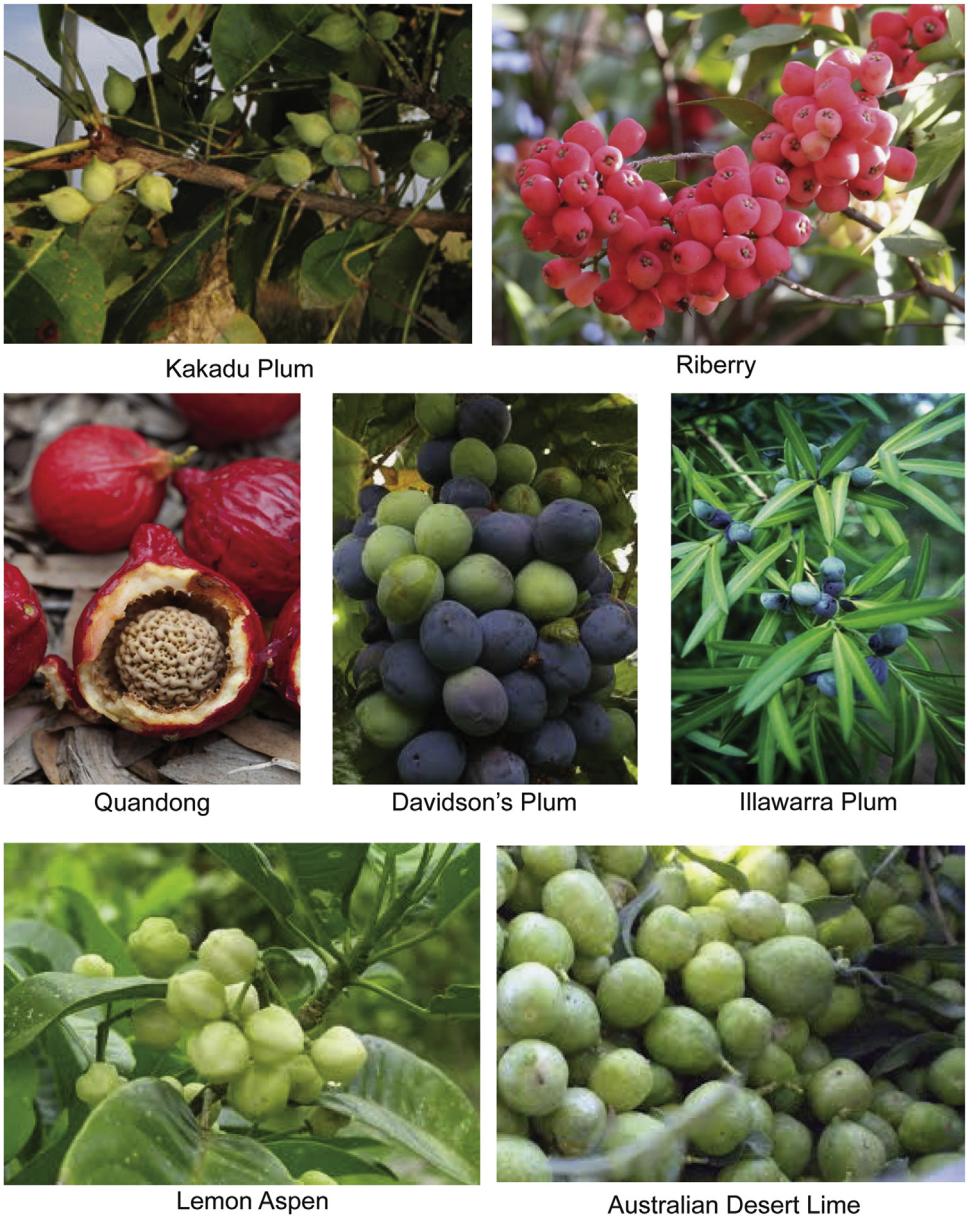

Fig. 9. Images of selected Australian native fruits.

The phytochemicals identified in Australian native fruits are diversified and their extracts show potential anti-cancer activity *in vitro* for certain types of cancers, particularly cancers of the gastrointestinal tract such as colorectal and gastric carcinomas (Table 6), indicating that Australian native fruits may also prove effective against pancreatic cancer. Several studies have been conducted to determine the phytochemical content of selected Australian fruits (Fig. 9), with initial findings indicating that Australian native fruits are rich in phenolic compounds and demonstrate potent antioxidant capacity (Table 6). Australian native fruits were found to contain a diversity of individual active components such as chlorogenic acid, quercetin, myricetin, rutin, and keampferol, earlier discussed for their anti-pancreatic cancer activity. Recent studies have revealed that extracts of selected Australian native fruits can supress the proliferation of several human cancer cells *in vitro*.

For example, the Kakadu plum has been demonstrated to contain high levels of total polyphenols, accounting for approximately 158 mg/g dried weight (DW) (Konczak et al., 2009), possessing levels comparable to that of green tea (Astill et al., 2001), but significantly higher than found in other native Australian fruits, such as lemon aspen, riberry and quandong (10, 24 and 33 mg/g DW, respectively) (Konczak et al., 2010). The Kakadu plum has been shown to possess high scavenging and antioxidant properties (Konczak and Roulle, 2011), while exhibiting strong pro-apoptotic activity against human promyelocytic leukaemia HL-60 cells. Kakadu plum extract induced apoptosis in HL-60 cells via DNA fragmentation and the activation of caspase-3, -7, and -9, as well as poly (ADP-ribose) polymerase (PARP) cleavage, suggesting the involvement of the mitochondrial mediated (intrinsic) apoptosis pathway (Tan et al., 2011). Further, Kakadu plum extract caused direct DNA damage in colon adenocarcinoma cells (HT-29), potentially during the period of cytokinesis, or via inhibition of cell cycle progression (Tan et al., 2011). In addition to polyphenolic compounds, the Kakadu plum has significantly high levels of ascorbic acid (Mohanty and Cock, 2012). Ascorbic acid is known to have cancer preventive potential due to its redox properties. Acting as a radical scavenger, it can reduce oxidative stress; thus

Table 7
Production and use of selected Australian native fruits (Ahmed and Johnson, 2000; CSIRO, 2006).

Common name	Food usage	Retain product	Annual production*
Kakadu plum	Fruit-type flavour in sweet and savoury products	Sauces, jams, preserves, in cosmetic products	2.5 tonnes
Quandong	Fruit-type flavour in sweet and savoury products	Liqueur, jams, sauces, confectionary, dairy products and baked goods	25 tonnes
Davidson's plum	Fruit-type flavour in sweet and savoury products	Jams, dipping sauce, wine, colouring, flavouring in sauces and drinks	4–6 tonnes
Illawarra plum	Fruit-type flavour in sweet and savoury products	Jams and conserves	2–4 tonnes
Lemon aspen	Citrus-type flavour in sweet and savoury products	Simmer sauces, chutneys and relishes, aspen flavoured mineral water	6–12 tonnes
Riberry	Fruit-type flavour in sweet and savoury products	Jams, conserves, chutneys and relishes	3–5 tonnes
Australian desert lime	Citrus flavour in sweet and savoury products	Jams and conserves, dipping sauces, and simmer sauces	10–15 tonnes

* Volume of fruits for trade recorded in 2001.

can be protective during the initiation and promotional stages of carcinogenesis (van Poppel and van den Berg, 1997). Furthermore, ascorbic acid has been reported to improve the efficacy of several chemotherapeutic agents such as procarbazin, asparaginase, vinblastine and gemcitabine (Verrax and Buc Calderon, 2008). Recently, Espey et al. (2011) demonstrated that combining pharmacological levels of ascorbic acid with gemcitabine results in a synergistic cytotoxic response in wide panel of pancreatic tumour cell lines, including gemcitabine resistant cells. Further, they showed that the gemcitabine-ascorbic acid combination treatment had an improved effect on the inhibition of growth of pancreatic tumour xenografts, when compared to gemcitabine alone suggesting that ascorbic acid has the potential to be used as an adjuvant to other chemotherapeutic strategies, particularly as it is safe, with few side effects (Cullen et al., 2011; Espey et al., 2011).

In addition, extract from the Illawarra plum fruit was found to exhibit greater anti-proliferative and pro-apoptotic activity in colon cancer cell lines than in normal cells (Tan et al., 2011). This inhibition of proliferation has been correlated with the high anthocyanin levels of the fruit, decreasing the number of cells in the G0/G1 phase while increasing the number of cells in S-phase, indicative of cell cycle arrest. This S-phase accumulation suggests a block in transition from S to G2, thereby causing an overall delay in the cell cycle and a decrease in cell proliferation (Lazze et al., 2004; Kundu and Surh, 2008; Gonzalez-Sarrias et al., 2012; Symonds et al., 2013). The Illawarra plum extract was also found to inhibit telomerase, increase histone deacetylase activity and decrease proliferation of colon cancer cells (Table 6). The observed decrease in hTERT expression and in telomere length following treatment with Illawarra plum extract would result in telomere shortening, repressed proliferation and an altered cell cycle, ultimately leading to apoptosis (Boklan et al., 2002; Symonds et al., 2013).

Studies on bioactive components in the quandong fruit are limited, with preliminary studies reporting that the fruit contained kaempferol, cyanidin-3-glucoside, rutin, vitamin E and malic acid (Konczak et al., 2010; Konczak and Roulle, 2011). Of note, kaempferol has been demonstrated to be anti-proliferative and pro-apoptotic in pancreatic cancer cells, as well as having a synergistic relationship with the chemotherapeutic agent 5-fluorouracil, with less cytotoxicity to normal cells (Zhang et al., 2008). Cyanidin-3-glucoside, has also been shown to have to an anti-tumour effect against cancers of the breast, lung, ovary and pancreas (Zhang et al., 2005; Chen et al., 2006; Luo et al., 2011), while also demonstrating inhibition of cell invasion and metastasis of gastric cancer cells via the reduction of matrix metalloproteinase-2 (MMP-2) levels (Sun et al., 2013).

Extracts of the Davidson's plum, rabbit eye blueberry, and southern highbush blueberry have been found to exhibit anti-proliferative effects against colorectal adenocarcinoma and gastric adenocarcinoma cells without a damaging effect on normal cells (Konczak et al., 2012), and we have recently demonstrated that a crude ethanol extract of Davidson's plum can reduce the viability

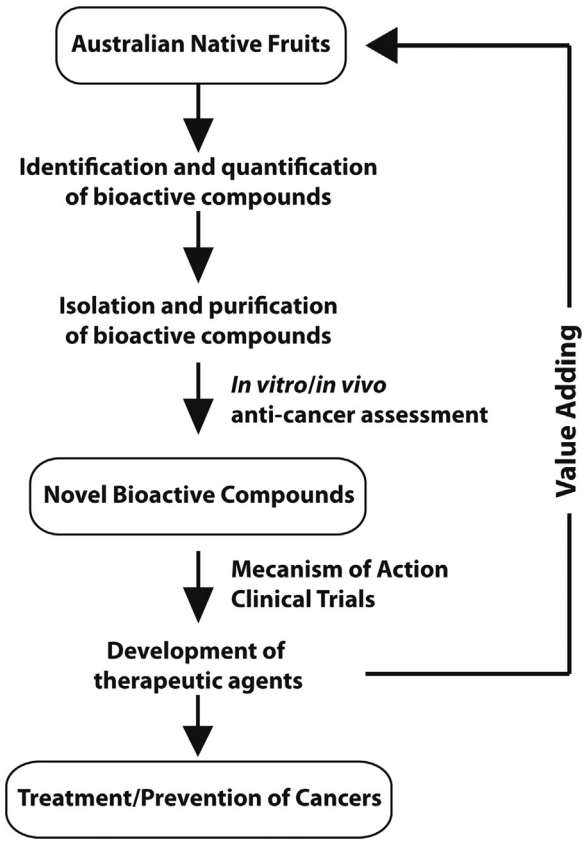

Fig. 10. A proposed trend for future studies on Australian native fruits.

of pancreatic cancer cells at a concentration between 100 and 200 μg/mL. We are currently isolating and identifying the active components of this crude extract for further anti-cancer investigations (*unpublished*).

The lemon aspen, riberry and the Australian desert lime have had little assessment thus far into their bioactive compound composition. The lemon aspen is reported to have a lower content of total phenolic compounds compared to the Davidson's and Kakadu plum, however demonstrated comparable antioxidant activity Konczak et al., 2009). The riberry contains lower levels of total phenolic compounds than other Australian native fruits such as the Davidson's plum, Illawarra plum and the Kakadu plum (Netzel et al., 2007). However, the riberry possesses a high total antioxidant activity (Konczak et al., 2009). Several bioactive components have been identified from the riberry fruit including cyanidin 3-galactoside, cyanidin 3-glucoside, rutin, and quercetin (Konczak et al., 2010), and as described above, these bioactive components have demonstrated anti-cancer activity. For example,

cyanidin 3-galactoside in combination with the bilberry extract mirtoselect, was found to show potential for the prevention of colorectal cancer (Cooke et al., 2006), while rutin has been shown to inhibit the proliferation of murine leukaemia WEHI-3 cells and promotes the immune response *in vivo* (Lin et al., 2009). The Australian desert lime has very high levels of vitamin C (ascorbic acid) (Konczak et al., 2009), which as described for the Kakadu plum, has potential anti-cancer activity due to its redox properties.

The fledging native foods industry is worth an estimated $14 million annually and is rapidly expanding (Ahmed and Johnson, 2000; CSIRO, 2006; RIRDC, 2008). Several tonnes of individual native fruits are being harvested annually for trading from both cultivation and through wild harvest (Table 7). Thus, there is an abundant source of native fruits produced from Australia annually.

With great potential for the discovery of the key phytochemicals from Australian native fruits as anti-cancer agents, including for pancreatic cancer, a trend for future studies on Australian native fruits is proposed in Fig. 10. We recommend to screen and identify the key phytochemicals from Australian native fruits and then using the safe and economical methods to isolate these bioactive compounds for testing their anti-cancer properties *in vitro* and *in vivo*. Further pre-clinical testing for the most effective compounds is also recommended for development of therapeutic agents for the treatment and prevention of cancers, including pancreatic cancer.

5. Conclusions and future considerations

Therapeutic agents, derived directly or indirectly (as semi-synthetic derivatives) from plant compounds, have played an important role in the treatment of cancers; however, only a small portion of the plant world has been examined for their phytochemical properties. Existing evidence has revealed that polyphenols have chemopreventive (both preventive and treatment) effects on pancreatic cancer, which is the most devastating cancer and is largely resistant to conventional therapeutic strategies. Preliminary studies on seven Australian native fruits have revealed that these native fruits show promise for the prevention and/or treatment of certain cancers, including pancreatic cancer, however to date, studies on these Australian native plants are limited, and most often limited to *in vitro* studies. Issues such as bioavailability *in vivo* must be considered and promptly assessed before translating the apparent effectiveness of extracts *in vitro* into *in vivo* clinical use. Nevertheless, most classes of polyphenols are sufficiently absorbed to exert a biological effect, and polyphenols have been demonstrated to cross the intestinal barrier and reach sufficient concentrations in the blood (Williamson and Manach, 2005), highlighting the great potential that these compounds possess.

Future studies are therefore recommended to: (1) screen the bioactive components from Australian native plants, especially plants which have been used as *traditional* remedies by the Aboriginal people to identify plants with high levels of valuable bioactive components; (2) develop safe, economical and effective methods to extract and isolate the valuable bioactive components from these plants; and (3) to investigate the link between these native plant extracts with various types of cancers, including pancreatic cancer. Therefore, more value can be added for the expansion of the Australian native plant industry, and importantly, novel anti-cancer agents can be identified from these Australian native fruits.

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