REVIEW

Dietary factors and pancreatic cancer: The role of food bioactive compounds

Jodee Johnson[1] *and Elvira Gonzalez de Mejia*[1,2]

[1] Division of Nutritional Sciences, University of Illinois at Urbana-Champaign, Urbana, IL, USA
[2] Department of Food Science and Human Nutrition, University of Illinois at Urbana-Champaign, Urbana, IL, USA

Pancreatic cancer is the fourth leading cause of cancer mortality among both men and women in the United States with a 5-year survival rate of only 4%. Several dietary factors may influence the risk of developing pancreatic cancer and its recurrence. Some of these factors may offer innovative therapies for prevention of this disease. The goal of this review is to provide an overview of pancreatic cancer, as well as current knowledge on the epidemiological, *in vitro*, *in vivo*, and clinical studies conducted about this disease using various dietary agents. The main focus is on food-based approaches for preventing this disease particularly, citrus fruits, and foods containing flavonoids, curcumin, folate and vitamin D.

Received: September 1, 2010
Revised: October 22, 2010
Accepted: October 26, 2010

Keywords:
Flavonoids / Food-based dietary agents / Pancreatic cancer

1 Introduction

Pancreatic cancer is the fourth leading cause of cancer death among both men and women in the United States [1]. This disease is so aggressive that it kills more than half of all its victims within 6 months of diagnosis, with the remaining patients having only a 5-year survival rate of 4%. Although no one knows the exact causes of pancreatic cancer, research shows that people with certain risk factors are more likely to develop this disease. The main risk factors of pancreatic cancer include age, smoking, type 2 diabetes, family history, race, obesity, poor physical activity, and chronic pancreatitis [2] (www.cancer.gov). Age is the most significant unmodifiable risk factor, whereas smoking is the most predominant modifiable risk factor [3] and changes in the diet may also play a role. Pancreatic cancer is often known as the silent killer because symptoms, when they occur at all, are typically vague and nonlocalizing. Some of these symptoms include jaundice, pain in the upper abdomen, weakness, loss of appetite, nausea, vomiting, and weight loss [2]. By the time most symptoms are noticeable, the cancer has already spread to other organs and surgical intervention is no longer a viable option [4]. It is because of such a poor outlook for patients diagnosed with pancreatic cancer that there is a need to expand our knowledge on different approaches that can be used to prevent and/or treat this disease. The goal of this review was to provide an overview of pancreatic cancer, as well as an analysis of current knowledge on food-based approaches for preventing pancreatic cancer, particularly the role of bioactive compounds in citrus fruits, flavonoids, curcumin, folate, and vitamin D.

Correspondence: Dr. Elvira Gonzalez de Mejia, Division of Nutritional Sciences, University of Illinois at Urbana-Champaign, 228 Edward R. Madigan Laboratory, MC-051, 1201 W. Gregory Drive, Urbana, IL 61801, USA
E-mail: edemejia@illinois.edu
Fax: +1-217-265-0925

Abbreviations: CI, confidence interval; **EGCG,** epigallocatechin 3-gallate; **K-ras,** Kirsten Rat Sarcoma virus; **NFκB,** nuclear factor κB; **PanIN,** pancreatic intraepithelial neoplasias; **STAT3,** signal transducer and activator of transcription 3; **WT1,** Wilms' tumor gene 1

2 Physiology of the pancreas

The pancreas is a glandular organ located deep within the abdomen. This 6-in organ consists of three main parts: the head, the body, and the tail, with the head being the widest part. The pancreas is composed of two glands that have two completely different functions. The endocrine gland, which comprises only 1–2% of the pancreas' mass, is made up of millions of cell clusters called islets of Langerhans. Its function is to produce and secrete into the blood stream hormones such as insulin, glucagon, somatostatin,

pancreatic polypeptide, and ghrelin. The exocrine gland, which comprises 90–95% of the pancreas' mass, is made up of cell clusters called acini that surround the islets of Langerhans. Its function is to synthesize and secrete digestive enzymes including trypsin, chymotrypsin, lipase, and amylase into the duodenum that help breakdown proteins, lipids, and carbohydrates [5].

3 Pancreatic cancer

3.1 The prevalence of pancreatic cancer

There are two types of pancreatic tumors: exocrine ductal epithelial adenocarcinoma and endocrine cancer, also called islet cell cancer. The more common of the two tumors is exocrine pancreatic cancer and about 95% of these tumors are pancreatic adenocarcinomas [6] (http://www.cancer.org). Of the people diagnosed with this disease, more than 90% are over the age of 55, with the average age of diagnosis being 72 years [6].

3.2 Pancreatic intraepithelial neoplasias and the development of pancreatic cancer

Pancreatic adenocarcinomas are believed to arise from noninvasive precursor lesions in the pancreatic ducts that undergo histological and genetic mutations toward invasive cancer. These histologically well-defined precursor lesions are termed pancreatic intraepithelial neoplasias (PanINs) [7, 8]. Figure 1 shows the three PanIN grades that normal ductal epithelium undergo before they become invasive adenocarcinoma. In PanIN-1A, the epithelial lesions are flat and composed of tall columnar cells with basally located nuclei and abundant mucin [8]. In PanIN-1B, the epithelial lesions are papillary, but otherwise identical to PanIN-1A. In these two early subcategories, mutations lead to the overexpression/amplification/activation of EGFR, Kirsten Rat Sarcoma virus (K-ras), Shh, Notch, and Wnt, and to the deletion or loss of function of p21, PTEN, Telomere, and attrition [7]. In PanIN-2, the epithelial lesions are papillary and have some nuclear abnormalities (loss of polarity, nuclear crowding, enlarged nuclei, pseudo-stratification, and hyperchromatism) [8]. In this intermediate grade, mutations lead to the overexpression/amplification/activation of Hes-1, cyclin D1, and ErbB2, and the loss of function of p16 [7]. In PanIN-3 (or carcinoma *in situ*), the epithelial lesions show the budding off of clusters of cells (cribriforming) into the lumen as well as luminal necrosis [8]. Mutations in PanIN-3 lead to overexpression/amplification/activation of c-Met, Ki-67, Topo IIα, mesothelin, and telomerase; and the deletion or loss of function of p53, BRCA2, Smad4, and TGF-βR [8].

3.3 K-ras signaling pathway in pancreatic cancer

One of the most frequently activated oncogenes in all human cancers is K-ras, with over 25% of cancers having a mutation in this gene. In pancreatic cancer, constitutively active K-ras is found in over 95% of tumors, making it a molecular signature of this disease [9]. K-ras, a member of the small GTPase superfamily, is 21 kDa membrane-bound protein. This protein is used to transmit signals from the extracellular to the intracellular environment and when it is in its active form, it mediates several cellular activities including proliferation, survival, migration, and metabolism [7, 10]. Normally, the K-ras activation pathway is regulated by GTPase activating proteins, but single-point mutations on K-ras codons 12, 13, or 61 render this protein resistant to GTPase activating proteins inactivation and therefore constitutively active [7]. K-ras is believed to be an initiator of pancreatic cancer due to the research conducted using

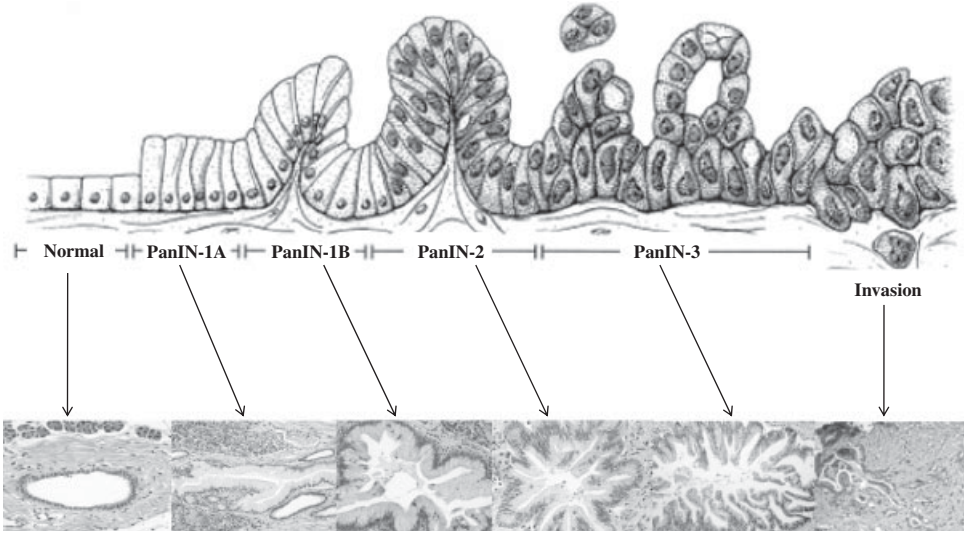

Figure 1. A schematic diagram and histopathological images that show the progression of normal pancreatic ducts into invasive pancreatic adenocarcinomas (adapted from [114], histopathological images from [8, 109, 115]).

multiple mouse models that show that mutations to this protein cause the formation of lesions that closely resemble human PanINs. Continuous production of K-ras has also been shown to be necessary in order to maintain tumor progression. However, the exact mechanism of how K-ras contributes to these factors of cancer is still unknown. What is known is that K-ras propagates at least part of its signal through three Ras pathways. The first pathway is the cell survival promoting pathway of phosphoinositide-3-kinase. The second is the RAF-MEK-ERK pathway and it plays an important role in cell proliferation. The third pathway is the Ral guanine nucleotide exchange factor pathway responsible for activating Ral guanine nucleotide dissociation stimulator (RalGDS), which in turn activates the G proteins, RalA, and RalB, which are critical for K-ras-induced transformation and tumorigenesis of human cells [7]. As K-ras plays such a key role in pancreatic cancer, there has been considerable interest in discovering compounds that can inhibit it and the pathways they affect. Figure 2 shows how some of the dietary factors discussed in this review affect K-ras and these three pathways.

3.4 Common pancreatic cancer-risk factors

There are several common risk factors that can contribute to the development of pancreatic cancer. They can be divided into two categories: unmodifiable and modifiable. Unmodifiable risk factors include heredity, age, sex, and race. Modifiable risk factors include smoking, obesity, and physical inactivity, type 2 diabetes, high fat diet, and excessive alcohol consumption [6].

3.5 Food-based approaches for treating pancreatic cancer

Every year, about $881 million is spent on pancreatic cancer treatment in the United States [11]. The main treatment options for patients with pancreatic cancer are surgery, chemotherapy, radiation, and targeted therapy. The treatment option that is best for the patient depends on the location of the tumor, whether or not the disease has spread, and the patient's age and general health [2].

There are two major diet-related prevention strategies involved in cancer research: cancer chemoprevention and dietary cancer prevention [12]. Cancer chemoprevention is defined as the use of natural, synthetic, or biologic chemical agents for pharmacologic intervention to prevent, inhibit, or reverse carcinogenesis [13]. Dietary cancer prevention, on the other hand, involves the modification of food consumption patterns that are often accompanied by lifestyle changes in order to decrease the risk [12, 14]. The use of food-based approaches for the prevention of pancreatic cancer has been explored in recent years based on the epidemiological evidence that shows an inverse association between consumption of fruits and vegetables and the risk of developing pancreatic cancer [15–17]. Figure 2 shows the structures of some of these compounds of interest.

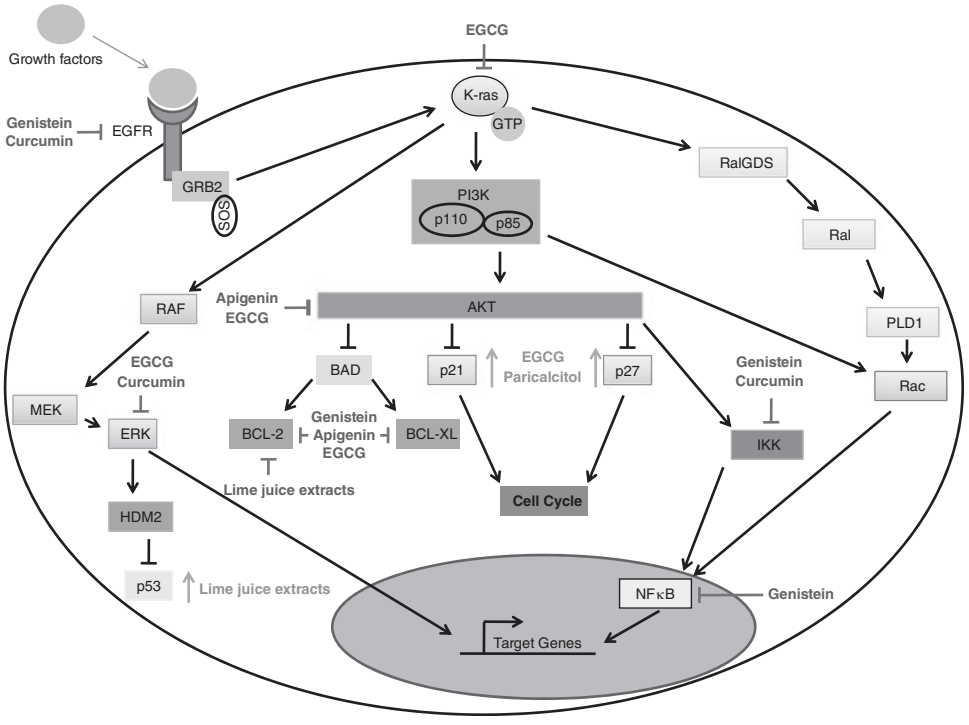

Figure 2. Modulation of K-ras and the signaling pathways it affects in pancreatic cancer cells by citrus fruit extracts, apigenin, EGCG, genistein, curcumin, maxacalcitol, and paricalcitol.

4 Pancreatic cancer and whole foods

4.1 Citrus fruits

Citrus fruits are one of the most important and largest fruit crops produced worldwide, with approximately 100 million metric tons produced annually [18]. This type of fruit is most commonly consumed as fresh produce and juice. It is known for its diverse and high phytonutrient content that contributes to its health benefits [19]. Flavonoids, one of the major classes of compounds in citrus, have been shown to have antioxidant, antiproliferative, antitumor, anti-inflammatory, and pro-apoptotic activities [20]. The most abundant flavonoids found in citrus are hesperidin, narirutin, neohesperidin, eriocitrin, neoeriocitrin, rutin, diosmin, neoponcirin, and nobiletin [19]. Carotenoids are also found in the abundance in citrus fruits, with over 115 of them that have been identified [21]. Numerous studies have demonstrated that high carotenoid intake may decrease the risk of cardiovascular disease, age-related macular degeneration, and cancer [22]. Among the carotenoids, β-carotene, lutein, zeaxanthin, β-cryptoxanthin, and lycopene are found to be the most in citrus fruits [19]. Citrus limonoids, a class of compounds that are responsible for the delayed bitterness in citrus juices, have been found to have several beneficial properties as well including, antioxidant, hypocholesterolemic, antiviral, insecticidal, and anticancer activities [23]. Limonin, nomilin, and obacunone are the major limonoids present in citrus [24].

Several case–control and cohort epidemiological studies have examined the effects of citrus fruits on the risk of developing pancreatic cancer [15–17, 25–32]. The majority of these studies show an inverse association between the consumption of citrus fruit and the risk of developing this disease. However, the existing data have inconsistencies and diversity in the study designs limit the ability to fully interpret the published observations. Relevant details about the studies are summarized in Tables 1 and 2. Five of the studies took place in the United States [17, 25–28], whereas the rest were conducted in Italy [15], Sweden [16], The Netherlands [29], Finland [30], China [31], and Japan [32]. All of the studies adjusted for age and cigarette smoking, except for that in [17] which did not. In all eleven of the studies, the results showed that the higher the consumption of citrus fruit the lower the risk of developing pancreatic cancer.

More recent studies have shown that citrus bioactive compounds have the ability to inhibit multiple stages of breast [33], colon [34], prostate [35], lung [36], and pancreatic cancers [37, 38]. In an *in vitro* investigation conducted by Patil *et al.* [37], the effects of freeze-dried lime (*Citrus aurantifolia* Swingle) juice extracted with chloroform, acetone, methanol, or methanol/water (8:2) on pancreatic cancer cells were tested. The results showed that all four lime juice extracts inhibited the growth of cancer cells in a dose-dependent manner, with the methanol extract having the highest activity. The protein levels of p53, Bax, Bcl-2, and caspase-3 demonstrated that the lime juice extracts favored the induction of apoptosis in the cancer cells. It was also determined by high-performance liquid chromatography that the bioactive components in the lime juice were the flavonoids: rutin, neohesperidin, hesperidin, and hesperetin; and the limonoids: limonexic acid, isolimonexic acid, and limonin. In another study conducted by the same research group [38], they found that limonoids (limonin glucoside, limonexic acid, isolimonexic acid, and limonin) extracted from the seeds of the same type of lime also inhibited pancreatic cancer cells through apoptosis.

5 Pancreatic cancer and bioactive foods components

5.1 Flavonoids

Flavonoids are the largest class of polyphenols with over 5000 of them described. They are water-soluble secondary metabolites that possess a common C6-C3-C6 structure and provide much of the flavor and color to fruits and vegetables. There are six major subclasses of flavonoids: flavones, flavonols, flavanones, flavanols, anthocyanidins, and isoflavones [39]. In humans, flavonoids have a wide range of bioactivities including anticancer, anti-inflammatory, and antihypertensive properties [40]. Table 3 summarizes the *in vitro* and *in vivo* studies that have been conducted on compounds in each of the subclasses of flavonoids and pancreatic cancer.

One class of flavonoids is the flavones and these include apigenin, luteolin, tangeretin, and nobiletin, among others. Apigenin, an isoconformer of the isoflavone genistein, has been shown to possess antioxidant properties as well as anti-inflammatory and anticarcinogenic effects [41]. In pancreatic cancer, apigenin has been shown to have an antiproliferative effect on cell growth by downregulating the expression of geminin protein and glucose uptake through inhibition of the GLUT-1 transporter [42, 43]. It has also been reported to induce cell-cycle arrest at G2/M phase through the downregulation of cyclin A and cyclin B, phosphorylated forms of cdc2, and cdc25 [44]. In addition, apigenin has been shown to enhance the inhibitory and apoptotic effects of the chemotherapeutic drug gemcitabine both *in vitro* and *in vivo* by downregulating nuclear factor κB (NFκB) activity with the suppression of Akt [45, 46].

The second class of flavonoids is the flavonols, which are commonly present in many fruits vegetables, and some examples are quercetin, myricetin, kaempferol, and rutin [47]. One flavonol of great interest due to its anticancer properties is quercetin. Quercetin has been shown to be a free-radical scavenging antioxidant, as well as having the ability to induce apoptosis and block different phases of the cell-cycle in a variety of cancer cell lines [48]. *In vitro* and *in vivo* quercetin has been shown to reduce apoptosis resistance in pancreatic cancer by downregulating Hsp70 protein [49]. In addition, it has been shown to inhibit the expression and function of P-glycoprotein in resistant to daunorubicin

Table 1. Summary of case–control citrus fruit and pancreatic cancer studies

Reference	Enrollment period	# of cases/# of controls	Age range	Gender	Factors controlled for in analysis of citrus fruit intake	Type of citrus fruit	Comparison of exposure level	OR (95% CI)[a)]
[15]	1991–2008	326/652	34–80	Italian male/female	Gender, age, cigarette smoking, alcohol consumption, body mass index, year of interview, education, self-reported history of diabetes, and total energy	Citrus fruits	0 servings/wk *versus* 10.5 servings/wk	OR: 0.92 (0.54–1.57)
[17]	1995–1999	526/1701	21–85	Male/female	Age, gender, and energy intake	Orange, grapefruit, orange juice, and grapefruit juice	<2 servings/day *versus* >4 servings/day	OR: 0.78 (0.58–1.0)
[25]	1980–1983	212/220	40–84	Caucasian male	Age, cigarette smoking, alcohol consumption, reported history of diabetes mellitus, educational level, and meat and vegetable consumption	Oranges, grapefruit, and orange juice	<5 times/month *versus* >20 times/month	OR: 0.6 (0.3–1.1)
[26]	1986–1989	436/2003	30–79	African American and Caucasian male/female	Age at diagnosis/interview, race, study area, calories from food, diabetes mellitus, cholecystectomy, body mass index, cigarette smoking, alcohol consumption, income (men), and marital status (women)	Grapefruit; oranges or tangerines	<1.5 servings/wk *versus* >4 servings/wk	OR: 0.9 in men, OR: 1.2 in women
[29]	1984–1988	164/480	35–79	Dutch male/female	Age, gender, response status, total smoking, and total energy	Citrus fruits	Q1 *versus* Q5 (by level of daily intake in grams)	OR:0.95
[31]	1990–1993	451/1552	30–74	Chinese male/female	Age, income, smoking, green tea drinking (females only), and response status	Oranges/tangerines	≤ 2 servings/month *versus* ≥ 4 servings/month	OR: 0.65 (0.42–0.99) in men, OR: 0.58 (0.34–0.99) in women

a) OR, odds ratio.

Table 2. Summary of cohort citrus fruit and pancreatic cancer studies

Reference	Enrollment period	# of cases/# of noncases	Age range	Gender	Factors controlled for in analysis of citrus fruit intake	Type of citrus fruit	Comparison of exposure level	HR/RR (95% CI)[a]
[16]	1998–2004	135/81 787	40–75	Swedish male/female	Age, gender, education, body mass index, physical activity, cigarette smoking status and pack years of smoking, history of diabetes, multivitamin supplement use, and intakes of total energy and alcohol	Oranges, grapefruits, orange juice, grapefruit juice, and other citrus fruits	<1 servings/wk *versus* ≥ 7 servings/wk	HR: 1.12 (0.68–1.83)
[27]	1993–1996	434/161 716	45–75	African American, Japanese American, Latino, Native Hawaiian and Caucasian male/female	Gender, time on study, race-ethnicity, age at cohort entry, smoking status, pack years of smoking, family history of pancreatic cancer, energy intake, intakes of red meat and processed meat, and body mass index	Citrus fruits	$<13.4\,g \cdot 1000\,kcal^{-1}\,day^{-1}$ *versus* $\geq 93.9\,g\ 1000\ kcal^{-1}\,day^{-1}$	RR: 1.08 (0.82–1.43)
[28]	1982	3751/ 1098 557	45–71 (male), 43–71 (female)	Male/female	Age, race, years of education, family history of pancreatic cancer in a first degree relative, history of gallstones, body mass index, cigarette smoking history, alcohol consumption, total red meat consumption, vegetable consumption, and history of diabetes	Citrus fruits and juices	Q1 *versus* Q4	RR: 1.0 (0.8–1.2) in men, RR: 0.9 (0.7–1.1) in women
[30]	1985–1988	163/26 948	50–69	Male smokers	Age, years of smoking, and energy intake by residue method (except coffee and tea)	Citrus fruits	<5.3 g/day *versus* >90.9 g/day	HR: 0.79 (0.47–1.31)
[32]	1988–1990	300/105 138	40–79	Japanese male/female	Age, area, and pack years of smoking	Citrus fruits	0–2/month *versus* almost every day	HR: 0.85 (0.47–1.51) in men, HR: 1.07 (0.57–1.98) in women

a) HR, hazard ratio; RR, relative risk.

Table 3. Summary of *in vitro* and *in vivo* anticarcinogenic activities of flavonoids against pancreatic cancer

Compound	Mechanism of antipancreatic cancer action (dose, exposure time, and route of administration)	Reference
Flavones	***In vitro* studies**	
Apigenin	Antiproliferative (100 μM for 24–72 h), inhibits DNA synthesis (6.5–100 μM for 24 h) and induces cell-cycle arrest at G2/M phase through downregulation of cyclin A and B, phosphorylated cdc2, cdc25A and cdc25C in AsPC-1, MIA PaCa-2, CD18, and S2-013 cells (100 μM for 24 h)	[44]
	Inhibits proliferation (5–100 μM for 72 h) and induces apoptosis alone (5–50 μM for 48 h), as well as enhances the inhibitory and apoptotic effects of gemcitabine through the downregulation of NFκB activity with suppression of Akt activation and the reduction of Bcl-2 expression in MIA PaCa-2 and AsPC-1 cells (25 or 50 μM apigenin with 0–10 μM gemcitabine for 72 h)	[45]
	Decreases glucose uptake through downregulation of GLUT-1 in CD18 and S2-013 cells and interferes with the PI3K/Akt pathway (6.5–100 μM for 24 h to assess glucose uptake, 6.5–50 μM for 3-24 h to assess GLUT-1 gene expression)	[43]
	Increases the anticancer effects of gemcitabine on AsPC-1 and CD18 cells through induction of both S and G2/M phase cell-cycle arrest and increased apoptosis; downregulates pAkt expression induced by gemcitabine (25 μM apigenin for 6 h followed by the addition of 10 μM gemcitabine for 24 h); inhibits proliferation of gemcitabine-resistant cell line AsPC-1 (25–100 μM apigenin 24 h)	[46]
	Downregulates geminin and Cdc6 at both mRNA and protein levels in the cell lines CD18 and S2-013 (25–50 μM for 24 h and 50 μM for 6–24 h); inhibits geminin promoter activity (50 μM for 6 h)	[42]
	***In vivo* studies**	
Apigenin	Potentiates the inhibitory effects of gemcitabine on tumor growth; abrogates gemcitabine-induced activation of Akt-NFκB pathway (50 mg/kg apigenin five times/wk with 125 mg/kg gemcitabine two times/wk for 3 wk, intraperitoneal injections, 4-wk-old male BALB/c nude mice)	[45]
Flavonols	***In vitro* studies**	
Kaempferol	Inhibits cell growth (17.5–70 μM for 1-4 days) and induces apoptosis (17.5–70 μM for 3 days) in MIA PaCa-2 and PANC-1 cells; provides an additive effect on the inhibition of MIA PaCa-2 cell proliferation when combined with 5-fluorouracil (35 μM kaempferol with 7.7 μM 5-fluorouracil for 1-5 days)	[51]
Quercetin	Antiproliferative effects on BxPC-3, MIA PaCa-2 and PANC-1 cells; induces apoptosis by upregulating caspase-3 and caspase-9 and downregulating Hsp70 (IC_{50} = 50 μM at 24 h for MIA PaCa-2 and PANC-1 cell lines)	[49]
	Inhibits expression and function of P-glycoprotein in resistant to daunorubicin pancreatic cancer cell line EPP85-181RDB, as well as decreases the expression of ABCB1 (IC_{50} = 12 μM at 72 h)	[50]
Rutin	Antiproliferative effects on PANC-28 cells (IC_{50} = 187.20, 49.47, and 41.73 μg/mL at 24, 48, and 72 h, respectively)	[37]
	***In vivo* studies**	
Quercetin	Decreases tumor growth and Hsp70 (50 mg/kg for 18 days subcutaneous injection, 6-wk-old male nude mice)	[49]
Flavanones	***In vitro* studies**	
Hesperidin	Antiproliferative effects on PANC-28 cells (IC_{50} = 147.28, 26.29, and 16.68 μg/mL at 24, 48, and 72 h, respectively)	[37]
Flavanols	***In vitro* studies**	
Catechin	Reduces cellular proliferation (100 μM, 24–72 h); induces early apoptosis in MIAPACA and PANC-1 cells (100 μM for 18 h)	[55]
EGCG	Induces antiproliferative effects on MIA PaCa-2 cells through apoptosis by caspase-3-mediated PARP cleavage (0.2 mM for 24 h); arrests cancer cells at an early phase of the cell-cycle; causes mitochondrial membrane depolarization (0.2 mM for 14 h) and BAX oligomerization (0.1 mM) which facilitate the release of cytochrome *c* into the cytosol; facilitates the activation of ROS-mediated JNK (0.1 mM for 24 h)	[111]
	Inhibits growth in PANC-1, MIA PaCa-2, AsPC-1, and Hs 766T cell lines (0–80 μM for 24 h); induces apoptosis through ROS-mediated caspase-3 and -9 activation (10–80 μM for 0–360 min for ROS activity; 0–80 μM for 12 h for caspase activity), increases expression of Bax, Bak, Bcl-X_S, and PUMA, and inhibits expression of Bcl-2 and Bcl-X_L (0–40 μM for 48 h); regulates MAP kinase pathways through the inhibition of Ras, Raf-1, ERK 1/2 and p90 RSK activities and the induction of MEKK1, JNK 1/2, p38 and cJUN activities (40 μM for 0–48 h); induces cell-cycle arrest at G1 phase through the upregulation of $p21^{/WAF1/CIP1}$ and $p27^{/KIP1}$ and the downregulation of cyclin D1, cdk4, and cdk6 (0–40 μM for 24 h for cell-cycle; 40 μM for 0–48 h for regulatory proteins)	[52]
	Mediates apoptosis in MIA PaCa-2 cells through the activation of caspase-8 and -9, the disappearance of Bid protein, the upregulation of death receptor-related genes and the downregulation of survivin (50 μg/mL for 8–24 h); provides synergistic effect when combined with TRAIL on apoptosis due to caspase-3 mediated PARP cleavage (50 μg/mL of EGCG and 5 ng/mL TRAIL for 16 h)	[112]
	Inhibits cell growth (IC_{50} < 50 μM at 48 h) in MIA PaCa-2 cells by binding directly to the C-terminal region of Hsp90 and preventing its association with the cochaperones p23 and Hsc 70 (60–200 μM for 0-24 h); decreases cellular levels of Hsp90 client proteins Her-2, Akt, Cdk4, Raf-1, and pERK (80 μM for 0–24 h or 60 μM/24 h for up to 72 h); induces apoptosis through the activation of caspase-3 (60 μM/24 h)	[54]

Table 3. Continued

Compound	Mechanism of antipancreatic cancer action (dose, exposure time, and route of administration)	Reference
Flavanols (cont.)	***In vivo* studies**	
EGCG	Decreases tumor growth in AsPC-1 xenografts through inhibition of cell proliferation shown by reduced Ki-67 and PCNA staining and induction of growth arrest caused by upregulating $p21^{/CIP1/WAF1}$ expression; induces apoptosis through caspase-3 activation; regulates MAP kinase pathways through the inhibition of ERK activity and the induction of JNK and p38 activities; inhibits angiogenesis by reducing the expression of vWF, VEGF and CD31; blocks metastasis by inhibiting the expression of matrix metalloproteinases MMP-2, -7, -9, and -12 (60–100 mg/kg, 5 days a wk for 6 wk, oral, 4–6 wk-old athymic nude mice)	[53]
Isoflavones	***In vitro* studies**	
Genistein	Inhibits cell growth (30 μM for 72–96 h), induces apoptosis (30 μM for 72–96 h or 50 μM for 72 h), and inhibits NFκB activity (30 or 50 μM for 2 h) in BxPC-3 cells; potentiates effects of cisplatin and docetaxel by inhibiting cell growth and inducing apoptosis (30 μM genistein for 24 h followed by 100 nM cisplatin or 1 nM docetaxel for 48 h); inhibits NFκB activity (30 μM of genistein for 24 h followed by 100 or 150 nM of cisplatin for 48 h)	[113]
	Enhances cell growth inhibition of gemcitabine on COLO 357 and L3.6pl cell lines (25 μM genistein for 24 h followed by 25 nM of gemcitabine for 72 h); abrogates gemcitabine-induced activation of NFκB DNA-binding activity (30 μM genistein for 48 h followed by 25 nM of gemcitabine for 6 or 24 h); sensitizes gemcitabine-treated cells to apoptosis by induction of caspase-3-mediated PARP cleavage and the downregulation of Bcl-2, Bcl-X_L, and p-Akt (30 μM genistein for 48 h followed by 25 nM or 100 nM gemcitabine for 24 h)	[58]
	Reduces NFκB activity in BxPC-3 cells thus downregulating Bcl-2 and Bcl-X_L (30 μM for 24 h); induces apoptosis (30 μM for 72 h); enhances the inhibitory effects of (−)-gossypol (20 μM genistein and 1.5 μM (−)-gossypol for 72 h)	[60]
	Inhibits cell growth of BxPC-3 cells (10–50 μM for 24–72 h); induces apoptosis through the downregulation of Notch-1 which leads to inhibition of IKK protein and therefore reduced NFκB activity (25 μM for 24–72 h)	[61]
	Downregulates Notch-1 activity thus leading to a reduction in Hes-1, Bcl-X_L and cyclin D1 (25 μM for 24–72 h); inhibits cell growth in BxPC-3 cells (15–50 μM for 72 h); induces apoptosis (25 μM for 24–72 h) and inhibits NFκB DNA-binding activity (10–50 μM for 48 h)	[62]
	Inhibits cell growth (0–50 μM for 24–72 h) and the activation of NFκB (25 and 50 μM for 72 h) in COLO 357 and L3.6pl cells; induces apoptosis through the downregulation of Bcl-2, Bcl-X_L, and p Akt, and the upregulation of caspase-3 (5–100 μM for 72 h); sensitizes COLO 357 and L3.6pl cells to cisplatin-induced growth inhibition (30 μM genistein for 24 h followed by 1 μM of cisplatin for 72 h); augments apoptosis by cisplatin (30 μM genistein for 24 h followed by coincubation with 1 and 2 μM of cisplatin for 72 h) through the upregulation of cleaved caspase-3 and cleaved PARP and the downregulation of Bcl-2 and Bcl-X_L; downregulates NFκB activation caused by cisplatin (30 μM genistein for 72 h followed by 2.5 μM cisplatin for 2.5 h)	[59]
	Potentiates the growth inhibition of erlotinib-treated cells (25 μM genistein and 2 μM erlotinib for 72 h); increases the apoptotic effect of erlotinib in BxPC-3 cells (25 μM genistein and 2 μM erlotinib for 72 h) through the downregulation of EGFR, pAkt, NFκB activation, and survivin; potentiates the growth inhibition and apoptotic effects of combined gemcitabine and erlotinib treatment in COLO 357 cells by downregulating EGFR, survivin, and Bcl-X_L (20 μM genistein, 1 μM erlotinib, and 10 nM gemcitabine for 72 h)	[57]
	Enhances growth inhibition and sensitizes the apoptotic effects of cisplatin on BxPC-3 cells (25 μM genistein for 24 h followed by 0.5 μM of cisplatin for 72 h); abrogates cisplatin-induced activation of NFκB activity thus downregulating Bcl-X_L and Bcl-2 (10–50 μM genistein for 24 h, followed by 0.5 μM of cisplatin for 72 h)	[56]
	Inhibits cell proliferation in BxPC-3, HPAC, MIA PaCa-2 and PANC-28 cell lines (10–100 μM for 72 h); induces apoptosis (25–100 μM for 72 h); downregulates expression of FoxM1 (25–100 μM for 72 h) thus leading to the inhibition of cdc25a, survivin, MMP-9, and VEGF (25–100 μM for 72 h); decreases the penetration of pancreatic cancer cells through the matrigel-coated membrane (50 μM)	[63]
	***In vivo* studies**	
Genistein	Reduces tumor weight when combined with gemcitabine treatment and inhibits gemcitabine-induced activation of NFκB activity (1 mg/day of genistein, orally, and 80 mg/kg body weight every other day of gemcitabine, intravenous injection, 13 days total, 4- to 6-wk-old ICR-SCID female nude mice)	[58]
	Decreases tumor weight when combined with cisplatin; abrogates cisplatin-mediated NFκB activation; increases apoptosis in cisplatin-treated tumors through the upregulation of PARP cleavage, and the downregulation of Bcl-X_L (9 mg/kg body weight of cisplatin as single intraperitoneal bolus injection and 1 mg/day of genistein for 10 days, orally, 4- to 6-wk-old ICR-SCID female mice)	[59]
	Reduces tumor weight when combined with cisplatin; abrogates NFκB activity induced by cisplatin (800 μg/kg genistein for 5 days orally and 9 mg/kg cisplatin given once as an intraperitoneal bolus injection, 4-wk-old ICR-SCID female mice)	[56]

PI3K, phosphoinositide-3-kinase, IKK, IκB kinase.

pancreatic cancer cell line EPP85-181RDB [50]. Another flavonol, kaempferol, has also been found to possess anticancer properties, such as the ability to inhibit DNA synthesis and growth in cancer cells. In pancreatic cancer cells, kaempferol has been shown to provide an additive inhibitory effect when combined with 5-fluorouracil [51].

The third class of flavonoids is flavanones, commonly represented in the diet by hesperidin, hesperetin, and naringenin. Hesperidin, along with the flavonol rutin have been recently discovered to have antiproliferative effects on pancreatic cancer cells [37]; however, more research needs to be conducted to determine their exact mechanisms of action.

Flavanols, the fourth class of flavonoids, have a 2-phenylchromanol skeleton. Examples of this class of compounds are catechin, epicatechin, epicatechin 3-gallate, epigallocatechin, and epigallocatechin 3-gallate (EGCG). EGCG, the major green tea catechin, has been found to act as an antioxidant, antiproliferative, antitumor, and antiangiogenic agent in several types of cancer. Specifically in pancreatic cancer, it has been reported to induce apoptosis, both *in vitro* and *in vivo*, through the activation of caspase-3, the upregulation of pro-apoptotic Bax, Bak, Bcl-X_S, and PUMA, and the downregulation of antiapoptotic Bcl-2 and Bcl-X_L [52–54]. Catechin, another green tea flavanol, has also been shown to have anticarcinogenic effects on pancreatic cancer by inducing early apoptosis [55].

The last class of flavonoids reported to have antipancreatic cancer effects is isoflavones. Isoflavones differ from the other classes of flavonoids due to the fact that they have the B-ring attached at the C3 position rather than at C2. Some naturally occurring isoflavones include genistein, daidzein, and genistin. Genistein, found in soybeans, has been shown to enhance the inhibitory and apoptotic effects of the chemotherapeutic drugs gemcitabine (*in vitro* and *in vivo*), erlotinib (*in vitro*), and cisplatin (*in vitro* and *in vivo*) by downregulating NFκB activity [56–59]. Most importantly, genistein has been shown to abrogate NFκB activity caused by gemcitabine and cisplatin [56, 58, 59]. *In vitro* studies on the use of genistein alone to treat pancreatic cancer have shown that it has the ability to inhibit cancer cell growth and induce apoptosis through the downregulation of FoxMI, NFκB, and Notch-1 activities [60–63]. In March 2010, a phase II clinical trial was completed on the use of genistein in combination with gemcitabine and erlotinib to treat patients with locally advanced or metastatic pancreatic cancer. The results of this study have not yet been published. As of July 2010, there is one phase II clinical trial recruiting that will look at the effect of genistein treatment on patients with resectable pancreatic cancer [64], (http://www.clinicaltrials.gov).

5.2 Curcumin

Curcumin is a fat-soluble polyphenolic compound that is the main and most active curcuminoid found in turmeric (*Curcuma longa* L.) [65]. This compound is commonly used as a spice in Asian countries as well as a natural food-coloring agent [66, 67]. Curcumin has been a bioactive compound of interest for many types of cancer including breast [68], prostate [69], oral [70], ovarian, endometrial [71], and others. The reason curcumin is so widely studied in a variety of cancers, as well as other diseases, is because of its many pharmacological properties including antioxidant, anti-inflammatory, antimicrobial, antitumor, antidepressant, and antiatherogenic activities [72, 73]. In pancreatic cancer studies, curcumin has been used as a bioactive agent in *in vitro*, *in vivo*, and phase I, II, and III clinical trials.

The anticancer effects of curcumin on pancreatic cancer *in vitro* have been widely researched and documented. Early studies on the use of curcumin on pancreatic cancer showed that it has the ability to suppress NFκB activity through the inhibition of IκB kinase and therefore decrease the expression of the NFκB-regulated gene products COX-2, prostaglandin E_2, and interleukin-8 [74]. Curcumin has been shown to inhibit ERK activity, as well as downregulate EGFR and Notch-1 signaling leading to increased apoptosis in pancreatic cancer [75, 76]. Curcumin has also been shown to augment the cytotoxic effect on pancreatic adenocarcinoma cell lines when used in combination with the chemotherapeutic drugs gemcitabine or celecoxib [77, 78]. A more recent study conducted by Glienke *et al.* [79] was aimed to determine the effect of curcumin on Wilms' tumor gene 1 (WT1), a gene frequently expressed in pancreatic cancer. The results showed that WT1 expression was able to be downregulated in a dose-dependent manner by curcumin. Another *in vitro* study conducted by the same research group [80] found that curcumin has the ability to inhibit signal transducer and activator of transcription 3 (STAT3) protein and induce apoptosis by the downregulation of the expression of the antiapoptotic gene Survivin/BIRC4 in pancreatic cancer cells. Sahu *et al.* [81] used the single dose of 2.5 μM of curcumin to determine the mechanism by which it causes G2/M phase cell-cycle arrest. The results showed that G2/M phase cell-cycle arrest was achieved by increased phosphorylation of cdc25C, Chk1, and ATM, as well as decreased DNA polymerase-β levels and expression of cyclin B1 and Cdk1. Finally, a recently published study showed that curcumin-encapsulated MePEG/PCL (40:60) diblock copolymeric micelles could have a promising future for the controlled delivery of curcumin as cancer therapy [72]. In this investigation, the authors found that the curcumin-encapsulated micelles had up to 2.95 times more uptake into the pancreatic cancer cells than the unmodified curcumin. The results from this study are of great importance because research has shown that curcumin, a naturally hydrophobic compound, has very poor bioavailability when administered alone either orally or intravenously [82].

Bar-Sela *et al.* [83] published a detailed review about the clinical trials that have been conducted or are currently ongoing that use curcumin as an anticancer agent. To summarize the completed trials, two research groups

published their results from their Phase II studies that used 8 g/day of curcumin as a treatment for patients with advanced pancreatic cancer. In the study conducted by Epelbaum *et al.* [84], they used a combination of curcumin and gemcitabine to treat 17 patients and the results showed that this combined treatment option is tolerable in patients but suggested that the oral dose of 8 g/day of curcumin should be reduced. In the study conducted by Dhillon *et al.* [85], they only used curcumin as the 1st line treatment for the 25 patients and the results showed that curcumin was able to downregulate the expression of NFκB, COX-2, and phosphorylated STAT3 in peripheral blood. As of July 2010, there are currently three ongoing clinical trials using curcumin as a treatment option for pancreatic cancer, two phase II, and one phase III [64]. The phase III clinical trial, being carried out at the Tev-Aviv Sourasky Medical Center in Israel, is the first one for the use of curcumin to treat pancreatic cancer. In this study, the researchers are using a combination of curcumin and the drugs gemcitabine and celecoxib to treat patients with advance or inoperable pancreatic cancer.

6 Pancreatic cancer and nutrients

6.1 Folate

Folate is a water-soluble B vitamin found in fortified cereal grains, leafy green vegetables, legumes, various seeds, and liver. There are two forms of folate, the naturally occurring form (folate, also used as the generalized term), and the synthetically produced form (folic acid). The bioavailability of folic acid is higher than folate because folic acid is nonconjugated and more stable than folate [86]. Folate plays a critical role in DNA synthesis, methylation and repair, and an imbalance in these three functions may contribute to carcinogenesis. In particular, a deficiency in folate has been implicated in increasing the risk of pancreatic cancer due to hypomethylation of DNA [86–88].

Several epidemiological studies have shown that a deficiency in folate is associated with an increased risk of pancreatic cancer [89–94]. Although most of these studies suggest that increased intake of folate may help reduce the risk of pancreatic cancer in both men and women, a recent prospective study conducted by Oaks *et al.* [89] suggests that only women benefit from higher folate intakes. In this study, they analyzed the pancreatic cancer risk in relation to folate intake by using a self-administered food-frequency questionnaire to collect dietary data from 1998 to 2005 and a mailed annual questionnaire to determine who developed the disease. The results from this study showed that women had a significantly decreased risk of pancreatic cancer when they consumed higher intakes of folate from foods containing naturally occurring folate or fortified with folic acid ($\geq$253.3 compared with $\leq$179.1 μg/d; hazard ratio = 0.47; 95% confidence interval (CI): 0.23–0.94). However, there was no significant association in men consuming higher levels of food folate ($\geq$229.6 compared with $\leq$158.0 μg/d; hazard ratio = 1.20; 95% CI: 0.70–2.04).

6.2 Vitamin D

Vitamin D is a fat-soluble vitamin found in very few natural dietary sources such as fatty fish and their oils, egg yolks, liver, and mushrooms. The main source of vitamin D comes from exposing the body to the ultraviolet rays from sunlight and this source accounts for over 90% of our required dietary intake [95]. There are two major pro-vitamins of vitamin D, vitamin D_2 (ergocalciferol), and vitamin D_3 (cholecalciferol). These pro-vitamins must undergo two hydroxylation steps, first in the liver and then in the kidney, before they can become the active form of vitamin D (1,25-dihydroxyvitamin D) [96].

Several epidemiological studies have reported that a sufficient vitamin D status is inversely associated with the risk of some cancers including colon, breast, prostate, and ovarian [97]. In two large prospective studies conducted by Skinner *et al.* [98], they hypothesized that higher vitamin D intake, either from food or supplements, would lead to a reduced risk of pancreatic cancer. The two cohort studies that provided the information for their analyses were the Nurses' Health Study, 75 427 women ages 38–65 years as of 1984, and the Health Professionals Follow-up Study, 46 771 men ages 40–75 years as of 1986. During 16 years of followup, they identified 365 incident cases of pancreatic cancer. The multivariate+multivitamin relative risks were adjusted for age (1-year intervals), time period (2-year intervals), total energy intake (kcal), cigarette smoking, history of diabetes, body mass index, height, region of residence (north, south), parity (among women), and the use of multivitamin supplements. The results from this study found that participants in the highest category of total vitamin D intake ($\geq$600 IU/d) had a pooled multivariate+multivitamin relative risk for pancreatic cancer of 0.59 (95% CI: 0.40–0.88) compared with the lowest category of total vitamin D intake ($<$150 IU/d). In another analyses conducted by Bao *et al.* [99] on data collected from the Nurses' Health Study (73 371 women) and the Health Professionals Follow-up Study (45 226 men), they assessed the relationship between predicted vitamin D status and the risk of pancreatic cancer. They identified 575 incident pancreatic cancer cases over 20 years of followup. In this study, they used plasma 25-hydroxyvitamin D as an indicator of vitamin D status. Briefly, they used a sample of 1095 men from the Health Professionals Followup Study who had available plasma 25-hydroxyvitamin D measurements and who were cancer free at the time of blood draw. They then calculated a 25-hydroxyvitamin D score using known predictors of vitamin D status for each individual and examined the predicted 25-hydroxyvitamin D levels in

relation to pancreatic cancer risk. Relative risks were adjusted for age, sex, race, height, cigarette smoking, and diabetes. The results from this study found that participants who had higher estimated 25-hydroxyvitamin D scores also had significant reduction in pancreatic cancer risk (relative risk of 0.65, 95% CI (0.50–0.86)).

In experimental studies, 1,25-dihydroxyvitamin D_3 (calcitriol) has been shown to induce differentiation and inhibition of various types of cancer cells including colon [100], breast [101], and prostate [102]. However, the use of 1,25-dihydroxyvitamin D_3 as an anticancer agent is limited because of its toxic hypercalcemia-inducing activity. To overcome this drawback, anticancer analogs of this compound that have less calcemic effects have been developed. For example, Kawa *et al.* [103] compared the effect of vitamin D_3 analog, 22-oxa-1, 25-dihydroxyvitamin D_3, maxacalcitol, with that of 1, 25-dihydroxyvitamin D_3 on treating nine different pancreatic cancer cell lines. In this study, *in vitro* assays showed that both maxacalcitol and calcitriol significantly inhibited the proliferation of the cancer cell lines Hs 700T, BxPC-3, and SUP-1 in a dose-dependent manner and caused G_1 phase cell-cycle arrest. *In vivo*, it was found that maxacalcitol significantly inhibited the growth of BxPC-3 xenografts, 38% of controls at the end of the experiment, while having no hypercalcemic effect. Calcitriol, on the other hand, was not able to significantly inhibit the growth of BxPC-3 xenografts but significantly induced the elevation of serum calcium. Schwartz *et al.* [104] conducted another study that compared the effects of the vitamin D analog 19-*nor*-1, 25-dihydroxyvitamin D_2 (paricalcitol) with calcitriol on pancreatic cancer. The results from this investigation showed that paricalcitol was able to inhibit the growth of pancreatic cancer *in vitro* in a dose-dependent manner similar to calcitriol through the upregulation of the cell-cycle inhibitors p21 and p27. *In vivo*, paricalcitol was shown to inhibit AsPC-1 xenografts at doses that did not induce hypercalcemia.

In 2009, the results were published from a phase II clinical trial that used the chemotherapeutic drug docetaxel enhanced with calcitriol to treat patients with locally advanced or metastatic pancreatic cancer [105]. In this study, 25 patients were given oral calcitriol 0.5 μg/kg on day 1, followed by docetaxel 36 mg/m^2 IV on day 2. This treatment was administered weekly for 3 wk, followed by 1 wk without treatment. The results found that three patients had a partial response (12%) to the combination treatment, seven patients had stable disease (28%), and nine patients frankly progressed (36%). This study was successful in increasing the time-to-progression of this disease from 1.5 to 3.6 months; however, the results were not comparable to the standard chemotherapy for pancreatic cancer. The current consensus is that gemcitabine should be used alone or in combinations with a platinum agent (oxaliplatin), erlotinib, or a fluoropyrimidine (5-fluorouracil or capecitabine), especially in selected patients with high-performance status [106–110].

7 Summary and conclusion

Pancreatic cancer is a devastating disease with a dismal outlook for diagnosed patients. Although there have not been a sufficient number of clinical trials, promising dietary factors to prevent pancreatic cancer include citrus fruits, flavonoids, curcumin, folate, and vitamin D. Curcumin is one of the most important bioactive compounds that have been studied for its chemoprotective effects on pancreatic cancer. *In vitro* studies have shown that curcumin has the ability to inhibit a diverse range of molecular targets in pancreatic cancer cells including NFκB, EGFR, WT1, and STAT3. Phase II clinical trials of curcumin have shown encouraging chemoprotective effects in patients with pancreatic cancer and have determined that curcumin can be safely administrated to patients at oral doses up to 8 g/d. However, in order to validate curcumin as a pharmaceutical for pancreatic cancer treatment, more large-scale trials are needed. Another important limitation of curcumin research is its poor bioavailability and more studies are needed to develop ways to effectively deliver curcumin to its target sites.

Several flavonoids found in a variety of fruits and vegetables have also been shown to inhibit pancreatic cancer at various molecular targets including cell-cycle, Akt, NFκB, ERK, and many others (Fig. 3). The isoflavone genistein is one of the more studied flavonoids in pancreatic cancer. It has been shown to effectively inhibit NFκB and its regulated genes *in vitro*, both alone and in combination with chemotherapeutic drugs. Another important finding about genistein is that it has the ability to abolish the activation of NFκB induced by the chemotherapeutic drugs gemcitabine and cisplatin when used as a pretreatment for either of them. Currently, there is one on-going phase II clinical trial on the use of genistein in treating resectable pancreatic cancer patients. However, more clinical trials are needed to explore the efficacy and application of genistein in treating pancreatic cancer.

The use of citrus fruit extracts to treat pancreatic cancer has become of interest only in the past few years. Using citrus fruit extracts instead of individual compounds to treat pancreatic cancer is of great interest because it allows the use of low doses of multiple bioactive compounds and nutrients instead of large doses of single compounds, and therefore reducing the possibility of reaching toxic effects. When comparing the inhibitory effects of different extraction methods of lime juice on pancreatic cancer, it was found that the methanol extract exhibited the highest inhibitory effect. Although the results from this study provide insight into the best options for extracting citrus fruits, more research needs to be conducted on various types of citrus fruits extracts and their mechanisms of action by which they affect pancreatic cancer.

Folate and vitamin D have good epidemiological evidence that shows that consumption of either of these nutrients leads to a reduced risk of pancreatic cancer. However, both of

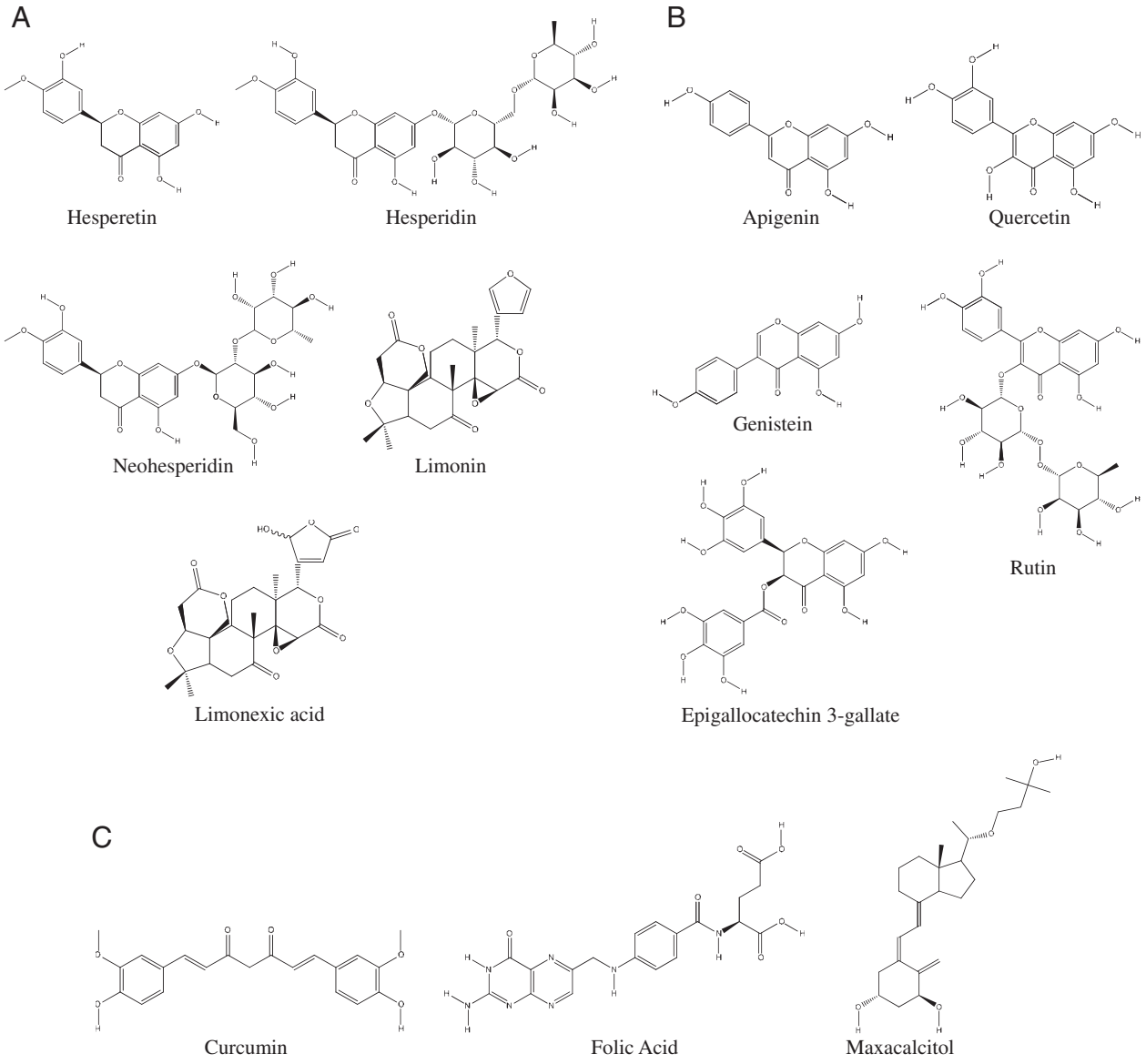

Figure 3. Structures of some compounds reviewed in this article were found to inhibit pancreatic cancer. (A) Citrus flavonoids and limonoids, (B) flavonoids, (C) curcumin, folic acid, and maxacalcitol.

the nutrients have few experimental studies needed to help draw conclusions about either of their impacts on pancreatic cancer. Another limitation for the use of vitamin D as an anticancer agent is that its active form causes toxic hypercalcemia-inducing activity. The use of vitamin D analogs instead of active vitamin D has been a proven way to overcome this limitation both *in vitro* and *in vivo*, while still having a negative impact on pancreatic cancer growth.

The role of food bioactive compounds in the prevention and/or treatment of pancreatic cancer is very promising. With a better understanding of how specific bioactive substances affect pancreatic cancer cell growth, scientists will be able to develop therapeutic treatment options that have less harmful side effects than current chemotherapeutic drugs.

The authors have declared no conflict of interest.

8 References

[1] Jemal, A., Siegel, R., Xu, J., Ward, E., Cancer statistics, 2010. *CA Cancer J. Clin.* 2010, *60*, 277–300.

[2] What you need to know about cancer of the pancreas, Available on the World Wide Web, National Cancer Institute 2010, Accessed May 2010.

[3] World Cancer Research Fund/American Institute for Cancer Research. *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*, AICR, Washington DC 2007.

[4] Hingorani, S., in: Lowy, A., Leach, S., Philip, P. (Eds.), *From Inception to Invasion: Modeling Pathways to Pancreatic Cancer – Pancreatic Cancer*, Springer Science+Business Media, LLC New York 2008, pp. 159–180.

[5] Dominguez-Bendala, J., in: Turksen, K. (Ed.), *The Pancreas – Pancreatic Stem Cells*, Humana Press, New York, NY 2009, pp. 1–10.

[6] Pancreatic Cancer Detailed Guide, Available on the World Wide Web, American Cancer Society 2010, Accessed May 2010, http://www.cancer.org.

[7] Boland, G., Thayer, S., in: Lowy, A., Leach, S., Philip, P. (Eds.), Molecular Signaling Pathways in Pancreatic Cancer – Pancreatic Cancer, Springer Science+Business Media, LLC New York, NY 2008, pp. 181–228.

[8] Hruban, R., Brune, K., Fukushima, N., Maitra, A., in: Lowy, A., Leach, S., Philip, P. (Eds.), *Pancreatic Intraepithelial Neoplasia – Pancreatic Cancer*, Springer Science+Business Media, LLC New York, NY 2008, pp. 41–52.

[9] Kranenburg, O., The KRAS oncogene: past, present, and future. *Biochim. Biophys. Acta* 2005, *1756*, 81–82.

[10] Shields, J., Pruitt, K., McFall, A., Shaub, A., Der, C., Understanding Ras: ''it ain't over 'til it's over''. *Trends Cell Biol.* 2000, *10*, 147–154.

[11] Wilson, L., Lightwood, J., Pancreatic cancer: total costs and utilization of health services. *J. Surg. Oncol.* 1999, *71*, 171–181.

[12] Singletary, K., Diet, Natural products and cancer chemoprevention. *J. Nutr.* 2000, *130*, 465S–466S.

[13] Tsao, A., Kim, E., Hong, W., Chemoprevention of cancer. *CA Cancer J. Clin.* 2004, *54*, 150–180.

[14] Schatzkin, A., Kelloff, G., Chemo- and dietary prevention of colorectal cancer. *Eur. J. Cancer* 1995, *31A*, 1198–1204.

[15] Polesel, J., Talamini, R., Negri, E., Bosetti, C. *et al.*, Dietary habits and risk of pancreatic cancer: an Italian case-control study. *Cancer Causes Control* 2010, *21*, 493–500.

[16] Larsson, S., Hakansson, N., Naslund, I., Bergkvist, L., Wolk, A., Fruit and vegetable consumption in relation to pancreatic cancer risk: a prospective study. *Cancer Epidemiol. Biomarkers Prev.* 2006, *15*, 301–305.

[17] Chan, J., Wang, F., Holly, F., Vegetable and fruit intake and pancreatic cancer in a population-based case-control study in the San Francisco bay area. *Cancer Epidemiol. Biomarkers Prev.* 2005, *15*, 2093–2097.

[18] FAO Statistical Yearbook 2005-2006. Food and Agriculture Organization of the United Nations.

[19] Wang, Y., Chuang, Y., Ku, Y., Quantitation of bioactive compounds in citrus fruits cultivated in Taiwan. *Food Chem.* 2007, *102*, 1163–1171.

[20] Buer, C., Imin, N., Djordjevic, M., Flavonoids: new roles for old molecules. *J. Integr. Plant Biol.* 2010, *52*, 98–111.

[21] Stewart, I., Wheaton, T., Conversion of β-citraurin to reticulataxanthin and β-apo-8′-carotenal to citranaxanthin during the isolation of carotenoids from citrus. *Phytochemistry* 1973, *12*, 2947–2951.

[22] Marti, N., Mena, P., Canovas, J., Micol, V., Saura, D., Vitamin C and the role of citrus juices as functional food. *Nat. Prod. Commun.* 2009, *4*, 677–700.

[23] Manners, G., Citrus limonoids: analysis, bioactivity, and biomedical prospects. *J. Agric. Food Chem.* 2007, *55*, 8285–8294.

[24] Tanaka, T., Kohno, H., Kawabata, K., Honjo, S. *et al.*, in: Berhow, M., Hasegawa, S., Manners, G. (Eds.), *Citrus Limonoids Obacunone and Limonin Inhibit the Development of a Precursor Lesion, Aberrant Crypt Foci, for Colon Cancer in Rats – Citrus Limonoids: Functional Chemicals in Agriculture and Food*, American Chemical Society, Washington DC 2000, pp. 145–163.

[25] Olsen, G., Mandel, J., Gibson, R., Wattenberg, L., Schuman, L., Nutrients and pancreatic cancer: a population-based case-control study. *Cancer Causes Control* 1991, *2*, 291–297.

[26] Silverman, D., Swanson, C., Gridley, G., Wacholder, S. *et al.*, Dietary and nutritional factors and pancreatic cancer: a case-control study based on direct interviews. *J. Natl. Cancer Inst.* 1998, *90*, 1710–1719.

[27] Nothlings, U., Murphy, S., Wilkens, L., Henderson, B., Kolonel, L., Dietary glycemic load, added sugars, and carbohydrates as risk factors for pancreatic cancer: the multiethnic cohort study. *Am. J. Clin. Nutr.* 2007, *86*, 1495–1501.

[28] Coughlin, S., Calle, E., Patel, A., Thun, M., Predictors of pancreatic cancer mortality among a large cohort of United States adults. *Cancer Causes Control* 2000, *11*, 915–923.

[29] Bueno de Mesquita, H., Masionneuve, P., Runia, S., Moerman, C., Intake of foods and nutrients and cancer of the exocrine pancreas: a population-based case-control study in the Netherlands. *Int. J. Cancer* 1991, *48*, 540–549.

[30] Stolzenberg-Solomon, R., Pietinen, P., Taylor, P., Virtamo, J., Albanes, D., Prospective study on diet and pancreatic cancer in male smokers. *Am. J. Epidemiol.* 2002, *155*, 783–792.

[31] Ji, B., Chow, W., Gridley, G., McLaughlin, J. *et al.*, Dietary factors and the risk of pancreatic cancer: a case-control study in Shanghai, China. *Cancer Epidemiol. Biomarkers Prev.* 1995, *4*, 885–893.

[32] Lin, Y., Kikuchi, S., Tamakoshi, A., Yagyu, K. *et al.*, Dietary habits and pancreatic cancer risk in a cohort of middle-aged and elderly Japanese. *Nutr. Cancer* 2006, *56*, 40–49.

[33] Sergeev, I., Ho, C., Li, S., Colby, J., Dushenkov, S., Apoptosis-inducing activity of hydroxylated polymethoxyflavones and polymethoxyflavones from orange peel in human breast cancer cells. *Mol. Nutr. Food Res.* 2007, *51*, 1478–1484.

[34] Jayaprakasha, G., Mandadi, K., Poulose, S., Jadegoud, Y. *et al.*, Novel triterpenoid from *Citrus aurantifolia* L.

possesses chemopreventive properties against human colon cancer cells. *Bioorg. Med. Chem.* 2008, *16*, 5939–5951.

[35] Tang, M., Ogawa, K., Asamoto, M., Hokaiwado, N. *et al.*, Protective effects of citrus nobiletin and auraptene in transgenic rats developing adenocarcinoma of the prostate (TRAP) and human prostate carcinoma cells. *Cancer Sci.* 2007, *98*, 471–477.

[36] Hung, J., Hsu, Y., Ko, Y., Tsai, Y. *et al.*, Didymin, a dietary flavonoid glycoside from citrus fruits, induces Fas-mediated apoptotic pathway in human non-small lung cancer cells *in vitro* and *in vivo*. *Lung Cancer* 2010, *68*, 366–374.

[37] Patil, J., Murthy, K., Jayaprakasha, G., Chetti, M., Patil, B., Bioactive compounds from Mexican lime (*Citrus aurantifolia*) juice induce apoptosis in human pancreatic cells. *J. Agric. Food Chem.* 2009, *57*, 10933–10942.

[38] Patil, J., Jayaprakasha, G., Murthy, K., Chetti, M., Patil, B., Characterization of *Citrus aurantifolia* bioactive compounds and their inhibition of pancreatic cancer cells through apoptosis. *Microchem. J.* 2010, *94*, 108–117.

[39] Ross, J., Kasum, C., Dietary flavonoids: bioavailability, metabolic effects, and safety. *Annu. Rev. Nutr.* 2002, *22*, 19–34.

[40] Gil-Izquierdo, A., Gil, M., Ferreres, F., Tomas-Barberan, F., *In vitro* availability of flavonoids and other phenolics in orange juice. *J. Agric. Food Chem.* 2001, *49*, 1035–1041.

[41] Kim, H., Mani, I., Iversen, L., Ziboh, V., Effects of naturally occurring flavonoids and bioflavonoids on epidermal cyclooxygenase and lipoxygenase from guinea pigs. *Prostaglandins Leukot. Essent. Fatty Acids* 1998, *58*, 17–24.

[42] Salabat, M., Melstrom, L., Strouch, M., Ding, X. *et al.*, Geminin is overexpressed in human pancreatic cancer and downregulated by the bioflavonoid apigenin in pancreatic cancer cell lines. *Mol. Carcinog.* 2008, *47*, 835–844.

[43] Melstrom, L., Salabat, M., Ding, X., Milam, B. *et al.*, Apigenin inhibits the GLUT-1 glucose transporter and the phosphoinositide 3-kinase/Akt pathway in human pancreatic cells. *Pancreas* 2008, *37*, 426–431.

[44] Ujiki, M., Ding, X., Salabat, M., Bentrem, D. *et al.*, Apigenin inhibits pancreatic cancer cell proliferation through G2/M cell cycle arrest. *Mol. Cancer* 2006, *5*, 76.

[45] Lee, S., Ryu, J., Lee, K., Woo, S. *et al.*, Enhanced anti-tumor effect of combination therapy with gemcitabine and apigenin in pancreatic cancer. *Cancer Lett.* 2008, *259*, 39–49.

[46] Strouch, M., Milam, B., Melstrom, L., McGill, J. *et al.*, The flavonoid apigenin potentiates the growth inhibitory effects of gemcitabine and abrogates gemcitabine resistance in human pancreatic cancer cells. *Pancreas* 2009, *38*, 409–415.

[47] Liu, H., Jiang, W., Xie, M., Flavonoids: recent advances as anticancer drugs. *Recent Pat. Anti-Cancer Drug Discov.* 2010, *5*, 152–164.

[48] Gibellini, L., Pinti, M., Nasi, M., Montagna, J. *et al.*, Quercetin and cancer chemoprevention. *eCam.* 2010, 1–14.

[49] Aghdassi, A., Phillips, P., Dudeja, V., Dhaulakhandi, D. *et al.*, Heat shock protein 70 increases tumorigenicity and inhibits apoptosis in pancreatic adenocarcinoma. *Cancer Res.* 2007, *67*, 616–625.

[50] Borska, S., Sopel, M., Chmielewska, M., Zabel, M., Dziegiel, P., Quercetin as a potential modulator of p-glycoprotein expression and function in cells of human pancreatic carcinoma line resistant to daunorubicin. *Molecules* 2010, *15*, 857–870.

[51] Zhang, Y., Chen, A., Li, M., Chen, C., Yao, Q., *Ginkgo biloba* extract kaempferol inhibits cell proliferation and induces apoptosis in pancreatic cancer cells. *J. Surg. Res.* 2008, *148*, 17–23.

[52] Shankar, S., Suthakar, G., Srivastava, R., Epigallocatechin-3-gallate inhibits cell cycle and induces apoptosis in pancreatic cancer. *Front. Biosci.* 2007, *12*, 5039–5051.

[53] Shankar, S., Ganapathy, S., Hingorani, S., Srivastava, R., EGCG inhibits growth, invasion, angiogenesis, and metastasis of pancreatic cancer. *Front. Biosci.* 2008, *13*, 440–452.

[54] Li, Y., Zhang, T., Jiang, Y., Lee, H. *et al.*, (−)-Epigallocatechin-3-gallate inhibits hsp90 function by impairing hsp90 association with cochaperones in pancreatic cancer cell line MIA PaCa-2. *Mol. Pharm.* 2009, *6*, 1152–1159.

[55] McMillan, B., Riggs, D., Jackson, B., Cunningham, C., McFadden, D., Dietary influence on pancreatic cancer growth by catechin and inositol hexaphosphate. *J. Surg. Res.* 2007, *141*, 115–119.

[56] Mohammad, R., Banerjee, S., Li, Y., Aboukameel, A. *et al.*, Cisplatin-induced antitumor activity is potentiated by the soy isoflavone genistein in BxPC-3 pancreatic tumor xenografts. *Cancer* 2006, *106*, 1260–1268.

[57] El-Rayes, B., Ali, S., Ali, I., Philip, P. *et al.*, Potentiation of the effect of erlotinib by genistein in pancreatic cancer: the role of Akt and nuclear factor-κB. *Cancer Res.* 2006, *66*, 10553–10559.

[58] Banerjee, S., Zhang, Y., Ali, S., Bhuiyan, M. *et al.*, Molecular evidence for increased antitumor activity of gemcitabine by genistein *in vitro* and *in vivo* using an orthotopic model of pancreatic cancer. *Cancer Res.* 2005, *65*, 9064–9072.

[59] Banerjee, S., Zhang, Y., Wang, Z., Che, M. *et al.*, *In vitro* and *in vivo* molecular evidence of genistein action in augmenting the efficacy of cisplatin in pancreatic cancer. *Int. J. Cancer* 2006, *120*, 906–917.

[60] Mohammad, R., Wang, S., Banerjee, S., Wu, X. *et al.*, Nonpeptidic small-molecule inhibitor of Bcl-2 and Bcl-X_L (−)-gossypol, enhances biological effect of genistein against BxPC-3 human pancreatic cancer cell line. *Pancreas* 2005, *31*, 317–324.

[61] Wang, Z., Zhang, Y., Banerjee, S., Li, Y., Sarkar, F., Inhibition of nuclear factor κB activity by genistein is mediated *via* Notch-1 signaling pathway in pancreatic cancer cells. *Int. J. Cancer* 2006, *118*, 1930–1936.

[62] Wang, Z., Zhang, Y., Li, Y., Banerjee, S. *et al.*, Down-regulation of Notch-1 contributes to cell growth inhibition and apoptosis in pancreatic cancer cells. *Mol. Cancer Ther.* 2006, *5*, 483–493.

[63] Wang, Z., Ahmad, A., Banerjee, S., Azmi, A. *et al.*, FoxM1 is a novel target of a natural agent of pancreatic cancer. *Pharm. Res.* 2010, *27*, 1159–1168.

[64] National Institute of Health, ClinicalTrials.gov, 2010, http://www.clinicaltrials.gov, accessed July 2010.

[65] Sharma, R., Gescher, A., Steward, W., Curcumin: the story so far. *Eur. J. Cancer* 2005, *41*, 1955–1968.

[66] Ammon, H., Wahl, M., Pharmacology of Curcuma longa. *Planta Med.* 1991, *57*, 1–7.

[67] Goel, A., Kunnumakkara, A., Aggarwal, B., Curcumin as ''curecumin'': from kitchen to clinic. *Biochem. Pharmacol.* 2008, *75*, 787–809.

[68] Hua, W., Fu, Y., Liao, Y., Xia, W. *et al.*, Curcumin induces down-regulation of EZH2 expression through the MAPK pathway in MDA-MB-435 human breast cancer cells. *Eur. J. Pharmacol.* 2010, *637*, 16–21.

[69] Hilchie, A., Furlong, S., Sutton, K., Richardson, A. *et al.*, Curcumin-induced apoptosis in PC3 prostate carcinoma cells is caspase-independent and involves cellular ceramide accumulation and damage to mitochondria. *Nutr. Cancer* 2010, *62*, 379–389.

[70] Shin, H., Kim, J., Lee, E., Kim, S., Inhibitory effect of curcumin on motility of human oral squamous carcinoma YD-10B cells *via* suppression of ERK and NF – κB activations. *Phytother. Res.* 2010, *24*, 577–582.

[71] Saydmohammed, M., Joseph, D., Syed, V., Curcumin suppresses constitutive activation of STAT-3 by up-regulating protein inhibitor of activated STAT-3 (PIAS-3) in ovarian and endometrial cancer cells. *J. Cell. Biochem.* 2010, *110*, 447–456.

[72] Mohanty, C., Acharva, S., Mohanty, A., Dilnawaz, F., Sahoo, S., Curcumin-encapsulated MePEG/PCL diblock copolymeric micelles: a novel controlled delivery vehicle for cancer therapy. *Nanomedicine* 2010, *5*, 433–449.

[73] Sarkar, F., Banerjee, S., Li, Y., Pancreatic cancer: pathogenesis, prevention and treatment. *Toxicol. Appl. Pharmacol.* 2007, *224*, 326–336.

[74] Li, L., Aggarwal, B., Shishodia, S., Abbruzzese, J., Kurzrock, R., Nuclear factor-κB and IκB kinase are constitutively active in human pancreatic cells, and their down-regulation by curcumin (diferuloylmethane) is associated with the suppression of proliferation and the induction of apoptosis. *Cancer* 2004, *101*, 2351–2362.

[75] Lev-Ari, S., Starr, A., Vexler, A., Karaush, V. *et al.*, Inhibition of pancreatic and lung adenocarcinoma cell survival by curcumin is associated with increased apoptosis, down-regulation of COX-2 and EGFR and inhibition of Erk1/2 activity. *Anticancer Res.* 26, *2006*, 4423–4430.

[76] Wang, Z., Zhang, Y., Banerjee, S., Li, Y., Sarkar, F., Notch-1 down-regulation by curcumin is associated with the inhibition of cell growth and the induction of apoptosis in pancreatic cancer cells. *Cancer* 2006, *106*. 2503–2513.

[77] Levi-Ari, S., Zinger, H., Kazanov, D., Yona, D. *et al.*, Curcumin synergistically potentiates the growth inhibitory and pro-apoptotic effects of celecoxib in pancreatic adenocarcinoma cells. *Biomed. Pharmacother.* 2005, *59*, S276–S280.

[78] Lev-Ari, S., Vexler, A., Starr, A., Ashkenazy-Voghera, M. *et al.*, Curcumin augments gemcitabine cytotoxic effect on pancreatic adenocarcinoma cell lines. *Cancer Invest.* 2007, *25*, 411–418.

[79] Glienke, W., Maute, L., Wicht, J., Bergmann, L., Wilms' tumour gene 1 (WT1) as a target in curcumin treatment of pancreatic cancer cells. *Eur. J. Cancer* 2009, *45*, 874–880.

[80] Glienke, W., Maute, L., Wicht, J., Bergmann, L., Curcumin inhibits constitutive STAT3 phosphorylation in human pancreatic cancer cell lines and downregulation of Survivin/BIRC5 gene expression. *Cancer Invest.* 2010, *28*, 166–171.

[81] Sahu, R., Batra, S., Srivastava, S., Activation of ATM/Chk1 by curcumin causes cell cycle arrest and apoptosis in human pancreatic cancer cells. *Br. J. Cancer* 2009, *100*, 1425–1433.

[82] Anand, P., Kunnumakkara, A., Newman, R., Aggarwal, B., Bioavailability of curcumin: problems and promises. *Mol. Pharm.* 2007, *4*, 807–818.

[83] Bar-Sela, G., Epelbaum, R., Schaffer, M., Curcumin as an anti-cancer agent: review of the gap between basic and clinical applications. *Curr. Med. Chem.* 2010, *17*, 190–197.

[84] Epelbaum, R., Vizel, B., Bar-Sela, G., Phase II study of curcumin and gemcitabine in patients with advanced pancreatic cancer. *J. Clin. Oncol.* 2008, *26*, Abstract 15619.

[85] Dhillon, N., Aggarwal, B., Newman, R., Wolff, R. *et al.*, Phase II trial of curcumin in patients with advanced pancreatic cancer. *Clin. Cancer Res.* 2008, *14*, 4491–4499.

[86] Shane, B., in: Alexopolous, Y., Hebberd, K., Vales, S. (Eds.), *Folic Acid, Vitamin B12, and Vitamin B6 – Biochemical, Physiological, and Molecular Aspects of Human Nutrition*, Saunders Elsevier, St. Louis, MO 2006, pp. 694–712.

[87] Mason, J., Choi, S., Folate and carcinogenesis: developing a unifying hypothesis. *Adv. Enzyme Regul.* 2000, *40*, 127–141.

[88] Friso, S., Choi, S., Gene-nutrient interactions and DNA methylation. *J. Nutr.* 2002, *132*, 2382S–2387S.

[89] Oaks, B., Dodd, K., Meinhold, C., Jiao, L. *et al.*, Folate intake, post-folic acid grain fortification, and pancreatic cancer risk in the prostate, lung, colorectal, and ovarian cancer screening trial. *Am. J. Clin. Nutr.* 2010, *91*, 449–455.

[90] Gong, Z., Holly, E., Bracci, P., Intake of folate, vitamins B_6, B_{12}, and methionine and risk of pancreatic cancer in a large population-based case-control study. *Cancer Causes Control* 2009, *20*, 1317–1325.

[91] Larsson, S., Håkansson, N., Giovannucci, E., Wolk, A., Folate intake and pancreatic cancer incidence: a prospective study of Swedish women and men. *J. Natl. Cancer Inst.* 2006, *98*, 407–413.

[92] Li, D., Ahmed, M., Li, Y., Jiao, L. *et al.*, 5, 10-Methylenetetrahydrofolate reductase polymorphisms and the risk of pancreatic cancer. *Cancer Epidemiol. Biomarkers Prev.* 2005, *14*, 1470–1476.

[93] Stolzenberg-Solomon, R., Albanes, D., Nieto, F., Hartman, T. *et al.*, Pancreatic cancer risk and nutrition-related methyl-group availability indicators in male smokers. *J. Natl. Cancer Inst.* 1999, *91*, 535–541.

[94] Stolzenberg-Solomon, R., Pietinen, P., Barrett, M., Taylor, P. *et al.*, Dietary and other methyl-group availability factors and pancreatic cancer risk in a cohort male smokers. *Am. J. Epidemiol.* 2001, *153*, 680–687.

[95] Holick, M., Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am. J. Clin. Nutr.* 2004, *80*, 1678S–1688S.

[96] Holick, M., in: Alexopolous, Y., Hebberd, K., Vales, S. (Eds.), *Vitamin D – Biochemical, Physiological, Molecular Aspects of Human Nutrition*, Saunders Elsevier St., Louis, MO 2006, pp. 863–883.

[97] Garland, C., Garland, F., Gorham, E., Lipkin, M. *et al.*, The role of vitamin D in cancer prevention. *Am. J. Public Health* 2006, *96*, 252–261.

[98] Skinner, H., Michaud, D., Giovannucci, E., Willett, W. *et al.*, Vitamin D intake and the risk for pancreatic cancer in two cohort studies. *Cancer Epidemiol. Biomarkers Prev.* 2006, *15*, 1688–1695.

[99] Bao, Y., Ng, K., Wolpin, B., Michaud, D. *et al.*, Predicted vitamin D status and pancreatic cancer risk in two prospective cohort studies. *Br. J. Cancer* 2010, *102*, 1422–1427.

[100] Akhter, J., Chen, X., Bowrey, P., Bolton, E., Morris, D., Vitamin D3 analog, EB1089, inhibits growth of subcutaneous xenografts of the human color cancer cell line, LoVo, in a nude mouse model. *Dis. Colon Rectum* 1997, *40*, 317–321.

[101] Abe-Hashimoto, J., Kikuchi, T., Matsumoto, T., Nishii, Y. *et al.*, Antitumor effect of 22-oxa-calcitrol, a noncalcemic analogue of calcitrol, in athymic mice implanted with human breast carcinoma and its synergism with tamoxifen. *Cancer Res.* 1993, *53*, 2534–2537.

[102] Polek, T., Murthy, S., Blutt, S., Boehm, M. *et al.*, Novel nonsecosteroidal vitamin D receptor modulator inhibits the growth of LNCaP xenograft tumors in athymic mice without increased serum calcium. *Prostate* 2001, *49*, 224–233.

[103] Kawa, S., Yoshizawa, K., Nikaido, T., Kiyosawa, K., Inhibitory effect of 22-oxa-1, 25-dihydroxyvitamin D_3, maxacalcitol, on the proliferation of pancreatic cancer cell lines. *J. Steroid Biochem. Mol. Biol.* 2005, *97*, 173–177.

[104] Schwartz, G., Eads, D., Naczki, C., Northrup, S. *et al.*, 19-Nor-1α, 25-dihydroxyvitamin D_2 (Paricalcitol) inhibits the proliferation of human pancreatic cancer cells *in vitro* and *in vivo*. *Cancer Biol. Ther.* 2008, *7*, 430–436.

[105] Blanke, C., Beer, T., Todd, K., Mori, M. *et al.*, Phase II study of calcitriol-enhanced docetaxel in patients with previously untreated metastatic or locally advanced pancreatic cancer. *Invest. New Drugs* 2009, *27*, 374–378.

[106] Rivera, F., Lopez-Tarruella, S., Vega-Villegas, M., Salcedo, M., Treatment of advanced pancreatic cancer: from gemcitabine single agent to combinations and targeted therapy. *Cancer Treat. Rev.* 2009, *35*, 335–339.

[107] Wong, H., Lemoine, N., Pancreatic cancer: molecular pathogenesis and new therapeutic targets. *Nat. Rev. Gastroenterol. Hepatol.* 2009, *6*, 412–422.

[108] Stathis, A., Moore, M., Advanced pancreatic carcinoma: current treatment and future challenges. *Nat. Rev. Clin. Oncol.* 2010, *7*, 163–172.

[109] O'Reilly, E., Refinement of adjuvant therapy for pancreatic cancer. *J. Am. Med. Assoc.* 2010, *304*, 1124–1125.

[110] Neoptolemos, J., Stocken, D., Bassi, C., Ghaneh, P. *et al.*, Adjuvant chemotherapy with fluorouracil plus folinic acid *versus* gemcitabine following pancreatic cancer resection: a randomized controlled trial. *J. Am. Med. Assoc.* 2010, *304*, 1073–1081.

[111] Qanungo, S., Das, M., Haldar, S., Basu, A., Epigallocatechin-3-gallate induces mitochondrial membrane depolarization and caspase-dependent apoptosis in pancreatic cancer cells. *Carcinogenesis* 2005, *26*, 958–967.

[112] Basu, A., Haldar, S., Combinatorial effect of epigallocatechin-3-gallate and TRAIL on pancreatic cancer cell death. *Int. J. Oncol.* 2009, *34*, 281–286.

[113] Li, Y., Ahmed, F., Ali, S., Philip, P. *et al.*, Inactivation of nuclear factor κB by soy isoflavone genistein contributes to increased apoptosis induced by chemotherapeutic agents in human cancer cells. *Cancer Res.* 2005, *65*, 6934–6942.

[114] Mihaljevic, A., Michalski, C., Friess, H., Kleeff, J., Molecular mechanism of pancreatic cancer-understanding proliferation, invasion, and metastasis. *Langenbecks Arch. Sur.* 2010, *395*, 295–308.

[115] Andea, A., Sarkar, F., Adsay, V., Clinicopathological correlates of pancreatic intraepithelial neoplasia: a comparative analysis of 82 cases with and 152 cases without pancreatic ductal adenocarcinoma. *Mod. Pathol.* 2003, *16*, 996–1006.

