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To cite this article: Mustafa B. A. Djamgoz & Valerie Jentzsch (2021): Integrative Management of Pancreatic Cancer (PDAC): Emerging Complementary Agents and Modalities, Nutrition and Cancer, DOI: [10.1080/01635581.2021.1934043](https://doi.org/10.1080/01635581.2021.1934043)

To link to this article: <https://doi.org/10.1080/01635581.2021.1934043>



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Published online: 04 Jun 2021.



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Integrative Management of Pancreatic Cancer (PDAC): Emerging Complementary Agents and Modalities

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ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC) is a devastating disease. The standard first-line treatment for PDAC is gemcitabine chemotherapy which, unfortunately, offers only limited chance of a lasting cure. This review further evaluates the hypothesis that the effectiveness of gemcitabine can be improved by combining it with evidence-based complementary measures. Previously, supported by clinical trial data, we suggested that a number of dietary factors and nutraceuticals can be integrated with gemcitabine therapy. Here, we evaluate a further 10 agents for which no clinical trials have (yet) been carried out but there are promising data from in vivo and/or in vitro studies including experiments involving combined treatments with gemcitabine. Two groups of complementary agents are considered: Dietary factors (resveratrol, epigallocatechin gallate, vitamin B9, capsaicin, quercetin and sulforaphane) and nutraceutical agents (artemisinin, garcinol, thymoquinone and emodin). In addition, we identified seven promising agents for which there is currently only basic (mostly in vitro) data. Finally, as a special case of combination therapy, we highlighted synergistic drug combinations involving gemcitabine with “repurposed” aspirin or metformin. We conclude overall that integrated management of PDAC currently is likely to produce the best outcome for patients and for this a wide range of complementary measures is available.

Abbreviations: AMPK: Adenosine Monophosphate Kinase; ASP: Aspirin; CAPS: Capsaicin; CSC: Cancer Stem Cell; DHA: Dihydroartemisinin; EGCG: Epigallocatechin Gallate; EMO: Emodin; EMT: Epithelial-Mesenchymal Transition; FOLFIRINOX: Folinic acid + Fluorouracil + Irinotecan + Oxaliplatin; GAR: Garcinol; GEM: Gemcitabine; MET: Metformin; NF- κ B: Nuclear Factor κ -light-chain-enhancer of activated B cells; PDAC: Pancreatic Ductal Adenocarcinoma; QUER: Quercetin; RAD: Radiation; RES: Resveratrol; ROS: Reactive Oxygen Species; SFN: Sulforaphane; TRAIL: Tumor Necrosis Factor-Related Apoptosis Inducing Ligand; TMQ: Thymoquinone

ARTICLE HISTORY

Received 17 December 2020



Accepted 10 May 2021

1. Introduction

Pancreatic cancer, the most common form of which is “pancreatic ductal adenocarcinoma” (PDAC), is one of the hardest to treat cancers both because of the difficulty of early diagnosis and the limited effectiveness of the available therapies (1–3). With a five-year survival rate of only some 6%, the associated mortality rates are regional (deaths per 100,000 people) being ca. 7.2 (Europe), 6.5 (North America) and 1.2 (East Africa) (4). PDAC is age-related; its incidence has been rising steeply for a number of years, and it is expected to become the most common cause of cancer-related deaths in the USA by 2030 (5). PDAC arises in the pancreatic ducts which perform the gland’s main exocrine functions. The liver is often the first major organ to be metastasized due to the proximity of the hepatic

portal vein (6). In fact, liver failure is frequently the first sign and the main cause of death from PDAC. In the context of integrated management, therefore, treatments should ideally protect also the liver.

The most common first-line treatment for PDAC is gemcitabine chemotherapy (7, 8). Gemcitabine is an “antimetabolite” pro-drug which becomes active once phosphorylated into diphosphate or triphosphate inside cells at very specific phases of the mitotic cycle. Thus, it works most effectively on fast-dividing cells, hence cancer cells. The basic mechanism of cell death is DNA damage (9). Apart from its inherent limited effectiveness and the common undesirable side effects of the treatment, use of gemcitabine suffers from the eventual onset of resistance to the drug. In these respects, therefore, any adjustment to gemcitabine chemotherapy that

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will increase its sensitivity (and hence lower its dosage of use) and lengthen its period of effectiveness (e.g., overcoming resistance) would be welcome. Our hypothesis is that these are possible by combining the gemcitabine chemotherapy with evidence-based complementary agents. Indeed, use of complementary agents in cancer treatment generally is increasingly, being favored by patients as well as by oncologists (10–14).

In the first instance, an association between dietary/nutritional lifestyle and PDAC is apparent epidemiologically from the fact that the PDAC incidence and mortality rates are much higher in relatively developed countries with diets rich in fatty, oily or sweet foods (4). Whilst our understanding of this association has come a long way over the years, we know much less about how dietary and nutraceutical agents, as well as lifestyle factors, could associate with PDAC during treatment (15). In our previous review, we advanced the hypothesis that the best outcome for PDAC currently would be obtained by integration of clinical medicine with evidence-based natural complementary agents and lifestyle factors (16). Of the former, 9 (six dietary and three nutraceutical compounds) were chosen based upon evidence from clinical trials as the essential criterion, as well as meta-analyses and in vivo and in vitro experiments. In addition, however, there is a range of natural agents that did not meet all of those strict criteria but may do so in the future as more evidence is gathered. Here, we evaluate this second group of “emerging” agents incorporating both dietary factors and nutraceuticals. For all these, there is both in vivo and/or in vitro evidence including combination treatments. In vivo animal models include molecularly appropriate transgenic models wherever possible. As regards in vitro experiments, the data used come mainly from human cells.

Central to our approach, again, is the epigenetic nature of cancer, including PDAC, which means that genes and their products can be regulated significantly including by dietary and lifestyle factors (16–20). Indeed, overall, ca. 40% of cancers are due to modifiable, hence reversible factors (www.cancer.org/latest-news/more-than-4-in-10-cancers-and-cancer-deaths-linked-to-modifiable-risk-factors.html). Not surprisingly, therefore, the link between nutrition and cancer has been questioned for over a century (21). Since pancreas is a strongly hormonal (both endocrine and exocrine) organ, PDAC would be expected to be particularly sensitive to the body's biochemistry and chemical balance (e.g., Refs. (22–25)).

2. Dietary Factors

In our previous review we considered dietary factors in 3 different categories (16). General/background conditioners included acidity, glycaemic index and cholesterol. As multifactorial foodstuffs, we covered red and processed meat, fish, fruit and vegetables, dairy, honey and coffee. Finally, as specific dietary agents the following satisfied our full criteria: Vitamins A, C, D, and E, curcumin and genistein. Here, we have accepted for further consideration six specific dietary factors for which significant in vivo and in vitro data were available. The emphasis again is on the possible potentiating effect of these agents on gemcitabine chemotherapy. Such dietary agents can also be taken as supplements.

2.1. Resveratrol

Resveratrol is a natural phytoalexin that is produced in plants as a defensive response against fungal infections and other environmental stressors. It is particularly abundant in the skin of red grapes, blueberries, raspberries, mulberries and nuts (Table 1A). Resveratrol has been shown to inhibit proliferation and invasiveness of PDAC cells by reducing “nuclear factor κ -light-chain-enhancer of activated B cells” (NF- κ B) expression, downregulating lipid metabolism and activating pro-apoptotic caspase-3 (25–27). Furthermore, markers of epithelial-mesenchymal transition (EMT), an early event in invasiveness, were suppressed (28). A synthetic, more stable derivative of resveratrol (triacetyl resveratrol) also selectively induced apoptosis in PDAC cells in vitro without affecting normal pancreatic ductal cells and this occurred via downregulation of hedgehog signaling (29). Combined treatment of PDAC cells with gemcitabine and resveratrol (i) increased apoptosis highly significantly and (ii) reduced gemcitabine resistance in vitro and this involved adenosine monophosphate kinase (AMPK) (30, 31). Also, in vitro, the inhibition of colony formation by gemcitabine was enhanced by resveratrol addition, again, involving an enhanced pro-apoptotic effect (Figure 1A) (27). Consistent with this, in an in vivo orthotopic mouse model of PDAC, the anti-tumorigenic effect of gemcitabine was potentiated by combination with resveratrol (Figure 1B) (32). These results were confirmed by Gupta *et al.* and Xu, Q. *et al.* (33, 34). Importantly, also, resveratrol suppressed both the “basal” stemness of PDAC cells and that promoted by gemcitabine (Figure 1C) (27). In addition, pterostilbene, a natural analogue derived from resveratrol, enhanced gemcitabine sensitivity in part by inhibiting expression of the multi-drug resistance gene, MDR1 (35).

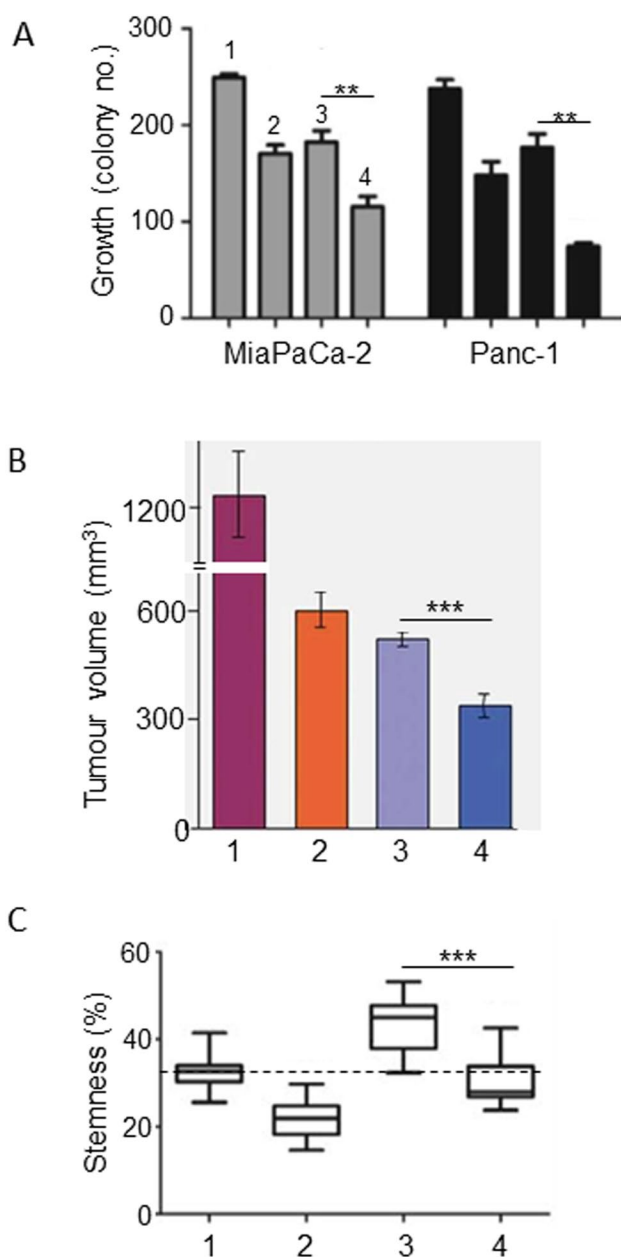


Figure 1. Effects of a dietary compound on PDAC: Resveratrol. For all parts of the figure (A to C), treatments were as follows: control (1), resveratrol (2), gemcitabine (3) and their combination (4). A. In vitro effects on growth (quantified as colony number) of treating two different human PDAC cell lines (MiaPaCa-2/gray bars and Panc-1/black bars) with resveratrol, gemcitabine and their combination. For both cell lines, the inhibition of growth was significantly greater for the combination than gemcitabine alone ($P < 0.01$). From Zhou, C *et al.* (27). B. In vivo growth of MiaPaCa-2 cells in an orthotopic xenograft model of PDAC. The inhibition of growth was significantly greater for the combination than gemcitabine alone ($P < 0.001$). Modified from Harikumar *et al.* (32). C. Assessment of stemness in PDAC cells obtained from tissue sections of KPC mice. Stemness was quantified as the Sox2-positive area, expressed as a percentage of total. Resveratrol significantly reduced the effect of gemcitabine in inducing stemness ($P < 0.001$), bringing it to control level. Dotted horizontal line denotes the median control level, as reference. From Zhou, C. *et al.* (27).

Interestingly, addition of resveratrol to the combined application of gemcitabine and capsaicin restored the effectiveness of chemotherapy and increased radio-sensitivity in in vivo (xenograft) models of human PDAC (36, 37). These studies would raise the possibility of extending the integrated management to triple (or more) combinations without incurring antagonism, as we suggested earlier (16). Finally, resveratrol reduced the undesirable side effects of chemotherapy on heart and liver by increasing the activity of antioxidant enzymes (38).

In conclusion, resveratrol has excellent properties both by itself as an anti-PDAC agent and for possible integration with gemcitabine chemotherapy in the future.

2.2. Epigallocatechin Gallate

Epigallocatechin gallate (EGCG) is abundant in teas, especially green tea, and fruits, especially berries (Table 1A). Epidemiological studies have shown beneficial effects of green tea on cancers of lung, breast, esophageal, stomach, liver and prostate (39, 40). As regards PDAC, however, such studies have given somewhat inconsistent results. Most meta-analyses concluded (i) that green tea consumption was not associated with PDAC risk and (ii) that high consumption was associated with slightly lower risk (41). This seemed more pronounced among Chinese populations (42, 43). Abe *et al.* recently evaluated the available epidemiological evidence for green tea consumption and showed that whilst PDAC risk was not affected, several other cancers were associated significantly with reduced risk (44). These included, importantly, liver cancer. Possible reasons for the discrepancy between the epidemiological data could include (i) the ranges of green tea consumption and (ii) compounding lifestyle factors especially smoking. Importantly, however, no adverse effect has been reported. Furthermore, green tea consumption could be beneficial indirectly by reducing the impact of diabetes, obesity and inflammation including pancreatitis (40, 45–47).

There is a wealth of in vitro evidence showing that green tea and one of its most active ingredients, EGCG, inhibit development and progression of cancer, including PDAC (48, 49). As regards “combination therapies,” an initial in vitro study suggested significant synergistic effects of gemcitabine with EGCG (over a range of concentrations). This involved increased expression of “signal transducer and activator of transcription 3” (STAT3) target genes and enhanced apoptosis (Figure 2A) (50). More recently, EGCG was able to enhance the gemcitabine-induced reduction in insulin-like

Table 1. Dietary and nutraceutical agents with emerging anti-PDAC effects.

A.			
Dietary agent	Formula	Mechanisms of action/Cellular effects	Food sources
Resveratrol	C ₁₄ H ₁₂ O ₃	Multiple – anti-inflammatory; antioxidant; inhibition of growth and stemness	Red grapes (especially the skin), blueberries, raspberries, nuts
EGCG	C ₂₂ H ₁₈ O ₁₁	Multiple – anti-inflammatory; antioxidant; anti-angiogenic; pro-apoptotic; effects on gene expression	Green tea; fruits (especially berries), nuts
Vitamin B9 (Folate)	C ₁₉ H ₁₉ N ₇ O ₆	Multiple – anti-proliferative and anti-migratory; modulator of angiogenesis, cytokine secretion, oxidative stress and immune response	Vegetables, (especially green leaf), whole grains, eggs, legumes, seeds, nuts
Capsaicin	C ₁₈ H ₂₇ NO ₃	Activator of vanilloid-type receptor-channel; pro-apoptotic; inhibitor of growth, angiogenesis	Cayenne (red) peppers and other chili peppers
Quercetin	C ₁₅ H ₁₀ O ₇	Multiple - anti-inflammatory; proteolytic enzyme inhibition; immune-stimulant; antioxidant	Apples, red grapes, cherries, red raspberry, onions
B.			
Nutraceutical agent	Formula	Mechanisms of action / Cellular effects	Source(s)
Artemisinin	C ₁₅ H ₂₂ O ₅	Multiple - pro-apoptotic; anti-proliferative; antioxidant; anti-angiogenic	Sweet wormwood (<i>Artemisia annua</i>)
Garcinol	C ₃₈ H ₅₀ O ₆	Multiple – antioxidant; anti-proliferative; anti-invasive; pro-apoptotic	Tropical fruit (<i>Garcinia indica</i>)
Thymoquinone	C ₁₀ H ₁₂ O ₂	Multiple – antioxidant; anti-proliferative; pro-apoptotic; immune modulator	Fennel flower (<i>Nigella sativa</i>)
Emodin	C ₁₅ H ₁₀ O ₅	Multiple – anti-proliferative; pro-apoptotic; anti-inflammatory; anti-invasive	Roots and bark of various plants (e.g. rhubarb, buckthorn, Japanese knotweed)

A. Dietary agents. B. Nutraceuticals. For both groups, chemical formulae, main mechanisms of action (cellular effects) and examples of their natural sources are given. Further details can be found in the main text.

growth factor receptor and Akt/protein kinase B signaling, and thus reduce cell migration and invasion in vitro (Figure 2B) (51). in vivo also (xenograft mouse model of PDAC), intraperitoneal EGCG downregulated glycolysis and potentiated the effect of gemcitabine, together reducing tumor weight by an additional ca. 30% (Figure 2C) (52).

In conclusion, the evidence for EGCG as an anti-PDAC agent is overall positive, albeit limited. The evidence is stronger for liver cancer. Hence, this agent would be worth considering for possible integration with gemcitabine chemotherapy in the future.

2.3. Vitamin B9

Vitamin B9 (folate) is one of eight B vitamins. It is abundant in foods such as citrus fruits, green leafy vegetables and legumes (Table 1A) (53). Taken as folic acid, it is converted to folate by the body. Folate deficiency has been shown to induce chromosomal breaks and mutations in tumor suppressor genes, hence its supplementation proved beneficial against PDAC (54). The level of reduced risk from increased folate intake varied between studies, but importantly, no adverse effect has been reported (53, 55). Lin, H. *et al.* found in a meta-analysis that a high intake of folate, especially as part of diet, reduced the relative risk of PDAC by as much as 34% (Figure 3) (53). This conclusion was supported by Yallem *et al.*, also reporting a significant inverse association between folate intake and PDAC (56). Studies have suggested that folate supplementation may be most beneficial when taken with certain

folate-rich foods, e.g., spinach and asparagus (56). Although vitamin B9 has not been tested in combination with gemcitabine systemically, it is one of the four components of the FOLFIRINOX regime, which is given to cases advanced (metastatic) PDAC. So, it can be considered acceptable for integrated management of PDAC.

In conclusion, we consider vitamin B9 to be an effective complement to gemcitabine chemotherapy of PDAC. We should note, however, that B vitamins are sometimes taken as a “complex” of the various forms, but this should best be avoided, since there is some evidence that B12 may promote cancer including PDAC (57). The latter is consistent with dietary sources of B12 (animal products such as meat, dairy etc.) also being undesirable (16).

2.4. Capsaicin

Capsaicin is the active ingredient of hot red peppers (Table 1A) (58). It has anticancer properties through its ability to induce cell cycle arrest and cause apoptosis (58). Capsaicin reduced the growth of PDAC xenografts in mice by promoting apoptosis mediated by caspase-3 and caspase-8 (59). Additionally, capsaicin downregulated PI3 kinase signaling, leading to an increase in cell cycle arrest. Through the inhibition of the mitochondrial electron transport chain, capsaicin could generate reactive oxygen species (ROS) and increase DNA damage, without affecting healthy pancreatic cells (60). There is no study on the possible effects of combining capsaicin with gemcitabine. However, in cases where gemcitabine monotherapy

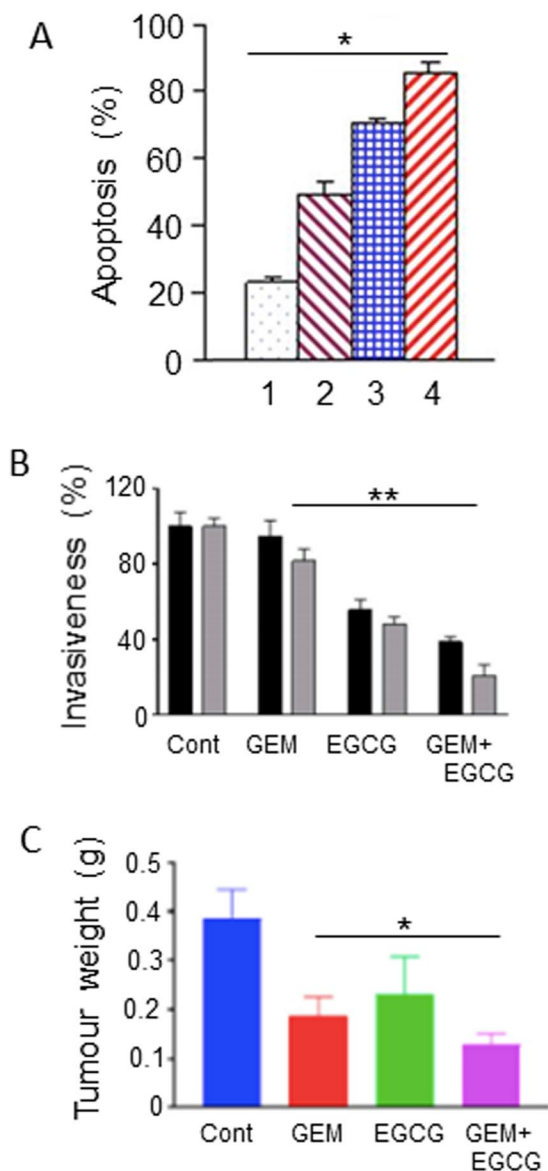


Figure 2. Effects of a dietary compound on PDAC: Epigallocatechin gallate. A. Apoptotic responses of Panc-1 cells to treatment with increasing concentrations of epigallocatechin gallate (EGCG) and combination with a fixed dose of gemcitabine (GEM). The histograms denote the following: GEM alone (1), GEM+EGCG (2-4, increasing concentrations of EGCG). Data represent mean \pm SD. There was a statistically significant difference between the effects of all the combinations compared with GEM alone ($P < 0.05$). From Tang *et al.* (50). B. Effects of GEM, EGCG and their combination on the invasiveness on two pancreatic cancer cell lines, Panc-1 (black histograms) and MiaPaCa-2 (gray histograms). Data represent mean \pm SD. Effects of the treatments are expressed as a percentage of control (Cont). For both cell lines, the effect of the combination was significantly greater than GEM alone ($P < 0.01$). From Wei, R. *et al.* (51). C. Effect of GEM, EGCG and their combination on tumorigenesis in a subcutaneous xenograft model of PDAC (KPC cells). "Cont" denotes control data from untreated animals. Data represent mean \pm SD. The decrease in tumor weight induced by the combination was greater than GEM alone ($P < 0.05$). From Wei, R. *et al.* (52).

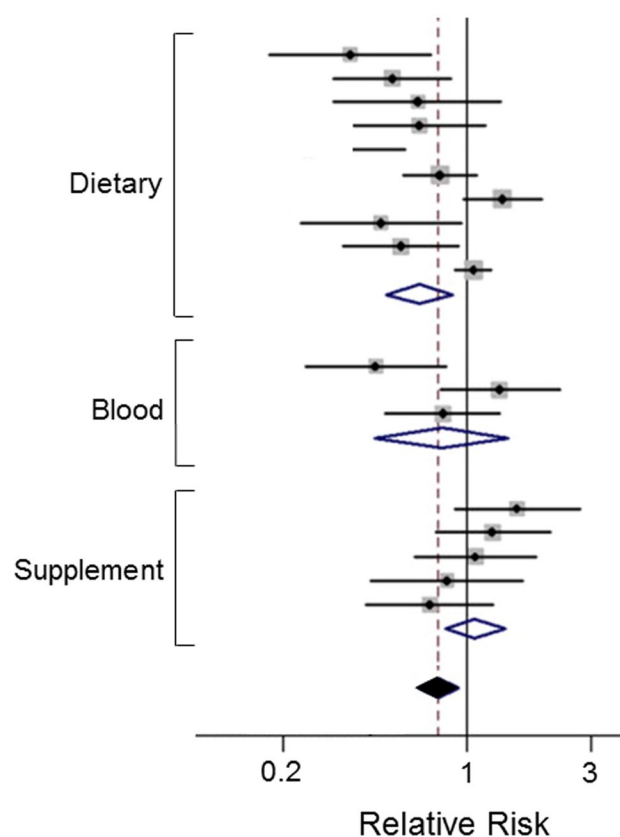


Figure 3. Effects of a dietary compound on PDAC: Vitamin B9. Meta-analysis of studies examining the effects of folate levels (assessed from dietary intake, blood levels and supplements) on pancreatic cancer risk. Diamonds indicate the average and the spread of the data. White diamonds relate to the individual data sets. Black diamond indicates overall significantly reduced relative risk, despite the noticeable variability across the three sets of studies. Modified from Lin, H. *et al.* (53), where further details and primary data can be found.

was ineffective, supplementation with capsaicin and resveratrol restored the full effectiveness of gemcitabine *in vivo* (Figure 4A) (37). This effect occurred through apoptosis. If, however, gemcitabine was at its full effectiveness, no increase following treatment with resveratrol and capsaicin was observed. Combinations of resveratrol and capsaicin were also able to sensitize some PDAC cell lines to radiotherapy, leading to further reduction in tumor volume *in vivo* (Figure 4B) (36). Capsaicin may also benefit patients through pain relief and reduction of inflammation (61).

In conclusion, capsaicin has excellent properties for possible integration into management of PDAC, both directly and as regards side effects of the treatment.

2.5. Quercetin

Quercetin (also known as sophoretin or meletin) belongs to the flavonoid group of polyphenols and

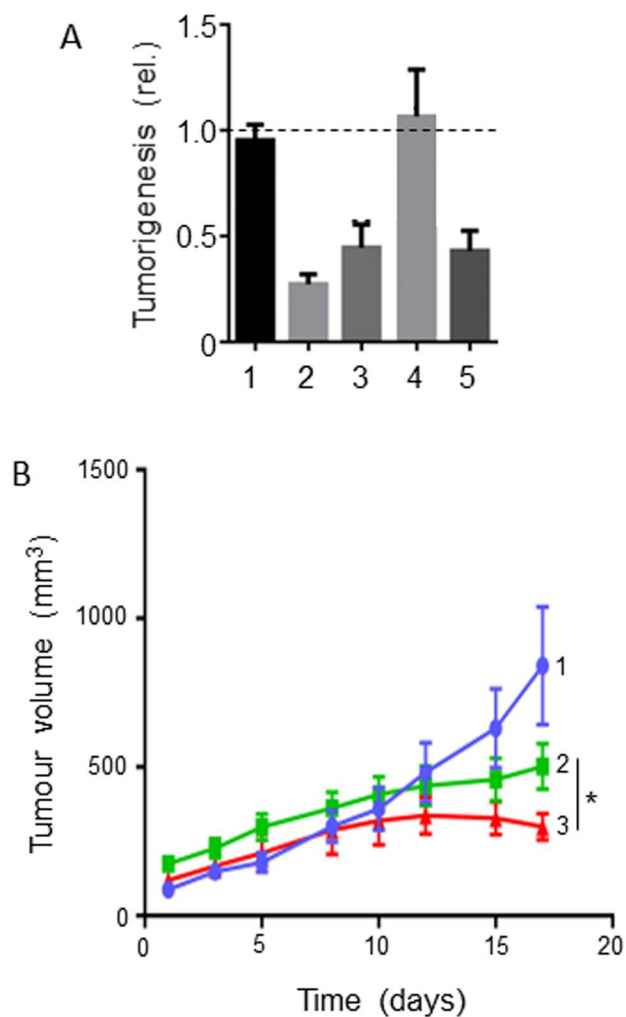


Figure 4. Effects of a dietary compound on PDAC: Capsaicin. A. Effects on tumorigenesis of treatment with gemcitabine coupled with capsaicin (CAPS) and resveratrol (RES) combined in a xenograft (Capan-2) model of pancreatic cancer. Tumorigenesis was quantified as tumor weight expressed relative to control. The treatments were as follows: control (1), high-dose GEM (2), high-dose GEM coupled with CAPS and RES combination (3), low-dose GEM (4), and low-dose GEM coupled with CAPS and RES combination (5). There was no added effect of treatment with high-dose GEM combined with CAPS + RES, suggesting a saturating effect of the chemotherapy (3 vs. 2). Although low-dose GEM had no effect on tumorigenesis (4), combination with CAPS + RES produced a marked inhibitory effect (5 vs. 4, statistics not specified). Dotted horizontal line indicates null effect. Modified from Vendrely *et al.* (37), where further details can be found. B. Tumorigenesis in a xenograft (Capan-2) model of pancreatic cancer. The treatments were as follows: control (1), 2 Gy radiotherapy (2), and radiotherapy with CAPS + RES (3). Data are presented as mean \pm SEM. The effect of the radiotherapy in suppressing tumorigenesis was potentiated significantly by combination with CAPS + RES (3 vs. 2; $P < 0.05$). From Vendrely *et al.* (36), where further details can be found.

found naturally in apples, grapes, red raspberry and onions (Table 1A). Although by itself it is not readily bioavailable, its various metabolites (present in systemic circulation after consumption) demonstrate significant biological (antioxidant and anti-inflammatory) activity. In vitro, quercetin suppressed a range of PDAC cell behaviors by regulating a variety of signaling pathways. Cell viability was suppressed dose-dependently (Figure 5A) (62, 64). Apoptotic cell death was increased significantly (Figure 5B) (e. g., Ref. (63)). The pro-apoptotic/anti-tumor effect of quercetin was confirmed in frozen tissue sections of human PDAC xenografts and shown to involve miR-let-7c as an intermediary (65). Importantly, also, in human primary PDAC cells, quercetin upregulated miR-200b-3p expression and inhibited Notch signaling, resulting in inhibition of stemness and self-renewal (66). Parallel to these effects, quercetin strongly down-regulated the expression of a range of EMT markers (Figure 5C) (28, 64). Consistent with these effects, taken together, cellular invasiveness was significantly decreased, and this was dose dependent (Figure 5D) (64).

There is also some evidence from human PDAC cells in vitro that quercetin potentiates the effectiveness of gemcitabine in inhibiting cell viability and promoting apoptosis (Figures 5A and B). Also, on two human PDAC cell lines, Serri *et al.* used biodegradable nanoparticles and showed, again, that quercetin could enhance the impact of gemcitabine on cell viability by 15–20% (67). Consistent with these results, Lan *et al.* showed that quercetin had a remarkable pro-apoptotic effect on a gemcitabine-resistant variant of Mia-Paca-2 cells (Figure 5E) (62). This was extended recently to several other gemcitabine-resistant PDAC as well as hepatocarcinoma cell lines by Liu ZJ *et al.* (68). This effect was revealed to involve the “receptor for advanced glycation end products” (RAGE) (62). In a further study, a natural isoform of quercetin, quercetin-3-O-glucoside, exhibited synergy with low concentrations of gemcitabine on human PDAC CFPAC-1 and SNU-213 cells in suppressing transverse migration induced by basic fibroblast growth factor (bFGF) (69).

In vivo, also, quercetin caused a significant reduction of tumor volume in a xenograft model of PDAC, again involving let-7c (Figure 5F) (65). However, less work has been done to test the possible effectiveness of combining quercetin with gemcitabine in vivo. In the one available study, Angst *et al.* showed in an orthotopic model of PDAC that quercetin maintained

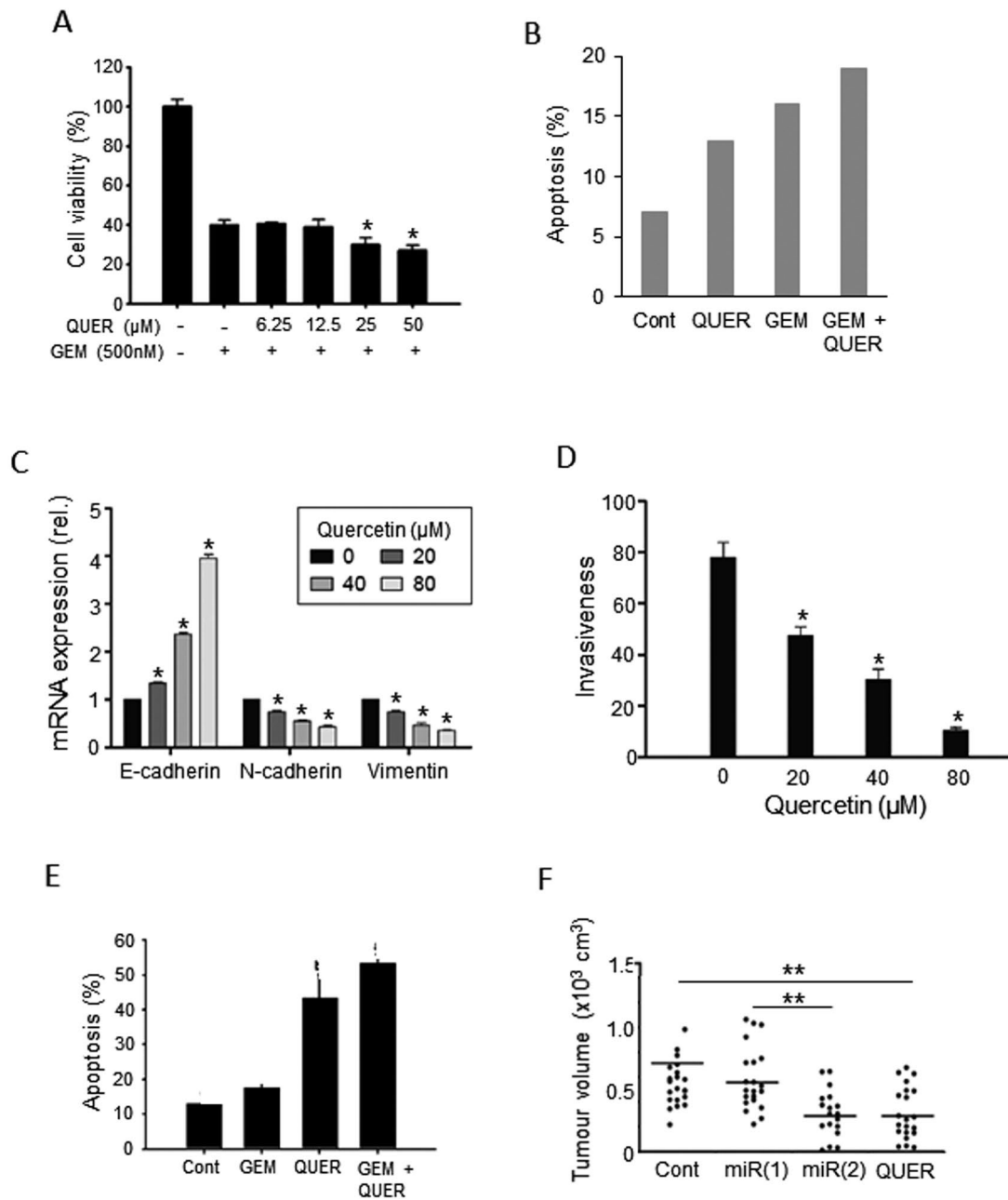


Figure 5. Effects of a dietary compound on PDAC: Quercetin. **A.** Cell viability of MiaPaCa-2 cells following treatment with increasing concentrations of quercetin (QUER) and gemcitabine (GEM). Cells were pretreated with quercetin at various concentrations for 24 h, and then treated with a fixed concentration of gemcitabine for 72 h. The effects of the combinations with 25 and 50 μM QUER were inferred to be significantly greater than GEM alone ($P < 0.05$). From Lan *et al.* (62). **B.** PANC-1 cell apoptosis. Effects of QUER and GEM, and their combination, on compared with control (Cont). Apoptosis was defined as the number of apoptotic cells expressed as a percentage of control. Modified from Lee *et al.* (63). **C.** Effects of treatment with increasing QUER concentrations on mRNA expression of EMT markers (E-cadherin, N-cadherin, and Vimentin) in PATU-8988 cells. Quercetin treatment resulted in dose-dependent reductions in expression of all three mRNAs. In all conditions and concentrations, treatment with quercetin was significant compared with the control ($P < 0.05$). From Yu *et al.* (64). **D.** Invasiveness (quantified arbitrarily as the number of invaded cells per field of view) in PATU-8988 cells treated with increasing concentrations of QUER. For all concentrations, treatment with quercetin produced a significantly greater reduction in invasiveness compared with the control ($P < 0.05$). From Yu *et al.* (64). **E.** Apoptosis (measured by annexin-V FITC) in gemcitabine-resistant MiaPaCa-2 cells. Cells were treated with QUER, GEM or their combination, compared with untreated Cont. The effect of the combination was markedly greater than gemcitabine alone (statistics not performed). From Lan *et al.* (62). **F.** Tumor volume in a xenograft model of human primary PDAC cells. AsanPaCa cells were implanted into chick embryos and left untreated (Cont) or treated with QUER. In a parallel experiment, the cells were processed so as to silence miR-let-7c (miR2), or its negative control (miR1). MiR2 and QUER treatment decreased tumor volume significantly compared to the relative controls ($P < 0.01$). From Nwaeburu *et al.* (65).

its anti-proliferative and pro-apoptotic effects and reduced tumor weight (70). In combination with gemcitabine, quercetin had a noticeably (ca. two-fold) greater effect on proliferative activity. In contrast, the additional effects of quercetin combined with gemcitabine on apoptosis and tumor weight were modest (ca. 10%). However, these effects did not reach significance, probably due to the limited number of animals used ($n=6$) and the inherent variability of in vivo testing especially with combinations of agents (70).

In conclusion, the evidence is consistent that quercetin suppresses PDAC and potentiates the effect of gemcitabine in vitro. In vivo, also, quercetin produces noticeable anti-PDAC effects, but more work is required to substantiate the evidence for the added benefit of combination with gemcitabine.

2.6. Sulforaphane

Cruciferous vegetables, named as such for their cross-shaped flowers, are rich in sulforaphane (other active ingredients include indole-3-carbinol and 3,3'-diindolylmethane). Sulforaphane-rich foods include broccoli, cabbage, cauliflower, brussels sprouts, collard greens and kale (Table 1A) (71). Appari *et al.* showed that three servings of cruciferous vegetables per day was associated with a 50% decrease in PDAC risk (72). A more extensive meta-analysis of four cohort and five case-control studies also found that a high intake of cruciferous vegetables decreased PDAC risk significantly by some 20% (71). This was extended to a clinical trial (<https://clinicaltrials.gov/ct2/show/NCT01879878>). Thus, Lozanovski *et al.* reported that PDAC patients consuming sulforaphanes (freeze-dried broccoli) whilst undergoing palliative chemotherapy experienced improved survival albeit for limited time (Figure 6A) (73). A range of anti-cancer modes of action has been associated with sulforaphane (76). In one study, indole-3-carbinol reduced the assembly of prostate cancer cells into organoids (77). This finding could be significant to PDAC due to some similarities with prostate cancer, especially hormone (insulin) sensitivity. Both are also cancers of affluence and express similar stem cell markers (78, 79). Sulforaphane suppressed the genetic damage of carcinogens, induced apoptosis and inhibited proliferation of PDAC cells, in culture as well as in vivo (80). Specifically, combining sulforaphane with “tumor necrosis factor-related apoptosis inducing ligand” (TRAIL) was able to reduce resistance to the drug (81). Furthermore, using a xenograft model of PDAC, synergy between sulforaphane and gemcitabine has been demonstrated in suppressing tumorigenesis and

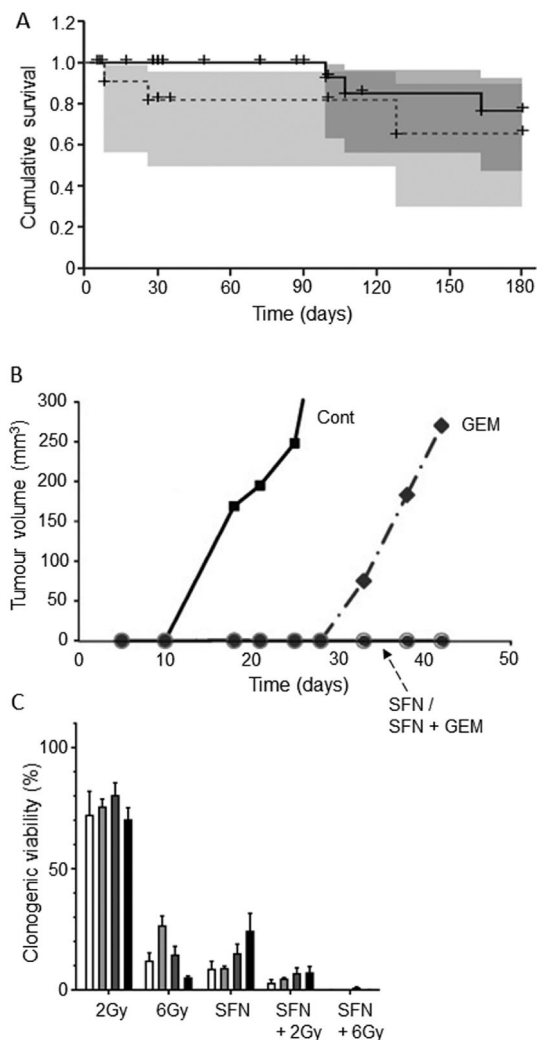


Figure 6. Effects of a dietary compound on PDAC: Sulforaphane. A. Kaplan-Meier analysis of cumulative survival of PDAC patients (undergoing palliative chemotherapy). Patients were treated with a sulforaphane preparation ($n=29$, solid line) compared with placebo ($n=11$, dotted line). Plus signs indicate patients who were lost to follow-up. The shaded areas denote 95% confidence intervals (dark gray for treatment, light gray for placebo). From Lozanovski *et al.* (73). B. Effects of 72-hour pretreatment of pancreatic CSC-like cells with sulforaphane (SFN), gemcitabine (GEM) and their combination on volume of tumors formed by subsequent injection (subcutaneous) into nude mice. Time indicated is from the day of inoculation. Control mice (Cont) were injected with untreated cells. Gemcitabine delayed tumorigenesis and its effect was potentiated by co-treatment with sulforaphane, suppressing tumorigenesis completely during the experimental period. Sulforaphane alone was also effective in completely suppressing the tumorigenesis. The data points for SFN and SFN + GEM (circles on the horizontal axis) were indistinguishable. From Kallifatidis *et al.* (74), where further details can be found. C. Effect of combining sulforaphane (SFN) with two doses of irradiation, 2 and 6 Grays (Gy), on clonogenic viability (“survival”), relative to control (100%). Four different cell lines were used (AsPC-1, BxPC-3, MiaPaCa-2 and Panc-1), each indicated as a histogram. The effects of the combination were clearly greater than radiotherapy alone (formal statistics not performed). Modified from Naumann *et al.* (75).

this involved suppression of Notch signaling and cancer stem cells (CSCs) (Figure 6B) (74). Finally, combining sulforaphane with radiotherapy suppressed PDAC cell viability by increasing cell cycle arrest (Figure 6C) (75). Interestingly, attempts are being made to develop stable synthetic variants of sulforaphane as anticancer drugs (<https://evgen.com/>).

In conclusion, the available evidence for sulforaphane is promising as regards its potential both as a preventative agent by itself as well as in combination with chemotherapy, including gemcitabine.

3. Nutraceutical Agents

Nutraceuticals are defined generally as natural substances that are not a part of normal diet but can be formulated and consumed as extracts or supplements. We have identified four nutraceutical compounds for which there are promising therapeutic effects (in vitro and/or in vivo) against PDAC and in some cases the associated organs, especially the liver (82). These are listed in Table 1B alongside their chemical formulae, main modes of action/cellular effects and natural sources.

3.1. Artemisinin

This compound is isolated from *Artemisia annua*, sweet wormwood, a herb commonly employed in traditional Chinese medicine against malaria (83). Artemisinin and its derivatives (e.g., dihydroartemisinin) produced a variety of in vitro and in vivo effects against PDAC, including inhibition of growth and induction of apoptosis (84–86). These effects have been associated with the upregulation of several miRNAs (83). It has also been suggested that artemisinin generates ROS to induce oxidative stress and thereby cell death in PDAC cell lines (87). Additionally, dihydroartemisinin increased T-cell proliferation and activity, which could promote an anticancer immune response (88). Importantly, dihydroartemisinin increased the sensitivity of PDAC in vitro and in vivo to therapies including gemcitabine and TRAIL (85, 89). In a xenograft model of PDAC, dihydroartemisinin significantly potentiated the effect of gemcitabine in suppressing tumorigenesis by some 25% (Figure 7A) (85). Histochemical analyses of the tissues from the in vivo experiments showed that the enhancing effect of dihydroartemisinin involved suppression of proliferation and increased apoptosis (Figure 7B and C) (85). Additionally, dihydroartemisinin was able to sensitize liver cancer cells to gemcitabine in vivo, thereby further reducing tumor burden significantly (90).

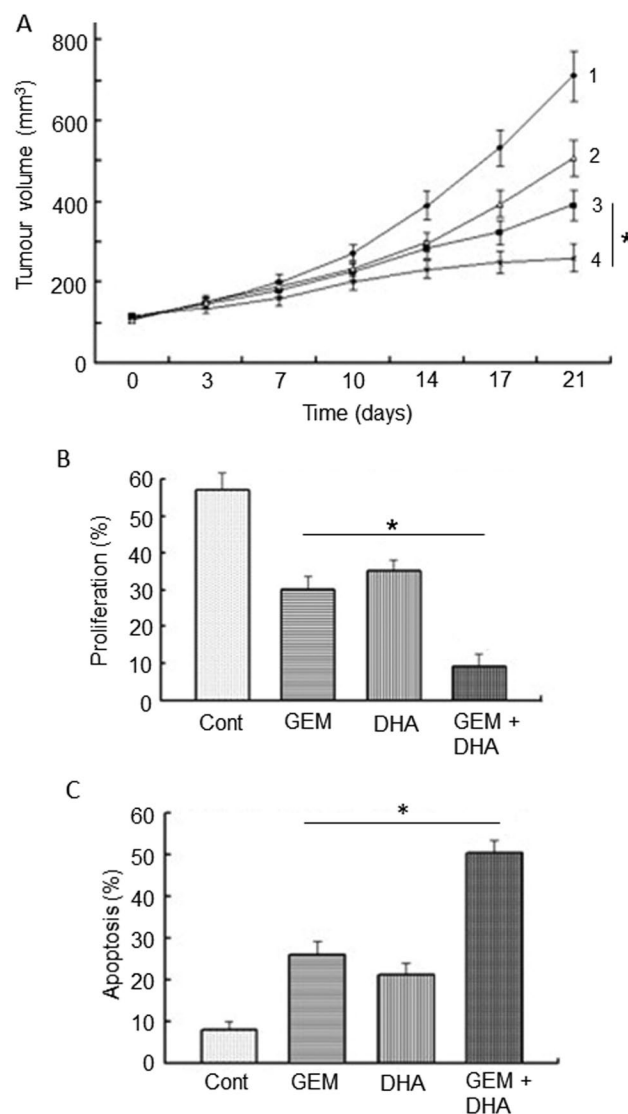


Figure 7. Effects of a nutraceutical compound on PDAC: Artemisinin. A. Effects of dihydroartemisinin (2), gemcitabine (3) and their combination (4) on volume of pancreatic cancer tumors; compared with control (1). BxPC-3 tumors were xenografted in nude mice. Data are presented as means \pm standard deviation. The effect of the combination was significantly greater than gemcitabine alone ($P < 0.05$). B & C. Effects of treatments on status of proliferation (B) and apoptosis (C) determined from tissue sections taken from the induced tumors in (A). Treatments were as follows: gemcitabine (GEM), dihydroartemisinin (DHA) and their combination (GEM + DHA), compared with control (Cont). Data are presented as means \pm standard deviation. For both parameters, the effect of the combination was greater than the effect of gemcitabine alone ($P < 0.05$). From Wang, SJ. *et al.* (85).

In conclusion, artemisinin and its derivatives can produce anti-PDAC effects and potentiate the effectiveness of gemcitabine. In addition, it may support liver function (Table 1B). Altogether, therefore, it has great promise for integration into chemotherapy of PDAC.

3.2. Garcinol

This is a derivative isolated from *Garcinia indica*, a plant of the mangosteen family, commonly known as “kokum”. It is a potent inhibitor of histone acetyltransferases, a modulator of gene expression, both in vitro and in vivo. Garcinol could produce a variety of anti-PDAC effects, promoting apoptosis by increasing activities of caspase-9 and caspase-3 In Vitro (91). By modulating the expression of miRNAs involved in chemoresistance, garcinol also allowed gemcitabine to become significantly more effective in suppressing proliferation and promoting apoptosis In Vitro (92). Importantly, garcinol could also suppress the self-renewal and tumor-forming ability of CSCs (93). Alone or in combination with gemcitabine, garcinol suppressed tumor growth in a transgenic (KPC) mouse model of PDAC (Figure 8A) (94). Furthermore, quantifying the stage of PDAC as pancreatic intraepithelial neoplasia (PanIN), combined treatment resulted in disease remaining in earlier stages. Thus, compared with gemcitabine treatment alone, PanIN lesions of all grades were consistently fewer in the combination treatment (Figure 8B) (94).

In conclusion, the available evidence suggests consistently that garcinol has significant effects against PDAC in vitro and in vivo and would seem ready to be tested in gemcitabine combination treatments.

3.3. Thymoquinone

This is an active ingredient isolated from the black seed, *Nigella sativa* (Table 1B). It has been investigated for its anti-oxidant and anti-inflammatory activities against PDAC, both in vitro and in vivo, and was found to be effective without significant side effects (95). Thymoquinone also has anticancer including anti-metastatic properties (96). Mahmoud & Abdelrazek reviewed these properties as well as the hepatoprotective effects of thymoquinone (97). Specifically, in PDAC, thymoquinone downregulated the expression of the anti-adhesive protein MUC4, thereby leading to decreased cell motility (98). Several studies have suggested a synergistic effect of thymoquinone in combination with gemcitabine. When these agents were combined in vitro, cell viability fell by more than 50% compared with monotherapy (Figure 9A) (99). In a xenograft model of PDAC, combination of thymoquinone with gemcitabine produced a significantly greater effect (by some 80%) on tumor weight compared with gemcitabine alone (Figure 9B) (99). This effect involved potentiation of caspase (3 and 9) activation, leading to apoptosis (100). This pro-apoptotic effect appeared to

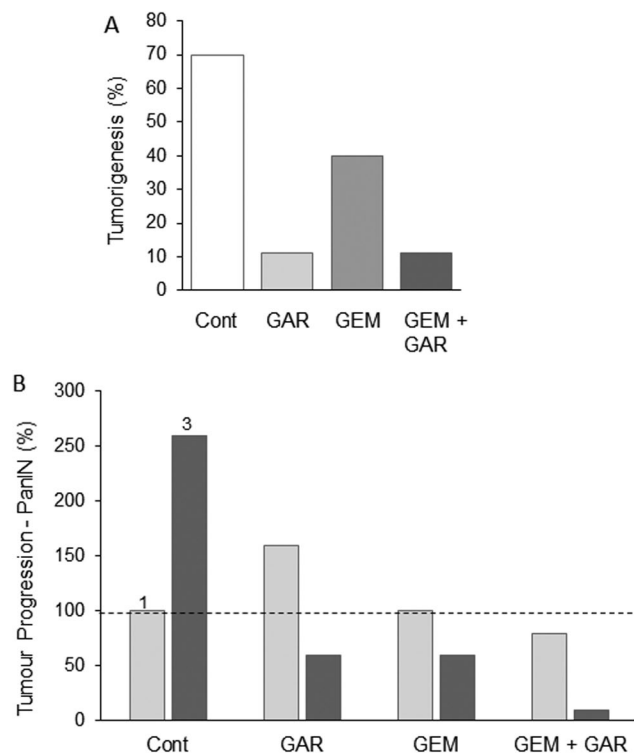


Figure 8. Effects of a nutraceutical compound on PDAC: Garcinol. A. Genetically engineered pancreatic cancer mouse model (KPC). Effects of treatment with garcinol (GAR), gemcitabine (GEM) and their combination on tumorigenesis over five weeks, quantified as the percentage of tumors which increased in size (determined by MRI). The combination produced about a four-fold greater effect than gemcitabine alone (statistics not available). B. Treatments as in (A), showing effects on tumor progression, quantified as the number of observed PanIN1 and PanIN3 lesions (light and dark bars, respectively, emphasized as 1 and 3 in the control data). Data are presented as a percentage of the PanIN1 level in control (Cont). Compared with gemcitabine alone, the combination produced consistently greater effects on both PanIN lesions, but noticeably more on PanIN3. However, significance was not reached, probably due to the limited number of animals used in the study ($n=8$ in each group) and the inherent variability of the pathology. Redrawn from data given in Saadat *et al.* (94).

be specific to PDAC cells (101). Thymoquinone-induced histone acetylation was proposed to be the basis of its synergy with gemcitabine (102).

In conclusion, from the available in vivo combination evidence, supported by in vitro data, we conclude that thymoquinone has excellent potential to be incorporated into an integrated management regimen for PDAC.

3.4. Emodin

This is a purgative resin from rhubarb (*Polygonum cuspidatum*), buckthorn and Japanese knotweed (*Fallopia japonica*) (Table 1B). By increasing activation of tumor

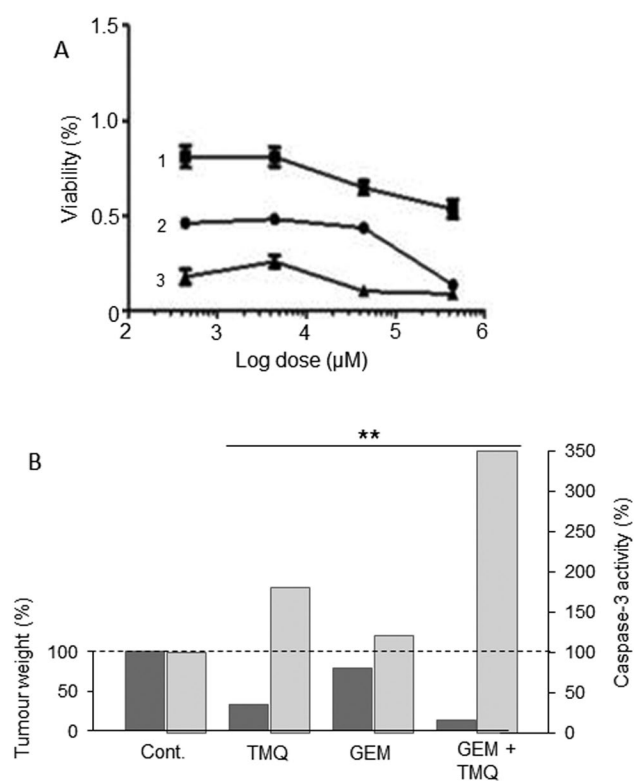


Figure 9. Effects of a nutraceutical compound on PDAC: Thymoquinone. **A.** Effects of gemcitabine (1), thymoquinone (2) and their combination (3) on the viability of PANC-1 cells. All treatments produced dose-dependent reduction in viability. The effects of the combination were markedly greater than gemcitabine alone at all concentrations tested. Calculations of the “combination index” confirmed significant synergy. From Pandita *et al.* (99), where further details can be found. **B.** Effects of thymoquinone (TMQ), gemcitabine (GEM) and their combination (GEM+TMQ), compared with control (Cont), in mice bearing orthotopically induced PANC-1 tumors. Data show effects on both tumor weight (lefthand axis, dark bars) and associated caspase-3 activity (righthand axis, light bars). In both cases, data are shown relative to the respective control level at 100%. For both parameters, the effects of the combination were significantly greater than treatment with gemcitabine alone ($P < 0.01$ for both). Replotted from data given in Mu *et al.* (100).

suppressor genes via DNA demethylation, emodin suppressed PDAC cell proliferation (103–105). In combined treatments in vitro, emodin “sensitized” a drug-resistant cell line to gemcitabine (Figure 10A) (105). In an orthotopic xenograft model of PDAC, emodin promoted the effect of gemcitabine in suppressing tumorigenesis (Figure 10B) (106). The effects of emodin involved increased apoptosis and inhibited angiogenesis with possible transcriptional control via NF- κ B (106–109). Finally, in a mouse model of PDAC, emodin dose-dependently decreased metastasis to liver by up to ca. 50% whilst “normalising” miR1271 expression and inhibiting EMT (107). In vitro and in vivo, liver cancer

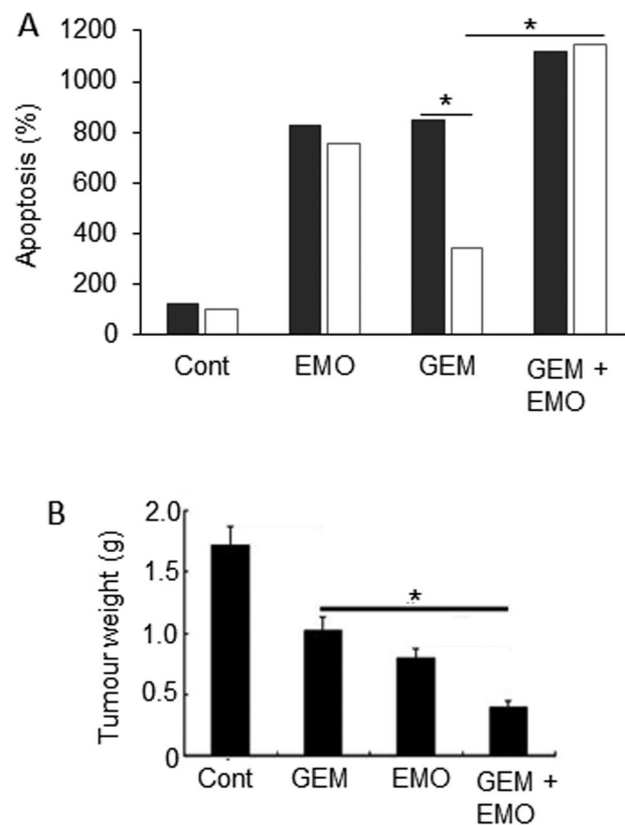


Figure 10. Effects of a nutraceutical compound on PDAC: Emodin. **A.** Bxpc-3 cells and their gemcitabine-resistant versions (Bxpc-3/Gem) (black and white bars, respectively). Effects of treatment of cells with emodin (EMO), gemcitabine (GEM) and their combination (GEM+EMO) on apoptosis. Data are plotted as a percentage of the control level for Bxpc-3 cells (at 100%). The effect of the combination was significantly greater than gemcitabine alone, but on the resistant cell line only ($P < 0.05$). The GEM-resistance of the Bxpc-3/Gem cell line was confirmed by significant lack of apoptotic response ($P < 0.05$). Replotted from data given in Zhang, W. *et al.* (104). **B.** Orthotopically induced pancreatic cancer in mice, treated with GEM, EMO and their combination. Tumor weights (in grams) were determined and compared with tumor-bearing control animals treated with saline only (Cont). The effect of the combination was significantly greater than gemcitabine alone ($P < 0.05$). Modified from Lin, SZ. *et al.* (106), where further details can be found.

itself benefited from emodin treatment which also enhanced the effectiveness of a biological (sorafenib) therapy (110). Finally, also in an in vivo mouse model, cachexia could be reversed by long-term treatment with emodin and this occurred through decreased hypoxia inducible factor (HIF) - 1 α signaling (111).

In conclusion, emodin can produce beneficial effects against PDAC, as well as liver cancer, by itself and can potentiate the effectiveness of gemcitabine in vitro and in vivo. Thus, it could be considered for clinical application.

4. Further Emerging Potential Complementary Agents

We should note that there are a number of other “agents” (dietary and nutraceutical) with anti-PDAC properties but for which evidence is mainly from In Vitro experiments and no In Vivo combination data are available. Such emerging agents are noted here with the expectation that the evidence in their favor could become stronger in time. Some examples of these emerging agents include the following.

4.1. Lycopene

This is the red pigment that gives red and pink fruit, such as tomatoes, watermelons, pink grapefruit and guava their characteristic color. A meta-analysis of 18 eligible studies concluded that lycopene intake and PDAC risk were inversely correlated (112). This conclusion was supported later by the mechanistic demonstration that lycopene induces apoptosis in PDAC cells (113). Thus, the overall evidence for the anti-PDAC role of lycopene is significant. However, it has never been tested in combination therapies. Lycopene can also protect against acute pancreatitis and diabetes (e.g., Refs. 114, 115). Accordingly, lycopene may currently be used in a preventative setting. Although it is not known if it would potentiate gemcitabine chemotherapy of PDAC, it could reduce or even prevent the side effects of chemotherapy due to its antioxidant and anti-inflammatory properties (116, 117).

4.2. Zinc

This is an essential mineral found naturally in high concentrations in oysters, crab, beans and pumpkin seeds. It is frequently mentioned as an anticancer agent but the evidence for its possible anti-PDAC effect is quite contradictory (118–120). This is probably due to the multi-faceted role of this metal as a structural component of many proteins and a co-factor in enzymatic reactions. Overall, a meta-analysis concluded that high consumption of zinc was associated with a decreased risk of PDAC (121). Consistent with this, more recent evidence has concluded that zinc dyshomeostasis (caused by the dysfunction of zinc transporters) can contribute to the initiation and/or progression of various cancers, including PDAC (122). Accordingly, the zinc ionophore, clioquinol, was suggested to be efficacious against PDAC (123). Furthermore, “Bhasma” (incinerated processed zinc widely used in Ayurveda for various ailments) could also be effective against PDAC (124). Finally, zinc

could protect against cachexia in PDAC (125). While there is no evidence for possible synergy between chemotherapy and zinc, it has been deemed acceptable for treatment of liver disease (126, 127).

4.3. Selenium

Selenium is a trace element that plants accumulate from soil and convert to organic forms. Thus, it is naturally present in many foods, especially Brazil nuts, seafood, pasta and eggs. Han X *et al.* originally reported anti-PDAC effects of selenium (128, 129). A meta-analysis and a later nested case-control study found no adverse effect on PDAC but a negative association was apparent for patients with body mass index (BMI) higher than 25 (130, 131). Beneficial effects and no adverse effects have also been reported against diabetes (132–134). However, high-level consumption could promote insulin resistance and should be avoided (135).

4.4. Magnesium

Magnesium-rich foods include dark-green leafy vegetables, seeds, wholegrains, fish and nuts. A recent study revealed significantly lower levels of magnesium in urine of PDAC patients compared to healthy controls (136). Consistent with this, a prospective cohort study showed that magnesium supplementation may help prevent PDAC (137). Mechanistic evidence suggested (i) that Mg^{2+} -permeant ion channels associate with PDAC (138) and (ii) that the Mg^{2+} transporter protein SLC41A1 could be a viable anti-PDAC target (139). Indirectly, also, magnesium may reduce the risk of PDAC through its well-established negative relationship with diabetes (140, 141).

4.5. Plumbagin

This is a derivative of naphthalene obtained from the roots of the “chitrak” that has been used in Ayurvedic medicine for more than 2,500 years. A bioinformatics study revealed several “mainstream” cancer signaling mechanisms whereby plumbagin could affect survival, apoptosis and metabolism in PDAC cells (142). Indeed, experimentally, plumbagin has been shown to inhibit the growth of PDAC cells (including CSCs) and induce autophagy in vitro and in vivo and may target the tumor suppressor p53 (142–145). Most recently, Pandey *et al.* showed that plumbagin induced apoptosis in PDAC cells both in monolayers and three-dimensional tumor spheroids (146). This effect

involved production of ROS and cleavage of caspases 3 and 9. Work is ongoing to develop nanoparticles of plumbagin as an anti-angiogenic drug (147).

4.6. Milk Thistle

This has been used as a traditional herbal remedy for almost 2000 years. Its active ingredient, silymarin (major constituent, silibinin/silybin) has been shown to inhibit proliferative activity and angiogenesis in models of PDAC (148). Silibinin also promoted viability and promoted apoptosis and autophagy in human PDAC cells (149). These effects were mediated by increased “stress-activated protein kinase” (JNK/SAPK) signaling. Used by itself, silibinin could suppress tumor growth and cachexia in *in vivo* mouse models of PDAC (150). Silibinin is also well known for its “hepatoprotective” property and for promoting liver regeneration (151). Indeed, a randomized phase two clinical trial on childhood acute lymphoblastic leukemia (ALL) undergoing chemotherapy employed in combination silymarin (milk thistle extract) with the aim of reducing liver toxicity and a positive effect was reported (<https://clinicaltrials.gov/ct2/show/NCT00055718>) (151).

4.7. Berberine

This is an isoquinoline alkaloid extracted from a variety of natural herbs (152). Its molecular targets include upregulation of tumor suppressor genes, activation of AMPK and downregulation of matrix metalloproteinase production, leading to decreased cellular proliferation and invasion (153). *In vitro*, berberine induced apoptosis and suppressed the CSC population in PDAC cell lines even more effectively than gemcitabine (154, 155). Another study showed that berberine inhibited PDAC cell viability by dysregulating cellular energetics by targeting citrate metabolism (156). *In vivo*, also, berberine could reduce tumor growth in mouse models of PDAC (157). In addition, berberine demonstrated insulin-regulating properties and could suppress PDAC also indirectly (158). Consistent with this, it could potentiate the therapeutic effect of metformin (see section 5.2) (159).

4.8. Ginseng

Panax ginseng (“ginseng”) is a perennial plant that grows in East Asia. It is a traditional medicinal herb with a unique family of active saponin ingredients called “ginsenosides”. It is available in various forms

(e.g., fresh, white, steamed, acid-processed and fermented) leading to a range ginsenoside compositions with diverse pharmacological properties (160). Yun & Choi found in an early case-control study concluded ginseng consumption would reduce the risk of PDAC and liver cancer (161, 162). Experimentally, extracts of ginseng (leaves, flowers and roots) and some nanoparticle preparations have been tested against various human PDAC cell lines and shown to inhibit cell viability, proliferation and angiogenesis whilst promoting apoptosis (e.g., Refs. 163–165). Some anti-PDAC effects have also been reported *in vivo* (166, 167). Furthermore, ginseng could delay the development of type 1 diabetes and pancreatitis, both PDAC risk factors, in rats (168, 169). Finally, ginseng has also been reported to enhance the effectiveness of *in vitro* gemcitabine (and some other chemotherapeutic agents) on PDAC cells as well as liver, lung and prostate cancers (170–172).

5. Drug Combinations

Drug combinations refer to more than one drug being taken together. Although this topic is outside the immediate scope of the current review, as another “combination,” we would like to highlight it here for awareness and possible benefit to patients (173). In fact, use of drug combinations is common in cancer therapy and is already applied to PDAC in the form of FOLFIRINOX. A novel approach is including in the combination a drug that has been developed and prescribed for conditions other than cancer (a practice known as “repurposing”). We highlight here two examples of such drug combinations.

5.1. Aspirin

This is a natural agent used commonly against pain and inflammation. Its general health benefits including anticancer properties have been highlighted over many years (174, 175). However, caution has also been expressed as regards its possible detrimental side effects on uncontrolled high blood pressure, bleeding disorders, asthma and stomach ulcers (176, 177). As regards PDAC, evidence suggests that high and medium usage (one or more 75 mg tablet a day) may reduce the risk by as much as 50%, the risk of those who stop taking it subsequently increasing (178, 179). This is through its inhibition of the COX-2 enzyme which indeed is upregulated in PDAC and may promote the disease by enhancing inflammation, a risk factor for PDAC (180). A negative association between

aspirin use and PDAC risk was demonstrated from a meta-analysis (Figure 11A) (181, 183). The association was stronger with increased frequency and duration of aspirin consumption (178, 181, 184). The apparent time-dependent correlation could be due to the fact that development of PDAC begins long before its diagnosis so, to derive benefit, consumption of aspirin should start well before occurrence (185).

In terms of “combination therapy,” aspirin proved an effective adjuvant to gemcitabine in the treatment of PDAC in an in vivo transgenic mouse model (186). This study also showed that the combined treatment prolonged survival by ca. 30% over gemcitabine treatment alone. In an extensive, combined in vitro and in vivo study, including cells taken from PDAC patients, aspirin (at clinical doses) enhanced the effectiveness of gemcitabine in suppressing tumorigenesis (Figure 11B) (182). The effect involved induction of apoptosis, reduction of cell viability and expression of proteins involved in inflammation and stem cell signaling (182). This study also showed that the aspirin + gemcitabine combination significantly prolonged the survival of mice, by some 40%, compared with gemcitabine alone (Figure 11C). Importantly, also, aspirin sensitized cells that were resistant to gemcitabine (182, 187). In a more recent phase 1b clinical trial, aspirin has been included as a part of an immunotherapy/vaccination regime against PDAC (Ref: CHUV-DO-0017_PC-PEPDC_2017) (188).

In conclusion, aspirin can be taken safely in a preventative setting and can also be used in combination with gemcitabine chemotherapy to improve treatment efficacy.

5.2. Metformin

Metformin is the most common oral drug prescribed for type II diabetes (189). Epidemiological evidence suggests that diabetics treated with metformin are less likely to develop PDAC (190). Indeed, meta-analyses revealed that metformin treatment increased survival in diabetic PDAC patients as well as presumed non-diabetics (190, 191).

By inhibiting oxidative phosphorylation, metformin reduces levels of the energy rich compound adenosine triphosphate (ATP) in cells, which in turn downregulates signaling mechanisms involved in cellular survival and proliferation (192). Consistent with this, a study on a transgenic mouse model found that metformin reduced PDAC incidence (quantified by PanIN pathology) by up to 50% (193). Importantly, in in

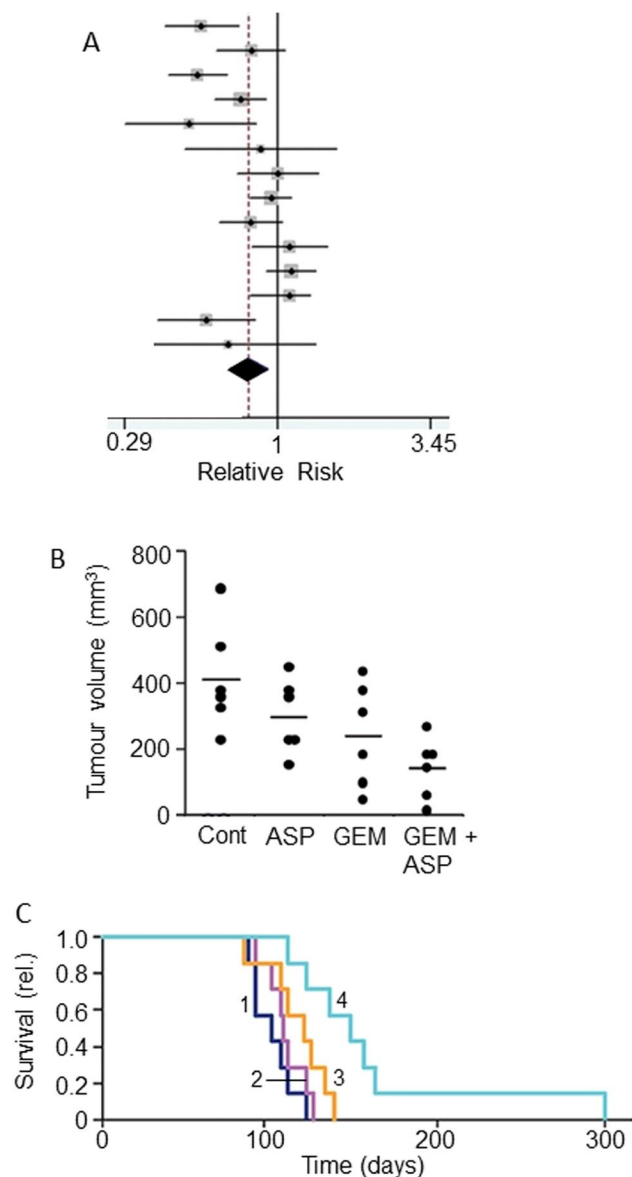


Figure 11. Drug combination: effects of combining aspirin with chemotherapy. A. Forest plot showing improved relative risk of pancreatic cancer resulting from taking aspirin. Diamond indicates the average and the spread of the data. From Qiao *et al.* (181), where further details and primary data can be found. B. Effects of aspirin (ASP), gemcitabine (GEM) and their combination (GEM + ASP) on volume of tumor induced by orthotopic inoculation of PANC-1 cells in immunodeficient mice. There was a clear trend in the data, the combination producing a significant effect compared to the control ($P < 0.05$). Although a marked difference between the effects of GEM + ASP and GEM alone was apparent, this did not reach significance, possibly because of the limited number of experimental animals involved ($n = 6$). C. Data from the same experiment as in (B) showing survival fraction for tumor-bearing mice treated with ASP (2), GEM (3) and their combination (4); control data are indicated as (1). The combination treatment significantly improved survival compared with GEM alone ($P < 0.05$). B and C, from Zhang, Y. *et al.* (182).

vivo mouse models of PDAC, metformin reduced CSC proliferation as well as infiltration and activation of tumor-associated macrophages which contribute to desmoplasia (194). Thus, metformin could induce stromal depletion and enhance penetration of a nanoparticulate form of gemcitabine (195).

There is also increasing evidence that metformin can enhance the effectiveness of gemcitabine (196, 197). Li, X. *et al.* performed a meta-analysis of rather disparate data and concluded that patients taking metformin (with or without chemotherapy) had improved

overall survival compared with a control group not taking metformin (Figure 12A) (198). Subgroup analysis showed that the effect of metformin correlated with tumor stage and was associated with improved survival in patients who had surgery or locally advanced cancer, but not in patients with metastatic disease (198).

The apparent improvement of effectiveness of chemotherapy by metformin is also supported by in vitro experiments involving several human PDAC cell lines (202, 203). In another study, even resistance to gemcitabine was reversed by metformin, albeit in vitro

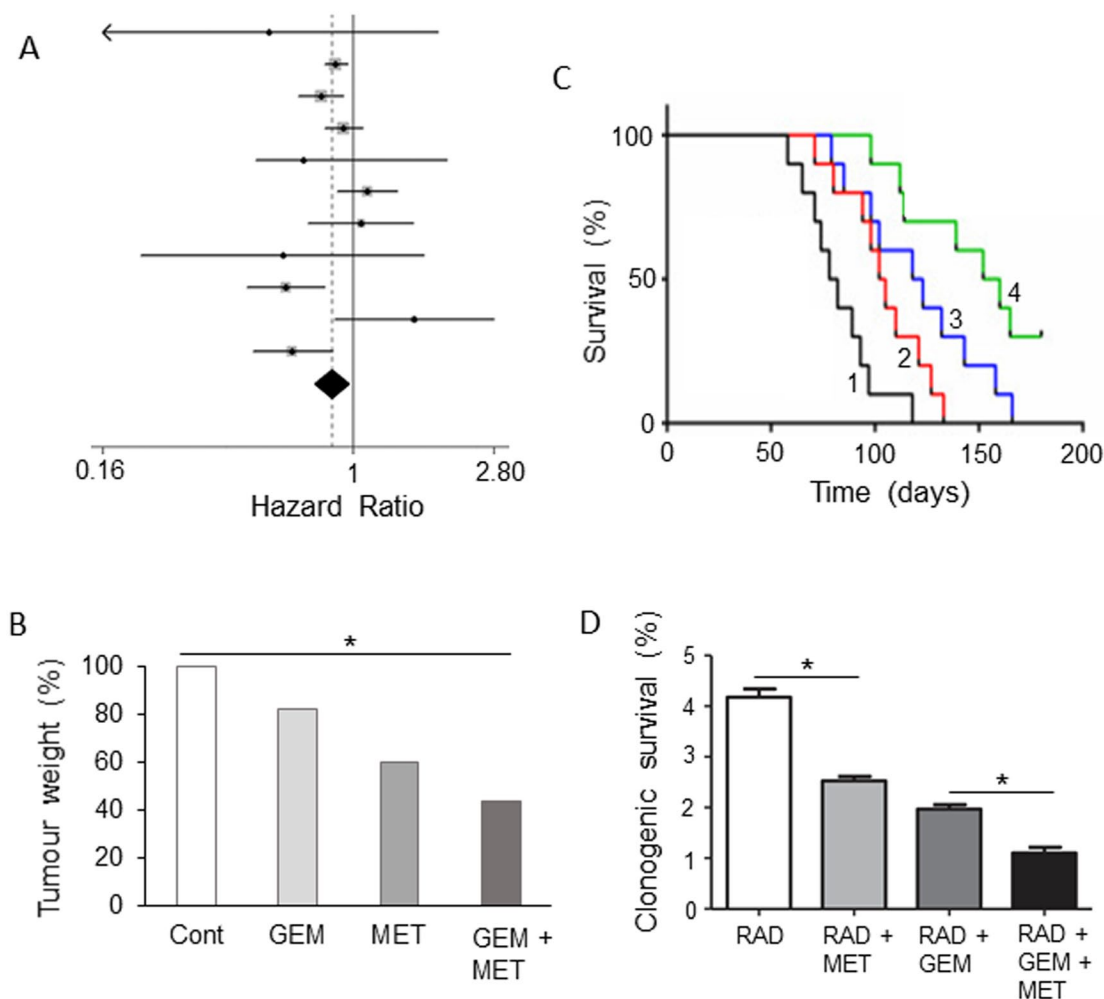


Figure 12. Drug combination: effects of adding metformin to chemotherapy. A. Forest plot demonstrating hazard ratios associated with use of metformin for pancreatic cancer patients. The average (indicated by the diamond) revealed significantly reduced risk ($P=0.01$). Modified from Li, X. *et al.* (198), where further details and primary data can be found. B. Effects of gemcitabine (GEM), metformin (MET) and their combination on tumor weight, compared with untreated controls (Cont), in a gemcitabine-resistant pancreatic cancer (BxG30) mouse xenograft model. Data are plotted relative to the control level at 100%. There was a clear trend, the combination producing a significant effect compared to the control ($P<0.05$). Although a noticeable difference between the effects of GEM+MET and GEM alone was apparent, this did not reach significance. Replotted from data given in Suzuki *et al.* (199). C. Kaplan-Meier survival analysis of KPC mice treated with control/sterile water (1), MET (2), GEM (3) and GEM+MET (4). There was a significant difference between the effects of the combination and GEM alone ($P<0.05$), confirming the beneficial effect of the combined treatment. Modified from Qian *et al.* (200). D. Effects combining metformin (MET) with irradiation (RAD) or RAD+GEM on clonogenic survival of MiaPaCa-2 cells. Survival was quantified as a percentage of total. Adding MET to both RAD or RAD+GEM produced a significant further decrease in survival ($P<0.05$ for both comparisons). Modified from Fasih *et al.* (201).

(204). Only one in vitro study reported inhibition of the pro-apoptotic effect of gemcitabine (205). However, this study involved (i) murine cell lines and (ii) the concentration of metformin used (20 mM) was rather high (cf. Ref. 192). Also, in an in vivo mouse xenograft model of PDAC, metformin demonstrated anti-tumor activity against a drug-resistant tumor (199). Combination of gemcitabine with metformin generated a noticeably further reduction in tumor weight, compared with the effect of gemcitabine alone (Figure 12B) (199). Furthermore, in xenograft and genetically engineered mouse models of PDAC, metformin enhanced significantly the effect of gemcitabine in improving survival (Figure 12C) (200). This enhancement effect was suggested to involve inhibition of CSCs and suppression of angiogenesis (200, 206).

Synergistic effects of combining metformin with radiation (plus gemcitabine in some cases) were observed in PDAC cells in vitro (Figure 12D) (201). This “radiosensitization” effect was thought to involve AMPK (201, 202).

Several clinical trials are evaluating the anti-PDAC potential of metformin by itself and in combined administration with chemotherapy (gemcitabine and *nab*-paclitaxel) and radiotherapy. The trials that have been concluded so far were those on late-stage or gemcitabine-resistant disease and, unfortunately, did not find significant improvement by adding metformin (207, 208). Other trials are still to report.

In conclusion, there is promising preclinical evidence that metformin can be added safely as an adjunct to chemotherapy of PDAC. Currently, this would appear more promising for early-stage disease.

6. Future Perspectives and Conclusion

In our previous study, supported by clinical trial data, we identified six dietary and three nutraceutical agents for integration with gemcitabine chemotherapy of PDAC (16). Here, based upon more limited available evidence, we evaluated another 10 agents (six dietary and four nutraceutical) which, in due course, may be added to the kind of integrative scheme we presented earlier. In fact, remembering the direness of PDAC, these 10 agents could even be introduced into integrated management now since, although the evidence in their favor is limited, there is no associated adverse effect. In addition to the incorporation of such agents, one should remember that integrative lifestyle factors should also be considered for completeness. These would include limited alcohol intake, no smoking, and regular exercise and avoiding obesity (16). In overall conclusion, cancer-causing processes can be

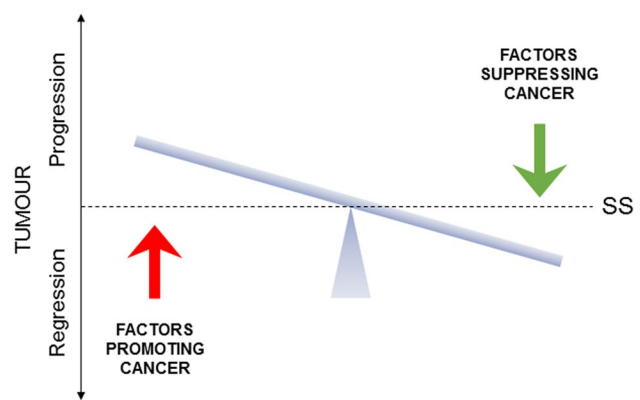


Figure 13. A schematic representation of the homeostatic balance of cancer. The figure illustrates that cancers are under the dynamic influence of opposite factors that promote or suppress the cancer. Depending on their balance, cancer will progress or regress. The horizontal bar indicates steady-state (SS), representing either a cancer-free or a benign state. The ultimate promise of integrated management of cancer is the possibility of living with cancer chronically as long as the balance is kept tilting away from “progression.” Adapted from Djamgoz and Plant (209).

suppressed, and current treatment methods can be potentiated significantly by integrating with complementary factors to the extent that it may ultimately be possible to live with cancer chronically (Figure 13) (209). In fact, any improvement to life expectancy would be hugely beneficial to PDAC patients as research continues intensely in this field and new clinical therapies as well as novel integration regimes can be expected.

In further evaluating the kinds of dietary and nutraceutical agents covered here, a number of issues should be born in mind. These were covered in some detail by Jentzsch *et al.* (16). Some key issues are the quality of the agents and the possible personalized nature of their effects. Future research should aim at ascertaining such issues as well as determining the molecular mechanisms/modes of action of the emerging agents and, most importantly, extending the evaluations to clinical trials.

In overall conclusion, both existing and emerging evidence strongly suggests that introduction of complementary agents and lifestyle factors into mainstream treatment of PDAC can produce significant beneficial effects, as regards both disease status and its side effects (16, 210).

Acknowledgments

This study was funded by The Sunflower Jam charity and is dedicated to the memory of Jon Lord. We thank Ms Vicky Lord and Ms Jacky Paice and, also, the College of

Medicine, Dr Michael Dixon in particular, for encouragement. Our research – *neuroscience solutions to cancer* – overall is supported by the Pro Cancer Research Fund (PCRF).

Conflict of Interest

The authors declare no conflict of interest.

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