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Baicalein – An Intriguing Therapeutic Phytochemical in Pancreatic Cancer

Graham Donald, Kathleen Hertzner, and Guido Eibl*

UCLA Center for Excellence in Pancreatic Diseases, Department of Surgery, David Geffen School of Medicine at UCLA, Los Angeles, California, USA

Abstract

Despite advances in therapy for many of the most common cancers, advances which have led to corresponding improvements in survival rates, progress on the pancreatic cancer front have been slow and mortality rates remain startlingly high. New therapeutic strategies are needed. Phytochemicals are naturally occurring, plant-based substances that have garnered much interest in the research world for their anti-cancer properties, both as therapeutics and as components of the diet for chemoprevention. One particularly ubiquitous group of phytochemicals is the polyphenolic flavonoids. Baicalein, one such flavonoid, which has been widely studied in several malignancies, shows potent activity against pancreatic adenocarcinoma in both *in vitro* and *in vivo* studies. The mechanisms by which baicalein accomplishes this have recently been elucidated, and is through an induction of apoptosis in pancreatic cancer cells that are fiercely resistant to cell death. Compounds such as baicalein, offer promise in dietary chemoprevention, as chemotherapeutic adjuvants, or as targeted therapy.

Keywords

Apoptosis; baicalein; bioavailability; pancreatic cancer; phytochemical; prevention; treatment

PANCREATIC CANCER

It is estimated that in 2012 nearly 44,000 Americans will be diagnosed with pancreatic adenocarcinoma (PDAC) and that over 37,000 people will die of this aggressive disease [1]. As the fourth most common malignancy in the United States, PDAC is unique from other cancers (e.g. prostate, breast, colon) in that the mortality of PDAC approaches its prevalence. The 1- and 5- year survival rates for PDAC are 80% and 4%, respectively, and this has been nearly unchanged for over 60 years [2]. This is partially because a majority of new diagnoses are advanced stage cases (either locally invasive or distantly metastasized) and thus not amenable to surgical therapy, which is currently the only hope for a cure. Early stage PDAC is rarely detected because there are no useful screening biomarkers or imaging techniques (e.g. colonoscopy or mammography) to discover the disease in its pre-malignant or pre-invasive stage, and patient's symptoms are often vague and non-specific, consisting of everything from abdominal or back pain to dyspepsia to unexplained weight loss. The classic presentation of pancreatic cancer is painless jaundice in the setting of a pancreatic

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*Address correspondence to this author at the Department of Surgery, David Geffen School of Medicine at UCLA, 675 Charles E Young Drive South, Los Angeles, CA 90095, USA; Tel: 310 825 5743; Fax: 310 206 2472; geibl@mednet.ucla.edu.

CONFLICT OF INTEREST

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head mass abutting and compressing the common bile duct, but this is often represents advanced disease.

Another reason that PDAC statistics are so grim is that the mainstay chemotherapeutic agent, gemcitabine, is largely ineffective, conferring only a marginal overall survival benefit [3]. Attempts at implementing targeted and combination therapies have been disappointing in their lack of efficacy or toxicity [4, 5]. Pancreatic cancer cells are highly resistant to traditional chemotherapy as they develop a variety of genetic alterations to evade apoptosis.

For these reasons, a change in physicians' strategies in managing PDAC is necessary, and chemoprevention with naturally occurring, low- to non-toxic substances, as well as dietary prevention, are promising avenues for which significant amounts of research have been conducted. As it is thought that the evolution from normal ductal tissue to metastatic disease *via* stepwise genomic mutations is an approximately 15-year process, there is a window during which these interventions may prove useful [6].

DIET AND BIOFLAVONOIDS

The association between diet and PDAC has been well established for over 20 years [7–19]. High fruit and vegetable intake with low amounts of fats, sugars, and meats have all been shown to be associated with lower rates of PDAC in epidemiologic, population-based studies. One particular group of nutrients, the phytonutrients, are found in high concentrations in vegetables, fruits, green tea, and many traditional Chinese herbal remedies, and these have been found to have multiple beneficial properties including anti-inflammatory, antifungal, anti-allergic, antioxidant, and anti-tumorigenic action. Their anti-cancer properties have been demonstrated both *in vitro* and *in vivo*.

Bioflavonoids are one such group of phytonutrients. Bioflavonoids, including quercetin, baicalein, apigenin, luteolin, and myricetin, are the most common polyphenolic compounds in nature and are found ubiquitously in plant life and also in wine, tea, citrus fruits, dark chocolate, and herbs Fig. (1) [20]. They have activity against a multitude of human diseases including an array of different malignancies [21–27]. Of these, one particular compound, baicalein, has been shown to be particularly efficacious against several cancers [28–33]. For example, baicalein has been shown to either decrease proliferation or induce apoptosis in multiple myeloma, prostate cancer, head and neck cancer, and breast cancer. It has also been shown to inhibit cancer cell migration and invasion in hepatoma cells, as well as in skin cancer and breast cancer cells.

BAICALEIN

Baicalein (5,6,7 trihydroxyflavone) is a component of the traditional herbal remedy known as Chinese skullcap (or Huang Qin). This plant, *Scutellaria baicalensis* (SB), is a member of the mint family and is used in Chinese and Japanese medicine for a variety of ailments, most commonly for chronic hepatitis as a component of Sho-saiko-to [34]. While over 50 flavonoids have been isolated from SB, baicalein in particular has been found to have antitumor properties in PDAC. Early research demonstrated a clear reduction in cellular proliferation in one human pancreatic cancer cell line, BxPC-3, when exposed to micromolar concentrations of the compound [35].

Later research revealed that this effect might be the result of the interplay between the lipoxygenase (LOX) pathway and baicalein [36–39]. High-fat diets, and particularly those high in polyunsaturated fatty acids (PUFAs), are associated with a higher risk of cancer, and we have shown this in a transgenic mouse model for PDAC. When fed with a high-fat diet, conditional KrasG12D mice grow larger tumors than mice fed with a normal diet

(unpublished data). PUFAs, some of which are substrates of the lipoxygenase pathway (including arachidonic acids), have been shown to enhance tumorigenesis in pancreatic cancer. Ding *et al.* found that both arachidonic acid and linoleic acid directly stimulate pancreatic cancer cell proliferation *in vitro*. Furthermore, they demonstrated that LOX-5 and LOX-12, enzymes in the LOX pathway, are up-regulated in human pancreatic cancer cells and that blockade of these enzymes with the LOX-12 specific inhibitor baicalein attenuates cancer cell growth. In a series of *in vitro* studies, they were able to demonstrate an induction of apoptosis and morphological changes by baicalein in four separate human pancreatic cell lines (HPAF, MiaPaca-2, Capan-2, and Panc-1).

Tong *et al.* produced similar studies investigating the mechanism for this induction *in vitro* and in xenograft models. They found after treatment with baicalein, human pancreatic cancer cells expressed decreased anti-apoptotic proteins Bcl-2 and Mcl-1 and increased pro-apoptotic protein bax. Furthermore, they found that baicalein induced cytochrome C release and caspase-9 activation, both of which are key signals in the apoptosis pathway. Xenograft models treated with daily baicalein gavage showed smaller tumors compared to controls.

Our own research confirmed the findings of these studies (namely that the antitumor properties of baicalein are attributable to a reduction in the pro-survival/anti-apoptotic Mcl-1 protein), but further elucidated the mechanism by which baicalein accomplishes this [40]. One mechanism whereby baicalein induces apoptosis is caspase-dependent, as inhibiting caspase activity diminishes the pro-apoptotic effect of the compound. Baicalein treated pancreatic cancer cells also showed a reduction in Mcl-1 mRNA, suggesting a transcriptional mechanism.

Multiple studies have shown how Mcl-1 expression (more so than other pro-apoptotic proteins) correlates with cancer cell resistance to chemotherapy and how inhibition of this protein sensitizes the cells to treatment by eliminating a barrier to apoptosis, both in the form of drugs and radiation [41–44]. We highlighted the importance of Mcl-1 as it confers chemoresistance to pancreatic cancer cells. We found that baicalein-induced apoptosis was attenuated with Mcl-1 overexpression and that genetic knockdown of Mcl-1 increased the rate of apoptosis.

The known effects of baicalein on the pancreatic cancer cell cycle are summarized in Fig. (2). Overall, baicalein abrogates pancreatic cancer cell growth in a variety of ways, namely by decreasing expression of protein that enables the cancer cell to evade pre-programmed cell death, by inducing mitochondrial-based apoptosis programs, and by inhibiting the lipoxygenase pathway as this pathway stimulates cell proliferation. It should be noted, however, that baicalein has been shown in other cancer types to act on other cellular targets besides those regulating apoptosis, such as through activation of the ERK pathway in melanoma, or through up-regulation in the expression of PRDX6 in colorectal cancer [45, 46].

BIOAVAILABILITY

Bioavailability is an important concept when considering polyphenolic compounds as therapies or for chemoprevention as it has previously been unknown whether the substances are absorbed in humans in pharmacologic concentrations into the bloodstream, tissues, and tumors. In general, it is thought that only 10% of ingested dietary polyphenols or their conjugates are found in the urine or plasma. Plasma concentrations in humans barely reach 1 μ M [47]. As a point of comparison, the concentrations at which we and others have found baicalein to be anti-proliferative *in vitro* are between 10 μ M and 100 μ M. Thus, the hurdles of low bioavailability of polyphenols aimed at being used for cancer prevention or therapy would need to be overcome. However, it is also possible that the putative anti-tumor effects

of baicalein (and other polyphenolic compounds) are mediated by metabolites that are not readily detected in plasma. It is established in both in rodents and in humans that a majority of baicalein in circulation is in the form of its metabolite, the O-glucuronide baicalin. It is possible that the antitumor properties of baicalein *in vivo* are due to baicalin as opposed to baicalein, as these compounds are inter-converted in the intestine by naturally occurring microbes [48, 49].

To address the concerns that baicalein will not achieve relevant anti-tumor concentrations *in vivo*, the measurement of baicalein (and metabolites) levels locally in the target tissue, e.g. pancreatic cancer, is imperative. There is some thought that the health effects of phytochemicals with low bioavailability are in fact mediated by their effects within the intestinal lumen and that high intestinal absorption is not entirely necessary for this class of compounds to exert their anti-tumor function.

We published a study measuring these levels in nude mice with subcutaneous xenograft tumors [50]. The mice ingested a diet contained 1% of *Scutellaria baicalensis* extract, 20% of which is the flavonoid baicalein, for 13 weeks. After sacrifice, baicalein was found in the plasma, the pancreas, and the xenografted pancreatic tumors in concentrations of 4.37 ± 1.69 $\mu\text{mol/Liter}$, 1.34 ± 0.50 nmol/gram of tissue, and 0.85 ± 0.02 nmol/gram of tumor tissue, respectively. This was measured using high-pressure liquid chromatography (HPLC).

There are numerous clinical trials that have been carried out or are ongoing to study the chemoprotective or chemosensitization/chemopotential of polyphenols [51]. For example, phase II trials studying the flavonoid genistein in both breast and pancreatic cancer patients using soybeans or soy products. The trial in pancreatic cancer did not show any increase in survival when genistein was added to a regimen of gemcitabine and erlotinib, but the trial included only cases of advanced pancreatic cancer and was thus not in the context of chemoprevention but rather chemopotential. Further studies are warranted.

FUTURE DIRECTIONS

To date no animal studies have been performed using a diet supplemented with pure baicalein, as opposed to *Scutellaria baicalensis* (which only has 20% baicalein), nor has any research been done to our knowledge examining the effect of baicalein on pancreatic cancer cell migration or invasion. Thus there is clearly a need to further the scientific knowledge of baicalein in this respect. Furthermore, there seems to be a need to initiate clinical trials using baicalein and other flavonoids examining the efficacy of pancreatic cancer *prevention* as opposed to *potentiation* with other therapeutic agents in advanced cases of cancer where differences in survival are unlikely to be seen.

Research is ongoing in our lab to further clarify the role of baicalein in PDAC. We are in the process of initiating an orthotopic xenograft model of PDAC using human cancer cells lines in SCID-mice and subjecting them to a low concentration, pure baicalein diet (as opposed to one composed of *Scutellaria baicalensis* extract) or a control diet with no known flavonoids. A pilot study feeding mice with this baicalein diet revealed no toxicities and was well tolerated by mice at the baicalein concentration that we selected. Furthermore, we are investigating the anti-migration properties of baicalein on human pancreatic cancer cells lines (unpublished). We have found that baicalein in low micromolar concentrations, at which there is no effect on cellular proliferation, may inhibit migration. This has also been shown to be the case in breast cancer cells *in vitro* [52].

CONCLUSION

PDAC is a heterogeneous and aggressive cancer with multiple phenotypes resulting from different genetic mutations, both from patient to patient and within the same tumor specimen. Despite the promising results of the aforementioned studies in regards to the potent anti-tumor activities of baicalein and its bioavailability and low-toxicity, it is currently unrealistic to imagine that naturally occurring substances such as baicalein could be utilized as monotherapy. However, because they are minimally toxic and the mechanisms by which they induce apoptosis in PDAC cells are known and proven to be efficacious in animal models of the disease, it is reasonable to imagine that they would be a useful adjuvant with more standard, synthetic chemotherapies. Furthermore, because the side effects of ingesting baicalein at the low micromolar concentrations necessary to induce apoptosis are minimal to none, there is the possibility of implementing baicalein into the diet as a nutritional supplement to protect against the development of pancreatic cancer.

Acknowledgments

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Fig. 1.

A 2-Dimensional representation of bioflavonoid family members: Quercetin, Baicalein, Myricetin, Apigenin, and Luteolin. Bioflavonoids are naturally occurring phytonutrients found in food and drink commonly consumed by humans, including wine, fruit, tea and chocolate. Members of this family of chemicals have shown anti-inflammatory, antioxidant, chemo-preventative, cardio-protective and anti-viral activity in the research setting. These compounds have been of great interest recently in multiple cancer research fields given studies exhibiting anti-cancer properties. Bioflavonoids share a common chemical structure built on phenolic and pyrane rings. Variations of these structures occur with the arrangements of multiple hydroxyl, methoxy and glycosidic side groups. During metabolism hydroxyl groups are added or modified *via* methylation, addition of sulfates, or glucuronidation.

Fig. 2.

A simplified schematic of apoptosis showing the effects of Baicalein on known apoptotic mediators. Baicalein has been shown to decrease the expression of Bcl-2 and the amount of Mcl-1, and increase the expression of Bax as well as activate caspase 9 and cytochrome C in *in vitro* work. In general, Mcl-2 and Bcl-2, along with other agents, are pro-survival mediators (A) and provide an environment that promotes cell survival. Alternatively, in a cell death environment, Bax and other proteins (not shown) lead to activation of cytochrome C and caspase 9, among others. In the presence of Baicalein (C), shown in red hexagons, Mcl-1 and bcl-2 are down-regulated, Bax levels are increased and this leads to activation of both cytochrome C and caspase 9, promoting cell death. Proteins are as labeled. Gray shading indicates inactive. Cyto C, cytochrome C. C9, caspase 9. B, baicalein.