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Dietary Manipulation for Therapeutic Effect in Prostate Cancer

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1. Introduction

Given that there is a wealth of literature on the potential effect of a wide variety of phytochemicals on the growth of prostate cancer cells, we have limited our discussion to arguably four of the most important: isoflavones, lycopene, resveratrol, and curcumin. The focus of this review is on the clinical pharmacology of these compounds, as there are already an extensive number of reviews in the literature on all of these compounds for various cancers, including our previous review of isoflavones in prostate cancer (de Souza et al., 2009). Here, we use the loose term “phytochemicals” to describe this group of plant-based compounds with biological activity *in vitro*, for simplicity. Like other phytochemicals, isoflavones, lycopene, resveratrol and curcumin have a wide variety of potential mechanisms of action in many different cancer cell lines. Many of these biological effects involve key components of signal transduction pathways within cancer cells, but in this review, we will be focusing on studies specifically in prostate cancer.

Reactive oxidative species (ROS) may have an overall contribution to the development of cancer (Kryston et al., 2011; Benhar et al., 2002), but the mechanism is far from clear, though the general thrust of the argument is that DNA damage wrought by ROS may be left unchecked or uncorrected by mismatch repair enzymes, thereby contributing to carcinogenesis (Benhar et al., 2002, Ziech et al., 2010, Kryston et al., 2011). However, it is also apparent that higher levels of ROS can activate intrinsic apoptosis (Benhar et al., 2002), which would imply that antioxidants should not be used indiscriminately as it could prevent a desirable outcome in cancer cells. The biological mechanisms underpinning some of the potential anti-oxidant mechanisms of phytochemicals are complex and as yet speculative, and will not be discussed here. Instead, readers are referred to recent reviews (Ziech et al., 2010; Kryston et al., 2011).

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Table 1 lists the major sources of our selected phytochemicals (Holden et al., 1999; Neveu et al., 2010; Nutrient Data, L. & Knovel, 2008; Tayyem et al., 2009), though we acknowledge that many other foods contain smaller amounts as well, though they are not reviewed here.

Food	Curcumin mg/100g	Lycopene mg/100g	Isoflavones mg/100g	Resveratrol mg/100g
Apricots, tinned		0.065		
Bilberry				0.67
Chocolate, dark				0.04
Cranberries, European				1.92
Curry	50-580			
Grape, black				0.15
Grapefruit, pink		1.3-1.5		
Guava, fresh		5.4		
Guava, juice		3.3		
Lingonberry				3.00
Peanut			0.02	0.08
Peanut butter			0.01	0.04
Pistachio			3.6	0.11
Red currant				1.57
Soy paste, miso			41.4	
Soybean, tofu,firm			22.5	
Soybean,tofu, silken			30.0	
Strawberry				0.35
Tomato, raw		3.0		
Tomato, boiled		4.4		
Tomato juice		9.3		
Tomato paste		6.5-29.3		
Tomato, sauce (ketchup)		17.0		
Tomato, tinned		9.7		
Turmeric powder	580-3,140			
Wine, Red				0.27
Wine, Rose				0.12
Wine, White				0.04

Table 1. Dietary sources of selected phytochemicals.

2. Isoflavones

Soy and soy products, rye bread, and red clover, are good sources of flavonoids (Adlercreutz, 2002). Flavonoids, in turn, are made up of isoflavones, flavonones, flavones,

flavonols, catechins, anthocyanins, and chalcones, of which the isoflavones are but a small part, though disproportionately studied. Isoflavone intake is approximately 50mg daily in Asia, about ten times more than in Western countries (Messina et al., 2006).

2.1 Pharmacology

There are many intermediates and metabolites of isoflavones produced in humans, but the majority have not been studied. Genistin, daidzin and glycitin are thought to be the predominant isoflavones found in soy foods, of which the glycoside moiety is the major form with anticancer activity. Through the action of α - glucosidase provided by gut bacteria, and hydrolysis, the conversion of glycosides to aglycones (Setchell et al., 2002; Yuan et al., 2007; Zubik & Meydani, 2003) allows absorption into the blood. One hypothesis for the variable absorption values obtained from studies is the variability of the gut microbacterial environment amongst humans. Some support for this concept was provided by Rufer et al., (2008), who gave pure daidzein in both its aglycone and glycoside forms to seven volunteer men in a randomized, double - blind study, at a dose of 1mg/kg. Bioavailability of the glycoside form was found to be 3-6 times higher than that of the aglycone form, with half - life measured at 6.4h for the glycoside and 8.9h for the aglycone. Given the differences recorded for maximum concentration (C_{max}) and urinary excretion, it is not unreasonable to speculate that this observation could be explained by the time taken by gut microflora to generate metabolites. Inter - individual variability in pharmacokinetic parameters was very high for these metabolites, which clearly could not be explained by differences in pharmacogenomic factors, due to the randomized crossover design.

There are few other pharmacokinetic reports of isoflavones and data are derived largely from single dose administration studies. In general, aglycones appear in the blood within two hours of ingestion (Atkinson et al., 2005; Franke et al., 1995; Richelle et al., 2002; Setchell et al., 2001). Peak plasma concentrations (C_{max}) for aglycones occur at 4-7h, whereas the corresponding time for glycosides is 8-11h, implying that the rate limiting step for absorption is initial hydrolysis of the isoflavone (Setchell et al., 2001; Zubik & Meydani, 2003). After about 48hrs, plasma concentrations are no longer detectable. In a study reported by Setchell et al., (2003), higher doses of isoflavones did not produce linear pharmacokinetic parameters, suggesting that uptake was rate - limiting and saturable. Administration of approximately 80mg isoflavones a day is thought to give concentrations of genistein and daidzein consistent with that found in patients on a high isoflavone diet (Howes et al., 2002).

2.2 *In vitro* data

The literature attests to a large array of potential biological effects of isoflavones, despite their similarity in chemical structure: genistein binds estrogen receptor better than daidzein (Kuiper et al., 1998) for example, and equol is more potent than daidzein in inhibiting prostate cancer cell growth (Hedlund et al., 2003). Genistein produces apoptosis in prostate cancer cells (Kyle et al., 1997), but it is also possible that low doses promote cancer cell growth while higher doses inhibit growth (Bergan et al., 1996). This apparently conflicting data is not limited to isoflavones, and if the potential biphasic effects of phytochemicals are true, the underlying mechanisms for this observation could represent an important area of future research.

Tyrosine kinase phosphorylation appears to be a key event influencing the fate of many cancer cells, and inhibition may increase apoptosis or inhibit prostate cancer cell growth. Some isoflavones appear to have this ability; for example, genistein has been shown to reduce FAK (focal adhesion kinase) activity just prior to apoptosis (Kyle et al., 1997). It can also transiently activate the FAK : beta - 1 - integrin complex (Bergan et al., 1996; Liu et al., 2000), which could theoretically help explain its ability to reduce metastases. Further, isoflavones may reduce activity of ERK1/2 and various cyclin dependent kinases (Agarwal et al., 2000). A range of other potential mechanisms for the growth inhibiting effects of isoflavones have been described (see Table 2).

2.3 *In vivo* data

Soy protein or biochanin A (another isoflavone) inhibits growth and increases apoptosis in the LNCaP prostate cancer xenograft model (Bylund et al., 2000; Rice et al., 2002). Dietary genistein supplementation can reduce the incidence of poorly differentiated adenocarcinoma in a transgenic strain of mice (Mentor-Marcel et al., 2001), and can improve survival. In a model where prostate cancer is induced by chemical carcinogens methyl nitrosourea (NMU) or 3,2-dimethyl-4-aminobiphenyl (DMAB) (Kato et al., 2000), soy protein or genistein can prevent growth (McCormick et al., 2007; Wang et al., 2002). Dose - response studies involving subcutaneously and orthotopically implanted tumours (Zhou et al., 1999; 2002) demonstrated clear reduction of tumor growth with a variety of isoflavone preparations, though changes in a variety of biomarkers were not consistent, and depended on the type of isoflavone preparation.

2.4 Clinical studies in prostate cancer

An interesting study of 40 men randomized post-prostatectomy to a low fat / high isoflavone diet (Li et al., 2008) or a control diet showed lower 6 month IGF-1 concentrations in the treatment group. Sera collected from treated patients were able to reduce *in vitro* growth of LNCaP cancer cells by 20%, suggesting biologically relevant concentrations were achieved. Soy has been shown to suppress growth of localized, but not for advanced disease (Kurahashi et al., 2007), perhaps not surprisingly, since prostate cancer is a heterogenous disease, and more advanced disease may have different underlying biology. Pharmacogenomic work suggests that the reduction in risk of prostate cancer may be positively associated with a greater ability to produce equol from other isoflavones (Akaza et al., 2002, 2004). "Nutrigenomic" factors may therefore play an important part in predicting those who might benefit from phytoestrogen supplementation (Steiner et al, 2008).

Many studies do not show evidence of benefit for isoflavones. One randomized, placebo-controlled trial of 12 weeks treatment with genistein in men with early prostate cancer found no significant difference in PSA levels between the treatment and placebo groups (Kumar et al., 2004), although the authors suggested that surrogate measures were being affected by treatment. Other trials support the idea that isoflavones, even given over relatively short periods of time, can possibly slow the rate of rise of PSA, though no statistically significant conclusions can be drawn (Dalais et al., 2004; Hussain et al., 2003; Maskarinec et al., 2006; Pendleton et al., 2008). Even by administering high doses, up to 600mg genistein daily, no statistically significant PSA changes were noted in a Phase I and

	Action	References
Androgen related functions		
5 α reductase	a. Inhibited by genistein	a. (Evans et al., 1995)
PART-1	a. Prostate androgen regulated transcript 1 inhibited by genistein and daidzein	a. (Yu et al., 2003)
AR	a. Transcriptionally downregulated by genistein b. In LNCaP cells, Lycopene inhibited AR gene element in a dose response manner c. Resveratrol inhibits AR transcription activity in LNCaP d. Curcumin downregulates AR gene expression in androgen dependent and castration resistant prostate cancer cells	a. (Davis et al., 2000; Takahashi et al., 2006; Tepper et al., 2007) b. (Zhang et al., 2010) c. (Wang et al., 2010) d. (Nakamura et al., 2002; Tsui et al., 2008)
PSA	a. mRNA expression and secretion reduced by genistein b. PSA mRNA not downregulated by lycopene in LNCaP c. Resveratrol downregulates expression in LNCaP cells d. Curcumin inhibits PSA expression	a. (Davis et al., 2000; Rice et al., 2007) b. (Peternac et al., 2008) c. (Hsieh & Wu, 2000; Mitchell et al., 1999) d. (Tsui et al., 2008)
Cell survival and proliferation		
DNA synthesis	b. Lycopene reduces DNA synthesis in primary cultures of prostate epithelia	b. (Barber et al, 2006)
Cyclins	a. Cyclin B downregulated by genistein b. Lycopene downregulates cyclin D1 c. C1/Cdk4 kinase and D1, E, B and cdk1 all downregulated by resveratrol in LNCaP lines; resveratrol increases cyclin A and cyclin E in LNCaP cells d. Curcumin downregulates cyclin expression	a. (Davis et al., 1998) b. (Palozza et al., 2010) c. (Benitez et al., 2007; Kuwajerwala et al., 2002) d. (Aggarwal et al., 2009)
Myt-1	a. Upregulated by genistein	a. (Touny & Banerjee, 2006)
Wee-1	a. Phosphorylation reduced by genistein	a. (Touny & Banerjee, 2006)
p21 ^{WAF1}	a. Upregulated by genistein c. Decreased by resveratrol in LNCaP d. Upregulated by curcumin	a. (Davis et al., 1998; Lian et al., 1998) c. (Benitez et al., 2007; Kuwajerwala et al., 2002; Mitchell et al., 1999) d. (Aggarwal et al., 2007)

p27 ^{Kip1}	a. Increased by genistein c. Upregulated by resveratrol in LNCaP only, not in PC-3 cells; repressed by resveratrol in LNCaP cells d. Upregulated by curcumin	a. (Bhatia & Agarwal, 2001; Kazi et al., 2003; Rice et al., 2007) c. (Benitez et al., 2007; Kuwajerwala et al., 2002) d. (Aggarwal et al., 2007)
Protein tyrosine kinase	a. Inhibition of EGF tyrosine kinase activation by genistein c. Resveratrol inhibits tyrosine kinase d. Curcumin inhibits EGF-R signaling	a. (Akiyama et al., 1987) c. (Sallman et al., 2007) d. (Dorai et al., 2000)
PTEN	a. Expression is induced by genistein and daidzein in PC3 and LNCaP	a. (Cao et al., 2006)
Akt	a. Inhibited by genistein b. Lycopene decreases AKT activation, leading to apoptosis in both androgen-responsive and independent PCa cells c. Inhibited by resveratrol d. Inhibited by curcumin; PI3K inhibited by curcumin	a. (Bemis et al., 2004; Li & Sarkar, 2002; El Touny & Banerjee, 2007; Park et al., 2005) b. (Ivanov et al., 2007) c. (Aziz et al., 2006; Chen et al., 2010) d. (Yu et al., 2008; Shankar & Srivastava, 2007)
mTOR	a. Inhibited by genistein c. Resveratrol inhibits mTOR d. Inhibited by curcumin in PC-3 cells,	a. (Rice et al., 2007) c. (Brito et al, 2009; Chen et al., 2010) d. (Yu et al., 2008)
MAPK	a. MAPK inhibited by genistein b. Lycopene, at least partially inhibits MAPK c. MAPK is inhibited by resveratrol d. P38 is activated by curcumin in PC3 cells	a. (Huang et al., 2005; Xu & Bergan, 2006) b. (Palozza et al., 2010) c. (Nguyen et al., 2008) d. (Hilchie et al., 2010)
ERK1/2	a. Inhibited by genistein; induced by isoflavones	a. (Agarwal, 2000; Bhatia & Agarwal, 2001; Wang et al., 2006; Wang et al., 2004)
JNK	a. Activation by genistein d. Activated by curcumin	a. (Lazarevic et al., 2008) d. (Hilchie et al., 2010)
NFκB	a. Inhibited by genistein and soy isoflavones b. Downregulated by resveratrol	a. (Davis et al., 1999; Li & Sarkar, 2002; Raffoul et al., 2007; Singh-Gupta et al., 2009) b. (Benitez et al., 2009)
IGF-1/R	a. Inhibition by genistein b. Lycopene decreases IGF-1R expression in PC-3 cells	a. (Takahashi et al., 2006, Wang et al., 2003) b. (Kanagaraj et al., 2007)

STAT	a. Activated by genistein c. Resveratrol inhibits Src and Jak kinases d. STAT 3 is inhibited by curcumin, but even more so by synthetic analogues of curcumin	a. (Pinski et al., 2006) c. (Sallman et al., 2007) d. (Lin et al., 2009)
TGF β	a. TGF β inhibited by genistein d. IL6 induction via TGF β inhibited via curcumin	a. (Xu & Bergan, 2006) d. (Park et al., 2003)
Apoptosis		
Mdm2	a. Downregulated by genistein d. mRNA reduced by Curcumin in a dose dependent manner	a. (Li et al., 2005) d. (Li et al., 2007)
Bax	a. Increased by genistein b. Lycopene upregulates Bax in LNCaP c. Increased due to resveratrol in LNCaP d. Curcumin upregulates	a. (Kazi et al., 2003) b. (Palozza et al., 2010) c. (Benitez et al., 2007) d. (Shankar & Srivastava, 2007)
Bcl-XL	a. Downregulated by genistein d. Down regulated by curcumin	a. (Li et al., 2001) d. (Shankar & Srivastava, 2007)
XIAP	a. Inhibited by phenoxodiol in ovarian cancer cells and melanoma cells c. Resveratrol promotes interaction of XIAP with Bax to cause apoptosis d. Inhibited by curcumin	a. (Alvero et al., 2006; Herst et al., 2007; Kamsteeg et al., 2003, Kluger et al., 2007; Sapi et al., 2004) c. (Gogada et al., 2011) d. (Deeb et al., 2007)
Caspases	a. Activated and caspase inhibition overcome by phenoxodiol in HN12 cells; Caspase mediation by genistein induced apoptosis c. Resveratrol activates caspase: 9,6,7 and 3 leading to apoptosis d. In PC-3 cells, apoptosis caused by curcumin is independent of caspases; In LNCaP curcumin initiates caspase-dependent mitochondrial death	a. (Aguero et al., 2005; Choueiri et al., 2006; Kumi-Diaka et al., 2000; Kumi-Diaka & Butler, 2000) c. (Benitez et al., 2007) d. (Hilchie et al., 2010) PC-3 results, (Shankar & Srivastava, 2007) LNCaP results
Other targets		
HIF1 α	a. Inhibition by genistein in PC3 cancer cells d. Curcumin inhibits gene transcription of HIF 1 alpha	a. (Singh-Gupta, 2009) d. (Thomas et al, 2008)

VEGF	a. Downregulated by genistein b. Inhibited by lycopene in xenografts c. Suppressed by resveratrol d. Inhibited by curcumin in LNCaP xenografts	a. (Cao et al., 2006; Guo et al., 2007; Li & Sarkar, 2002) b. (Yang, 2011) c. (Ganapathy et al., 2010) d. (Shankar et al., 2007)
ER β	a. Antagonist and partial agonist by genistein; expression reduced by genistein d. Estradiol binding inhibited by > 85% in PC-3 cells	a. (Booth et al., 2006; Cao et al., 2006; Kuiper et al., 1998; Pike et al., 1999; Wang et al., 2006) d. (Shenouda, et al., 2004)
COX-2	a. mRNA and protein expression reduced by genistein in LNCaP and PC3	a. (Swami et al., 2009)
Sphingosine Kinase	a. Inhibited by phenoxodiol in endothelial cells c. Inhibited by resveratrol	a. (Gamble et al., 2006) c. (Brizuela, 2010)
TNOX	a. Inhibited by phenoxodiol	a. (Davies & Bozzo, 2006; DeLuca et al., 2005)
Focal adhesion kinase	a. Activity reduced by genistein	a. (Kyle et al., 1997)
Hypermethylation	a. Reversal of DNA methyltransferase activity by genistein	a. (Fang et al., 2007; Skogseth et al., 2005)
MMP	a. MMP2 and 9 downregulated by genistein; MMP2 expression inhibited by phenoxodiol c. MMP3 and MMP9 suppressed by resveratrol d. Curcumin inhibited expression of MMP2 and MMP9	a. (Gamble et al., 2006; Huang et al., 2005; Kumi-Diaka, 2006; Li & Sarkar, 2002 ; Xu & Bergan, 2006) c. (Ganapathy et al., 2010) d. (Hong et al., 2006)
Urokinase plasminogen activator	a. Inhibited by genistein b. Lycopene upregulates UPA receptor	a. (Jarred et al., 2002) b. (Forbes et al., 2003)

Table 2. Selected molecular targets of phytochemicals in prostate cancer cells: (a), (b), (c), (d) refer to isoflavone, lycopene, resveratrol, and curcumin related literature, respectively. While many of these targets have been shown to be relevant in other cancer cell lines, here we have focused on publications on prostate cancer cell lines.

pharmacokinetic study (Fischer et al., 2004), though serum dehydroepiandrosterone was reduced by 31.7% ($P = 0.0004$) at the end of the study, and estrogenic side effects were encountered. Biologically relevant concentrations of genistein, commensurate with *in vitro* activity, can be achieved with high doses of genistein - enriched isoflavone extracts (Takimoto et al., 2003). Peak plasma concentrations reached between 4.3 and 16.3 μ M at doses up to 8mg/kg orally (equivalent to 560mg for a 70kg person) in this study.

3. Lycopene

Once water is reduced, the lycopene content of tomato products surpasses all other foods, weight for weight. Although lycopene melts at 172-173 degrees Celsius (Zapalis & Beck, 1985), processing and cooking improves availability of tomato-sourced lycopene. Being fat soluble, tomato sources of lycopene are best absorbed when cooked or consumed with a fat, such as with olive oil in Mediterranean cooking (Itsiopoulos et al., 2009). As lycopene synthesis correlates with tomato ripening, it is older, vine ripened-in-the sun tomatoes that offer the highest lycopene content (Ronen et al., 1999). Other sources of lycopene, in descending order of content are: guava, watermelon, pink grapefruit (Mangels et al., 1993), apricots (Curl, 1960) and rosehips (Böhm et al., 2003).

3.1 Pharmacology

Lycopene is a non-provitamin A carotenoid. The frequency of light absorption, due to its alternating double bond system, defines visual color ranging from pink through to deep red. Once consumed, lycopene micelles are believed to be formed by bile salts and along with fat, pass from the mucosa and into general circulation via low-density lipoproteins (Sharma & Goswami, 2011). It is the only carotenoid associated with plasma cholesterol level (Campbell et al., 1994). Within the body, lycopene is preferentially stored in the liver, seminal vesicles and the prostate tissue. In particular it becomes localized to the nuclear membrane and the nuclear matrix, suggesting that it may have a receptor or transporter role. In Western populations, blood lycopene concentrations range from 0.29-0.60 μM , with a half-life of 2-3 days (Schwedhelm et al., 2003).

A Phase I single-dose study on lycopene pharmacokinetics using increasing doses from 10 to 120 mg found dose dependent half-lives between 28 and 62 hours. Lycopene peaks between 16 and 33 hours after dosing levels of 0.075 to 0.21 μM (Gustin et al., 2004).

3.2 *In vitro* data

Like other phytochemicals, many potential mechanisms of action have been put forward to explain the anticancer properties of lycopene. Of relevance to prostate cancer, lycopene has been shown to inhibit DNA synthesis (Barber et al., 2006). Lycopene also inhibits growth of hormone-dependent LNCaP and C4-2 prostate cancer cell lines without affecting PSA mRNA expression (Peternac et al., 2008), and increases expression of PPARgamma and LXRalpha in LNCaP cells (Yang et al., 2011). It also inactivates Ras and reduces NFkappaB, as well as inducing apoptosis in LNCaP cells (Palozza et al., 2010). While it can reduce Akt activation (Ivanov et al., 2007), its ability to induce apoptosis may be cell line-dependent. Other potential mechanisms of action by lycopene in prostate cancer are listed in Table 2.

In combination with docetaxel, lycopene inhibits growth of hormone independent prostate cancer DU145 cells through insulin-like growth factor 1 receptors leading to downstream inhibition of survivin expression and subsequent apoptosis (Tang et al., 2011).

Almost certainly, variations in experimental conditions, doses and techniques could contribute to these apparent biological effects. At physiological concentrations, however, lycopene may not have growth inhibitory effects on a variety of cell lines (Burgess et al., 2008). This was confirmed recently in experiments where supraphysiological concentrations

were required to reduce growth, possibly through alterations in the cell cycle (Ford et al., 2011).

3.3 *In vivo* data

Athymic mice models used by Yang et al., (2011) show strong inhibition of PC3 xenograft growth by high doses of lycopene (16 mg/kg), possibly via increased levels of insulin-like growth factor-binding protein 3, or a reduction in plasma vascular endothelial growth factor (VEGF) levels. In a provocative study of androgen expressing prostate cancer cell lines treated with serum from rats fed a control diet, or diets supplemented with red, or yellow tomato (containing no lycopene), connexin43 (a protein regulating cell growth) was upregulated by both the red and yellow tomato supplemented diet (Gitenay et al., 2007). This suggests tomato compounds other than lycopene may have a role in reducing prostate cancer cell growth; one such candidate might be FruHis, a carbohydrate derivative found in tomato products (Mossine et al., 2008). However, in humans at least, dietary lycopene has been shown to affect gene expression, regardless of whether it is included in its food matrix (Talvas et al., 2010)

In a transgenic mouse model, early intervention with selenium, vitamin E and lycopene supplements was able to significantly reduce prostate cancer and liver metastases (Venkateswaran et al, 2009). Limpens et al., (2006) had earlier reached the same conclusion, but they did not see any activity from the single agents. Naturally, it is difficult to know how much the additional supplements contributed to prostate cancer control, though both groups suggest the combination was important. Not all data are supportive of the growth inhibitory effect of lycopene however, possibly because of differences in the rat model used by Imaida et al., (2001).

3.4 Clinical studies in prostate cancer

Mills et al., (1989), through the Seventh Day Adventist men study, showed a link between low prostate cancer risk and frequent tomato consumption, along with beans, lentils and peas, raisins, dates, and other dried fruit. Giovannucci et al., (2007) performed an analysis on data from the Health Professionals study and found that higher tomato sauce (assumed to be lycopene) intake correlated inversely with prostate cancer incidence; indeed, this was only one of four factors (in addition to African American race, positive family history, and alpha-linolenic acid intake) that predicted for incidence and advanced prostate cancer.

In a small, randomized trial of 30mg lycopene supplementation over 3 weeks prior to prostatectomy, margin positivity at surgery was reduced by lycopene, though no other endpoints were affected (Kucuk et al., 2001). The study was extremely small, and no conclusions can be drawn.

Zhang et al., (2010) recently reported a study in 41 men with localized prostate cancer given 10mg lycopene once a day. Seventy percent of men had a reduced slope of PSA rise, and 21% had a decrease in their PSA levels. However, scant details were available for the study, and we do not know whether there were confounding variables; further, this would appear to be the same patient population as in a previous publication (Barber et al., 2006). In a study of 41 men with localised prostate cancer (Barber et al., 2006) given 20 mg lycopene daily, nearly 70% of patients had a slower rate of PSA rise post-treatment. A study in 20

consecutive men with hormone refractory prostate cancer treated with lycopene 10mg daily had shown a response rate (complete and partial) of 35% (Ansari et al., 2004). However, this phenomenal response rate has not been able to be repeated. Indeed, Vaishampayan et al., (2007) reported a study in 38 men with hormone sensitive and resistant cancer randomized to the lycopene alone arm and found only PSA stabilization, without any patient qualifying for a partial response. Adding soy isoflavones (to men randomized to the other arm) did not appear to improve outcome. Another study in 46 patients with androgen-independent prostate cancer prescribed 15mg lycopene daily found only one patient with a PSA response; toxicity included mainly grade 1-2 diarrhea, nausea, flatulence, and abdominal distension (Jatoi et al., 2007).

4. Resveratrol

Resveratrol is a phytoalexin found in the skins and seeds of red grapes *Vitaceaea vinifera*. Therefore, red wines are especially rich in resveratrol, as is grape juice (Romero-Perez, 1999). Other sources include lentils (as resveratrol-3-O-glucoside), peanuts, dark chocolate and berries (Neveu, 2010).

4.1 Pharmacology

Resveratrol is well-absorbed, but has poor bioavailability due to extensive first pass metabolism by the liver.

A pharmacokinetic study of trans-resveratrol (25, 50, 100 or 150mg single doses, repeated over 13 dosings) showed C_{max} detected 48 to 90 minutes post-dosing (Almeida et al., 2009), but there was wide interindividual variability reported, also noted in another pharmacokinetic study (Nunes et al., 2009). In another study in 40 healthy volunteers given a single dose ten times the quantities used in the previous study (500, 1000, 2,500 or 5,000mg), peak plasma concentrations were achieved in 90 minutes, and were associated with a range of plasma resveratrol concentrations between 73 and 539 ng/mL (Boocock et al., 2007). Absorption may be faster after oral dosing (Goldberg et al., 2003), possibly due to delayed absorption by food (Vaz-da-Silva et al., 2008).

Resveratrol is rapidly metabolized. Radioactively labeled carbon-14 distribution studies (Vitrac et al., 2003) have been performed in mice with trans-resveratrol; it distributes to the stomach, intestines, liver and kidney, regions of highest uptakes. Mice, like men (de Santi et al., 2000 a,b,c) also form both sulfur and glucuronide conjugates, but a proportion remains unchanged as trans-resveratrol. A toxicological study with trans-resveratrol (as resVida®) in rats over 4 weeks has tested up to 300 mg/kg/d, with no observed serious adverse events (Edwards et al., 2011).

A phase I trial and repeated dose study to determine safety, pharmacokinetics and the effect on insulin-like growth factor (IGF) axis by resveratrol was recently reported (Brown et al., 2010). Doses of 0.5, 2.5 or 5.0 g per day over 29 days was given to forty volunteers. Levels of resveratrol metabolites in plasma were about 20 times higher than that of free resveratrol, and a reduction of circulating plasma IGF-1 and IGFBP-3 was noted ($P < 0.04$ in both). It is not clear to what extent the metabolites contributed to the fall in plasma IGF-1 and IGFBP-3 levels.

4.2 *In vitro* data

Resveratrol results in dose-dependent inhibition of PI3K and pAkt in LNCaP cells that in turn modulates anti-apoptotic bcl2 family proteins (Aziz et al., 2006). Resveratrol reduces ERK 1/2 activation in PC3 cells (Stewart & O'Brian, 2004) amongst many other targets; some of these are listed in Table 2. For example, resveratrol also reduces the activity of clusterin by functioning as a tyrosine kinase inhibitor (Sallman et al., 2007), phosphoAkt and mTOR (Chen et al., 2010), and NFkB (Benitez et al., 2009). Resveratrol causes growth inhibition in typical prostate cancer cell lines: PC-3, DU145, and LNCaP (Hsieh & Wu, 1999), but interestingly, whole cranberry extract (containing resveratrol) was also effective in inducing apoptosis (Maclean et al., 2011). As in all whole-food extract studies, however, there is no certainty that the molecule of interest is responsible for the effect seen.

4.3 *In vivo* data

In a PC3 xenograft study, resveratrol alone inhibited tumour growth, enhanced TRAIL induced apoptosis, and inhibited angiogenesis (Ganapathy et al., 2010). Resveratrol is also able to reduce or delay prostate cancer in the TRAMP mouse model (Slusarz et al., 2010), possibly via inhibition of HedgeHog signaling. Conflicting evidence was provided by Wang et al., (2008), who found that resveratrol increased angiogenesis and inhibited apoptosis, at least in LNCaP xenografts.

4.4 Clinical studies in prostate cancer

A review on clinical trials of resveratrol has already been recently published (Patel et al., 2011), and will not be discussed in detail here. Selected prostate cancer trials are listed in Table 3.

Resveratrol dosing studies have been performed at up to 5 grams per day. However, mild gastrointestinal side effects (abdominal pain, nausea, diarrhea) were common in subjects administered resveratrol at a dose 1g daily (Brown et al., 2010; Elliott et al., 2009; la Porte et al., 2010). A Phase I study of resveratrol in 10 volunteers demonstrated that even at the highest 5 g per day cohort, saturation kinetics were not observed (Boocock et al., 2007) and that plasma concentrations remained quite low, 500 ng/mL. This possibly is considerably less than the 5 μ M concentration required for *in vitro* activity, but six plasma and urine metabolites were identified; whether these compounds contribute to the anticancer activity of resveratrol remains unknown. Two monoglucuronide metabolites of resveratrol area under the curve concentrations were 23-fold higher than that of cis-resveratrol (Boocock et al., 2007). Inter-individual pharmacokinetic variability has been found to be high (Almeida et al., 2009). Complicating the picture is that other phytochemicals ingested in the diet, such as quercetin and to a lesser degree, kaempferol, fisetin, apigenin and myricetin, may inhibit phenol sulfotransferase and in doing so, increase resveratrol absorption (de Santi et al., 2000 a, b).

As the studies in Table 3 have noted, data for resveratrol are not all favourable or particularly convincing. The reasons are not well understood, but could include ineffective plasma concentrations derived from inadequate doses, inter-individual pharmacokinetic

Intervention / Diet	Design	Outcome	Reference
Isoflavones			
	N=34. Randomized crossover trial. 6 week intervention	Reduced cholesterol but no change in PSA	(Urban et al., 2001)
Single dose formulations of genistein, daidzein, glycitein	Pharmacokinetic study	Mean elimination half - lives of genistein was 3.2h and daidzein was 4.2h	(Busby et al., 2002)
160mg daily of red clover isoflavone preparation (genistein, daidzein, formonnetin, biochanin A)	N=38, pilot study of treatment prior to prostatectomy. 18 treated vs 18 untreated patients. Non - randomized and non - blinded study	Apoptosis in treated patient specimens significantly higher than controls. No changes in PSA, testosterone.	(Jarred, 2002)
Soy isoflavone preparation for 3 - 6 months	N=41, Pilot study in 3 groups (watchful waiting, rising PSA after local therapy, hormone insensitive)	Reduction of rate of rise of PSA in whole group. Serum genistein concentrations increased from 0.11 to 0.65 μ M and daidzein from 0.11 to 0.51 μ M. PSA stabilization in 83% of hormone sensitive group and 35% hormone insensitive patients	(Hussain et al., 2003)
Single doses of two soy isoflavone preparations	N=13. Phase I dose escalation with genistein at 2, 4, 8mg/kg.	Cmax between 4.3 and 16.3 μ M, half - life between 15 and 22h.	(Takimoto et al., 2003)
Approximately 300mg or 600mg genistein and daidzein in soy formulation	N=20. Phase I multiple dose, orally over 84 days	31% reduction in dehydroepiandrosterone. Possibly slowing of PSA rise (non - significant)	(Fischer et al., 2004)
Soy vs Soy + linseed vs wheat in bread diet	N=29, Pilot study. randomized comparison prior to prostatectomy	-12% and 24% change in PSA and free/total ratio respectively. In favour of phytoestrogen activity.	(Dalais et al., 2004)
Genistein - rich extract for 6 months	N=62, range of rising PSA states including post - prostatectomy, off cycle during intermittent hormones, surveillance.	One patient had PSA decline >50% and 8 patients had PSA decline <50%.	(de Vere White et al., 2004)
60mg soy isoflavone preparation	N=59 evaluable patients who completed 12 weeks treatment. Gleason grade 6 or less.	Reduction of testosterone in 61% of treatment group vs 33% of controls. PSA stabilization in 69% of treatment group vs 55% controls.	(Kumar et al., 2004)
Supplement of soy, isoflavones, lycopene, silymarin, antioxidants	N=46 (intent to treat). Randomized, double blind, crossover analysis. 10 week treatment periods separated by 4 week washout	Statistically significant reduction in slope of PSA induced by treatment. Increase in PSA doubling time from 445 to 1150 days (2.6 fold) with supplement	(Schroder et al., 2005)

Intervention / Diet	Design	Outcome	Reference
240mg clover phytoestrogens daily for 2 weeks prior to prostatectomy	N=20, pilot study, placebo controlled.	Non - significant decline in testosterone levels, but compensated rise in LH levels	(Rannikko et al., 2006)
High or low soy diet for 3 months	N=24, randomized crossover to alternative diet after 1 month washout	Decline of PSA (not significant) of 14% while on high soy diet	(Maskarinec et al., 2006)
Lycopene with or without soy isoflavones for 6 months	N=71, includes hormone sensitive and resistant patients. Randomized trial.	95% of patients in lycopene group and 67% of patients in the combined group achieved PSA stabilization.	(Vaishampayan et al., 2007)
80mg daily, purified isoflavones	N=50 men with prostate cancer Gleason grad 6 or less completed treatment. Randomized, placebo controlled, double blind	No changes in sex hormones or PSA over 12 weeks	(Kumar et al., 2007)
Soy milk 3 times daily for 12 months	N=20, open label study observing rate of PSA rise after local therapy	Regression modeling showed slowing of the rate of PSA rise, from 56% per year to 20% per year while on study	(Pendleton et al., 2008)
Soy isoflavone supplement for 2 -4 weeks prior to prostatectomy	N=25 (12 placebo, 13 soy). Randomized, double blind, placebo controlled	Tissue COX-2 mRNA expression were reduced by soy isoflavones. Statistically significant correlation between isoflavone levels and p21 mRNA expression in the treatment group.	(Swami et al., 2009)
Soy vs Soy + linseed vs wheat in bread diet	N=29, Pilot study. randomized comparison prior to prostatectomy	-12% and 24% change in PSA and free/total ratio respectively. In favour of phytoestrogen activity.	(Dalais et al., 2004)
Lycopene			
15 mg Lycopene daily for 6 months	N=18, Phase II pilot study in men with advanced hormone refractory disease. 29% withdrew from the study before the end of the 6 month observation period.	Endpoints included PSA progression rate, QOL, analgesic use. Stable PSA noted in 29%, but otherwise no benefit.	(Schwenke, et al., 2009)
30 mg/d lycopene supplement tomato oleoresin (LycoRed®)	N=105. Randomized Phase II, placebo controlled, double blind study in African Americans. 21 day treatment prior to prostate biopsy.	Mean Plasma lycopene concentration 0.74 to 1.43 $\mu\text{mol/L}$ ($P < 0.0001$), Mean Prostate tissue lycopene 0.45 to 0.59 pmol/mg . No significant changes in 8-oxo-deoxyguanosine or malondialdehyde was seen.	(van Breemen et al., 2011)

Intervention / Diet	Design	Outcome	Reference
3 months of 30mg lycopene per day, 3g fish oil per day, or placebo	N = 69 (22 on lycopene, 21 on fish oil, 26 placebo). Randomized, Phase II double-blind trial.	IGF-1 and COX-2 gene expression did not change compared to placebo in men with early stage, low grade prostate cancer.	(Chan et al., 2011)
10mg daily for 3 months	N=20, metastatic hormone refractory prostate cancer	One patient (5%) with complete response, 6 with partial response (30%)	(Ansari & Gupta, 2004)
10mg daily	N=41, localized prostate cancer on surveillance	Regression slopes of (log) PSA vs time decreased in 26/37 (70%, 95% CI: 53–84%) of the patients after supplementation and in eight cases (21%) the post-treatment slope was negative	(Barber et al., 2006)
15mg, 30mg, or 45mg for 30 days	N=45, randomized to one of 3 doses of lycopene prior to prostatectomy	No toxicity, but reduced serum free testosterone and increased total estradiol was noted.	(Kumar et al., 2008)
Resveratrol			
Trans-resveratrol at: 0, 25, 50, 100 and 150 mg, 6 times/d for 13 doses-	Double blind, randomized, placebo controlled Healthy volunteers, N=40, as 4 x 10 per group 5 males Phase I	Mean plasma concentration was 3.9, 7.4, 23.1 and 63.8 ng/mL and peaked in 0.8-1.5 hours post dose: Mean area under curve for plasma, post the 13 th dose was 3.1, 11.2, 33.0 and 78.9 ng/mL; coefficients of variation >40% Adverse events were mild and similar between groups, but low plasma concentrations achieved	(Almeida, et al., 2009)
2 g resveratrol BID over 8 days	N=8 Healthy subjects Steady state and pharmacokinetics study Tolerability with food, quercetin and alcohol Phase I	6/8 has loose stool or mild diarrhea at the start of the study 1 subject developed rash and headache	(la Porte et al., 2010)
Up to 975 mg/d as: 25, 50, 100, 150 mg given 6 times per day over 2 days	N=8 Healthy volunteers Double blind Randomized Placebo-controlled Phase I 4 men, one per dosing level	Mild adverse events experienced; low plasma concentrations achieved	(Almeida, , 2009)
28 day x 36 µg resveratrol per day- as Chardonnay cava wine containing <i>trans</i> -resveratrol, <i>cis</i> -resveratrol, and <i>cis</i> -piceid	Healthy volunteers Phase I	Decrease in inflammatory markers: IL-6, high sensitivity CRP, intercellular adhesion molecule-1 (ICAM-1), monocyte chemo attractant protein 1 (MCP-1)	(Soleas et al., 2002)
270 mg/d resveratrol over 7 days	N=19 Phase I	"did not cause discomfort"	(Wong et al., 2010)

Intervention / Diet	Design	Outcome	Reference
2.5 versus 5 g per day for 28 days	N = Healthy volunteers Phase I	Mild and reversible AEs	(Elliott et al., 2009)
Single resveratrol doses of 0.5, 1, 2.5 and 5 g using 500 mg capsules	Healthy volunteers 10/level = 40 Pharmacokinetic study and metabolite	6 metabolites found in urine and plasma No serious adverse events Peak Plasma 539 ng/mL 1.5 hour post dose, peak AUC for metabolites were up to 23 time that of resveratrol, rapid urinary excretion.	(Boocock et al., 2007)
25mg to 5 g resveratrol	Dose escalation Phase I 40 Healthy volunteers	No evidence of saturation with a continuing linear response-very limited plasma concentrations, at high 5 g intake only 500 ng/mL levels achieved	(Boocock et al., 2007a,b)
500 mg caps resveratrol At 0.5, 1, 1.25 or 5.0 g once daily over 29 days	Healthy adults 22 Males, 18 Females Safety, Pharmacokinetics Phase I	Lower IGF-1 and IGFBP-3 in plasma. In all ,28/40 healthy adults had at least one adverse event,: nausea, diarrhea or abdominal pain, all above 1 g daily	(Brown et al., 2010)
Curcumin			
Soy isoflavones (40mg) + Curcumin (100mg) or placebo for 6 months	Randomised trial, N=85 men who had previous prostate biopsies but were negative for cancer and PIN.	PSA reduction was greater in subgroup of men who had higher baseline PSA value, but overall, there was no statistical difference between those who had supplements and those on placebo	(Ide et al., 2010)

Table 3. Selected clinical trials of phytochemicals in prostate cancer.

and pharmacodynamic variability, and other factors such as drug interaction. For example, resveratrol has been shown to inhibit cytochrome P 450; 3A4, 2D6, 2C9 and alternately induce 1A2 (Chow et al., 2010), a key factor that has not been taken into account in many clinical studies. Theoretically, interactions with concomitant medications whilst on trial may therefore result in either unwanted toxicity or reduced concentrations of resveratrol.

5. Curcumin

Curcumin is only found as an active component of whole or ground turmeric, within the rhizome or root nodule, specifically of two branches of the ginger family, Zingiberaceas, of the species, *Curcuma longa* Linneas, *Curcuma aromatica* or *Curcuma zantorrhiza* and in tropical ginger, *Zingiber cassumaunar*. In India, turmeric in dried curry powders range considerably from 10 to 32% (Govindarajan, 1980).

5.1 Pharmacology

Structurally, curcumin (diferuloylmethane, a polyphenolic molecule) is a diketone and can also be classified as a phenylpropanoid. It is known to have poor solubility and poor

bioavailability (Anand et al., 2007). Absorption and transformation occurs at the intestinal wall, where enzymes such as sulfotransferases, UDP-glucosyltransferase, and P450 ensure its rapid breakdown (Ireson et al., 2002). Pharmacokinetic studies, including Phase I and other trials confirm the poor bioavailability of the compound (Cheng et al., 2001; Sharma et al., 2004; Garcea et al., 2005; Garcea et al., 2004). Data from these studies show that curcumin seems to be absorbed from the gut within 1-2hrs, and doses up to 8000mg have produced minimal toxicity. Nausea and diarrhea have been the principal toxicities encountered. Vareed et al (2008) studied doses of either 10g or 12g in volunteers, and found C_{max} to be around 1.7-2.3 ug/mL, with time taken to reach maximum concentration (T_{max}) and half-life estimated to be 3.3h and 6.8h, respectively. Sharma et al., (2004) studied escalating doses in a Phase I trial up to 3.6g daily and found no dose-limiting toxicity. Mild nausea and diarrhea was encountered, but plasma concentrations of only around 10nM could be elicited in this study; nevertheless, inducible PGE₂ production was reduced by about 50-60% at that dose level.

5.2 *In vitro* data

There is a wealth of literature on the potential mechanism of action of curcumin *in vitro* (see Table 2), but it is not clear which is the predominant mode of action. It is highly likely that different mechanisms of action exist for different cell lines. Curcumin can inhibit Akt and mTOR in PC3 cell lines (Yu et al., 2008), and enhance Apo2L/TRAIL induced apoptosis, at least in ovarian cancer cells (Wahl et al., 2007). EF24, a curcumin analogue, and curcumin itself can inhibit HIF1alpha gene transcription in PC3 prostate cancer cells (Thomas et al., 2008). Teiten et al., (2011) showed that curcumin induced cell cycle arrest in G₂ phase and could modulate Wnt signaling in androgen-dependent prostate cancer cells, but not in androgen-independent cells.

Apoptotic and growth inhibitory pathways are affected by curcumin in numerous ways (Ravindran et al., 2009). One example is its ability to abrogate survival mechanisms via suppression of constitutive and inducible NF-kappaB activation (Mukhopadhyay et al., 2001). It can also induce apoptosis of DU145 and LNCaP, associated with reduction of expression of Bcl2 and bcl-xL (Mukhopadhyay et al., 2001).

5.3 *In vivo* data

Curcumin inhibits LNCaP xenograft growth, induces apoptosis, and sensitizes tumours to TRAIL induced apoptosis (Shankar et al., 2007). Others have also demonstrated the growth inhibitory properties of curcumin *in vivo* (Barve et al., 2008; Khor et al., 2006), possibly via antiangiogenic mechanisms such as reduction of MMP-2 and MMP-9 expression (Hong et al., 2006). Liposomal encapsulation of curcumin, particularly in combination with resveratrol, significantly reduces prostate cancer tumours *in vivo* (Narayanan et al., 2009).

5.4 Clinical studies

Despite the intense interest in curcumin as a possible cancer prevention agent, there is a surprising lack of clinical data in prostate cancer. Efforts have focused on improving bioavailability by incorporating curcumin in nanoparticles, or developing more potent analogues. Whilst ongoing trials in prostate cancer are yet to be reported, the only trial we

could find described a randomized study of the combination of soy isoflavone and curcumin compared to placebo in men who did not have prostate cancer after undergoing prostate biopsy (Ide et al., 2010); its relevance for prostate cancer can therefore be questioned.

6. Studies on the the combination of phytochemicals and androgen ablation

Even though androgen suppression for metastatic disease is effective treatment, invariably, castrate resistance develops. However the recent development of new drugs that act on the androgen receptor (AR) suggest that there is still a role for androgen manipulation beyond the point traditionally defined as “castration resistance”. As a result, there is renewed interest in whether phytochemicals modulate androgen receptor function in prostate cancer. It appears each phytochemical discussed in this review accomplishes androgen receptor inhibition, but all may use different mechanisms. For example, isoflavones have been shown to reduce androgen receptor transcription (Gao et al., 2004), and down regulate prostate androgen-regulated transcript-1 gene expression (Yu et al, 2003), whereas androgen receptor gene element is inhibited by lycopene in a dose-dependent manner in studies with LNCaP cells (Zhang et al., 2010). Lycopene appears to interact with AR by affecting β -catenin nuclear localization and inhibiting IGF-1 stimulated prostate cancer growth (Kucuk et al., 2002; Liu et al 2008). Resveratrol functions include the inhibition of androgen receptor transcription activity (Wang et al., 2010; Shi et al 2009) and down regulation of PSA expression (Mitchell at al, 1999; Hsieh & Wu, 2000) as tested in LNCaP cell lines. Others have shown that it also inhibits DNA binding of androgen receptor (Harada et al., 2011). Finally, androgen receptor function is inhibited by curcumin in LNCaP (Tsui et al., 2008) and in PC3 (Nakamura et al., 2002) cell lines. Curcumin appears to down regulate transactivation and expression of AR and AR-related cofactors, including activator protein-1 (AP-1), NF- κ B, and cAMP response element binding protein (CREB) (Nakamura et al., 2002).

Burich et al., (2008), showed that the combination of genistein combined polysaccharide (GCP) and bicalutamide had enhanced activity against LNCaP and LNCaPR237H cell lines. Presumably, the basis of synergistic activity observed was the ability of GCP to downregulate AR and suppress mTOR (Tepper et al., 2007).

7. Studies on the combination of phytochemicals and chemotherapy

In many clinical studies, the possibility that something other than the phytochemical of interest, obtained from the diet, may influence outcome has probably not been given sufficient weight in the literature. Given that foods contain many phytochemicals other than those proposed to have anti-cancer activity, it is surprising to find little work on the potential synergistic or antagonistic interactions between different phytochemicals on cancer cell lines. Further, since many experiments involve unspecified doses, sources and contents of phytochemicals, it is not possible to conclude whether true synergistic growth inhibition occurs when these agents are used in combination.

Synergy or enhanced activity has been reported in prostate cancer cell lines using isoflavones in combination with paclitaxel (Ping et al., 2010), radiation (Raffoul et al., 2007), and docetaxel (Burich et al., 2008). Phenoxodiol, a novel isoflavone, in combination with

cisplatin has been shown to be synergistic against DU145 cells and probably additive in PC3 cells (McPherson et al., 2009). *In vivo* combination therapy of soy isoflavones and radiation for prostate cancer has also been investigated, with favorable effects on the control of the disease (Raffoul et al., 2007; Wang et al., 2006).

Docetaxel effect in castration-resistant prostate cancer patients was improved by lycopene via insulin-like growth factor 1 receptor perturbation (Tang et al., 2011). Using an animal model to confirm these findings, a 38% improvement over docetaxel was found ($P=0.047$). Lycopene appeared to work by inhibiting IGF-1 stimulation and increasing expression and secretion of IGF-BP3. Downstream effects included reduced AKT kinase activity and survivin production and increased apoptosis.

Resveratrol enhances ionizing radiation - induced cell death in DU145 cells, which are thought to be relatively radiation-resistant (Scarlati et al., 2007), and as previously noted, enhances TRAIL-induced apoptosis *in vivo* (Ganapathy et al., 2010). Radiosensitisation properties, at least in PC3 cells, also appear to belong to curcumin (Chendil et al., 2004; Li et al., 2007), and like resveratrol, curcumin also enhances TRAIL-induced apoptosis in prostate cancer cells (Deeb et al., 2005). Synergy between curcumin and a number of cytotoxic agents including doxorubicin, 5FU and paclitaxel occurs in PC3 and DU145 cells (Hour et al., 2002), as well as gemcitabine in PC3 (Li et al., 2007).

The advantage of finding synergy lies in an increased benefit: risk ratio if compounds being combined are more effective (synergistic) without necessarily being more toxic, particularly if they are known to be well-tolerated as single agents. Further, because some phytochemicals have poor bioavailability, the discovery of synergistic interactions with other phytochemicals in prostate cancer gives rise to the hypothesis that therapeutic effects may be obtained from a variety of combinations, even though individual phytochemicals may have questionable clinical effect.

8. Conclusions

The literature surrounding the idea of using phytochemicals for the prevention of prostate cancer is considerable, yet there are disproportionately few clinical studies, and just about none that show a convincing effect for biological outcomes in a clinical setting. Showing meaningful outcomes in a prostate cancer prevention trial with phytochemicals would ideally involve a prospective, randomized, placebo controlled trial that would require large numbers of patients to provide statistical power. Given that prostate cancer patients can live for many years, long-term follow up, is also required. Both of these requirements make such studies extremely difficult to mount. Nevertheless, many have investigated the effect of phytochemical administration in men with established prostate cancer (see Table 3). The lack of standardization in endpoints (eg. PSA, sex hormone changes) means that drawing systematic conclusions from such data is problematic, if not impossible. Other flaws in these studies include short-term administration of the phytochemical in question, highly variable sources, preparations and combinations, underpowered studies, and almost certainly inadequate dosing and scheduling of these compounds. However, the wealth of preclinical literature concerning the potential use and mechanisms of action of phytochemicals for prostate cancer will no doubt continue to provide impetus for therapeutic trials for some time to come. There are some serious pharmacological challenges in simply administering a

single agent though, and it remains to be seen whether new approaches such as developing analogues of phytochemicals, or improving their bioavailability through better formulations will ultimately prove successful.

9. Acknowledgements and statement of conflict of interest

Carol Gano is funded by an Australian Postgraduate scholarship. Prof. de Souza is a holder of a project grant from the Prostate Cancer Foundation of Australia, and a Translational Cancer Research Grant from the NSW Cancer Institute. Prof. de Souza was a consultant in 2002 for Novogen Pty Ltd, the manufacturer of phenoxodiol.

10. References

- Adlercreutz, H. "Phyto-Oestrogens and Cancer." *Lancet Oncol* 3, no. 6 (2002): 364-73.
- Agarwal, C., Y. Sharma & R. Agarwal. "Anticarcinogenic Effect of a Polyphenolic Fraction Isolated from Grape Seeds in Human Prostate Carcinoma Du145 Cells: Modulation of Mitogenic Signaling and Cell-Cycle Regulators and Induction of G1 Arrest and Apoptosis." *Mol Carcinog* 28, no. 3 (2000): 129-38.
- Aggarwal, B. B., S. Banerjee, U. Bharadwaj, B. Sung, S. Shishodia & G. Sethi. "Curcumin Induces the Degradation of Cyclin E Expression through Ubiquitin-Dependent Pathway and up-Regulates Cyclin-Dependent Kinase Inhibitors P21 and P27 in Multiple Human Tumor Cell Lines." *Biochem Pharmacol* 73, no. 7 (2007): 1024-32.
- Aggarwal, B. B. & B. Sung. "Pharmacological Basis for the Role of Curcumin in Chronic Diseases: An Age-Old Spice with Modern Targets." *Trends Pharmacol Sci* 30, no. 2 (2009): 85-94.
- Aguero, M. F., M. M. Facchinetti, Z. Sheleg & A. M. Senderowicz. "Phenoxodiol, a Novel Isoflavone, Induces G1 Arrest by Specific Loss in Cyclin-Dependent Kinase 2 Activity by P53-Independent Induction of P21waf1/Cip1." *Cancer Res* 65, no. 8 (2005): 3364-73.
- Akaza, H., N. Miyanaga, N. Takashima, S. Naito, Y. Hirao, T. Tsukamoto, T. Fujioka, M. Mori, W. J. Kim, J. M. Song & A. J. Pantuck. "Comparisons of Percent Equol Producers between Prostate Cancer Patients and Controls: Case-Controlled Studies of Isoflavones in Japanese, Korean and American Residents." *Jpn J Clin Oncol* 34, no. 2 (2004): 86-9.
- Akaza, H., N. Miyanaga, N. Takashima, S. Naito, Y. Hirao, T. Tsukamoto & M. Mori. "Is Daidzein Non-Metabolizer a High Risk for Prostate Cancer? A Case-Controlled Study of Serum Soybean Isoflavone Concentration." *Jpn J Clin Oncol* 32, no. 8 (2002): 296-300.
- Akiyama, T., J. Ishida, S. Nakagawa, H. Ogawara, S. Watanabe, N. Itoh, M. Shibuya & Y. Fukami. "Genistein, a Specific Inhibitor of Tyrosine-Specific Protein Kinases." *J Biol Chem* 262, no. 12 (1987): 5592-5.
- Almeida, L., M. Vaz-da-Silva, A. Falcao, E. Soares, R. Costa, A. I. Loureiro, C. Fernandes-Lopes, J. F. Rocha, T. Nunes, L. Wright & P. Soares-da-Silva. "Pharmacokinetic and Safety Profile of Trans-Resveratrol in a Rising Multiple-Dose Study in Healthy Volunteers." *Mol Nutr Food Res* 53 Suppl 1 (2009): S7-15.

- Alvero, A. B., D. O'Malley, D. Brown, G. Kelly, M. Garg, W. Chen, T. Rutherford & G. Mor. "Molecular Mechanism of Phenoxodiol-Induced Apoptosis in Ovarian Carcinoma Cells." *Cancer* 106, no. 3 (2006): 599-608.
- Anand, P., A. B. Kunnumakkara, R. A. Newman & B. B. Aggarwal. "Bioavailability of Curcumin: Problems and Promises." *Mol Pharm* 4, no. 6 (2007): 807-18.
- Ansari, M. S. & N. P. Gupta. "Lycopene: A Novel Drug Therapy in Hormone Refractory Metastatic Prostate Cancer." *Urol Oncol* 22, no. 5 (2004): 415-20.
- Atkinson, C., C. L. Frankenfeld & J. W. Lampe. "Gut Bacterial Metabolism of the Soy Isoflavone Daidzein: Exploring the Relevance to Human Health." *Exp Biol Med (Maywood)* 230, no. 3 (2005): 155-70.
- Aziz, M. H., M. Nihal, V. X. Fu, D. F. Jarrard & N. Ahmad. "Resveratrol-Caused Apoptosis of Human Prostate Carcinoma LNCaP Cells Is Mediated Via Modulation of Phosphatidylinositol 3'-Kinase/Akt Pathway and Bcl-2 Family Proteins." *Molecular Cancer Therapeutics* 5, no. 5 (2006): 1335-41.
- Barber, N. J., X. Zhang, G. Zhu, R. Pramanik, J. A. Barber, F. L. Martin, J. D. H. Morris & G. H. Muir. "Lycopene Inhibits DNA Synthesis in Primary Prostate Epithelial Cells *in Vitro* and Its Administration Is Associated with a Reduced Prostate-Specific Antigen Velocity in a Phase I Clinical Study." *Prostate Cancer Prostatic Dis* 9, no. 4 (2006): 407-13.
- Barve, A., T. O. Khor, X. Hao, Y. S. Keum, C. S. Yang, B. Reddy & A. N. Kong. "Murine Prostate Cancer Inhibition by Dietary Phytochemicals--Curcumin and Phenylethylisothiocyanate." *Pharm Res* 25, no. 9 (2008): 2181-9.
- Bemis, D. L., J. L. Capodice, M. Desai, R. Buttyan & A. E. Katz. "A Concentrated Aglycone Isoflavone Preparation (Gcp) That Demonstrates Potent Anti-Prostate Cancer Activity *in Vitro* and *in Vivo*." *Clin Cancer Res* 10, no. 15 (2004): 5282-92.
- Benhar, M., D. Engelberg & A. Levitzki. "Ros, Stress-Activated Kinases and Stress Signaling in Cancer." *EMBO Rep* 3, no. 5 (2002): 420-5.
- Benitez, D. A., M. A. Hermoso, E. Pozo-Guisado, P. M. Fernandez-Salguero & E. A. Castellon. "Regulation of Cell Survival by Resveratrol Involves Inhibition of Nf Kappa B-Regulated Gene Expression in Prostate Cancer Cells." *Prostate* 69, no. 10 (2009): 1045-54.
- Benitez, D. A., E. Pozo-Guisado, A. Alvarez-Barrientos, P. M. Fernandez-Salguero & E. A. Castellon. "Mechanisms Involved in Resveratrol-Induced Apoptosis and Cell Cycle Arrest in Prostate Cancer-Derived Cell Lines." *J Androl* 28, no. 2 (2007): 282-93.
- Bergan, R., E. Kyle, P. Nguyen, J. Trepel, C. Ingui & L. Neckers. "Genistein-Stimulated Adherence of Prostate Cancer Cells Is Associated with the Binding of Focal Adhesion Kinase to Beta-1-Integrin." *Clin Exp Metastasis* 14, no. 4 (1996): 389-98.
- Bhatia, N. & R. Agarwal. "Detrimental Effect of Cancer Preventive Phytochemicals Silymarin, Genistein and Epigallocatechin 3-Gallate on Epigenetic Events in Human Prostate Carcinoma Du145 Cells." *Prostate* 46, no. 2 (2001): 98-107.
- Böhm, V., K. Fröhlich & R. Bitsch. "Rosehip -- a "New" Source of Lycopene?" *Molecular Aspects of Medicine* 24, no. 6 (2003): 385-89.
- Boocock, D. J., G. E. Faust, K. R. Patel, A. M. Schinas, V. A. Brown, M. P. Ducharme, T. D. Booth, J. A. Crowell, M. Perloff, A. J. Gescher, W. P. Steward & D. E. Brenner. "Phase I Dose Escalation Pharmacokinetic Study in Healthy Volunteers of Resveratrol, a Potential Cancer Chemopreventive Agent." *Cancer Epidemiol Biomarkers Prev* 16, no. 6 (2007): 1246-52.

- Boocock, D. J., K. R. Patel, G. E. Faust, D. P. Normolle, T. H. Marczylo, J. A. Crowell, D. E. Brenner, T. D. Booth, A. Gescher & W. P. Steward. "Quantitation of Trans-Resveratrol and Detection of Its Metabolites in Human Plasma and Urine by High Performance Liquid Chromatography." *J Chromatogr B Analyt Technol Biomed Life Sci* 848, no. 2 (2007): 182-7.
- Booth, N.L., C.R. Overk, P. Yao, J.E. Burdette, D. Nikolic, S. Chen, J.L. Bolton, R.B. van Breemen, G.F. Pauli and N.R. Farnsworth. "The Chemical and Biologic Profile of a Red Clover (*Trifolium pratense* L.) Phase II Clinical Extract" *The Journal of Alternative and Complementary Medicine* no.12 (2006): 133-139.
- Brito, P. M., R. Devillard, A. Negre-Salvayre, L. M. Almeida, T. C. Dinis, R. Salvayre & N. Auge. "Resveratrol Inhibits the Mtor Mitogenic Signaling Evoked by Oxidized Ldl in Smooth Muscle Cells." *Atherosclerosis* 205, no. 1 (2009): 126-34.
- Brizuela, L., A. Dayon, N. Doumerc, I. Ader, M. Golzio, J. C. Izard, Y. Hara, B. Malavaud & O. Cuvillier. "The Sphingosine Kinase-1 Survival Pathway Is a Molecular Target for the Tumor-Suppressive Tea and Wine Polyphenols in Prostate Cancer." *FASEB J* 24, no. 10 (2010): 3882-94.
- Brown, V. A., K. R. Patel, M. Viskaduraki, J. A. Crowell, M. Perloff, T. D. Booth, G. Vasilinin, A. Sen, A. M. Schinas, G. Piccirilli, K. Brown, W. P. Steward, A. J. Gescher & D. E. Brenner. "Repeat Dose Study of the Cancer Chemopreventive Agent Resveratrol in Healthy Volunteers: Safety, Pharmacokinetics, and Effect on the Insulin-Like Growth Factor Axis." *Cancer Res* 70, no. 22 (2010): 9003-11.
- Burgess, L.C., E. Rice, T. Fischer, J.R. Seekins, T.P. Burgess, S.J. Sticka & K. Klatt. "Lycopene Has Limited Effect on Cell Proliferation in Only Two of Seven Human Cell Lines (Both Cancerous and Noncancerous) in an *in Vitro* System with Doses across the Physiological Range." *Toxicology in Vitro* 22, no. 5 (2008): 1297-300.
- Burich, R.A., W.S. Holland, R.L. Vinall, C. Tepper, R.W. De Vere White & P.C. Mack. "Genistein Combined Polysaccharide Enhances Activity of Docetaxel, Bicalutamide and Src Kinase Inhibition in Androgen-Dependent and Independent Prostate Cancer Cell Lines." *BJU International* 102, no. 10 (2008): 1458-66.
- Busby, M. G., A. R. Jeffcoat, L. T. Bloedon, M. A. Koch, T. Black, K. J. Dix, W. D. Heizer, B. F. Thomas, J. M. Hill, J. A. Crowell & S. H. Zeisel. "Clinical Characteristics and Pharmacokinetics of Purified Soy Isoflavones: Single-Dose Administration to Healthy Men." *American Journal of Clinical Nutrition* 75, no. 1 (2002): 126-36.
- Bylund, A., J. X. Zhang, A. Bergh, J. E. Damber, A. Widmark, A. Johansson, H. Adlercreutz, P. Aman, M. J. Shepherd & G. Hallmans. "Rye Bran and Soy Protein Delay Growth and Increase Apoptosis of Human LNCaP Prostate Adenocarcinoma in Nude Mice." *Prostate* 42, no. 4 (2000): 304-14.
- Campbell, D. R., M. D. Gross, M. C. Martini, G. A. Grandits, J. L. Slavin & J. D. Potter. "Plasma Carotenoids as Biomarkers of Vegetable and Fruit Intake." *Cancer Epidemiol Biomarkers Prev* 3, no. 6 (1994): 493-500.
- Cao, F., T. Y. Jin & Y. F. Zhou. "Inhibitory Effect of Isoflavones on Prostate Cancer Cells and Pten Gene." *Biomed Environ Sci* 19, no. 1 (2006): 35-41.
- Chan, J. M., V. Weinberg, M. J. Magbanua, E. Sosa, J. Simko, K. Shinohara, S. Federman, M. Mattie, M. Hughes-Fulford, C. Haqq & P. R. Carroll. "Nutritional Supplements, Cox-2 and Igf-1 Expression in Men on Active Surveillance for Prostate Cancer." *Cancer Causes & Control* 22, no. 1 (2011): 141-50.

- Chen, Q., S. Ganapathy, K. P. Singh, S. Shankar & R. K. Srivastava. "Resveratrol Induces Growth Arrest and Apoptosis through Activation of Foxo Transcription Factors in Prostate Cancer Cells." *PLoS One* 5, no. 12 (2010): e15288.
- Chendil, D., R. S. Ranga, D. Meigooni, S. Sathishkumar & M. M. Ahmed. "Curcumin Confers Radiosensitizing Effect in Prostate Cancer Cell Line Pc-3." *Oncogene* 23, no. 8 (2004): 1599-607.
- Cheng, A. L., C. H. Hsu, J. K. Lin, M. M. Hsu, Y. F. Ho, T. S. Shen, J. Y. Ko, J. T. Lin, B. R. Lin, W. Ming-Shiang, H. S. Yu, S. H. Jee, G. S. Chen, T. M. Chen, C. A. Chen, M. K. Lai, Y. S. Pu, M. H. Pan, Y. J. Wang, C. C. Tsai & C. Y. Hsieh. "Phase I Clinical Trial of Curcumin, a Chemopreventive Agent, in Patients with High-Risk or Pre-Malignant Lesions." *Anticancer Res* 21, no. 4B (2001): 2895-900.
- Choueiri, T. K., R. Wesolowski & T. M. Mekhail. "Phenoxodiol: Isoflavone Analog with Antineoplastic Activity." *Curr Oncol Rep* 8, no. 2 (2006): 104-7.
- Chow, H. H., L. L. Garland, C. H. Hsu, D. R. Vining, W. M. Chew, J. A. Miller, M. Perloff, J. A. Crowell & D. S. Alberts. "Resveratrol Modulates Drug- and Carcinogen-Metabolizing Enzymes in a Healthy Volunteer Study." *Cancer Prev Res (Phila)* 3, no. 9 (2010): 1168-75.
- Curl, A.L.. "The Carotenoids of Apricots." *Journal of Food Science* 25, no. 2 (1960): 190-96.
- Dalais, F. S., A. Meliala, N. Wattanapenpaiboon, M. Frydenberg, D. A. Suter, W. K. Thomson & M. L. Wahlqvist. "Effects of a Diet Rich in Phytoestrogens on Prostate-Specific Antigen and Sex Hormones in Men Diagnosed with Prostate Cancer." *Urology* 64, no. 3 (2004): 510-5.
- Davies, S. L. & J. Bozzo. "Spotlight on Tnox: A Tumor-Selective Target for Cancer Therapies." *Drug News Perspect* 19, no. 4 (2006): 223-5.
- Davis, J. N., O. Kucuk & F. H. Sarkar. "Genistein Inhibits Nf-Kappa B Activation in Prostate Cancer Cells." *Nutr Cancer* 35, no. 2 (1999): 167-74.
- Davis, J. N., N. Muqim, M. Bhuiyan, O. Kucuk, K. J. Pienta & F. H. Sarkar. "Inhibition of Prostate Specific Antigen Expression by Genistein in Prostate Cancer Cells." *International Journal of Oncology* 16, no. 6 (2000): 1091-7.
- Davis, J. N., B. Singh, M. Bhuiyan & F. H. Sarkar. "Genistein-Induced Upregulation of P21waf1, Downregulation of Cyclin B, and Induction of Apoptosis in Prostate Cancer Cells." *Nutr Cancer* 32, no. 3 (1998): 123-31.
- De Luca, T., D. M. Morre, H. Zhao & D. J. Morre. "Nad⁺/Nadh and/or Coq/Coqh₂ Ratios from Plasma Membrane Electron Transport May Determine Ceramide and Sphingosine-1-Phosphate Levels Accompanying G1 Arrest and Apoptosis." *BioFactors* 25, no. 1-4 (2005): 43-60.
- de Santi, C., A. Pietrabissa, F. Mosca & G. M. Pacifici. "Glucuronidation of Resveratrol, a Natural Product Present in Grape and Wine, in the Human Liver." *Xenobiotica* 30, no. 11 (2000): 1047-54.
- de Santi, C., A. Pietrabissa, R. Spisni, F. Mosca & G. M. Pacifici. "Sulphation of Resveratrol, a Natural Compound Present in Wine, and Its Inhibition by Natural Flavonoids." *Xenobiotica* 30, no. 9 (2000): 857-66.
- — —. "Sulphation of Resveratrol, a Natural Product Present in Grapes and Wine, in the Human Liver and Duodenum." *Xenobiotica* 30, no. 6 (2000): 609-17.
- de Souza P., Russell, P. J., Kearsley, J.H., Howes, L.G. "Clinical pharmacology of isoflavones and its relevance for potential prevention of prostate cancer" *Nutrition Reviews* 68 no. 9 (2010): 542-555.

- Deeb, D., H. Jiang, X. Gao, S. Al-Holou, A. L. Danyluk, S. A. Dulchavsky & S. C. Gautam. "Curcumin [1,7-Bis(4-Hydroxy-3-Methoxyphenyl)-1-6-Heptadine-3,5-Dione; C₂₁H₂₀O₆] Sensitizes Human Prostate Cancer Cells to Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand/Apo2l-Induced Apoptosis by Suppressing Nuclear Factor-Kappab Via Inhibition of the Prosurvival Akt Signaling Pathway." *Journal of Pharmacology and Experimental Therapeutics* 321, no. 2 (2007): 616-25.
- Deeb, D. D., H. Jiang, X. Gao, G. Divine, S. A. Dulchavsky & S. C. Gautam. "Chemosensitization of Hormone-Refractory Prostate Cancer Cells by Curcumin to Trail-Induced Apoptosis." *J Exp Ther Oncol* 5, no. 2 (2005): 81-91.
- deVere White, R. W., R. M. Hackman, S. E. Soares, L. A. Beckett, Y. Li & B. Sun. "Effects of a Genistein-Rich Extract on PSA Levels in Men with a History of Prostate Cancer." *Urology* 63, no. 2 (2004): 259-63.
- Dorai, T., N. Gehani & A. Katz. "Therapeutic Potential of Curcumin in Human Prostate Cancer. ii. Curcumin Inhibits Tyrosine Kinase Activity of Epidermal Growth Factor Receptor and Depletes the Protein." *Molecular Urology* 4, no. 1 (2000): 1-6.
- Edwards, J. A., M. Beck, C. Riegger & J. Bausch. "Safety of Resveratrol with Examples for High Purity, Trans-Resveratrol, Resvida." *Annals of the New York Academy of Sciences* 1215, no. 1 (2011): 131-37.
- El Touny, L. H. & P. P. Banerjee. "Akt Gsk-3 Pathway as a Target in Genistein-Induced Inhibition of Tramp Prostate Cancer Progression toward a Poorly Differentiated Phenotype." *Carcinogenesis* 28, no. 8 (2007): 1710-7.
- Elliott, P. J., S. M. Walpole, L. Morelli, P. D. Lambert, W. Lunsman, C. H. Westphal & S. Lavu. "Resveratrol/Srt501 Sirtuin Sirt1 Activator Treatment of Type 2 Diabetes." *Drugs of the Future* 34, no. 4 (2009): 291-95.
- Evans, B. A., K. Griffiths & M. S. Morton. "Inhibition of 5 Alpha-Reductase in Genital Skin Fibroblasts and Prostate Tissue by Dietary Lignans and Isoflavonoids." *J Endocrinol* 147, no. 2 (1995): 295-302.
- Fang, M., D. Chen & C. S. Yang. "Dietary Polyphenols May Affect DNA Methylation." *Journal of Nutrition* 137, no. 1 Suppl (2007): 223S-28S.
- Fischer, L., C. Mahoney, A. R. Jeffcoat, M. A. Koch, B. E. Thomas, J. L. Valentine, T. Stinchcombe, J. Boan, J. A. Crowell & S. H. Zeisel. "Clinical Characteristics and Pharmacokinetics of Purified Soy Isoflavones: Multiple-Dose Administration to Men with Prostate Neoplasia." *Nutr Cancer* 48, no. 2 (2004): 160-70.
- Forbes, K., K. Gillette & I. Sehgal. "Lycopene Increases Urokinase Receptor and Fails to Inhibit Growth or Connexin Expression in a Metastatically Passaged Prostate Cancer Cell Line: A Brief Communication." *Exp Biol Med (Maywood)* 228, no. 8 (2003): 967-71.
- Ford, N. A., A. C. Elsen, K. Zuniga, B. L. Lindshield & J. W. Erdman, Jr. "Lycopene and Apo-12'-Lycopenal Reduce Cell Proliferation and Alter Cell Cycle Progression in Human Prostate Cancer Cells." *Nutr Cancer* 63, no. 2 (2011): 256-63.
- Franke, A. A., L. J. Custer, C. M. Cerna & K. Narala. "Rapid Hplc Analysis of Dietary Phytoestrogens from Legumes and from Human Urine." *Proc Soc Exp Biol Med* 208, no. 1 (1995): 18-26.
- Gamble, J. R., P. Xia, C. N. Hahn, J. J. Drew, C. J. Drogemuller, D. Brown & M. A. Vadas. "Phenoxodiol, an Experimental Anticancer Drug, Shows Potent Antiangiogenic Properties in Addition to Its Antitumour Effects." *Int J Cancer* 118, no. 10 (2006): 2412-20.

- Ganapathy, S., Q. Chen, K.P. Singh, S. Shankar & R.K. Srivastava. "Resveratrol Enhances Antitumor Activity of Trail in Prostate Cancer Xenografts through Activation of Foxo Transcription Factor." *PLoS One* 5, no. 12 (2010): e15627.
- Gao, S., G. Z. Liu & Z. Wang. "Modulation of Androgen Receptor-Dependent Transcription by Resveratrol and Genistein in Prostate Cancer Cells." *Prostate* 59, no. 2 (2004): 214-25.
- Garcea, G., D. P. Berry, D. J. Jones, R. Singh, A. R. Dennison, P. B. Farmer, R. A. Sharma, W. P. Steward & A. J. Gescher. "Consumption of the Putative Chemopreventive Agent Curcumin by Cancer Patients: Assessment of Curcumin Levels in the Colorectum and Their Pharmacodynamic Consequences." *Cancer Epidemiol Biomarkers Prev* 14, no. 1 (2005): 120-5.
- Garcea, G., D. J. Jones, R. Singh, A. R. Dennison, P. B. Farmer, R. A. Sharma, W. P. Steward, A. J. Gescher & D. P. Berry. "Detection of Curcumin and Its Metabolites in Hepatic Tissue and Portal Blood of Patients Following Oral Administration." *Br J Cancer* 90, no. 5 (2004): 1011-5.
- Giovannucci, E. "Does Prostate-Specific Antigen Screening Influence the Results of Studies of Tomatoes, Lycopene, and Prostate Cancer Risk?" *J Natl Cancer Inst* 99, no. 14 (2007): 1060-2.
- Gitenay, D., B. Lyan, J. Talvas, A. Mazur, S. George, C. Caris-Veyrat & E. Rock. "Serum from Rats Fed Red or Yellow Tomatoes Induces Connexin43 Expression Independently from Lycopene in a Prostate Cancer Cell Line." *Biochem Biophys Res Commun* 364, no. 3 (2007): 578-82.
- Gogada, R., V. Prabhu, M. Amadori, R. Scott, S. Hashmi & D. Chandra. "Resveratrol Induces P53-Independent, X-Linked Inhibitor of Apoptosis Protein (Xiap)-Mediated Bax Protein Oligomerization on Mitochondria to Initiate Cytochrome C Release and Caspase Activation." *J Biol Chem* 286, no. 33 (2011): 28749-60.
- Goldberg, D. M., J. Yan & G. J. Soleas. "Absorption of Three Wine-Related Polyphenols in Three Different Matrices by Healthy Subjects." *Clin Biochem* 36, no. 1 (2003): 79-87.
- Govindarajan, V. S. "Turmeric--Chemistry, Technology, and Quality." *Crit Rev Food Sci Nutr* 12, no. 3 (1980): 199-301.
- Guo, Y., S. Wang, D. R. Hoot & S. K. Clinton. "Suppression of Vegf-Mediated Autocrine and Paracrine Interactions between Prostate Cancer Cells and Vascular Endothelial Cells by Soy Isoflavones." *J Nutr Biochem* 18, no. 6 (2007): 408-17.
- Gustin, D. M., K. A. Rodvold, J. A. Sosman, V. Diwadkar-Navsariwala, M. Stacewicz-Sapuntzakis, M. Viana, J. A. Crowell, J. Murray, P. Tiller & P. E. Bowen. "Single-Dose Pharmacokinetic Study of Lycopene Delivered in a Well-Defined Food-Based Lycopene Delivery System (Tomato Paste-Oil Mixture) in Healthy Adult Male Subjects." *Cancer Epidemiol Biomarkers Prev* 13, no. 5 (2004): 850-60.
- Harada, N., K. Atarashi, Y. Murata, R. Yamaji, Y. Nakano & H. Inui. "Inhibitory Mechanisms of the Transcriptional Activity of Androgen Receptor by Resveratrol: Implication of DNA Binding and Acetylation of the Receptor." *J Steroid Biochem Mol Biol* 123, no. 1-2 (2011): 65-70.
- Hedlund, T. E., W. U. Johannes & G. J. Miller. "Soy Isoflavonoid Equol Modulates the Growth of Benign and Malignant Prostatic Epithelial Cells *in Vitro*." *Prostate* 54, no. 1 (2003): 68-78.
- Herst, P. M., T. Petersen, P. Jerram, J. Baty & M. V. Berridge. "The Antiproliferative Effects of Phenoxodiol Are Associated with Inhibition of Plasma Membrane Electron

- Transport in Tumour Cell Lines and Primary Immune Cells." *Biochem Pharmacol* 74, no. 11 (2007): 1587-95.
- Hilchie, A. L., S. J. Furlong, K. Sutton, A. Richardson, M. R. Robichaud, C. A. Giacomantonio, N. D. Ridgway & D. W. Hoskin. "Curcumin-Induced Apoptosis in Pc3 Prostate Carcinoma Cells Is Caspase-Independent and Involves Cellular Ceramide Accumulation and Damage to Mitochondria." *Nutr Cancer* 62, no. 3 (2010): 379-89.
- Holden, J.M., A.L. Eldridge, G.R. Beecher, I. M. Buzzard, S. Bhagwat, C.S. Davis, L.W. Douglass, S. Gebhardt, D. Haytowitz & S. Schakel. "Carotenoid Content of U.S. Foods: An Update of the Database." *Journal of Food Composition and Analysis* 12, no. 3 (1999): 169-96.
- Hong, S. I., H. J. Kwak, M. J. Park, H. Cho, C. M. Park, S. I. Moon, H. C. Lee, I. C. Park, M. S. Kim & C. H. Rhee. "Transforming Growth Factor-Beta 1 Induces Tissue Inhibitor of Metalloproteinase-1 Expression Via Activation of Extracellular Signal-Regulated Kinase and Sp1 in Human Fibrosarcoma Cells." *Molecular Cancer Research* 4, no. 3 (2006): 209-20.
- Hour, T. C., J. Chen, C. Y. Huang, J. Y. Guan, S. H. Lu & Y. S. Pu. "Curcumin Enhances Cytotoxicity of Chemotherapeutic Agents in Prostate Cancer Cells by Inducing P21(Waf1/Cip1) and C/Ebpbeta Expressions and Suppressing Nf-Kappab Activation." *Prostate* 51, no. 3 (2002): 211-8.
- Howes, J., M. Waring, L. Huang & L. G. Howes. "Long-Term Pharmacokinetics of an Extract of Isoflavones from Red Clover (*Trifolium Pratense*)." *J Altern Complement Med* 8, no. 2 (2002): 135-42.
- Hsieh, T. C. & J. M. Wu. "Differential Effects on Growth, Cell Cycle Arrest, and Induction of Apoptosis by Resveratrol in Human Prostate Cancer Cell Lines." *Exp Cell Res* 249, no. 1 (1999): 109-15.
- — —. "Grape-Derived Chemopreventive Agent Resveratrol Decreases Prostate-Specific Antigen (PSA) Expression in LNCaP Cells by an Androgen Receptor (Ar)-Independent Mechanism." *Anticancer Res* 20, no. 1A (2000): 225-8.
- Huang, X., S. Chen, L. Xu, Y. Liu, D. K. Deb, L. C. Plataniias & R. C. Bergan. "Genistein Inhibits P38 Map Kinase Activation, Matrix Metalloproteinase Type 2, and Cell Invasion in Human Prostate Epithelial Cells." *Cancer Res* 65, no. 8 (2005): 3470-8.
- Hussain, M., M. Banerjee, F. H. Sarkar, Z. Djuric, M. N. Pollak, D. Doerge, J. Fontana, S. Chinni, J. Davis, J. Forman, D. P. Wood & O. Kucuk. "Soy Isoflavones in the Treatment of Prostate Cancer." *Nutr Cancer* 47, no. 2 (2003): 111-7.
- Ide, H., S. Tokiwa, K. Sakamaki, K. Nishio, S. Isotani, S. Muto, T. Hama, H. Masuda & S. Horie. "Combined Inhibitory Effects of Soy Isoflavones and Curcumin on the Production of Prostate-Specific Antigen." *Prostate* 70, no. 10 (2010): 1127-33.
- Ireson C.R., DJL Jones, S. Orr, MWH Coughtrie, DJ Boocock, ML Williams, PB Farmer, WP Steward & A J Gescher. "Metablisim of the Cancer Chemopreventive Agent Curcumin in Human and Rat Intestine." *Ca Epi Bio & Prev* 11 (2002) :105- 111.
- Imaida, K., S. Tamano, K. Kato, Y. Ikeda, M. Asamoto, S. Takahashi, Z. Nir, M. Murakoshi, H. Nishino & T. Shirai. "Lack of Chemopreventive Effects of Lycopene and Curcumin on Experimental Rat Prostate Carcinogenesis." *Carcinogenesis* 22, no. 3 (2001): 467-72.
- Itsiopoulos, C., A. Hodge & M. Kaimakamis. "Can the Mediterranean Diet Prevent Prostate Cancer?" *Molecular Nutrition & Food Research* 53, no. 2 (2009): 227-39.

- Ivanov, N. I., S. P. Cowell, P. Brown, P. S. Rennie, E. S. Guns & M. E. Cox. "Lycopene Differentially Induces Quiescence and Apoptosis in Androgen-Responsive and -Independent Prostate Cancer Cell Lines." *Clin Nutr* 26, no. 2 (2007): 252-63.
- Jarred, R. A., M. Keikha, C. Dowling, S. J. McPherson, A. M. Clare, A. J. Husband, J. S. Pedersen, M. Frydenberg & G. P. Risbridger. "Induction of Apoptosis in Low to Moderate-Grade Human Prostate Carcinoma by Red Clover-Derived Dietary Isoflavones." *Cancer Epidemiol Biomarkers Prev* 11, no. 12 (2002): 1689-96.
- Jatoi, A., P. Burch, D. Hillman, J. M. Vanyo, S. Dakhil, D. Nikcevich, K. Rowland, R. Morton, P. J. Flynn, C. Young & W. Tan. "A Tomato-Based, Lycopene-Containing Intervention for Androgen-Independent Prostate Cancer: Results of a Phase II Study from the North Central Cancer Treatment Group." *Urology* 69, no. 2 (2007): 289-94.
- Kamsteeg, M., T. Rutherford, E. Sapi, B. Hanczaruk, S. Shahabi, M. Flick, D. Brown & G. Mor. "Phenoxodiol--an Isoflavone Analog--Induces Apoptosis in Chemoresistant Ovarian Cancer Cells." *Oncogene* 22, no. 17 (2003): 2611-20.
- Kanagaraj, P., M. Vijayababu, B. Ravisankar, J. Anbalagan, M. Aruldas & J. Arunakaran. "Effect of Lycopene on Insulin-Like Growth Factor-I, Igf Binding Protein-3 and Igf Type-I Receptor in Prostate Cancer Cells." *Journal of Cancer Research and Clinical Oncology* 133, no. 6 (2007): 351-59.
- Kato, K., S. Takahashi, L. Cui, T. Toda, S. Suzuki, M. Futakuchi, S. Sugiura & T. Shirai. "Suppressive Effects of Dietary Genistin and Daidzin on Rat Prostate Carcinogenesis." *Jpn J Cancer Res* 91, no. 8 (2000): 786-91.
- Kazi, A., K. G. Daniel, D. M. Smith, N. B. Kumar & Q. P. Dou. "Inhibition of the Proteasome Activity, a Novel Mechanism Associated with the Tumor Cell Apoptosis-Inducing Ability of Genistein." *Biochem Pharmacol* 66, no. 6 (2003): 965-76.
- Khor, T.O., Y.-S. Keum, W. Lin, J.-H. Kim, R. Hu, G. Shen, C. Xu, A. Gopalakrishnan, B. Reddy, X. Zheng, A.H. Conney & A.-N. T. Kong. "Combined Inhibitory Effects of Curcumin and Phenethyl Isothiocyanate on the Growth of Human Pc-3 Prostate Xenografts in Immunodeficient Mice." *Cancer Research* 66, no. 2 (2006): 613-21.
- Kluger, H. M., M. M. McCarthy, A. B. Alvero, M. Sznol, S. Ariyan, R. L. Camp, D. L. Rimm & G. Mor. "The X-Linked Inhibitor of Apoptosis Protein (Xiap) Is up-Regulated in Metastatic Melanoma, and Xiap Cleavage by Phenoxodiol Is Associated with Carboplatin Sensitization." *J Transl Med* 5 (2007): 6.
- Kryston, T. B., A.B. Georgiev, P. Pissis, and A.G. Georgakilas. "Role of Oxidative Stress and DNA Damage in Human Carcinogenesis." *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis* 711, no. 1-2 (2011): 193-201.
- Kucuk, O., F. H. Sarkar, Z. Djuric, W. Sakr, M. N. Pollak, F. Khachik, M. Banerjee, J. S. Bertram & D. P. Wood, Jr. "Effects of Lycopene Supplementation in Patients with Localized Prostate Cancer." *Exp Biol Med (Maywood)* 227, no. 10 (2002): 881-5.
- Kucuk, O., F. H. Sarkar, W. Sakr, Z. Djuric, M. N. Pollak, F. Khachik, Y. W. Li, M. Banerjee, D. Grignon, J. S. Bertram, J. D. Crissman, E. J. Pontes & D. P. Wood, Jr. "Phase II Randomized Clinical Trial of Lycopene Supplementation before Radical Prostatectomy." *Cancer Epidemiol Biomarkers Prev* 10, no. 8 (2001): 861-8.
- Kuiper, G. G., J. G. Lemmen, B. Carlsson, J. C. Corton, S. H. Safe, P. T. van der Saag, B. van der Burg & J. A. Gustafsson. "Interaction of Estrogenic Chemicals and Phytoestrogens with Estrogen Receptor Beta." *Endocrinology* 139, no. 10 (1998): 4252-63.

- Kumar, N. B., K. Besterman-Dahan, L. Kang, J. Pow-Sang, P. Xu, K. Allen, D. Riccardi & J. P. Krischer. "Results of a Randomized Clinical Trial of the Action of Several Doses of Lycopene in Localized Prostate Cancer: Administration Prior to Radical Prostatectomy." *Clin Med Urol* 1 (2008): 1-14.
- Kumar, N. B., A. Cantor, K. Allen, D. Riccardi, K. Besterman-Dahan, J. Seigne, M. Helal, R. Salup & J. Pow-Sang. "The Specific Role of Isoflavones in Reducing Prostate Cancer Risk." *Prostate* 59, no. 2 (2004): 141-7.
- Kumar, N. B., J. P. Krischer, K. Allen, D. Riccardi, K. Besterman-Dahan, R. Salup, L. Kang, P. Xu & J. Pow-Sang. "A Phase II Randomized, Placebo-Controlled Clinical Trial of Purified Isoflavones in Modulating Steroid Hormones in Men Diagnosed with Localized Prostate Cancer." *Nutr Cancer* 59, no. 2 (2007): 163-8.
- Kumi-Diaka, J. & A. Butler. "Caspase-3 Protease Activation During the Process of Genistein-Induced Apoptosis in Tm4 Testicular Cells." *Biol Cell* 92, no. 2 (2000): 115-24.
- Kumi-Diaka, J., N. A. Sanderson & A. Hall. "The Mediating Role of Caspase-3 Protease in the Intracellular Mechanism of Genistein-Induced Apoptosis in Human Prostatic Carcinoma Cell Lines, Du145 and LNCaP." *Biol Cell* 92, no. 8-9 (2000): 595-604.
- Kumi-Diaka, J. K., M. Hassanhi, K. Merchant & V. Horman. "Influence of Genistein Isoflavone on Matrix Metalloproteinase-2 Expression in Prostate Cancer Cells." *J Med Food* 9, no. 4 (2006): 491-7.
- Kurahashi, N., M. Iwasaki, S. Sasazuki, T. Otani, M. Inoue & S. Tsugane. "Soy Product and Isoflavone Consumption in Relation to Prostate Cancer in Japanese Men." *Cancer Epidemiol Biomarkers Prev* 16, no. 3 (2007): 538-45.
- Kuwajerwala, N., E. Cifuentes, S. Gautam, M. Menon, E. R. Barrack & G.P.V. Reddy. "Resveratrol Induces Prostate Cancer Cell Entry into S Phase and Inhibits DNA Synthesis." *Cancer Research* 62, no. 9 (2002): 2488-92.
- Kyle, E., L. Neckers, C. Takimoto, G. Curt & R. Bergan. "Genistein-Induced Apoptosis of Prostate Cancer Cells Is Preceded by a Specific Decrease in Focal Adhesion Kinase Activity." *Molecular Pharmacology* 51, no. 2 (1997): 193-200.
- la Porte, C., N. Voduc, G. Zhang, I. Seguin, D. Tardiff, N. Singhal & D. W. Cameron. "Steady-State Pharmacokinetics and Tolerability of Trans-Resveratrol 2000 Mg Twice Daily with Food, Quercetin and Alcohol (Ethanol) in Healthy Human Subjects." *Clin Pharmacokinet* 49, no. 7 (2010): 449-54.
- Lazarevic, B., S. J. Karlson & F. Saaticioglu. "Genistein Differentially Modulates Androgen-Responsive Gene Expression and Activates Jnk in LNCaP Cells." *Oncol Rep* 19, no. 5 (2008): 1231-5.
- Li, M., Z. Zhang, D. L. Hill, X. Chen, H. Wang & R. Zhang. "Genistein, a Dietary Isoflavone, Down-Regulates the Mdm2 Oncogene at Both Transcriptional and Posttranslational Levels." *Cancer Res* 65, no. 18 (2005): 8200-8.
- Li, M., Z. Zhang, D.L. Hill, H. Wang & R. Zhang. "Curcumin, a Dietary Component, Has Anticancer, Chemosensitization, and Radiosensitization Effects by Down-Regulating the Mdm2 Oncogene through the Pi3k/Mtor/Ets2 Pathway." *Cancer Research* 67, no. 5 (2007): 1988-96.
- Li, X., M. Marani, R. Mannucci, B. Kinsey, F. Andriani, I. Nicoletti, L. Denner & M. Marcelli. "Overexpression of Bcl-X(L) Underlies the Molecular Basis for Resistance to Staurosporine-Induced Apoptosis in Pc-3 Cells." *Cancer Res* 61, no. 4 (2001): 1699-706.

- Li, Y. & F. H. Sarkar. "Down-Regulation of Invasion and Angiogenesis-Related Genes Identified by Cdna Microarray Analysis of Pc3 Prostate Cancer Cells Treated with Genistein." *Cancer Lett* 186, no. 2 (2002): 157-64.
- Li, Z., W. J. Aronson, J. R. Arteaga, K. Hong, G. Thames, S. M. Henning, W. Liu, R. Elashoff, J. M. Ashley & D. Heber. "Feasibility of a Low-Fat/High-Fiber Diet Intervention with Soy Supplementation in Prostate Cancer Patients after Prostatectomy." *Eur J Clin Nutr* 62, no. 4 (2008): 526-36.
- Lian, F., M. Bhuiyan, Y. W. Li, N. Wall, M. Kraut & F. H. Sarkar. "Genistein-Induced G2-M Arrest, P21waf1 Upregulation, and Apoptosis in a Non-Small-Cell Lung Cancer Cell Line." *Nutr Cancer* 31, no. 3 (1998): 184-91.
- Limpens, J., F. H. Schroder, C. M. de Ridder, C. A. Bolder, M. F. Wildhagen, U. C. Obermuller-Jevic, K. Kramer & W. M. van Weerden. "Combined Lycopene and Vitamin E Treatment Suppresses the Growth of Pc-346c Human Prostate Cancer Cells in Nude Mice." *Journal of Nutrition* 136, no. 5 (2006): 1287-93.
- Lin, L., B. Hutzen, S. Ball, E. Foust, M. Sobo, S. Deangelis, B. Pandit, L. Friedman, C. Li, P.-K. Li, J. Fuchs & J. Lin. "New Curcumin Analogues Exhibit Enhanced Growth-Suppressive Activity and Inhibit Akt and Signal Transducer and Activator of Transcription 3 Phosphorylation in Breast and Prostate Cancer Cells." *Cancer Science* 100, no. 9 (2009): 1719-27.
- Liu, X., J. D. Allen, J. T. Arnold & M. R. Blackman. "Lycopene Inhibits Igf-I Signal Transduction and Growth in Normal Prostate Epithelial Cells by Decreasing Dht-Modulated Igf-I Production in Co-Cultured Reactive Stromal Cells." *Carcinogenesis* 29, no. 4 (2008): 816-23.
- Liu, Y., E. Kyle, R. Lieberman, J. Crowell, G. Kelloff & R. C. Bergan. "Focal Adhesion Kinase (Fak) Phosphorylation Is Not Required for Genistein-Induced Fak-Beta-1-Integrin Complex Formation." *Clin Exp Metastasis* 18, no. 3 (2000): 203-12.
- MacLean, M. A., B. E. Scott, B. A. Deziel, M. C. Nunnolley, A. M. Liberty, K. T. Gottschall-Pass, C. C. Neto & R. A. Hurta. "North American Cranberry (*Vaccinium Macrocarpon*) Stimulates Apoptotic Pathways in Du145 Human Prostate Cancer Cells *in Vitro*." *Nutr Cancer* 63, no. 1 (2011): 109-20.
- Mangels, A. R., J. M. Holden, G. R. Beecher, M. R. Forman & E. Lanza. "Carotenoid Content of Fruits and Vegetables: An Evaluation of Analytic Data." *J Am Diet Assoc* 93, no. 3 (1993): 284-96.
- Maskarinec, G., Y. Morimoto, S. Hebshi, S. Sharma, A. A. Franke & F. Z. Stanczyk. "Serum Prostate-Specific Antigen but Not Testosterone Levels Decrease in a Randomized Soy Intervention among Men." *Eur J Clin Nutr* 60, no. 12 (2006): 1423-9.
- McCormick, D. L., W. D. Johnson, M. C. Bosland, R. A. Lubet & V. E. Steele. "Chemoprevention of Rat Prostate Carcinogenesis by Soy Isoflavones and by Bowman-Birk Inhibitor." *Nutr Cancer* 57, no. 2 (2007): 184-93.
- McPherson, R. A., P. T. Galettis & P. L. de Souza. "Enhancement of the Activity of Phenoxodiol by Cisplatin in Prostate Cancer Cells." *Br J Cancer* 100, no. 4 (2009): 649-55.
- Mentor-Marcel, R., C. A. Lamartiniere, I. E. Eltoum, N. M. Greenberg & A. Elgavish. "Genistein in the Diet Reduces the Incidence of Poorly Differentiated Prostatic Adenocarcinoma in Transgenic Mice (Tramp)." *Cancer Res* 61, no. 18 (2001): 6777-82.
- Messina, M., C. Nagata & A. H. Wu. "Estimated Asian Adult Soy Protein and Isoflavone Intakes." *Nutr Cancer* 55, no. 1 (2006): 1-12.

- Mills, P. K., W. L. Beeson, R. L. Phillips & G. E. Fraser. "Cohort Study of Diet, Lifestyle, and Prostate Cancer in Adventist Men." *Cancer* 64, no. 3 (1989): 598-604.
- Mitchell, S. H., W. Zhu & C. Y. Young. "Resveratrol Inhibits the Expression and Function of the Androgen Receptor in LNCaP Prostate Cancer Cells." *Cancer Res* 59, no. 23 (1999): 5892-5.
- Mossine, V. V., P. Chopra & T. P. Mawhinney. "Interaction of Tomato Lycopene and Ketosamine against Rat Prostate Tumorigenesis." *Cancer Res* 68, no. 11 (2008): 4384-91.
- Mukhopadhyay, A., C. Bueso-Ramos, D. Chatterjee, P. Pantazis & B. B. Aggarwal. "Curcumin Downregulates Cell Survival Mechanisms in Human Prostate Cancer Cell Lines." *Oncogene* 20, no. 52 (2001): 7597-609.
- Nakamura, K., Y. Yasunaga, T. Segawa, D. Ko, J. W. Moul, S. Srivastava & J. S. Rhim. "Curcumin Down-Regulates Ar Gene Expression and Activation in Prostate Cancer Cell Lines." *International Journal of Oncology* 21, no. 4 (2002): 825-30.
- Narayanan, N. K., D. Nargi, C. Randolph & B. A. Narayanan. "Liposome Encapsulation of Curcumin and Resveratrol in Combination Reduces Prostate Cancer Incidence in Pten Knockout Mice." *Int J Cancer* 125, no. 1 (2009): 1-8.
- Neveu, V., Perez-Jiménez J., Vos F., Crespy V., du Chaffaut L., Mennen L., Knox C., Eisner R., Cruz J., Wishart D., Scalbert A. (2010) "Phenol-Explorer: an online comprehensive database on polyphenol contents in foods." *Database*, doi: 10.1093/database/ bap024.
- Neveu, V., J. Perez-Jimenez, F. Vos, V. Crespy, L. du Chaffaut, L. Mennen, C. Knox, R. Eisner, J. Cruz, D. Wishart & A. Scalbert. "Phenol-Explorer: An Online Comprehensive Database on Polyphenol Contents in Foods." *Database (Oxford)* 2010 (2010): bap024.
- Nguyen, T. H., F. B. Mustafa, S. Pervaiz, F. S. Ng & L. H. Lim. "Erk1/2 Activation Is Required for Resveratrol-Induced Apoptosis in Mda-Mb-231 Cells." *International Journal of Oncology* 33, no. 1 (2008): 81-92.
- Nunes, T., L. Almeida, J. F. Rocha, A. Falcao, C. Fernandes-Lopes, A. I. Loureiro, L. Wright, M. Vaz-da-Silva & P. Soares-da-Silva. "Pharmacokinetics of Trans-Resveratrol Following Repeated Administration in Healthy Elderly and Young Subjects." *Journal of Clinical Pharmacology* 49, no. 12 (2009): 1477-82.
- Nutrient Data, Laboratory, and Knovel. "USDA Database for the Isoflavone Content of Selected Foods." U.S. Dept. of Agriculture; http://ezproxy.uws.edu.au/login?url=http://www.knovel.com/web/portal/browse/display?_EXT_KNOVEL_DISPLAY_bookid=3708.
- Palozza, P., M. Colangelo, R. Simone, A. Catalano, A. Boninsegna, P. Lanza, G. Monego & F. O. Ranelletti. "Lycopene Induces Cell Growth Inhibition by Altering Mevalonate Pathway and Ras Signaling in Cancer Cell Lines." *Carcinogenesis* 31, no. 10 (2010): 1813-21.
- Park, J. I., M. G. Lee, K. Cho, B. J. Park, K. S. Chae, D. S. Byun, B. K. Ryu, Y. K. Park & S. G. Chi. "Transforming Growth Factor-Beta1 Activates Interleukin-6 Expression in Prostate Cancer Cells through the Synergistic Collaboration of the Smad2, P38-Nf-Kappab, Jnk, and Ras Signaling Pathways." *Oncogene* 22, no. 28 (2003): 4314-32.
- Park, S.-S., Y.-N. Kim, Y.K. Jeon, Y.A. Kim, J.E. Kim, H. Kim & C.W. Kim. "Genistein-Induced Apoptosis Via Akt Signaling Pathway in Anaplastic Large-Cell Lymphoma." *Cancer Chemotherapy and Pharmacology* 56, no. 3 (2005): 271-78.

- Patel, K. R., E. Scott, V. A. Brown, A. J. Gescher, W. P. Steward & K. Brown. "Clinical Trials of Resveratrol." *Ann N Y Acad Sci* 1215 (2011): 161-9.
- Pendleton, J. M., W. W. Tan, S. Anai, M. Chang, W. Hou, K. T. Shiverick & C. J. Rosser. "Phase II Trial of Isoflavone in Prostate-Specific Antigen Recurrent Prostate Cancer after Previous Local Therapy." *BMC Cancer* 8 (2008): 132.
- Peternac, D., I. Klima, M. G. Cecchini, R. Schwaninger, U. E. Studer & G. N. Thalmann. "Agents Used for Chemoprevention of Prostate Cancer May Influence PSA Secretion Independently of Cell Growth in the LNCaP Model of Human Prostate Cancer Progression." *Prostate* 68, no. 12 (2008): 1307-18.
- Pike, A. C., A. M. Brzozowski, R. E. Hubbard, T. Bonn, A. G. Thorsell, O. Engstrom, J. Ljunggren, J. A. Gustafsson & M. Carlquist. "Structure of the Ligand-Binding Domain of Oestrogen Receptor Beta in the Presence of a Partial Agonist and a Full Antagonist." *EMBO J* 18, no. 17 (1999): 4608-18.
- Ping, S. Y., T. C. Hour, S. R. Lin & D. S. Yu. "Taxol Synergizes with Antioxidants in Inhibiting Hormal Refractory Prostate Cancer Cell Growth." *Urol Oncol* 28, no. 2 (2010): 170-9.
- Pinski, J., Q. Wang, M. L. Quek, A. Cole, J. Cooc, K. Danenberg & P. V. Danenberg. "Genistein-Induced Neuroendocrine Differentiation of Prostate Cancer Cells." *Prostate* 66, no. 11 (2006): 1136-43.
- Raffoul, J. J., S. Banerjee, M. Che, Z. E. Knoll, D. R. Doerge, J. Abrams, O. Kucuk, F. H. Sarkar & G. G. Hillman. "Soy Isoflavones Enhance Radiotherapy in a Metastatic Prostate Cancer Model." *Int J Cancer* 120, no. 11 (2007): 2491-8.
- Rannikko, A., A. Petas, T. Raivio, O. A. Janne, S. Rannikko & H. Adlercreutz. "The Effects of Short-Term Oral Phytoestrogen Supplementation on the Hypothalamic-Pituitary-Testicular Axis in Prostate Cancer Patients." *Prostate* 66, no. 10 (2006): 1086-91.
- Ravindran, J., S. Prasad & B. B. Aggarwal. "Curcumin and Cancer Cells: How Many Ways Can Curry Kill Tumor Cells Selectively?" *AAPS J* 11, no. 3 (2009): 495-510.
- Rice, L., R. Handayani, Y. Cui, T. Medrano, V. Samed, H. Baker, N. J. Szabo, C. J. Rosser, S. Goodison & K. T. Shiverick. "Soy Isoflavones Exert Differential Effects on Androgen Responsive Genes in LNCaP Human Prostate Cancer Cells." *Journal of Nutrition* 137, no. 4 (2007): 964-72.
- Rice, L., V. G. Samed, T. A. Medrano, C. A. Sweeney, H. V. Baker, A. Stenstrom, J. Furman & K. T. Shiverick. "Mechanisms of the Growth Inhibitory Effects of the Isoflavonoid Biochanin a on LNCaP Cells and Xenografts." *Prostate* 52, no. 3 (2002): 201-12.
- Richelle, M., S. Pridmore-Merten, S. Bodenstab, M. Enslin & E. A. Offord. "Hydrolysis of Isoflavone Glycosides to Aglycones by Beta-Glycosidase Does Not Alter Plasma and Urine Isoflavone Pharmacokinetics in Postmenopausal Women." *Journal of Nutrition* 132, no. 9 (2002): 2587-92.
- Romero-Perez, A. I., M. Ibern-Gomez, R. M. Lamuela-Raventos & M. C. de La Torre-Boronat. "Piceid, the Major Resveratrol Derivative in Grape Juices." *J Agric Food Chem* 47, no. 4 (1999): 1533-6.
- Ronen, G., M. Cohen, D. Zamir & J. Hirschberg. "Regulation of Carotenoid Biosynthesis During Tomato Fruit Development: Expression of the Gene for Lycopene Epsilon-Cyclase Is Down-Regulated During Ripening and Is Elevated in the Mutant Delta." *Plant J* 17, no. 4 (1999): 341-51.
- Rufer, C. E., A. Bub, J. Moseneder, P. Winterhalter, M. Sturtz & S. E. Kulling. "Pharmacokinetics of the Soybean Isoflavone Daidzein in Its Aglycone and

- Glucoside Form: A Randomized, Double-Blind, Crossover Study." *American Journal of Clinical Nutrition* 87, no. 5 (2008): 1314-23.
- Sallman, D. A., X. Chen, B. Zhong, D. L. Gilvary, J. Zhou, S. Wei & J. Y. Djeu. "Clusterin Mediates Trail Resistance in Prostate Tumor Cells." *Mol Cancer Ther* 6, no. 11 (2007): 2938-47.
- Sapi, E., A. B. Alvero, W. Chen, D. O'Malley, X. Y. Hao, B. Dwipoyono, M. Garg, M. Kamsteeg, T. Rutherford & G. Mor. "Resistance of Ovarian Carcinoma Cells to Docetaxel Is Xiap Dependent and Reversible by Phenoxodiol." *Oncol Res* 14, no. 11-12 (2004): 567-78.
- Scarlatti, F., G. Sala, C. Ricci, C. Maioli, F. Milani, M. Minella, M. Botturi & R. Ghidoni. "Resveratrol Sensitization of Du145 Prostate Cancer Cells to Ionizing Radiation Is Associated to Ceramide Increase." *Cancer Lett* 253, no. 1 (2007): 124-30.
- Schroder, F. H., M. J. Roobol, E. R. Boeve, R. de Mutsert, S. D. Zuijdgheest-van Leeuwen, I. Kersten, M. F. Wildhagen & A. van Helvoort. "Randomized, Double-Blind, Placebo-Controlled Crossover Study in Men with Prostate Cancer and Rising PSA: Effectiveness of a Dietary Supplement." *Eur Urol* 48, no. 6 (2005): 922-30; discussion 30-1.
- Schwedhelm, E., R. Maas, R. Troost & R. H. Boger. "Clinical Pharmacokinetics of Antioxidants and Their Impact on Systemic Oxidative Stress." *Clin Pharmacokinet* 42, no. 5 (2003): 437-59.
- Schwenke, C., B. Ubrig, P. Thurmann, C. Eggersmann & S. Roth. "Lycopene for Advanced Hormone Refractory Prostate Cancer: A Prospective, Open Phase II Pilot Study." *Journal of Urology* 181, no. 3 (2009): 1098-103.
- Setchell, K. D., N. M. Brown, P. Desai, L. Zimmer-Nechemias, B. E. Wolfe, W. T. Brashear, A. S. Kirschner, A. Cassidy & J. E. Heubi. "Bioavailability of Pure Isoflavones in Healthy Humans and Analysis of Commercial Soy Isoflavone Supplements." *Journal of Nutrition* 131, no. 4 Suppl (2001): 1362S-75S.
- Setchell, K. D., N. M. Brown, L. Zimmer-Nechemias, W. T. Brashear, B. E. Wolfe, A. S. Kirschner & J. E. Heubi. "Evidence for Lack of Absorption of Soy Isoflavone Glycosides in Humans, Supporting the Crucial Role of Intestinal Metabolism for Bioavailability." *American Journal of Clinical Nutrition* 76, no. 2 (2002): 447-53.
- Setchell, K. D., M. S. Faughnan, T. Avades, L. Zimmer-Nechemias, N. M. Brown, B. E. Wolfe, W. T. Brashear, P. Desai, M. F. Oldfield, N. P. Botting & A. Cassidy. "Comparing the Pharmacokinetics of Daidzein and Genistein with the Use of ¹³C-Labeled Tracers in Premenopausal Women." *American Journal of Clinical Nutrition* 77, no. 2 (2003): 411-9.
- Shankar, S., Q. Chen, I. Siddiqui, K. Sarva & R. K. Srivastava. "Sensitization of Trail-Resistant LNCaP Cells by Resveratrol (3, 4', 5 Tri-Hydroxystilbene): Molecular Mechanisms and Therapeutic Potential." *J Mol Signal* 2 (2007): 7.
- Shankar, S. & R. K. Srivastava. "Involvement of Bcl-2 Family Members, Phosphatidylinositol 3'-Kinase/Akt and Mitochondrial P53 in Curcumin (Diferulolylmethane)-Induced Apoptosis in Prostate Cancer." *International Journal of Oncology* 30, no. 4 (2007): 905-18.
- Sharma, N. & U. Goswami. "Functioning of Lycopene in Mammalian System: A Review." *Proceedings of the Zoological Society* 64, no. 1 (2011): 1-7.
- Sharma, R. A., S. A. Euden, S. L. Platton, D. N. Cooke, A. Shafayat, H. R. Hewitt, T. H. Marczylo, B. Morgan, D. Hemingway, S. M. Plummer, M. Pirmohamed, A. J.

- Gescher & W. P. Steward. "Phase I Clinical Trial of Oral Curcumin: Biomarkers of Systemic Activity and Compliance." *Clin Cancer Res* 10, no. 20 (2004): 6847-54.
- Shenouda, N. S., C. Zhou, J. D. Browning, P. J. Ansell, M. S. Sakla, D. B. Lubahn & R. S. Macdonald. "Phytoestrogens in Common Herbs Regulate Prostate Cancer Cell Growth *in Vitro*." *Nutr Cancer* 49, no. 2 (2004): 200-8.
- Shi, W. F., M. Leong, E. Cho, J. Farrell, H. C. Chen, J. Tian & D. Zhang. "Repressive Effects of Resveratrol on Androgen Receptor Transcriptional Activity." *PLoS One* 4, no. 10 (2009): e7398.
- Singh-Gupta, V., H. Zhang, S. Banerjee, D. Kong, J. J. Raffoul, F. H. Sarkar & G. G. Hillman. "Radiation-Induced Hif-1alpha Cell Survival Pathway Is Inhibited by Soy Isoflavones in Prostate Cancer Cells." *Int J Cancer* 124, no. 7 (2009): 1675-84.
- Skogseth, H., E. Larsson & J. Halgunset. "Inhibitors of Tyrosine Kinase Inhibit the Production of Urokinase Plasminogen Activator Human Prostatic Cancer Cells." *Apmis* 113, no. 5 (2005): 332-39.
- Slusarz, A., N. S. Shenouda, M. S. Sakla, S. K. Drenkhahn, A. S. Narula, R. S. MacDonald, C. L. Besch-Williford & D. B. Lubahn. "Common Botanical Compounds Inhibit the Hedgehog Signaling Pathway in Prostate Cancer." *Cancer Res* 70, no. 8 (2010): 3382-90.
- Soleas, G.J., L. Grass, P.D. Josephy, D.M. Goldberg & E.P. Diamandis. "A Comparison of the Anticarcinogenic Properties of Four Red Wine Polyphenols." *Clinical Biochemistry* 35, no. 2 (2002): 119-24.
- Steiner, C., S. Arnould, A. Scalbert & C. Manach. "Isoflavones and the Prevention of Breast and Prostate Cancer: New Perspectives Opened by Nutrigenomics." *Br J Nutr* 99 E Suppl 1 (2008): ES78-108.
- Stewart, J. R. & C. A. O'Brian. "Resveratrol Antagonizes Egr-Dependent Erk1/2 Activation in Human Androgen-Independent Prostate Cancer Cells with Associated Isozyme-Selective Pkc Alpha Inhibition." *Invest New Drugs* 22, no. 2 (2004): 107-17.
- Swami, S., A.V. Krishnan, J. Moreno, R.S. Bhattacharyya, C. Gardner, J.D. Brooks, D.M. Peehl & D. Feldman. "Inhibition of Prostaglandin Synthesis and Actions by Genistein in Human Prostate Cancer Cells and by Soy Isoflavones in Prostate Cancer Patients." *International Journal of Cancer* 124, no. 9 (2009): 2050-59.
- Takahashi, Y., S. D. Hursting, S. N. Perkins, T. C. Wang & T. T. Wang. "Genistein Affects Androgen-Responsive Genes through Both Androgen- and Estrogen-Induced Signaling Pathways." *Mol Carcinog* 45, no. 1 (2006): 18-25.
- Takimoto, C. H., K. Glover, X. Huang, S. A. Hayes, L. Gallot, M. Quinn, B. D. Jovanovic, A. Shapiro, L. Hernandez, A. Goetz, V. Llorens, R. Lieberman, J. A. Crowell, B. A. Poisson & R. C. Bergan. "Phase I Pharmacokinetic and Pharmacodynamic Analysis of Unconjugated Soy Isoflavones Administered to Individuals with Cancer." *Cancer Epidemiol Biomarkers Prev* 12, no. 11 Pt 1 (2003): 1213-21.
- Talvas, J., C. Caris-Veyrat, L. Guy, M. Rambeau, B. Lyan, R. Minet-Quinard, J. M. Lobaccaro, M. P. Vasson, S. George, A. Mazur & E. Rock. "Differential Effects of Lycopene Consumed in Tomato Paste and Lycopene in the Form of a Purified Extract on Target Genes of Cancer Prostatic Cells." *American Journal of Clinical Nutrition* 91, no. 6 (2010): 1716-24.
- Tayyem, R. F., D.D. Heath, W.K. Al-Delaimy, C.L. Rock. "Curcumin Content of Turmeric and Curry Powders" *Nutrition and Cancer* Vol. 55, no. 2, (2009) : 126-131.

- Tang, Y., B. Parmakhtiar, A. R. Simoneau, J. Xie, J. Fruehauf, M. Lilly & X. Zi. "Lycopene Enhances Docetaxel's Effect in Castration-Resistant Prostate Cancer Associated with Insulin-Like Growth Factor I Receptor Levels." *Neoplasia* 13, no. 2 (2011): 108-19.
- Teiten, M. H., F. Gaascht, M. Cronauer, E. Henry, M. Dicato & M. Diederich. "Anti-Proliferative Potential of Curcumin in Androgen-Dependent Prostate Cancer Cells Occurs through Modulation of the Wntless Signaling Pathway." *International Journal of Oncology* 38, no. 3 (2011): 603-11.
- Tepper, C.G., R.L. Vinall, C.B. Wee, L. Xue, X.-B. Shi, R. Burich, P.C. Mack & R.W. de Vere White. "Gcp-Mediated Growth Inhibition and Apoptosis of Prostate Cancer Cells Via Androgen Receptor-Dependent and -Independent Mechanisms." *The Prostate* 67, no. 5 (2007): 521-35.
- Thomas, S. L., D. Zhong, W. Zhou, S. Malik, D. Liotta, J. P. Snyder, E. Hamel & P. Giannakakou. "Ef24, a Novel Curcumin Analog, Disrupts the Microtubule Cytoskeleton and Inhibits Hif-1." *Cell Cycle* 7, no. 15 (2008): 2409-17.
- Touny, L. H. & P. P. Banerjee. "Identification of Both Myt-1 and Wee-1 as Necessary Mediators of the P21-Independent Inactivation of the Cdc-2/Cyclin B1 Complex and Growth Inhibition of Tramp Cancer Cells by Genistein." *Prostate* 66, no. 14 (2006): 1542-55.
- Tsui, K. H., T. H. Feng, C. M. Lin, P. L. Chang & H. H. Juang. "Curcumin Blocks the Activation of Androgen and Interleukin-6 on Prostate-Specific Antigen Expression in Human Prostatic Carcinoma Cells." *J Androl* 29, no. 6 (2008): 661-8.
- Urban, D., W. Irwin, M. Kirk, M. A. Markiewicz, R. Myers, M. Smith, H. Weiss, W. E. Grizzle & S. Barnes. "The Effect of Isolated Soy Protein on Plasma Biomarkers in Elderly Men with Elevated Serum Prostate Specific Antigen." *J Urol* 165, no. 1 (2001): 294-300.
- Vaishampayan, U., M. Hussain, M. Banerjee, S. Seren, F. H. Sarkar, J. Fontana, J. D. Forman, M. L. Cher, I. Powell, J. E. Pontes & O. Kucuk. "Lycopene and Soy Isoflavones in the Treatment of Prostate Cancer." *Nutr Cancer* 59, no. 1 (2007): 1-7.
- van Breemen, R. B., R. Sharifi, M. Viana, N. Pajkovic, D. Zhu, L. Yuan, Y. Yang, P. E. Bowen & M. Stacewicz-Sapuntzakis. "Antioxidant Effects of Lycopene in African American Men with Prostate Cancer or Benign Prostate Hyperplasia: A Randomized, Controlled Trial." *Cancer Prev Res (Phila)* 4, no. 5 (2011): 711-8.
- Vareed, S. K., M. Kakarala, M. T. Ruffin, J. A. Crowell, D. P. Normolle, Z. Djuric & D. E. Brenner. "Pharmacokinetics of Curcumin Conjugate Metabolites in Healthy Human Subjects." *Cancer Epidemiol Biomarkers Prev* 17, no. 6 (2008): 1411-7.
- Vaz-da-Silva, M., A. I. Loureiro, A. Falcao, T. Nunes, J. F. Rocha, C. Fernandes-Lopes, E. Soares, L. Wright, L. Almeida & P. Soares-da-Silva. "Effect of Food on the Pharmacokinetic Profile of Trans-Resveratrol." *Int J Clin Pharmacol Ther* 46, no. 11 (2008): 564-70.
- Venkateswaran, V., L. H. Klotz, M. Ramani, L. M. Sugar, L. E. Jacob, R. K. Nam & N. E. Fleshner. "A Combination of Micronutrients Is Beneficial in Reducing the Incidence of Prostate Cancer and Increasing Survival in the Lady Transgenic Model." *Cancer Prev Res (Phila)* 2, no. 5 (2009): 473-83.
- Vitrac, X., A. Desmouliere, B. Brouillaud, S. Krisa, G. Deffieux, N. Barthe, J. Rosenbaum & J. M. Merillon. "Distribution of [¹⁴C]-Trans-Resveratrol, a Cancer Chemopreventive

- Polyphenol, in Mouse Tissues after Oral Administration." *Life Sci* 72, no. 20 (2003): 2219-33.
- Wahl, H., L. Tan, K. Griffith, M. Choi & J. R. Liu. "Curcumin Enhances Apo21/Trail-Induced Apoptosis in Chemoresistant Ovarian Cancer Cells." *Gynecol Oncol* 105, no. 1 (2007): 104-12.
- Wang, J., I. E. Eltoun & C. A. Lamartiniere. "Genistein Alters Growth Factor Signaling in Transgenic Prostate Model (Tramp)." *Molecular and Cellular Endocrinology* 219, no. 1-2 (2004): 171-80.
- Wang, J., I.-E. Eltoun & C.A. Lamartiniere. "Dietary Genistein Suppresses Chemically Induced Prostate Cancer in Lobund-Wistar Rats." *Cancer Letters* 186, no. 1 (2002): 11-18.
- Wang, S., V. L. DeGross & S. K. Clinton. "Tomato and Soy Polyphenols Reduce Insulin-Like Growth Factor-I-Stimulated Rat Prostate Cancer Cell Proliferation and Apoptotic Resistance *in Vitro* Via Inhibition of Intracellular Signaling Pathways Involving Tyrosine Kinase." *Journal of Nutrition* 133, no. 7 (2003): 2367-76.
- Wang, T. T., T. S. Hudson, T. C. Wang, C. M. Remsberg, N. M. Davies, Y. Takahashi, Y. S. Kim, H. Seifried, B. T. Vinyard, S. N. Perkins & S. D. Hursting. "Differential Effects of Resveratrol on Androgen-Responsive LNCaP Human Prostate Cancer Cells *in Vitro* and *in Vivo*." *Carcinogenesis* 29, no. 10 (2008): 2001-10.
- Wang, T. T., N. W. Schoene, Y. S. Kim, C. S. Mizuno & A. M. Rimando. "Differential Effects of Resveratrol and Its Naturally Occurring Methylether Analogs on Cell Cycle and Apoptosis in Human Androgen-Responsive LNCaP Cancer Cells." *Mol Nutr Food Res* 54, no. 3 (2010): 335-44.
- Wang, Y., J. J. Raffoul, M. Che, D. R. Doerge, M. C. Joiner, O. Kucuk, F. H. Sarkar & G. G. Hillman. "Prostate Cancer Treatment Is Enhanced by Genistein *in Vitro* and *in Vivo* in a Syngeneic Orthotopic Tumor Model." *Radiat Res* 166, no. 1 Pt 1 (2006): 73-80.
- Wong, Y., G. Osmond, K. I. Brewer, D. S. Tyler & M. B. Andrus. "Synthesis of 4'-Ester Analogs of Resveratrol and Their Evaluation in Malignant Melanoma and Pancreatic Cell Lines." *Bioorganic & Medicinal Chemistry Letters* 20, no. 3 (2010): 1198-201.
- Xu, L. & R. C. Bergan. "Genistein Inhibits Matrix Metalloproteinase Type 2 Activation and Prostate Cancer Cell Invasion by Blocking the Transforming Growth Factor Beta-Mediated Activation of Mitogen-Activated Protein Kinase-Activated Protein Kinase 2-27-Kda Heat Shock Protein Pathway." *Molecular Pharmacology* 70, no. 3 (2006): 869-77.
- Yang, C. M., I. H. Lu, H. Y. Chen & M. L. Hu. "Lycopene Inhibits the Proliferation of Androgen-Dependent Human Prostate Tumor Cells through Activation of Ppargamma-Lxralpha-Abca1 Pathway." *J Nutr Biochem* (2011).
- Yang, C. M., Y. T. Yen, C. S. Huang & M. L. Hu. "Growth Inhibitory Efficacy of Lycopene and Beta-Carotene against Androgen-Independent Prostate Tumor Cells Xenografted in Nude Mice." *Mol Nutr Food Res* 55, no. 4 (2011): 606-12.
- Yu, L., G. L. Blackburn & J. R. Zhou. "Genistein and Daidzein Downregulate Prostate Androgen-Regulated Transcript-1 (Part-1) Gene Expression Induced by Dihydrotestosterone in Human Prostate LNCaP Cancer Cells." *Journal of Nutrition* 133, no. 2 (2003): 389-92.

- Yu, S., G. Shen, T. O. Khor, J. H. Kim & A. N. Kong. "Curcumin Inhibits Akt/Mammalian Target of Rapamycin Signaling through Protein Phosphatase-Dependent Mechanism." *Mol Cancer Ther* 7, no. 9 (2008): 2609-20.
- Yuan, J. P., J. H. Wang & X. Liu. "Metabolism of Dietary Soy Isoflavones to Equol by Human Intestinal Microflora--Implications for Health." *Mol Nutr Food Res* 51, no. 7 (2007): 765-81.
- Zapalis, Charles. *Food Chemistry and Nutritional Biochemistry / Charles Zapalis, R. Anderle Beck*. Edited by R. Anderle Beck. New York :: Wiley, 1985.
- Zhang, X., Q. Wang, B. Neil & X. Chen. "Effect of Lycopene on Androgen Receptor and Prostate-Specific Antigen Velocity." *Chin Med J (Engl)* 123, no. 16 (2010): 2231-6.
- Zhou, J. R., E. T. Gugger, T. Tanaka, Y. Guo, G. L. Blackburn & S. K. Clinton. "Soybean Phytochemicals Inhibit the Growth of Transplantable Human Prostate Carcinoma and Tumor Angiogenesis in Mice." *Journal of Nutrition* 129, no. 9 (1999): 1628-35.
- Zhou, J. R., L. Yu, Y. Zhong, R. L. Nassr, A. A. Franke, S. M. Gaston & G. L. Blackburn. "Inhibition of Orthotopic Growth and Metastasis of Androgen-Sensitive Human Prostate Tumors in Mice by Bioactive Soybean Components." *Prostate* 53, no. 2 (2002): 143-53.
- Ziech, D., R. Franco, A.G. Georgakilas, S. Georgakila, V. Malamou-Mitsi, O. Schoneveld, A. Pappa & M.I. Panayiotidis. "The Role of Reactive Oxygen Species and Oxidative Stress in Environmental Carcinogenesis and Biomarker Development." *Chemico-Biological Interactions* 188, no. 2 (2010): 334-39.
- Zubik, L. & M. Meydani. "Bioavailability of Soybean Isoflavones from Aglycone and Glucoside Forms in American Women." *American Journal of Clinical Nutrition* 77, no. 6 (2003): 1459-65.

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Cancer Prevention - From Mechanisms to Translational Benefits

Edited by Dr. Alexandros G. Georgakilas

ISBN 978-953-51-0547-3

Hard cover, 476 pages

Publisher InTech

Published online 20, April, 2012

Published in print edition April, 2012

This unique synthesis of chapters from top experts in their fields targets the unique and significant area of cancer prevention for different types of cancers. Perspective readers are invited to go through novel ideas and current developments in the field of molecular mechanisms for cancer prevention, epidemiological studies, antioxidant therapies and diets, as well as clinical aspects and new advances in prognosis and avoidance of cancer. The primary target audience for the book includes PhD students, researchers, biologists, medical doctors and professionals who are interested in mechanistic studies on cancer prevention and translational benefits for optimized cancer treatment.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Carol A Gano, Kieran Scott, Joseph Bucci, Heather Greenfield, Qihan Dong and Paul L de Souza (2012). Dietary Manipulation for Therapeutic Effect in Prostate Cancer, *Cancer Prevention - From Mechanisms to Translational Benefits*, Dr. Alexandros G. Georgakilas (Ed.), ISBN: 978-953-51-0547-3, InTech, Available from: <http://www.intechopen.com/books/cancer-prevention-from-mechanisms-to-translational-benefits/dietary-manipulation-for-therapeutic-effect-in-prostate-cancer>

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