Inflammation and Cancer – Therapeutic Implications

The relationship of inflammation to the malignant process, both in the initiation, promotional, and metastatic phases has been of great interest to conventional and integrative cancer physicians. Numerous reviews have been published detailing this area of research (1, 2, 3). The association has been studied in various aspects. The use of aspirin and NSAIDS has been shown to decrease the risk of developing various malignancies, including colon (4), lung (5), prostate and breast (2). There has been some conflicting evidence suggesting a possible increase of non-hodgkins lymphoma (6), though this was complicated by studying patients with rheumatoid arthritis, who have altered immune functioning. There are also very well known associations of various diseases of chronic inflammation and the subsequent development of malignancies of these organs. These diseases include inflammatory bowel disease, hepatitis B and C, Barretts esophagus, Helicobacter Pylori gastritis, and chronic obstruction pulmonary disease. Various chronic infections, including hepatitis B and C, Epstein Barr, schistosomiasis, and human papilloma virus are associated with the subsequent development of malignancies (1).

It is well known and studied that tumor tissue from various different sites, including brain, breast, colorectal, gastric, cervical, endometrium, head and neck, lung, pancreatic, prostate, and bladder (2) demonstrates an increased concentration of inflammatory substances. Comparing normal tissue, tissue adjacent to dysplastic colorectal tissue, and tissue adjacent to malignant colorectal tissue and malignant colorectal shows an increasing concentration of COX 2 staining as the tissue becomes more abnormal (2).

The connection between inflammation and cancer had already been hypothesized by Virchow in 1863, based on his hypothesis that some types of irritants, together with the tissue injury and the ensuing inflammation they cause, enhance cell proliferation. Cancer has also been described as “wounds that fail to heal”. The environment around a wound includes inflammatory cells, growth factors and demonstrates active new tissue formation. Combining enhanced proliferation with an environment that promotes DNA mutations, such as free radicals and inflammatory cells, potentiates and promotes the risk of a malignancy developing. The biochemical and molecular role of inflammatory substances in various phases of malignant development has been explained in detail by Coussens: “The protumor actions of inflammatory cells include releasing growth and survival factors, promoting angiogenesis and lymphangiogenesis, stimulating DNA damage, remodeling the extracellular matrix to facilitate invasion, coating tumor cells to make available receptors for disseminating cells via lymphatics and capillaries, and evading host defence mechanisms.” (1).

It should be noted, however, that there is an obvious paradox in the relationship of inflammation and malignancies. The inflammatory reaction is obviously essential to immune functioning, and central to the ability of the immune surveillance system to destroy cancer cells at early stages. Various treatment strategies are directed towards increasing, rather than decreasing, the immune response. These include the use of toxins such as Coley’s toxin (7, 8, 9), the use of monoclonal antibodies enabling the effective activity of the host immune system against the tumor, and tumor vaccines. The paradox might lie in the following observations: Firstly, there is an inherent difference in an acute as opposed to a chronic inflammatory reaction. The therapeutic strategies that employ proinflammatory mechanisms take advantage of an acute inflammation process. The type of inflammation typically found surrounding tumor cells are of a chronic nature. Secondly, the inflammatory and immune systems are very complex and differentiated. An acute inflammatory response usually involves upregulation of pro-inflammatory cytokines, Th1 lymphocytes and a cell mediated immune response. If the inflammatory response becomes chronic, the presence of COX 2 enzymes can inhibit these responses, and subsequently change the inflammatory environment into one where Th2 lymphocytes, and a humoral mediated immune response are dominant (3). This then leads to the state of tumor enhancing effects discussed above. Vaccines (10), as well as various natural substances such as mistletoe and mushrooms (see appropriate sections), can induce a proinflammatory response. There is thus the question if inflammatory cells are friends or foes of malignancies. As explained above, an acute

inflammatory response is likely helpful, whereas a chronic response is deleterious. This distinction is very important therapeutically, as many integrative cancer treatment strategies can employ agents that are pro acute-inflammatory (mushrooms, mistletoe, avemar), as well as agents that are anti chronic-inflammatory (w-3 fatty acids, curcumin, boswellia, substances that inhibit NFkappaB) concurrently.

Inflammation, analogous to the immune response described above, is a complex phenomenon, with numerous biochemical substances playing important roles. These include eicosanoids such as prostaglandins, which are produced from essential fatty acids, and involve cyclooxygenase and lipoxygenase activity (COX 1 and 2, LOX). Various cytokines such as tumor necrosis factor, interleukins and interferons are also involved. In addition, signaling molecules such as NFkappaB are important. These interact in complex ways. The body as a whole, as well as many of the substances mentioned demonstrate a "yin-yang" cybernetic aspect of balancing proinflammatory and anti-inflammatory processes. For instance, as is discussed below, some fatty acids (w-6) and prostaglandins (series 2 and 4) are proinflammatory, whereas other fatty acids (w-3), and prostaglandins (series 1 and 3) are anti-inflammatory.

Eicosanoids, cyclooxygenases and lipoxygenases

Detailed descriptions of fatty acid biochemical transformations are described in many sources (2). In short, w-3 fatty acids derived from fish and flax oils (alpha linolenic acid, EPA, DHA) lead to relatively anti-inflammatory results, whereas w-6 fatty acids derived from dairy and meat (arachidonic acid), or many vegetable oils(linoleic acid) lead to a proinflammatory state. The transformation of these fatty acids into prostaglandins is dependent on COX 1 and 2 enzymes, whereas their transformation into leukotrienes is dependent on LOX enzymes. Therefore, the eventual production of prostaglandins or leukotrienes is dependent on (1) variable dietary and supplement intake of fatty acids, and (2) various substances, both pharmaceutical and natural, which impact on COX and LOX enzymes.

The intake of fatty acids, either through diet or supplements, is described in detail in the section on fatty acids. In this section we will discuss substances which impact on COX and LOX enzymes. Although the greatest attention has been paid to the use of COX 2 inhibitors, many authors point out that if only the COX pathway is blocked, it's likely that the substrates will then preferentially travel down the leukotriene cascade, and produce analogous potent inflammatory leukotrienes (2). There is abundant evidence that leukotrienes are just as important as prostaglandins in promoting inflammation (11, 12,13). There is significant interest in dual COX/LOX inhibitors (14). In addition to being significantly safer, these dual inhibitors block a much wider range of eicosanoid related inflammatory pathways. Whereas conventional pharmaceutical agents are directed towards either COX (celecoxib) or LOX (zileuton), various natural agents, such as curcumin, effect both pathways. With this said, unexpected, worrisome adverse effects can occur with the manipatulation of these pathways. The increase of cardiovascular events seen with prolonged use of valecoxib (and possibly the entire class of targeted COX-2 inhibitors), and it's subsequent removal from the market, points to this uncertainty. Cardiovascular diseases such as coronary artery disease, as well as malignant diseases, have chronic inflammation implicated as part of their etiology, and COX 2 inhibition would have been thought to be beneficial. It's not clear if the adverse effects are due to some specific aspect of valecoxib, or are a generalized effect of COX 2 inhibitors. One can speculate, if the latter is the case, that it would be more beneficial to have dual COX and LOX inhibition,as discussed above.

In addition to the use of specific herbs with antiinflammatory properties, attention should also be paid to the use of antioxidants. Various studies show an inverse relationship between the level of antioxidants and the level of inflammation (15, 16). This is also true for critical trace elements like selenium and zinc (17), which can be augmented through supplements. These trace elements are essential components of internally produced antioxidants such as glutathione and superoxide dismutase.

Curcumin

In many ways, curcumin, which is derived from turmeric (curcuma longa), the spice used in cooking with curry, is an ideal anti-inflammatory agent. It has a long history of safe use in Ayurvedic medicine, and has potent anti-inflammatory and antioxidant properties. Curcumin inhibits COX and LOX as well as the signaling molecule NFkB (2,18), which is central to most inflammatory processes. In vitro studies have shown antiproliferative effects in numerous cancer cell lines, as well as other studies showing induction of cell cycle arrest and apoptosis. Curcumin has also been shown to block the expression of glutathione S transferase, which could be of significant import in chemotherapy resistance (19). However, it's essential to note that most studies of curcumin have been done in vitro and vivo. This is significant because there are troubling questions regarding the absorption of curcumin through the GI tract (20,21,22). A large amount of curcumin taken orally undergoes conjugation, and subsequent formation of different metabolites in the GI tract (22). Despite poor absorption, there is suggestive evidence of clinical activities in human studies (20). Mice had melanoma cells implanted and were treated with oral curcumin. A tendency towards decreased development of lung metastases, as well as an improvement in life span was found (23). Protection against radiation induced DNA damage was shown with oral administration of curcumin (24). An examination of the use of cisplatin against fibrosarcoma in rats showed increased efficacy when combined with oral curcumin (25). Unfortunately, there are not any studies which investigate the effects of the metabolites of curcumin, which could conceivably be active agents. Different pharmacologic formulations should also be considered (26). Shoba showed in a study with rats, that administering Curcumin together with piperine, a substance found in black peppers (available in the US as bioperine) led to significantly enhanced absorption and bioavailability (27). Black pepper has the ability to increase absorption, inhibit the transport out of the cell, and inhibit glucuronidation . Curcumin has been shown to be very safe at doses up to 8,000 mg/day in humans. The typical therapeutic dose is thought to be between 1-3 grams/day (28).

Boswellia and LOX inhibitors

The most well known herbal 5-lipoxygenase inhibitor is Boswellia (frankincense), which contains boswellic acids. Various studies have shown beneficial effects on other inflammatory conditions including arthritides. Gupta studied asthmatic patients treated with 350 mg of boswellic acid TID and noted significant improvements compared to placebo (29). Gerhardt studied patients with Crohns disease and noted similar improvement compared to patients treated with sulfasalazine (30). Zhao showed induction of differentiation and apoptotic effects in melanoma and fibrosarcoma cells (31). Studies have demonstrated effects with leukemic cell lines (32,33). Janssen studied the use of H15, a boswellic acid compound, in children with brain edema due to tumors and found a possible beneficial clinical effect (34). Streffer also found benefit in patients with tumor related brain edema (35).Winking found survival and shrinkage benefits in rats with implanted gliomas (36). The dosage range of boswellic acid content is 1-2.4 grams, with the usual dose of 1.8 grams (28).

Another interesting natural substance, with dual COX/LOX inhibitory properties, is the New Zealand green lipped mussel, perna canaliculus. Clinical and laboratory benefits have been noted in asthma (37), and osteoarthritis (38).

PPAR agonists

Peroxisome proliferator activated receptors (PPAR) are a nuclear receptor family which has generated significant interest in numerous clinical areas, including diabetes, obesity, and malignancies. Glitazone medications, used as insulin sensitizers with diabetic patients, are PPAR gamma agonists that are readily available and widely prescribed. Fibrates, PPAR beta agonists,used in hyperlipidemias, are also commonly prescribed. These have been shown to have anti-inflammatory and antiproliferative effects (39,40). PPAR agonists have also been

shown to inhibit NFkappaB formation (41). NFkappa B, a group of transcription factors, is intimately involved with inflammatory processes and discussed in more detail below.

Proteolytic enzyme therapy

The oral use of proteolytic enzymes, including plant based enzymes like bromelain and papain, as well as pancreatic enzymes such as trypsin and chymotrypsin, is widespread in alternative cancer treatment. The most well known preparations are the german preparations, wobenzyme and wobemugos. There are other proprietary preparations available. The mode of action is postulated to be anti-inflammatory, though they have also shown fibrinolytic and platelet aggregation inhibitory activities (42). There are some unique uses of this therapy, most importantly by Gonzales and Isaacs, who have reported very intriguing results in a pilot study of patients with pancreatic cancer (43). The use of these preparations will be reviewed in more detail in the section discussing miscellaneous therapeutic approaches.

Flavonoids

Many plant substances contain flavonoid like substances, including green tea (polyphenols), red wine (resveratrol), and onions and apples (quercetin). These have been shown to have numerous effects relevant to inflammation, including the downregulation of NFkB by resveratrol (44), and green tea (45), as well as also being potent antioxidants. The use of these agents is commonly part of a general integrative treatment protocol. They are discussed in more detail in the section on flavonoids.

NFkappaB

NFkappaB (NFkB) is a transcription factor generating considerable interest for it's role in oncogenesis. "NF-κB activation has been connected with multiple aspects of oncogenesis, including the control of apoptosis, the cell cycle, differentiation, and cell migration. Additionally, activation of NF-κB in cancer cells by chemotherapy or by radiation can blunt the ability of the cancer therapy to induce cell death" (46). Many natural substances have been found to downregulate NFkB production, including curcumin (18), green tea (47), resveratrol (48), and tetrathiomolybdate (49), an important copper chelator and antioangiogenesis compound discussed in detail elsewhere (see section). Oxidative stress has also been shown to upregulate NFkB (50). Many treatments commonly recommended in integrative oncology protocols have the effect of blocking NFkB activation, either through their antiinflammatory or antioxidant effects. An unwanted effect of chemotherapy and radiation therapy is the increase in NFkB activity. The use of NFkB inhibitors, such as are found in integrative protocols, during active chemotherapy and radiation therapy, has the potential to act as treatment sensitizers. This is described in more detail below.

Concurrent use with conventional treatment modalities

Conventional treatment strategies most commonly involve surgery, radiation, and/or chemotherapy. Immune related conventional strategies are discussed in the introductory section above and in the summary section below.

The use of anti-inflammatory approaches with surgery is to be recommended. Excessive tissue damage leads to increased free radical production and excessive catabolism. The approaches discussed above can modify these. Care needs to be given to the use of substances which can thin the blood, such as w-3 fatty acids and vitamin E.

The use of radiation therapy produces a secondary inflammatory reaction, with production of substances such as prostaglandin E and other inflammatory cytokines, as well as NFkB. These substances can interfere with the efficacy of radiation and chemotherapy. The use of COX-2 inhibitors has been shown to enhance radiation sensitivity (50, 51).

The presence of significant inflammation can contribute to chemotherapy toxicity (52). The presence of inflammatory compounds can interfere with chemotherapy efficacy. Combining curcumin with cisplatinum enhances the efficacy of cisplatinum (53). COX and LOX inhibitors were found to effect the efficacy of numerous chemotherapy agents in a positive way when used in various combinations (54).

As opposed to the controversy regarding the use of antioxidants concurrently with radiation or chemotherapy, there does not appear to be either a theoretical or evidence based reason to withhold anti-inflammatory treatments. The available research suggests that they will produce a synergistic benefit when used with radiation and chemotherapy.

Therapeutic strategies to counter chronic inflammation

As discussed above, the approach to chronic inflammation, with the aim to counter proliferation, local and metastatic spread, angiogenesis, and to foster differentiation and apoptosis, can be multifaceted, involving dietary measures, the use of various supplements including fatty acids, antioxidants, and herbs, as well as the use of various pharmaceuticals, most specially COX and LOX inhibitors.

The dietary approach emphasizes a diet that is high in antioxidants, flavonoids and w-3 fatty acids, and low in arachidonic acid containing foods, especially animal products.

The use of supplements involves antioxidants, both vitamins and herbs such as resveratrol and green tea, fish or flax oil supplements containing w-3 fatty acids, and different herbs. The herbs used typically have COX and LOX inhibiting activity, and downregulate the transcription factor NFkB. Most commonly, these include the use of curcumin and boswellia. As noted above, there are unresolved issues regarding the absorption of curcumin and it's effects in the intact organism, as opposed to it's clearly demonstrated effects in experimental cell lines, in vivo and in vitro systems.

Pharmaceuticals of considerable interest include aspirin, NSAIDS and selective COX 2 inhibitors. LOX inhibitors might also be of benefit. The class of drugs known as PPAR agonists, which include glitazones commonly used as insulin sensitizers, and fibrates used for hyperlipidemias, are a new class of medications shown to downregulate inflammation and various growth promoting activities.

Depending on the stage and aggressivity of the malignancy, these varied approached can be combined in different ways. Their use in combination, though rational and intriguing, has not been studied in any significant way. It's a ripe and potentially very fruitful area for research.

Caution should be entertained regarding using anti-inflammatory approaches when treatment methods that promote acute inflammation, such as monoclonal antibodies and vaccines, are employed. Inhibiting inflammation has the potential to interfere with the proinflammatory effects of these immunological methods. In these situations, immunostimulatory agents that also lead to acute immune and inflammatory reactions should be considered. These combinations, however, have not been studied formally.

The Use of Antiinflammatory Substances in Patients Receiving Chemotherapy and Radiation Therapy

Many naturally occurring products, such as herbs and foods, have significant antioxidant as well as anti-inflammatory properties. In contrast to the paucity of literature and theoretical concerns regarding the use of antioxidants such as those mentioned above, there is substantial supportive literature and and an absence of compelling theoretical concern regarding concurrent use of anti-inflammatory substances during chemo/radiation therapy.

Mohammed et al, treated diffuse large cell lymphoma cells with genistein (an isoflavone from soy), CHOP, or CHOP and genistein. At 30 micro M, compared to CHOP alone, genistein with CHOP inhibited the growth significantly, induced G(2)-M arrest, increased Bax:Bcl-2 ratio, decreased NF-kappaB DNA binding, and induced apoptosis. Genistein also inhibited NF-kappaB DNA binding in vivo, whereas CHOP enhanced it (56). A murine model of lung carcinoma was studied comparing standard chemo/radiation therapy with or without genistein. Genistein statistically enhanced the benefit of the treatment regimen (57). Prostate cancer cells were treated with radiation therapy without or without curcumin. "Compared to cells that were irradiated alone (SF(2)=0.635; D(0)=231 cGy), curcumin at 2 and 4 microM concentrations in combination with radiation showed significant enhancement to radiation-induced clonogenic inhibition (SF(2)=0.224: D(0)=97 cGy and SF(2)=0.080: D(0)=38 cGy) and apoptosis. It has been reported that curcumin inhibits TNF-alpha-induced NFkappaB activity that is essential for Bcl-2 protein induction. In PC-3 cells, radiation upregulated TNF-alpha protein leading to an increase in NFkappaB activity resulting in the induction of Bcl-2 protein. However, curcumin in combination with radiation treated showed inhibition of TNF-alpha-mediated NFkappaB activity resulting in bcl-2 protein downregulation. Bax protein levels remained constant in these cells after radiation or curcumin plus radiation treatments. However, the downregulation of Bcl-2 and no changes in Bax protein levels in curcumin plus radiation-treated PC-3 cells, together, altered the Bcl2 : Bax ratio and this caused the enhanced radiosensitization effect. In addition, significant activation of cytochrome c and caspase-9 and -3 were observed in curcumin plus radiation treatments. Together, these mechanisms strongly suggest that the natural compound curcumin is a potent radiosensitizer, **and it acts by overcoming the effects of radiation-induced prosurvival gene expression** in prostate cancer." (58) This explanation highlights the reason why these natural agents appear to enhance the effect of chemo/radiation therapy. Chemo/radiation therapy appears to elicit a counter response in the organism of producing prosurvival mechanisms, such as increased production of NFkB and AP-1, which act to counteract the apoptotic effect of the treatments. Numerous natural substances inhibit signaling molecules and genes such as NFkB and AP-1 and block this escape mechanism. It's to be noted that multiple drug resistance also involves this mechanism, and therefore these natural substances have the potential to be beneficial in this scenario. In this context, Curcumin has been shown to have beneficial effects on Glutathione, another important component related to multiple drug resistance (59). Various other substances, such as green tea (60), resveratrol from grape seeds (61), silymarin from milk thistle (62), and ganoderma mushroom (63), show similar effects.

Bibliography

1) Coussens, L. M., and Werb, Z. – Nature 420, 860 - 867 (19 December 2002);
2) Wallace J.M. – Integrative Cancer Therapies 1(1);2002, pp. 7-37
3) O'Byrne KJ, and Dalgleish AG – British Journal of Cancer (2001) 85(4); 473-483
4) Chan TA - The Lancet Oncology Vol 3, #3, March 2002
5) Moysich KB; Menezes RJ; Ronsani A; Swede H; Reid ME; Cummings KM; Falkner KL; Loewen GM; Bepler G – BMC Cancer - 26-NOV-2002; 2(1): 31
6) Cerhan JR, Anderson KE, Janney CA, Vachon CM, Witzig TE, Habermann TM - Int J Cancer. 2003 Sep 20;106(5):784-8
7) Mizuno D, Soma G - Mol Biother. 1992 Dec;4(4):166-9
8) Hobohm U - Cancer Immunol Immunother. 2001 Oct;50(8):391-6
9) Wiemann B, Starnes CO - Pharmacol Ther. 1994;64(3):529-6
10) Dredge K, Marriott JB, Todryk SM, Dalgleish AG - Cancer Immunol Immunother. 2002 Nov;51(10):521-31. Epub 2002 Sep 20
11) Myers CE, Ghosh J - Eur Urol. 1999;35(5-6):395-8
12) Romano, M and Claria, J - The FASEB Journal. 2003;17:1986-1995
13) Kennedy TJ, Chan CY, Ding XZ, Adrian TE - Expert Rev Anticancer Ther. 2003 Aug;3(4):525-36
14) Julemont F, Dogne JM, Pirotte B, de Leval X - Mini Rev Med Chem. 2004 Aug;4(6):633-8

15) McMillan DC, Talwar D, Sattar N, Underwood M, O'Reilly DS, McArdle C - The relationship between reduced vitamin antioxidant concentrations and the systemic inflammatory response in patients with common solid tumours Clin Nutr. 2002 Apr;21(2):161-4

16) Talwar D, Ha TK, Scott HR, Cooney J, Fell GS, O'Reilly DS, Lean ME, McMillan DC - Effect of inflammation on measures of antioxidant status in patients with non-small cell lung cancer Am J Clin Nutr. 1997 Nov;66(5):1283-5

17) Sattar N, Scott HR, McMillan DC, Talwar D, O'Reilly DS, Fell - Nutr Cancer. 1997;28(3):308-12

18) Plummer SM; Holloway KA; Manson MM; Munks RJ; Kaptein A; Farrow S; Howells L - Oncogene - 28-OCT-1999; 18(44): 6013-20

19) Annelyse Duvoixa, Franck Morceaua, Sylvie Delhallea, Martine Schmitza, Michaël Schnekenburgera, Marie-Madeleine Galteaub, Mario Dicatoa and Marc Diederich - Biochemical Pharmacology Volume 66, Issue 8 , 15 October 2003, Pages 1475-1483

20) Wahlstrom B, Blennow G - Acta Pharmacol Toxicol (Copenh). 1978 Aug;43(2):86-92

21) Sharma RA, McLelland HR, Hill KA, Ireson CR, Euden SA, Manson MM, Pirmohamed M, Marnett LJ, Gescher AJ, Steward WP - Clin Cancer Res. 2001 Jul;7(7):1894-900

22) Ireson CR, J - ones DJ, Orr S, Coughtrie MW, Boocock DJ, Williams ML, Farmer PB, Steward WP, Gescher AJ - Cancer Epidemiol Biomarkers Prev. 2002 Jan;11(1):105-11

23) Menon LG, Kuttan R, Kuttan G - Cancer Lett. 1995 Aug 16;95(1-2):221-5

24) Thresiamma KC, George J, Kuttan R - J Exp Clin Cancer Res. 1998 Dec;17(4):431-4

25) Navis I, Sriganth P, Premalatha B - Pharmacol Res. 1999 Mar;39(3):175-9

26) Kumar V, Lewis SA, Mutalik S, Shenoy DB, Venkatesh, Udupa N - Indian J Physiol Pharmacol. 2002 Apr;46(2):209-17

27) Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS. - Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers.

28) Boik J – Natural Compounds in Cancer Therapy Oregon Medical Press 2001 p 280

29) Gupta I, Gupta V, Parihar A, Gupta S, Ludtke R, Safayhi H, Ammon HP - Eur J Med Res. 1998 Nov 17;3(11):511-4

30) Gerhardt H, Seifert F, Buvari P, Vogelsang H, Repges R - Z Gastroenterol. 2001 Jan;39(1):11-7

31) Zhao W, Entschladen F, Liu H, Niggemann B, Fang Q, Zaenker KS, Han R - Cancer Detect Prev. 2003;27(1):67-75

32) Yongkui Jinga, d, *, Shigeo Nakajoc, Lijuan Xiaa, Kusuyasu Nakayac, Qicheng Fangb, Samuel Waxmand and Rui Hana - Leukemia Research Volume 23, Issue 1 , January 1999, Pages 43-50

33) Hostanska K, Daum G, Saller R - Anticancer Res. 2002 Sep-Oct;22(5):2853-62.

34) Janssen G, Bode U, Breu H, Dohrn B, Engelbrecht V, Gobel U - Klin Padiatr. 2000 Jul-Aug;212(4):189-95

35) Streffer JR, Bitzer M, Schabet M, Dichgans J, Weller M - Neurology. 2001 May 8;56(9):1219-21

36) Winking M, Sarikaya S, Rahmanian A, Jodicke A, Boker DK - J Neurooncol. 2000;46(2):97-103

37) Emelyanov A, Fedoseev G, Krasnoschekova O, Abulimity A, Trendeleva T, Barnes PJ - Eur Respir J. 2002 Sep;20(3):596-600

38) Cho SH, Jung YB, Seong SC, Park HB, Byun KY, Lee DC, Song EK, Son JH - Allerg Immunol (Paris). 2003 Jun;35(6):212-6

39) Schmidt S, Moric E, Schmidt M, Sastre M, Feinstein DL, Heneka MT - J Leukoc Biol. 2004 Mar;75(3):478-485. Epub 2003 Dec 04

40) Mendez M, LaPointe MC - Hypertension. 2003 Oct;42(4):844-50. Epub 2003 Jul 28

41) Dehmer T, Heneka MT, Sastre M, Dichgans J, Schulz JB – J Neurochem. 2004 Jan;88(2):494-501

42) Leipner J, Saller R - Drugs. 2000 Apr;59(4):769-80

43) Gonzalez NJ, Isaacs LL - Nutr Cancer. 1999;33(2):117-24

44) Vayalil PK, Mittal A, Katiyar SK - Carcinogenesis. 2004 Jan 23

45) Hastak K, Gupta S, Ahmad N, Agarwal MK, Agarwal ML, Mukhtar H - Oncogene. 2003 Jul 31;22(31):4851-9

46) Albert S. Baldwin - J Clin Invest, February 2001, Volume 107, Number 3, 241-246

47) Lin JK - Arch Pharm Res. 2002 Oct;25(5):561-71

48) Shu-Huei Tsai1, Shoei-Yn Lin-Shiau2 and Jen-Kun Lin - British Journal of Pharmacology 126:673-680 (1999)

49) Pan Q, Bao LW, Merajver SD - Mol Cancer Res. 2003 Aug;1(10):701-6.

50) Klaunig JE, Kamendulis LM - Annu Rev Pharmacol Toxicol. 2004;44:239-67 - Annu Rev Pharmacol Toxicol. 2004;44:239-67

51) Petersen C, Baumann M, Petersen S - Curr Med Chem Anti-Canc Agents. 2003 Sep;3(5):354-9

52) Asea A, Mallick R, Lechpammer S, Ara G, Teicher BA, Fiorentino S, Stevenson MA, Calderwood SK - Int J Hyperthermia. 2001 Sep-Oct;17(5):401-14

53) Kellie A Slaviero a Stephen J Clarke b Laurent P Rivory - The Lancet Oncology Volume 4 • Number 4 • April 2003

54) Navis I, Sriganth P, Premalatha B – Pharmacol Res. 1999 Mar;39(3):175-9

55) Teicher BA, Korbut TT, Menon K, Holden SA, Ara G - Cancer Chemother Pharmacol. 1994;33(6):515-22 a,

56) Mohammad RM, Al-Katib A, Aboukameel A, Doerge DR, Sarkar F, Kucuk O - Genistein sensitizes diffuse large cell lymphoma to CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy Mol Cancer Ther. 2003 Dec;2(12):1361-8

57) McDonnell CO, Holden G, Sheridan ME, Foley D, Moriarty M, Walsh TN, Bouchier-Hayes DJ - Improvement in efficacy of chemoradiotherapy by addition of an antiangiogenic agent in a murine tumor model J Surg Res. 2004 Jan;116(1):19-23

58) Damodaran; Ranga, Rama S; Meigooni, David; Sathishkumar, Sabapathi; Ahmed, Mansoor M **-** Curcumin confers radiosensitizing effect in prostate cancer cell line PC-3 Oncogene Volume 23, Issue 8 , February 26, 2004, Pages 1599-1607

59) Annelyse Duvoixa, Franck Morceaua, Sylvie Delhallea, Martine Schmitza, Michaël Schnekenburgera, Marie-Madeleine Galteaub, Mario Dicatoa and Marc Diederich - Induction of apoptosis by curcumin: mediation by glutathione S-transferase P1-1 inhibition Biochemical Pharmacology Volume 66, Issue 8 , 15 October 2003, Pages 1475-1483

60) Gupta S, Hastak K, Afaq F, Ahmad N, Mukhtar H - Essential role of caspases in epigallocatechin-3-gallate-mediated inhibition of nuclear factor kappa B and induction of apoptosis Essential role of caspases in epigallocatechin-3-gallate-mediated inhibition of nuclear factor kappa B and induction of apoptosis

61) Vayalil PK, Mittal A, Katiyar SK - Proanthocyanidins from grape seeds inhibit expression of matrix metalloproteinases in human prostate carcinoma cells which is associated with the inhibition of activation of MAPK and NF{kappa}B Carcinogenesis. 2004 Jan 23

62) Tyagi AK, Agarwal C, Chan DC, Agarwal R - Synergistic anti-cancer effects of silibinin with conventional cytotoxic agents doxorubicin, cisplatin and carboplatin against human breast carcinoma MCF-7 and MDA-MB468 cells Oncol Rep. 2004 Feb;11(2):493-9

63) Sliva D. Labarrere C. Slivova V. Sedlak M. Lloyd FP Jr. Ho NW. - Ganoderma lucidum suppresses motility of highly invasive breast and prostate cancer cells Biochemical & Biophysical Research Communications. 298(4):603-12, 2002 Nov 8