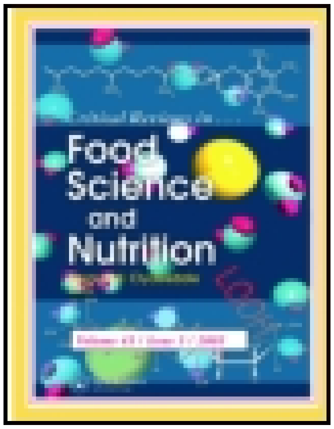

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The Role of Dietary Polyphenols in the Moderation of the Inflammatory Response in Early Stage Colorectal Cancer

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Abstract

Current focus in colorectal cancer management is on reducing overall mortality by increasing the number of early stage cancers diagnosed and treated with curative intent. Despite the success of screening programmes in down-staging colorectal cancer, interval cancer rates are substantial and other strategies are desirable.

Sporadic colorectal cancer is largely associated with lifestyle factors including diet. Polyphenols are phytochemicals ingested as part of a normal diet which are abundant in plant foods including fruits/berries and vegetables. These may exert their anti-carcinogenic effects via the modulation of inflammatory pathways. Key signal transduction pathways are fundamental to the association of inflammation and disease progression including those mediated by NF-κB and STAT, PI3K and COX.

Our aim was to examine the evidence for the effect of dietary polyphenols intake on tumour and host inflammatory responses to determine if polyphenols may be effective as part of a dietary intervention. There is good epidemiological evidence of a reduction in colorectal cancer risk from case-control and cohort studies assessing polyphenol intake. It would be premature to suggest a major public health intervention to promote their consumption however, dietary change is safe and feasible, emphasising the need for further investigation of polyphenols and colorectal cancer risk.

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Keywords

Colorectal cancer

Colonic polyps

Inflammation

Immune response

Signaling pathways

Lifestyle factors

Polyphenol

Flavonoid

Diet

Abbreviations

AICR, American Institute for Cancer Research; Bcl, B-cell lymphoma; COX2, Cyclo-oxygenase-2; COXIB, cyclo-oxygenase 2 inhibitor; CRC, colorectal cancer; CRP, C-reactive protein; DSS, dextran sulphate sodium; EGCG, epigallocatechin-3-gallate; EGF, epidermal growth factor; EPIC, European Prospective Investigation into Cancer and Nutrition; GM-CSF, granulocyte macrophage colony stimulating factor; IBD, inflammatory bowel disease; IL, interleukin; ICAM, intracellular adhesion molecule; JAK, janus kinase; k-RAS, Kirsten rat sarcoma viral oncogene homolog; MDM-2, mouse double minute 2 homolog; MMP, matrix metalloproteinase; NAG, non-steroidal anti-inflammatory drug-activated gene; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NOS, nitrous oxide synthase; NSAIDs, Non-steroidal anti-inflammatory drugs; PDGF, platelet derived growth factor; PGE, prostaglandin E; PI3K, phosphatidylinositol 3-kinase; PIK3CA, phosphatidylinositol-4,5-bisphosphonate 3-kinase catalytic subunit alpha polypeptide; STAT, signal transducer and activator of transcription; TGF, transforming growth factor; TNF-α, tumor necrosis factor-α; UC, ulcerative colitis; VCAM, vascular cell adhesion protein; VEGF, vascular endothelial growth factor; WCRF, World Cancer Research Fund

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Introduction

Colorectal cancer (CRC) is the 2nd most common cause of cancer-related death in the UK (2010) accounting for around 10% of all cancer deaths with 41,000 new cases diagnosed per year in the UK and 16,000 deaths (CRUK, 2012a). Only a small percentage (5-10%) of cases of colorectal cancer arise in patients with known hereditary syndromes while the majority of cases are sporadic, arising due to multiple alterations and mutations promoting initiation and progression of the dysplasia-cancer sequence (Fearon, 2011b).

One strategy to improve outcomes is to focus on reducing overall colorectal cancer mortality by increasing the number of early stage cancers diagnosed and treated with curative intent, therefore reducing cancer specific mortality. For example, with current standard treatment, reported 5 year survival rates for stages TNM I, II, III and IV disease are 93%, 77%, 48% and 7% respectively (CRUK, 2012b). There is good evidence that screening for colorectal cancer increases the number of early-stage cancers diagnosed and the number of precancerous adenomas removed and as a result leads to a reduction of cancer specific mortality (Johnson et al., 2010; Ellul et al., 2010). There was an overall reduction of colorectal cancer mortality of 25% in those who took up testing based on biennial screening (Hewitson et al., 2007).

Despite the success of the colorectal cancer screening program in down-staging colorectal cancer, interval cancer rates are still substantial accounting for 31.2% of cancers diagnosed in the screened population in the 1st round in Scotland, 47.7% in the second round and 58.9% in the third (Steele et al., 2012). With the shift to diagnosis at an earlier stage, a new focus on prevention of recurrence of colorectal cancer is of considerable interest and therefore, other strategies to reduce colorectal cancer risk and disease recurrence after surgery with curative intent are desirable.

Sporadic colorectal cancer appears to be largely associated with lifestyle factors including several dietary components, alcohol and tobacco consumption and sedentary lifestyle (Theodoratou et al., 2014; Park et al., 2012; Chan et al., 2011). The evidence for these associations is convincing, with a 10% decreased risk of CRC per 10g/day increase in intake of dietary fibre, 41% increased risk of CRC for the groups that drank the most alcohol in one large analysis of CRC cases (Cho et al., 2004), 38% increased risk of CRC for an increase of 40 cigarettes/day (Liang et al., 2009) and an 11% decreased risk of CRC and 12% decreased risk of colon cancer per 30 minutes/day of physical activity (WCRF, 2011). Since colorectal cancer develops from a precursor lesion, with approximately 8% of polyps greater than 1cm developing into cancer at 10 years (Stryker et al., 1987), there is the potential advantage that lifestyle interventions may alter the natural history of the disease. Patients with polyps are at an increased risk of developing further polyps and therefore at higher risk of subsequently developing colorectal cancer (Cairns et al., 2010).

Only a few studies investigate the relationship between diet and CRC recurrence; however patients diagnosed with CRC have been shown to be motivated to adjust their dietary and physical activity levels after diagnosis (Patterson et al., 2003; Reedy et al., 2005). Dietary and lifestyle interventions are an attractive option since they are likely to lead to other beneficial effects on health and these may, in part, exert their anti-carcinogenic effects via the modulation of inflammatory pathways involved in the initiation and progression of colorectal carcinogenesis.

The concept that diet may influence colorectal cancer risk is not new; initial observations of the relative rarity of colorectal cancers in African populations that consume a high fibre diet has been published for over 40 years (Burkitt, 1969). Red meat intake has also been implicated as a risk factor for CRC and many epidemiological studies associate an increase in colon cancer or adenoma risk with greater intake of red meat. In the EPIC study, the absolute risk of developing CRC within 10 years for a 50 year old participant was 1.71% for the highest category of red and processed meat intake and 1.28% for the lowest category (Norat et al., 2005). A recent prospective study of > 500,000 individuals from 10 European populations in the EPIC study showed a 40% reduced risk of CRC with the highest intake of fibre, and high fruit and vegetable intake was also associated with a modest risk reduction (Bingham et al., 2003). Polyphenols / phenolics have recently attracted attention as potential agents in the modification of inflammation in early stage colorectal cancer and given that inflammation has been identified as the seventh hallmark of cancer, this may be one mechanism by which they may reduce colorectal cancer risk. There is evidence of their effect on inflammation-associated pathways and they have low toxicity profiles compared with current anti-inflammatory medications. Therefore, the aim of the present review was to examine the evidence for the effect of dietary polyphenols on both the tumour and host inflammatory signal transduction pathways in order to determine if polyphenols may be effective as part of a dietary intervention in the context of a colorectal cancer screening programme.

Inflammation in colorectal cancer

Inflammation has recently been recognized as the seventh hallmark of cancer and current evidence suggests a role for inflammation in the pathogenesis (Colotta et al., 2009) and progression of CRC (Hanahan and Weinberg, 2011). In sporadic colorectal cancer, an accumulation of mutations in oncogenes and tumor suppressor genes such as adenomatous polyposis coli (APC) and β-catenin promotes the transition from dysplastic crypt foci to adenoma and subsequent aberrant genetic alterations including loss of p53 function and K-Ras activation encourage progression to colorectal carcinoma (Fearon, 2011a). Inflammation also has a significant role to play in influencing this process (Terzic et al., 2010; Pages et al., 2010): progression to neoplasia is dependent on growth and pro-survival signals from the tumor microenvironment, secreting factors that recruit inflammatory cells and activate stromal cells.

It has long been recognized by pathologists that some cancers are infiltrated by cells of the innate and adaptive immune system identical to inflammatory conditions in non-neoplastic tissues (Dvorak, 1986). With improvement in laboratory techniques, it has become evident that inflammation is a component of virtually all neoplastic processes. Conclusions drawn from early studies suggested that this ‘immune reaction’ reflected an anti-tumoral response by the immune system in an attempt to eliminate the tumor. However, there is now compelling evidence to suggest that the tumor-associated inflammatory response, on the contrary, can enhance tumorigenesis and progression (Hanahan and Weinberg, 2011). Immune cells, predominantly of the innate immune system have significant roles to play in neoplastic progression and include infiltration with neutrophils and macrophages and pro-inflammatory cytokines such as IL-6, IL-1, TNF-α, EGF and VEGF, which may lead to angiogenesis, cell proliferation and tumorigenesis (Knupfer and Preiss, 2010; Roxburgh and McMillan, 2012). Key signal transduction pathways

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are likely to be fundamental to the association of inflammation and disease progression in colorectal cancer (Figure 1) and in particular, the activation of NF-κB and STAT, PI3K and cyclo-oxygenase pathways in the tumor cells and their microenvironment (stroma and inflammatory cell infiltrate). Evidence that colorectal cancer may arise on a bed of inflammation and is not merely an ‘epiphenomenon’ is supported by the fact that there is a strong association between the duration and extent of mucosal inflammation in inflammatory bowel disease and the development of colorectal cancer (McAllister and Weinberg, 2014). In keeping with this concept, the overall risk of colorectal cancer in those with IBD has decreased markedly in the past few decades and this may be a result of improved therapies and better control of colonic inflammation associated with chronic inflammatory disease (Jess et al., 2012).

NF-kB

NF-κB is a family of dimers that are regulators of infection and inflammation and have been identified as a key component of the signal transduction pathways that occur when inflammation progresses to malignancy (Lu et al., 2006). Under normal resting conditions, NF-κB resides in the cytoplasm until it is activated to translocate to the nucleus, where it is involved in the expression of genes which suppress apoptosis, induce cellular transformation, proliferation, invasion, metastasis, chemo- and radio-resistance and inflammation (Aggarwal and Shishodia, 2006). There are multiple factors that are known to activate the NF-κB pathway including inflammatory stimuli, cytokines, viruses and carcinogens. The resulting activation of target genes such as cyclin D1, apoptosis suppressor proteins (Bcl-2/Bcl-XL), MMP, VEGF and

IL-6 may be critical in the development of aggressive cancers (Aggarwal and Shishodia, 2006). NF-κB has effects on both tumor cells and tumor associated inflammatory cells and therefore, NF-κB has become a target in the development of novel strategies to prevent and treat cancer (Sarkar and Li, 2008). It has been shown to be activated to a greater degree in colorectal tumor specimens than in normal tissue and the degree of activation increased with stage of cancer (Kojima et al., 2004).

STAT

Signal transducer and activator of transcription (STAT) proteins are transcription factors. They prevent apoptosis, therefore encouraging cell survival and growth through increased expression of Bcl-2 and Bcl-X (Aggarwal and Shishodia, 2006). STAT3 is activated by many growth factors and cytokines including IL-11, IL-22, EGF, TGF-α or PDGF receptors (Yu et al., 2009). Once activated, STAT3 induces expression of anti-apoptotic genes, proliferative genes such as Cyclin D1 or c-Myc and vascular endothelial growth factor (VEGF) which is responsible for angiogenesis (Terzic et al., 2010). In the tumor cells themselves, STAT3 inhibits apoptosis by up-regulating pro-survival Bcl-2 proteins (Stephanou et al., 2000; Bromberg et al., 1999). Furthermore, STAT3 induces tumour-associated inflammation by upregulating chemokines capable of attracting immune and inflammatory cells that further enhance STAT3 activity through the production of IL-6, IL-11 and other cytokines (Yu et al., 2009).

In this way, STAT3 has the ability to control and shape the tumor micro-environment. Activation of STAT3 can also lead to prolonged activation of NF-κB, therefore tumor promotion

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and metastasis (Lee et al., 2009). Studies have suggested that STAT3 activation in colorectal cancer is increased and this was in a stage specific manner, with more STAT3 identified in the poorly differentiated tumors as well as those of a more progressed T-stage (Baral et al., 2009; Park et al., 2008).

PI3k

Phosphatidylinositol 3-kinase (PI3K) signaling pathways serve an important role in carcinogenesis (Samuels et al., 2004) regulating cell growth, differentiation, survival, proliferation and migration and mutations in PIK3CA, the gene encoding phosphatidylinositol-4,5-bisphosphonate 3-kinase catalytic subunit alpha polypeptide, are present in 15-20% of colorectal cancers (Barault et al., 2008; Liao et al., 2012b; Whitehall et al., 2012). The up-regulation of PI3K enhances prostaglandin-endoperoxide synthase 2 (PTGS2) also known as COX-2, and therefore PGE2 synthesis leading to inhibition of apoptosis in colon-cancer cells (Kaur and Sanyal, 2010). Studies have shown that aspirin may suppress cancer cell growth by blocking the PI3K pathway and inducing apoptosis (Uddin et al., 2010). Furthermore, regular aspirin use after diagnosis of colorectal cancer was associated with longer survival in those patients with mutated PIK3CA colorectal cancer (Liao et al., 2012a).

The direct tumoral effects of the PI3K pathway include inhibition of apoptosis, increased cellular proliferation and growth and a reduction in cell-cycle arrest (Le and Fodde, 2008). The PI3K pathway is involved in the function of leukocytes and endothelial cells and they appear to be crucial mediators of inflammatory reactions (Le and Fodde, 2008). As a vital signaling

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pathway in the innate immune response, PI3K is involved in chemotaxis of neutrophils and macrophages to the site of inflammation (Hirsch et al., 2000) and this may be another mechanism by which it is involved in carcinogenesis.

Cyclo-oxygenase

Cyclo-oxygenase-2 (COX2) is an inducible mediator of prostaglandin synthesis and the pro-neoplastic effects of COX2 are mediated by the prostanoid PGE2, its major end product. COX2 has been shown to be over-expressed in colorectal cancers (Sheehan et al., 1999; Dimberg et al., 1999) as has PGE2 (Taketo, 1998; Kawamori et al., 2003) and its expression is associated with tumor invasiveness and metastatic potential (Church et al., 2003; Fujita et al., 1998; Tsujii et al., 1997). Much of the evidence describing the role of COX-2 in carcinogenesis derives from observing the actions of COX-2 inhibitors. The direct tumoral effects of COX-2 inhibitors may be related to the inhibition of COX-mediated synthesis of PGE2, which has been shown to increase tumor cell proliferation, decrease apoptosis, increase angiogenesis and increase chemo- and radio-resistance (Park et al., 2014). The interactions between tumor and host cells are mediated by growth factors and cytokines, which act as paracrine factors for endothelial and stromal cells (Kai et al., 2005). Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to decrease serum markers of inflammation including C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) in patients with advanced cancer (Senovilla et al., 2012).

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Cyclo-oxygenase inhibitors have therefore been proposed as an option for chemoprevention of colorectal cancer. Both selective inhibitors (such as celecoxib) and nonspecific inhibitors (for example aspirin) reduced the incidence of colorectal cancer (Flossmann et al., 2007; Chan et al., 2005) and the incidence of and recurrence of adenomatous polyps, established as precursors of colorectal cancer, were inversely associated with the regular use of NSAIDs (Tangrea et al., 2003; Johnson et al., 2010).

Moderation of the Inflammatory Response in Colorectal Cancer

Attempts have been made to manipulate the inflammatory response in colorectal cancer and there is epidemiological evidence to support the roles of lifestyle, medication use and diet in colorectal cancer risk and its prevention (Chan and Giovannucci, 2010).

A recent meta-analysis found that aspirin use is associated with a pooled risk ratio of 0.83 (95% CI, 0.72-0.96) for any adenoma and 0.72 (95% CI, 0.57-0.90) for advanced adenomas (Cole et al., 2009) although there was evidence of between-study heterogeneity (I^2-= 60.1% for any adenoma and 65.4% for advanced lesions). Other randomised control trials found that long-term use of aspirin protects against colorectal cancer in a dose-dependent manner (Flossmann et al., 2007). There have been many observational studies supporting the role of non-aspirin and non-COX-2 selective NSAIDs in colorectal cancer prevention; however, randomised trial data are limited. The most compelling hypothesis on the proposed mechanisms by which NSAIDs reduce the risk of colorectal neoplasia is related to their anti-inflammatory effect via the inhibition of COX-2. Moderation of the inflammatory response with medications such as aspirin

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and non-steroidal anti-inflammatory drugs are associated with substantial reductions in colorectal cancer risk although their utility may be affected by the associated risks and side-effect profile such as bleeding, peptic ulceration and cardiovascular events with COXIBs .

The role of environmental factors in the development of colorectal cancer is supported by the global variation in the incidence of CRC and its change on migration (Ladabaum et al., 2014). Many of the lifestyle risk factors associated with CRC including obesity, low levels of physical activity, alcohol consumption and smoking are associated with the activation of one or more of the above inflammatory pathways. An inverse association between levels of physical activity and the risk of colon cancer has been one of the most consistently observed (Colbert et al., 2001; Colditz et al., 1997) with a recent meta-analysis demonstrating that physically active individuals had a 20-30% lower risk of colon cancer compared to less active individuals (Wolin et al., 2009). The mechanisms by which physical activity reduces the risk of CRC are not yet fully understood, however, it may be in part due to a reduction in systemic inflammation which is largely mediated through the inhibition of COX-2 (Chan and Giovannucci, 2010).

The second World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) report advised that there is convincing evidence that red meat and processed-meat intake and higher alcohol intake are associated with a higher colorectal cancer risk whilst dietary fibre is associated with a lower risk. The evidence that milk and calcium as well as non-starchy vegetables, fruit and fish are associated with a lower risk of colorectal cancer is less convincing. Whilst there are several suggested mechanisms by which alteration of dietary intake may act to reduce the risk of colorectal cancer, including anti-oxidant and gut modulatory properties, an anti-inflammatory effect exerted by certain dietary compounds appears to play an important role.

Another mechanism by which dietary components may be linked to the development of colorectal cancer may involve the intestinal microbiota. Several studies have found differences in the population of bacteria in those with and those without CRC (Azcarate-Peril et al., 2011) and intestinal microbes may act as pro-carcinogens by inducing pro-inflammatory cytokines, whilst dietary modification can alter the number and type of micro-organisms present.

Polyphenols and cancer associated inflammation

Polyphenols are phytochemicals abundant in plant foods and can be considered as 4 main classes: flavonoids, phenolic acids, stilbenes and lignans. Polyphenolic compounds are characterised by a benzene ring with one or more hydroxyl groups attached and can be isolated from plant sources including fruits and vegetables, berries and seeds and some beverages such as tea, green tea, red wine and coffee. Dietary polyphenols have been shown to have anti-carcinogenic and anti-inflammatory effects through various mechanisms involving signalling cascades and transcription factors (Marzocchella et al., 2011).

The biological effects of polyphenols that contribute to their role in the inhibition of carcinogenesis include anti-oxidant, anti-inflammatory and phytoestrogenic properties and an ability to inhibit cellular proliferation, invasion, angiogenesis and metastasis and promote apoptosis (Qu et al., 2005; Danbara et al., 2005).

Flavonoids are ingested as part of a normal diet and it is therefore logical that they have been suggested to play a role in the modulation of intestinal inflammation. The bioavailability of polyphenolic compounds is low and therefore they remain in the lumen where they are degraded and metabolized by gut bacteria to phenolic metabolites. Administration of polyphenols was effective at preventing and treating intestinal inflammation in rodents models of IBD where acute or chronic colitis was induced by intra-rectal administration of dinitrobenzene sulphate (Oz et al., 2005; Kim et al., 2005) and addition of dextran sulphate sodium (DSS) to drinking water (Camuesco et al., 2004).

Several *in vivo* animal studies have been performed with naturally occurring polyphenols demonstrating their therapeutic effects in different disease models, particularly those with where an inflammatory component is pertinent. One such example is Rheumatoid Arthritis, and various flavonoids and related polyphenols have been demonstrated to reduce arthritis induced inflammation (Wang et al., 2008; Elmali et al., 2007; Tang et al., 2007). Cardiovascular disease is another condition which evidence suggests is prevented by dietary polyphenolic compounds and the mechanisms by which they exert this action appears to be at least in part anti-inflammatory because the levels of ICAM-1 and VCAM-1 in atherosclerotic blood vessels were reduced (Gonzalez et al., 2011).

Although the literature is still lacking evidence from trials involving human subjects, several human studies have reported that polyphenolic compounds may reduce the secretion of pro-inflammatory cytokines (Chun et al., 2008; Bobe et al., 2010a) and the molecular mechanisms by which polyphenols may exert their anti-inflammatory effects are multiple including the attenuation of signal transduction pathways, the cyclooxygenase and lipooxygenase pathways in particular (Wang et al., 2006).

In the context of benign inflammatory disease, a 6-month placebo-controlled trial of curcumin therapy in 89 patients with quiescent ulcerative colitis (UC) found a decreased relapse rate in those who were treated with curcumin (Hanai et al., 2006). Relapse was seen in 5% of those treated with curcumin and 21% of the placebo group.

Of the entire gastrointestinal tract, the large intestine may be exposed to the highest concentration of flavonoids due to their poor availability (Halliwell et al., 2000) and there is a growing body of evidence from human studies that certain polyphenolic compounds are associated with a reduced risk of colorectal cancer (Rossi et al., 2006; Theodoratou et al., 2007). Furthermore, case-control studies comparing dietary polyphenol intake in those diagnosed with colorectal cancer, with a control group, using food frequency questionnaires have demonstrated that the consumption of certain polyphenols was low in CRC cases versus controls and these are outlined in Table 2.

This presents an interesting concept, that dietary alteration to a diet high in polyphenols such as fruits and vegetables, berries, tea and coffee may be effective in modulating inflammatory responses and therefore decreasing the risk of advanced and high-risk colorectal adenoma recurrence (Bobe et al., 2010a; Bobe et al., 2008) and colorectal cancer (Rossi et al., 2006; Theodoratou et al., 2007) without the adverse effects that have been associated with some of the agents currently under investigation for chemoprevention in colorectal carcinogenesis.

The effect of polyphenols on signal transduction pathways important in tumor growth and inflammation in CRC

The anti-inflammatory activities of polyphenols can be related to the arachidonic acid-dependent pathway (COX, lipo-oxygenase and phospholipase A2 inhibition) or arachidonic independent pathways involving nitrous oxide synthase (NOS), NF-κB and NAG (Biesalski, 2007). Despite this, the evidence for polyphenols as anti-inflammatory agents remains limited and most studies have been performed *in vitro* and have concentrated on one specific polyphenolic compound (Table 1).

NF-kB

Dietary polyphenols such as resveratrol (Manna et al., 2000), green tea catechins (Yang et al., 2001) and curcumin (Singh and Aggarwal, 1995) are potent inhibitors of the NF-κB signaling pathway in human and animal cell lines in vitro and the mechanisms by which they exert this effect are becoming better understood. These substances may intervene at any step in the NF-κB signaling pathway, for example, inhibition of the translocation of NF-κB to the nucleus or inhibition of any of the initial stimulatory signal transduction pathways or transcription factors. Curcumin (the main polyphenolic in turmeric) is one such example which has been shown to mediate its chemotherapeutic effects by NF-κB inhibition and by inhibition of NF-κB regulated gene products such as COX-2, adhesion molecules, MMPs, iNOS, Bcl-2 and TNF (Shishodia et al., 2005).

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STAT

Dietary polyphenols epigallocatechin-3-gallate (EGCG) from green tea (Masuda et al., 2001), resveratrol (Wung et al., 2005) and curcumin (Bharti et al., 2003) have been shown to suppress the activation of STAT in tumor cells in human malignancy. EGCG was shown to down-regulate the phosphorylation of STAT3 whilst resveratrol inhibited IL-6 induced ICAM-1 gene expression partly by interfering with STAT3 phosphorylation.

PI3k

There is little in the way of evidence to support the inhibition of PI3k by polyphenolic compounds. Li et al demonstrated down-regulation of the oncogene MDM2 by curcumin via the PI3K signaling pathway and when activated, this pathway is known to promote cell survival and proliferation (Li et al., 2007). This effect was noted in human cancer cell lines as well as normal cell lines. Further work on colorectal cancer cells treated with curcumin demonstrated an inhibitory effect on cell growth in a time and dose-dependent manner via the PI3k/Akt pathway (Johnson et al., 2009).

Another polyphenol, quercetin, has been shown to exert a protective effect against COX-2 expression and PGE2 production by targeting the PI3K signaling pathway in rat liver epithelial cells and this may contribute to its chemopreventive potential (Lee et al., 2010).

Cyclo-oxygenase

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Dietary polyphenols have been shown to exert their anti-inflammatory effects through inhibition of COX-2 at the transcriptional and enzyme level (Biesalski, 2007). Many dietary polyphenols have demonstrated this ability to inhibit COX-2 in vitro including green tea extract enriched with catechin and epigallocatechin gallate (EGCG) which inhibited COX-2 expression in mouse skin (Kundu et al., 2003) and genistein, quercetin, kaempferol and resveratrol were found to down-regulate COX-2 promoter activity in human colon cancer cells (Mutoh et al., 2000).

NSAID activated gene-1 is a member of the TGF-β superfamily proteins and is another factor involved in the inflammatory response. It is activated by NSAIDs and also by several dietary compounds. Induction of NAG-1 can induce apoptosis and promote anti-tumorigenic activity (Baek et al., 2004). Baek et al have demonstrated that green tea polyphenol, epicatechin gallate, induces the expression of NAG-1 in colon cancer cells (Baek et al., 2004).

Polyphenols & the systemic inflammatory response

Cytokine concentrations measured in the serum or in the tumor itself may be utilized as markers of inflammation and may be an indicator of the risk of neoplastic change or progression (Pellegrini et al., 2006). In human studies, elevated serum levels of IL-6, CRP and TNF-α were associated with the presence of colorectal adenomas (Kim et al., 2008).

Interleukin-6

Interleukin-6 is a pro-inflammatory cytokine, the primary source of which are monocytes and macrophages during acute inflammation and T cells during chronic inflammation and it may act as a tumor promoter in colorectal neoplasms (Naugler and Karin, 2008; Heikkila et al., 2008). Activation of IL-6 activates Janus kinases (JAK) and STATs, which are involved in the regulation of cell proliferation and apoptosis (Hodge et al., 2005). There is a growing body of evidence that IL-6 is over-expressed in colorectal cancer tissue (Chung et al., 2006; Kinoshita et al., 1999) and, further to this, increased concentrations of IL-6 were associated with poorer survival and high-risk pathological factors such as T-stage, nodal status and vascular invasion (Chung et al., 2006). Similarly, there is reliable evidence that circulating concentrations of IL-6 are elevated in patients with colorectal cancer when compared to normal controls and, again, this is associated with poorer survival, tumor size and T-stage (Belluco et al., 2000; Galizia et al., 2002; Chung and Chang, 2003; Nikiteas et al., 2005). In addition to colorectal adenocarcinoma, IL-6 concentrations were also associated positively with the presence of colorectal adenoma in a colonoscopy-based study in North Carolina (Kim et al., 2008).

The evidence in humans that the consumption of dietary polyphenols decreases circulating levels of inflammatory markers such as IL-6 remains inconclusive (Song et al., 2005; Chun et al., 2008). Recently, Bobe et al (Bobe et al., 2010a) investigated whether serum IL-6 was associated with colorectal adenoma recurrence and flavonol intake in order to determine whether measuring serum levels would serve as an indicator of risk or recurrence. They found that a high intake of flavonols was inversely associated with serum IL-6 concentrations and advanced and high risk adenoma recurrence and concluded that dietary flavonols could serve as a method to prevent colorectal cancer and that serum IL-6 levels may serve as an indicator of risk and of response (Bobe et al., 2010a).

CRP

C-reactive protein is a nonspecific marker of systemic inflammation and it has been widely used to detect and monitor systemic inflammatory responses with extensive research supporting the fact that CRP levels are higher in cancer patients than healthy subjects. Several large cohort studies have identified a link between pre-cancer inflammation as measured by the CRP and colorectal cancer risk (Prizment et al., 2011; Allin et al., 2009). Furthermore, the systemic inflammatory response measured by circulating CRP levels, is a predictor of recurrence and overall survival in those with colorectal cancer.

Population-based observational and randomized control trials have found that an inverse relationship between the serum CRP concentration and dietary intake of substances high in polyphenols exists (De Bacquer et al., 2006; Steptoe et al., 2007; Chun et al., 2008). Chun et al (Chun et al., 2008) analyzed the dietary flavonoid intakes of over 8000 American adults. Total flavonoid and individual flavonoid compounds (quercetin, kaempferol, malvidin, peonidin, daidzein and genistein) had inverse associations with serum CRP concentration.

TNF

TNF is produced during the initial inflammatory response, initiating the production of cytokines and chemokines and increasing vascular permeability therefore promoting inflammation, angiogenesis and tumor dissemination (Li et al., 2009; Balkwill, 2009). Its

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expression increases during colon tumorigenesis and interference with TNF signaling with a soluble decoy receptor decreased tumorigenicity and tumor growth (Popivanova et al., 2008). Polyphenol ellagic acid has been shown to reduce the expression of COX-2, iNOS, IL-6 and TNF-α in a rat model of colon cancer (Umesalma and Sudhandiran, 2010).

Other studies have reported that concentrations of IL-8, IL-10, IL-12, granulocyte macrophage colony stimulating factor (GMCSF) and TNF-α are higher in those individuals with colorectal adenomas (Berghella et al., 1997) however, more recent studies were unable to associate serum concentration of IL-1, 2, 8, 10, GM-CSF, IF-ɣ or TNF-α with an elevated risk of colorectal adenoma recurrence, despite decrease cytokine concentrations during high flavonol consumption (Bobe et al., 2010b).

Dietary Polyphenols and Colorectal Neoplasia Risk in Observational Studies

There is epidemiological evidence from a limited number of case-control and cohort studies (Table 2), which have assessed the relationship between dietary flavonoid intake and colorectal cancer or colorectal adenomas. Flavonols are one class of dietary polyphenols that have been investigated for their ability to reduce the risk of colorectal adenoma recurrence in the Polyp Prevention Trial (Bobe et al., 2008). Bobe and colleagues found that a higher intake of flavonols was associated with a 76% decrease in the risk of advanced adenoma recurrence. They hypothesized that this may also apply in colorectal adenocarcinoma given that in cell culture more progressed tumor cells were more sensitive to flavonols (Jeong et al., 2009).

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Hoensch and colleagues investigated the recurrence risk of neoplasia in patients with resected colorectal cancer and after polypectomy in those who were treated with a mixture of flavonoids (apigenin and epigallocatechin-gallate) as compared to a matched control group. This study was unique in that it involved a nutritional intervention using a flavonoid supplement. 36 patients had resected colon cancer and 51 had undergone polypectomy (Hoensch et al., 2008). Both the treated group and the untreated controls were monitored with a surveillance colonoscopy for 3-4 years and also by questionnaire. The combined recurrence rate for neoplasia (cancer and adenoma) was 7% in the treated group compared to 47% in the control group. Therefore, they concluded that treatment with flavonoids could reduce the recurrence rate of neoplasia in those with resected colon cancer.

Conclusion

Over the past decade there has been an increased appreciation that inflammation has a significant role to play in human carcinogenesis and there is a significant body of evidence to support the role of the host inflammatory response in the progression of cancer of the colon and rectum. Various methods of favorably manipulating cancer-associated inflammation have shown promise including aspirin, statins and other non-steroidal anti-inflammatory drugs. Lifestyle factors also play a role in the development of colorectal cancer including obesity, lack of exercise, alcohol consumption and dietary intake. Further to this, dietary polyphenolic compounds have been shown to act at multiple key steps in carcinogenesis and inflammation and therefore a role in colorectal cancer prevention has been suggested.

The current evidence from epidemiological studies on the association of dietary flavonol intake and colorectal cancer or adenoma risk is limited and much of the current research concentrates on isolated flavonoids. Although positive associations between a reduction in risk and many polyphenolic compounds have been demonstrated, the data is inconsistent and many find this positive association with only one compound out of several tested.

As there are relatively few human studies at the time of writing conferring the benefit of a diet rich in polyphenols in those who have colorectal adenomas or adenocarcinoma, it would be premature to suggest a major public health intervention to promote their consumption. However, dietary change is both safe and feasible and this emphasizes the need for further investigation of dietary polyphenols and their association with colorectal cancer risk. This data would be essential in formulating dietary recommendations for the general public and for those who are at an increased risk of colorectal adenoma or carcinoma and this may complement the current bowel screening program to work towards a shift to earlier stage diagnosis of colorectal cancer.

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Table 1: Mechanisms of chemoprevention by polyphenols in *in vitro* cell lines

Authors	**Cell Type**	**Poyphenol (s)**	**Outcomes**
Kundu et al (2003) (Kundu et al., 2003)	Mouse skin	Catechin Epigallocatechin gallate	Inhibition of COX-2 expression
Mutoh et al (2000) (Mutoh et al., 2000)	Human colon cancer DLD-1 cells	Quercetin, kaempferol, genistein, resveratrol, resorcinol	Inhibition of COX-2 expression
Suh et al (2009) (Suh et al., 2009)	Human colon cancer HT29 cells	Fisetin	Apoptosis & down regulation of COX-2 protein expression in colon cancer cells
Li et al (2007) (Li et al., 2007)	Human prostate cancer cell lines	Curcumin	Reduced oncogene MDM2 via PI3K signaling
Johnson et al (2009) (Johnson et al., 2009)	Colorectal cancer cells	Curcumin	Inhibitory effect on cell growth via PI3K/Akt pathway
Lee et al (2010) (Lee et al., 2010)	Rat liver epithelial cells	Quercetin	Protective effect of quercetin against COX-2 expression by targeting

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			PI3K
Manna et al (2000) (Manna et al., 2000)	Human cells lines (lymphoma, epithelial cells)	Resveratrol	Inhibition of TNF induced activation of NF-κB
Singh et al (1995) (Singh and Aggarwal, 1995)	Human leukemia cell line	Curcumin	Inhibition of NF-κB
Yang et al (2001) (Yang et al., 2001)	Rat intestinal epithelial cell line	ECGC	Inhibition of I kappa B kinase complex mediated activation of NF-κB
Bharti et al (2003) (Bharti et al., 2003)	Human malignant melanoma cell lines	Curcumin	Inhibition of IL-6 induced STAT3 phosphorylation
Masuda et al (Masuda et al., 2001)	Head and neck squamous cell carcinoma cell line	EGCG	Suppression of the activation of STAT3
Wung et al (2005) (Wung et al., 2005)	Bovine aortic endothelial cells	Resveratrol	Inhibition of phosphorylation and of activation of STAT3
Baek et al (2004) (Baek et al., 2004)	Human colon cancer cells (HCT-116)	Catechins	ECG induced expression of NAG-1

Martinez-Florez et al (2005) (Martinez-Florez et al., 2005)	Rat hepatocytes	Quercetin	Inhibition of iNOS expression by quercetin

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Table 2: Clinical studies reporting an association between intake of dietary polyphenols and colorectal cancer/adenoma risk

Authors	**Sample Size**	**Methods**	**Outcomes**	**Association**	**Strength of Association**
Akhter et al (2008) (Akhter et al., 2008)	886	Prospective cohort study	Association of isoflavone intake with CRC risk	Intake of isoflavones is associated with reduced risk of proximal colon cancer in men only	HR in highest quartile 0.55 (5% CI 0.33-0.92) for proximal cancer in men only (P= 0.007)
Akhter (2009) (Akhter et al., 2009)	721 cases 697 controls	Case-control study	Association of isoflavone intake & colorectal adenoma risk	There is an inverse association between dietary isoflavone intake and colorectal adenoma and it was more	OR 0.7 (95% CI 0.51-0.96) for highest vs lowest quartile of isoflavone intake P=0.03 overall and 0.49 (0.27-090) in women (P=0.03)

				pronounced in women	
Arts (2002) (Arts et al., 2002)	33,339 (635 colon cancers)	Cohort study	Association of dietary catechin intake and cancer incidence amongst postmenopausal women	Rectal cancer but not colon cancer was inversely associated with catechin intake	RR 0.55 for highest quartile of intake (P= 0.02) for rectal cancer only
Bobe (2008) (Bobe et al., 2008)	958 cases 947 control s	Randomize d, multicentre nutritional intervention trial	Association of flavonoids with adenoma recurrence	High intake of flavonols and isoflavonoids were associated with reduced incidence of advanced adenoma recurrence	OR 0.24 (95% CI 0.11-0.53) for highest vs lowest quartile for flavonols (P=0.0006) & 0.46 (0.22-0.95) for isoflavonoids (P=0.01)
Budhathoki (2011) (Budhathoki et al., 2011)	816 cases 815 control	Case-control study	Association of soy food and isoflavone intake and CRC	High intake of soy food and isoflavones were inversely	OR for highest vs lowest quintile 0.65 (95% CI 0.41-1.03), p=0.03

	s		risk	associated with colorectal cancer risk in men and post-menopausal women	for soy foods & 0.68 (0.42-1.10) p= 0.051 for isoflavones in men & 0.60 (0.29-1.25) p=0.053 & 0.68 (0.33-1.40) p= 0.049 in postmenopausal women
Cotterchio (2006) (Cotterchio et al., 2006)	1095 cases 1890 controls	Case-control study	Association of dietary phytoestrogens and colorectal cancer risk	Dietary lignan and isoflavone intake were associated with reduced risk of colorectal cancer	OR 0.73 (95% CI 0.56-0.94) p= 0.01for highest vs lowest lignan intake & 0.71 (0.58-0.86) p<0.01 for isoflavones
Djuric (2012) (Djuric et al., 2012)	1163 cases 1501 controls	Case-control study	Association of dietary intake of quercetin and risk of colorectal	Protective effective of quercetin on risk of proximal colon cancer	OR 0.49 (95% CI 0.32-0.73) P=0.006) with high fruit intake, 0.44 (0.27-0.72)

			cancer	only when fruit intake high and tea intake low	P= 0.003with high healthy eating index & 0.51 (0.26-1.00) P=0.044 when tea intake was low
Kyle (2010) (Kyle et al., 2010)	264 cases 408 controls	Case-control study	Evaluation of the association of four flavonoid subclasses and the risk of colorectal cancer	Non-tea flavonol, specifically quercetin were associated with reduced colorectal cancer risk	OR 0.6 (95% CI 0.4-1.0) for non-tea flavonol & 0.5 (0.3-0.8) P<0.01 for colon cancer with high levels of non-tea quercetin intake
Rossi (2006) (Rossi et al., 2006)	1953 cases 4154 controls	Case-control study	Association of flavonoid intake and colorectal cancer risk	Reduced risk colorectal cancer with high intake isoflavones, anthocyanidins, flavones, flavonols	OR 0.76 (95% CI 0.63-0.91) P=0.001 for isoflavones, 0.67 (0.54-0.82) P<0.001 for anthocyanidins, 0.78 (0.65-0.93)

					P=0.004 for flavones, 0.64 (0.54-0.77) P<0.001 for flavonols
Simons (2009) (Simons et al., 2009)	2485 cases	Cohort study	Association of flavonol, flavones & catechin intake with CRC risk	Total catechin and epicatechin intake was associated with rectal cancer in men with BMI>25 and total catechin, kaempferol, myricetin was associated with colorectal cancer in women BMI<25	Total catechin/epicatechin in male rectal cancer with BMI>25 HR 0.63 (0.36-1.08) P=0.04. Total catechin in female colon cancer with BMI<25 HR= 0.62 (0.43-0.91) P=0.04 for highest vs lowest quintiles
Theodoratou (2007) (Theodorato	1456 cases 1456	Case-control study	Association of flavonoid intake with CRC risk	Increased consumption of flavonols,	OR 0.73 P=0.0121 for flavonols, 0.68 P=0.001 for

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u et al., 2007)	controls			quercetin, catechin & epicatechin were associated with a reduction in colorectal cancer risk	quercetin, 0.68 P<0.0005 for catechin, 0.74, P=0.019 for epicatechin & 0.78 P=0.031 for procyanidins.
Ward (2010) (Ward et al., 2010)	221 cases 886 controls	Case-control study	Association of risk of colorectal cancer relative to phyto-oestrogen intake	Colorectal cancer risk was inversely associated with enterolactone & entrolignans in women only	OR 0.33 (0.14-0.74) P=0.008 for enterolactone & 0.32 (0.13-0.79) P=0.013 for enterolignans
Yang, G (2009) (Yang et al., 2009)	68412 (321 CRC)	Cohort study	The relationship between intake of soy foods/isoflavones and colorectal cancer risk	Soy foods/isoflavones reduced the risk of colorectal cancer in postmenopausal women	RR 0.67 (95% CI 0.49-0.90) for highest vs lowest tertile p=0.008

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Zamora-Ros (2013) (Zamora-Ros et al., 2013)	424 cases 401 controls	Case-control study	Relationship between dietary flavonoid and lignin intakes and the risk of colorectal cancer	Intake of total dietary flavonoids and lignans was inversely associated with colorectal cancer risk	OR 0.59 95% CI 0.35-0.99) for flavonoids P=0.04, 0.59 (0.34-0.99) for lignans P=0.03

Figure 1

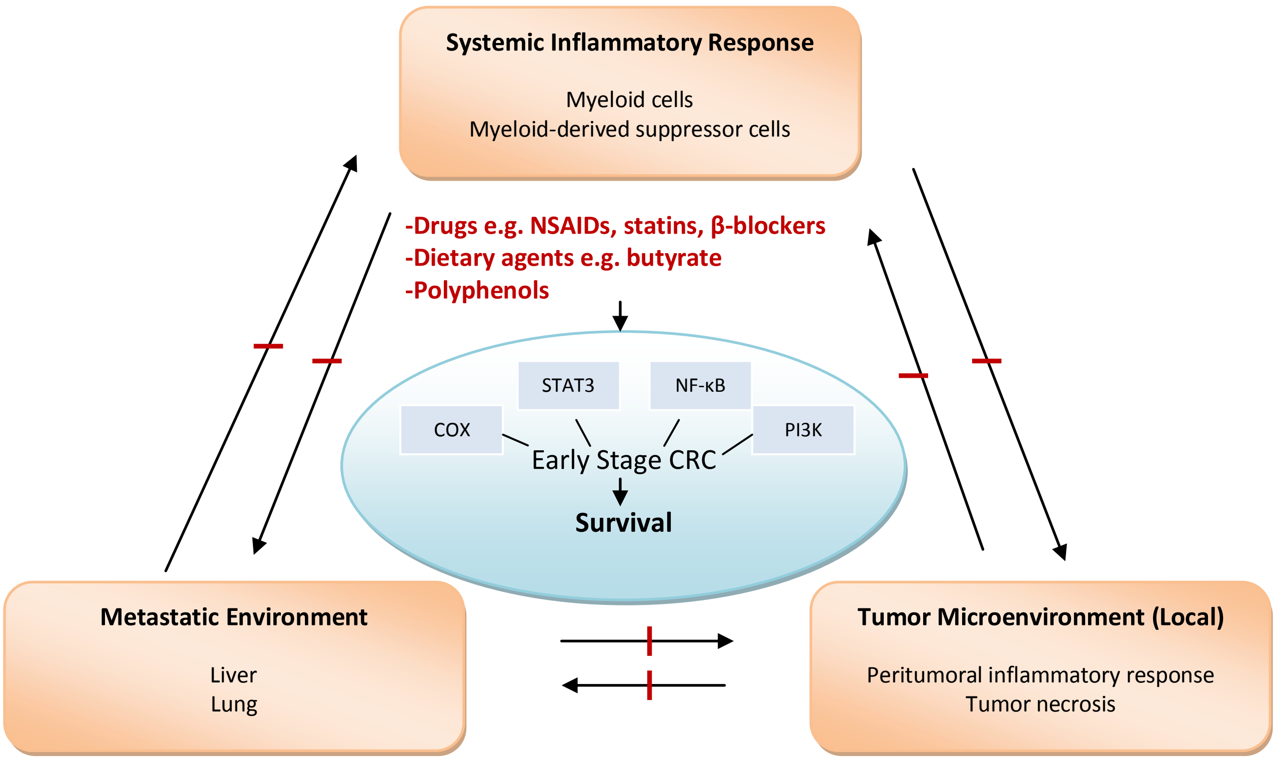

Figure 1: The inflammatory response promotes tumor development and progression, and tumor development and progression induces the inflammatory response. Local and systemic inflammatory states and the mediators released enhance metastogenesis. Furthermore, tumor progression and metastasis promotes the local and systemic inflammatory response (Mantovani et al., 2008, Chechlinska et al., 2010). This vicious circle can be interrupted by various agents and there has been recent interest in their administration with the aim of attenuating the inflammatory response associated with carcinogenesis, slowing progression or preventing recurrence and therefore potentially improving survival.

Figure 2

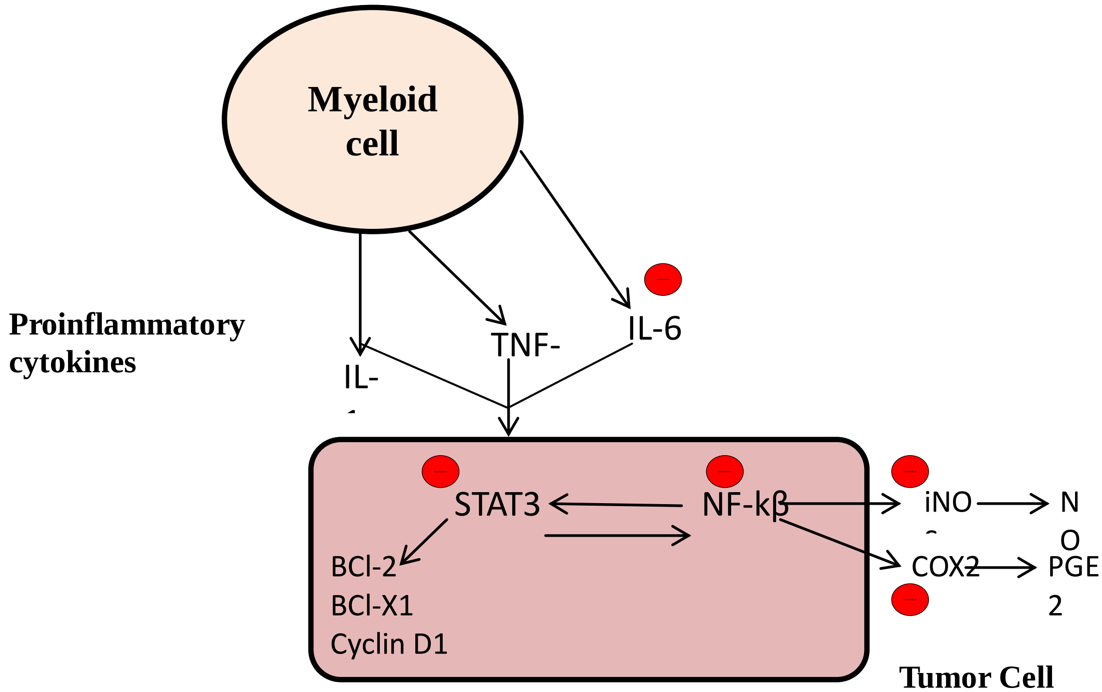

Figure 2: Mechanisms of inhibition of inflammation in cancer by dietary polyphenols

Signal transducer and activation of transcription 3 (STAT3) and nuclear factor-kβ (NF-Kβ) are induced in cancer cells by pro-inflammatory cytokines. This results in the suppression of apoptosis and the promotion of cell cycle progression and cell proliferation. Various dietary polyphenolic compounds have been demonstrated to inhibit these inflammatory pathways ( ), ultimately reducing cancer-associated inflammation and therefore reducing the incidence of neoplasia.