**Natural Medicine**

***Perspective Review***

# Rationale for the Use of Natural Anti-Inflammatory Agents in Cancer Chemotherapy

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## Abstract

**Chemotherapeutic drugs have been conventionally used for the cancer treatments, but the efficacy of the therapy remains problematic. It has been strongly suggested that the anti-inflammatory drugs, such as COX-2 inhibitors, may enhance the anti-cancer efficacy of chemotherapeutic drugs and reduce the chemo-resistance. Herein, the rational of the use of anti-inflammatory agents in the cancer treatment is summarized. One of the most important inflammatory processes occurs during metabolism of the eicosanoids, which involved arachidonic acid (AA), cyclooxygenase 2 (COX-2), prostaglandins (PGs) and leukotriens (LTs). As the results of excessive up-regulation of COX-2 and production of PGE2, for example, the harmful inflammation may promote the cancer development. The inflammation also involve in the drug resistance of the chemotherapy. In fact, many in vitro and in vivo studies have showed the positive potentials using COX-2 inhibitors in the cancer treatment. However, the regular anti-inflammatory agents, mainly COX-2 inhibitors, may induce serious damages to stomach, kidney and heart, which have restricted the clinical uses of these drugs. For the reason, growing numbers of studied have targeted on the natural anti-inflammatory substances and expected to find the effective adjuvant to the chemotherapeutic drugs without the safety concern. On the other hand, the counteraction between the chemotherapy and natural substances has been concerned clinically. Therefore, the natural substances, which were studied for their anti-inflammation effects, are listed. The potential enhancing effects of some of the national anti-inflammatory agents on chemotherapeutic agents are reviewed. A guideline for clinical use of these natural agents with chemotherapy is suggested although limited clinical trial data available. In conclusion, the existing evidences suggest that some natural anti-inflammatory substances have potential to be used as adjuvant agents to enhance the efficacy and reduce the resistance of the chemotherapy. But more research and clinical trials are needed to support the suggestions.**

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## Introduction

Growing evidence shows that inflammation not only contributes to cancer development, but also affects chemotherapy efficacy and resistance. It has been well documented that cyclooxygenase 2 (COX-2) plays an important role in the inflammatory pathway.[1-3] Intensive studies have targeted anti-inflammatory agents, particularly COX-2 inhibitors, as new adjuvant agents in chemotherapy.[4-6] Although numerous studies have suggested a role of COX-2 inhibitors in chemoprevention, serious side effects involving the heart, kidneys and stomach have hindered their clinical application.[7,8] Therefore, mounting interest has shifted to investigating natural substances that possess anti-inflammation and COX-2 inhibiting effects but less toxicity and side effects. Moreover, these natural substances may also convey multiple beneficial pharmacological effects, including immune function enhancement and cancer growth inhibition.

## COX-2, Inflammation, and Cancer

Normal inflammation is a necessary protective response to harmful stimuli to the body, such as infectious pathogens and toxic chemicals. However, prolonged or excessive inflammation is believed to be a possible contributor to angiogenesis and cancer development.[9-12] One of the most important inflammatory processes occurs during metabolism of the eicosanoids, which include prostaglandins (PGs) and leukotriens (LTs). Arachidonic acid (AA) is the precursor of eicosanoids on cell membranes and is enzymatically metabolized to PGs and LTs by cycloxygenase (COX) and lipoxygenase respectively. Multiple molecules or pro-inflammatory factors in the COX-2 pathway are involved in the inflammation process (**Figure 1**). Some of these factors play important roles in the formation, development and metastasis of cancer.[1] A new generation of pharmaceutical anti-cancer drugs has been developed to target the molecules which are involved in the COX-2 pathway, including PGE-2, tyrosine kinase, growth factors and angiogenesis.[3,10,13] COX-2 plays a central role in controlling and modulating the speed of the biochemical cascade in the eicosanoid pathway, particularly in the production of PGE-2.[14-20] PGE-2, one of the downstream products of COX-2, is a key stimulator of inflammation, cell migration and proliferation, while inhibiting cell death. Pro-inflammatory stimulators result in COX-2 and PGE-2 over-production, and cancer may occur as a result of inflammation.[21,22] A number of clinical investigations have demonstrated high COX-2 activity in patients with a variety of cancers, including colorectal, gastric, breast, non-small cell lung, ovarian, hepatocellular, pancreatic, bladder, skin cancers, and particularly, 80-90% of colon cancer patients.[23-28] Epidemiologic studies suggest that non-steroid anti-inflammatory drugs (NSAIDs), including aspirin and indomethacin, have significant preventative effects on certain types of cancer.[29,30] The activity of COX-2 can be stimulated by a variety of interior and exterior factors. The external COX-2 stimulators include Epstein-Barr virus, Streptococcus pneumoniae, phorbol ester and desferrioxamine. These factors may trigger AA release and the expression of COX-2 enzyme.[31] In epithelial colon cancer, the epidermal growth factor receptor (EGFr) activates tyrosine kinase resulting in excessive up-regulation of COX-2 expression. Consequently, this process results in up-regulation of PGE2, which is believed to be a possible contributor to tumor metastasis.[32] Other studies suggest that COX-2 is sensitive to hypoxia and oxygen-derived free radical injury, showing elevated levels in hypoxic conditions.[33-35] In response to pro-inflammatory stimuli, phagocytic cells of the immune system require rapid consumption of $O_2$ and comprise a major source of free radicals in the body. The lipid bilayer of the cell membrane is easily damaged by exposure to excessive levels of free radicals. As a result, AA on the cell membrane is released into cytosol and triggers the eicosanoid cascade. COX-2 up-regulators also include NO, epithelial growth factor, lipopolysacharide, omega-6 fatty acids, IL-4, IL-1β, IL-6, TGF-β and TNF-α.[36-39] Conversely, chemicals that inhibit COX-2 function also exist in our body and include substances such as omega-3 fatty acids, melatonin, pyruvate and IFN-β.[40]

Thus it is reasonable to postulate that many natural antioxidants may contribute to cancer prevention by modulating COX-2 activity and inflammation.

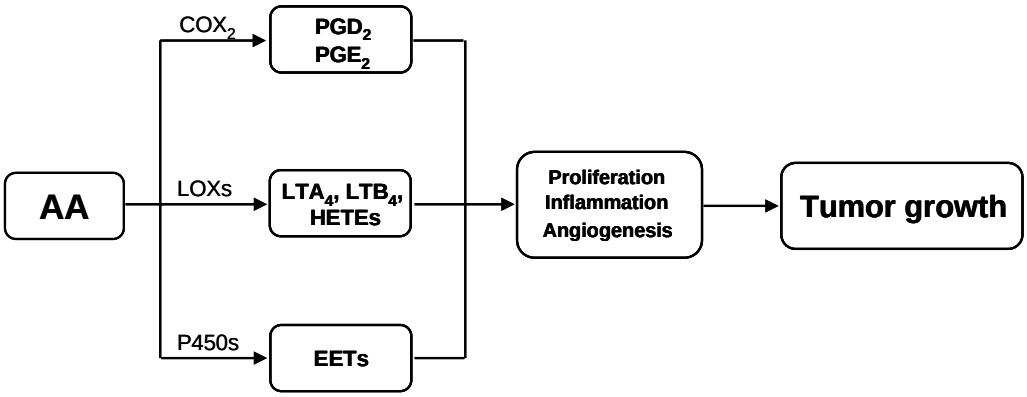


**Figure 1.** Overview of eicosanoid metabolism and its relationship with cancer. AA, arachidonic acid; COX2, cyclooxygenase; EET, epoxyeicosatrienoic acids; HETE, hydroxyeicosatetraenoic acids; LOXs, lipoxygenases; LT, leukotriene; PG, prostaglandin; TX, thromboxane.

## Benefits and Limitations of COX-2 Inhibitors on Chemotherapy

A number of NSAIDs and specific COX-2 inhibitors have been investigated for their anti-cancer properties and their adjuvant roles in chemotherapy. Celecoxib, aspirin and indomethacin are among the most frequently reported agents. Recent evidence indicates that potential benefits may be achieved by combining COX-2 inhibitors with certain chemotherapeutic agents. A clinical study revealed that Celecoxib enhanced colorectal tumor response to capecitabine and increased the median time to tumor progression (6 vs. 3 months, $P = 0.002$) as compared to capecitabine alone.[41] In addition to increasing efficacy Celecoxib may also reduce the side effects of chemotherapy in colon cancer.[42] COX-2-induced anti-apoptosis has been shown to be mediated by the release of $PGE_2$ and subsequent cAMP-dependent cellular inhibitors of apoptosis protein induction. Correspondently, NSAIDs may disrupt this pathological apoptotic process, thereby enhancing the efficacy of chemotherapy for colon cancer.[43]

Bcl-2, an oncogene, confers resistance to multiple chemotherapeutic treatments in a variety of cancers, including breast, lung, prostate cancers and leukemia. Down regulation of Bcl-2 may improve the cytotoxicity of chemotherapeutic agents in several cancer cell lines.[44,45] Selective COX-2 inhibitors SC-58125 and NS-398 can down regulate Bcl-2 and promote apoptosis in LNCaP cells, an epithelial cell line derived from a human prostate carcinoma.[46] Compared to taking indomethacin, adriamycin or cisplatin administrated alone, which showed limited effects in inhibiting the growth of the C20 tumors, a combination of two of these medications demonstrated synergistic effects. The effects accompanied with the expression of monocyte chemotactant protein-1 (MCP-1).[47] Interestingly, NSAID and COX-2 specific inhibitors have shown several COX-2 independent properties, suggesting that multiple COX-2 independent targets should also be investigated in future studies.[14,20]

Chemotherapeutic drug resistance is a constant challenge in clinical cancer treatment, particularly for metastatic carcinoma. Inflammation and pro-inflammatory cytokines are strong intrinsic factors promoting multiple drug resistance (MDR).[48] A number of studies have demonstrated that chemotherapy may induce the activities of COX-2 and inflammation stimulating the P-Glycoprotein involved in MDR, which transports drug out of the cancer cells. COX-2 inhibitors, particularly celecoxib, counteract MDR.[49,50]

It is not surprising that tumors may selectively respond to different combinations of chemotherapeutic agents and COX-2 inhibitors. Kobayashi et al., tested different combinations of chemotherapeutic agents including Adriamycin, 5-fluorouracil, cisplatin and vincristine for their efficacies on the growth of human pulmonary adenocarcinoma cells. The anti-inflammatory agents examined included aspirin, ibuprofen, sulindac, and indomethacin. The result showed that the combination of indomethacin and vincristine produced the most effective anticancer effects, compared with the other 10 chemotherapeutic agents and 5 anti-inflammatory agent combinations.[51] Their results also suggest that individual natural anti-COX-2 agents need should be tested specifically with each chemotherapeutic agent on tumor targets.

The side effects of the chemical COX-2 inhibitors have restricted their clinical usage on cancer prevention and treatment. COX-2 inhibitors showed many serious complications in altering the normal body's homeostasis.[7] For example, coxibs, including celecoxib, rofecoxib and valdecoxib, increase atherosclerosis, thrombogenesis, cardiovascular disease and even cardiac attack by inhibiting the generation of prostacyclin (PGI2) and mitochondrial oxidative phosphorylation.[52] COX-2 inhibitors may also cause a marked decline in glomerular filtration rate and lead to acute renal failure.[8] Therefore, natural anti-inflammatory agents with COX-2 inhibitory effects have become potential substitutes because of their excellent safety record.

## Chemoprevention with Natural Anti-Inflammatory Substances

A growing number of natural substances have been discovered with anti-inflammatory and COX-2 inhibiting effects. The potential of these natural anti-inflammatory agents on chemoprevention has been under investigation worldwide. A long list of herbs has been described with anti-COX-2 effects. These substances are used as either food supplements such as green tea, ginger, grape seeds and holy basil, or regarded as therapeutic herbs such as salvia miltiorrhiza bunge, fevervew, nettle leaf, oregano, rosemary, giardina C. butyrate, stylopine, chelidonium majus, ginsenoside Rh, scutellaria bacalensis, phellodendron amurense, cyanidin, carthamus tinctorius, carthamus tinctorius L. seed, anthocyanidin and willow bark.[32, 53-60]

Turmeric or *curcuma longa* has been used in China and India as a food spice and anti-inflammatory medicine for generations. Since the anti-COX-2 effect of turmeric was discovered by scientists at Vanderbilt University, Cornell University and University of Leicester in England, a growing body of reports have confirmed that turmeric is a strong anti-inflammation agent. The active anti-inflammation component is curcumin, which is about 50% as effective as cortisone. A number of publications have reported the anti-cancer effects of turmeric and encouraging synergistic effect with chemotherapy.[61-63]

A number of studies on *coptis* (*coptis Chinensis*, Huang Lian), a common herb in beberidaceae, has also drawn interest. *Coptis* is a commonly used anti-inflammatory herb in traditional Chinese medicine. Modern medical research reveals that both *coptis* and berberine, the major alkaloid in *Coptis*, possess multiple pharmacological properties, including anti-inflammation, anti-infection and anti-cancer effects.[64] The mechanism of the anti-inflammation effect may

be related to COX-2 inhibition and the anti-oxidant properties of berberine.[65-68] Several investigations have demonstrated the anti-cancer potential of *coptis* and berberine in *in vitro* and *in vivo* studies.[68-70] Studies conducted in our lab and by others have shown *coptis* and berberine-induced apoptosis in breast cancer cells.[71,72]

The role of omega-3 on inflammation and cancer modulation has been neglected until the last decade. Omega-3 can effectively inhibit COX mediated AA metabolism and PGE-2 inducible cancer.[73,74] Conversely, a high omega-6, low omega-3 diet may promote cancer.[75] The omega-3 enriched plants, such as flaxseed and *Perilla frutescens* seed have also been under investigations for their supplemental benefits in cancer treatment.[76, 77]

So far, no natural compounds are effective enough to replace current chemotherapeutic drugs. However, the combination of chemotherapeutic drugs with natural anti-inflammatory agents demonstrates encouraging potential. This integrated cancer treatment approach has been adopted in China for at least 40 years. However, these herbal compounds usually contain several herbs with different functions in addition to anti-inflammatory compounds. So far, most of the investigations on chemoprevention with natural COX-2 agents have been restricted to the laboratory. The role of natural anti-inflammatory agents in cancer treatment has not been well established. Curcumin was reported to have synergistic effects in chemoprevention,[78] although several earlier reports indicated the opposite.[79,80,81] A possible explanation for these disparate results could be that most natural compounds that inhibit COX-2 are antioxidants as well, and there is much debate regarding whether antioxidants counteract the efficacy of chemotherapy. It is recognized that one of the important mechanisms by which chemotherapy induces apoptosis is the generation of intracellular reactive oxygen species (ROS).[82] Antioxidants might counteract chemotherapy this way. Conversely, several recent studies support the thesis that antioxidants can enhance the anti-cancer effects of chemotherapy.[83,84,85] Block KI analyzed the results of antioxidant applications during chemotherapies from selected 19 trials of 845 articles. Only randomized, controlled clinical trials that reported survival and/or tumor response were included in the final tally. Antioxidants evaluated included glutathione, melatonin, vitamin A, vitamin C, N-acetylcysteine, vitamin E, ellagic acid and antioxidant mixture. None of the trials reported evidence of significant decreases in efficacy from antioxidant supplementation during chemotherapy. Many of the studies indicated that antioxidant supplementation resulted in either increased survival times, increased tumor responses, or both, as well as fewer toxicities than controls; however, lack of adequate statistical power was a consistent limitation.[86]

To avoid the worry that the herbs may counteract with the efficacy of the chemotherapy, we suggest that natural supplements may be taken after chemotherapeutic agents no longer be active in the body, which could range from hours to a few days. The information of pharmacodynamics of the agents, such as bioavailability, half-life time, maximum concentration in the plasma, should be searched before natural supplements are administered. In this way, natural anti-inflammatory agents or antioxidants can yield their benefits without the concern of interaction with chemotherapy. On the other hand, we assume that unhealthy level of ROS and free radicals should be reduced during the intervals of chemotherapies, so as to avoid the continuous damage to the immune function and general homeostasis of the body. Furthermore, the natural agents may eliminate the inflammation produced from chemotherapy which may result in chemo-resistance.[87,88]

## Prospective Research

Recent data reveals clues that anti-inflammatory drugs, which can interfere with multiple pro-inflammatory targets on the eicosanoid cascade, showed more therapeutic potential for cancer treatment. For example, a combined EGFR and COX-2 inhibitor treatment has the potential to be a new therapy for non-small cell lung cancer.[14] Berberine not only reduces production of PGE2 but also enhances IL-12 and INF-β, which could explain its effect on apoptosis of ER positive breast cancer cells.[72] Recently, we have discovered that berberine and coptis significantly improved the anticancer effects of estrogen receptor antagonists, tamoxifen and fulvestrant on MCF-7 breast cancer cells. The molecular mechanism underlying such action of these herbs may be the results of the down-regulation of EGFR, HER2 and bcl-2, and up-regulation of IFN-β and p21.[89] Many *in vitro* and *in vivo* studies show that Celecoxib possesses the most potent synergistic chemotherapy effects. Celecoxib can inhibit COX-2 generation, while inhibiting IL-8, TNF-α, NF-κB and apoptotic-related proteins.[15] The above reports suggest that an experimental model for multiple inflammation-cancer molecular targets should be established for evaluating the role of natural anti-inflammatory agents on cancer treatment.

What would be the real advantage of studying on the natural anti-inflammatory agents for the cancer treatment? A proposed optimal anti-inflammatory agent should be a multiple targeted inflammatory signal pathway modulator: a. properly down-regulating the excessive the gene expressions on the eicosanoid signal pathway, including COX-2, PGE-2, angiogenesis, tyrosine kinas and IL-1; b. promote INF-β and IL-18 at the same time. To formulate such an natural COX-2 inhibitor "cocktail" seems much easier than to formulate a chemical compound for the same purpose, considering less side effect and toxicity of the most natural compounds and enriched clinical experiences in using the compound herbal formulas.[90]

More investigations are needed to avoid the unexpected toxicity and possible lower therapeutic efficacy of chemotherapy resulting from herb-chemotherapeutic drug interactions. Almost all herb-chemotherapeutic drug interactions occur at the pharmacokinetic level, which

involves cytochrome P450 (CYP) metabolizing enzymes or phase II enzymes. Some investigators have reported the effects of herbs on the specific CYP or multiple CYP enzymes.[91,92] Based on these studies, a preliminary evaluation for herb-chemotherapeutic agent interaction could be derived to guide the clinical uses of the herbs in combination with chemotherapy before considering the clinical trial.

In summary, the application of natural anti-inflammatory agents in chemotherapy may open a new field for the treatment of cancer. However, more studies, especial well-designed clinical trials in using the anti-inflammatory natural substances with chemotherapy are needed to define the optimal integrated approach for various cancer types.

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