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## Could the cancer be a chronic immune disorder? rather than a serious malignant disease

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### ABSTRACT

Despite what is known about the cancer as a malignant dangerous disease treated classically by surgery, chemotherapy and radiotherapy which have a drastic consequences, demaging effect on rapidly growing immune cells e.g. bone marrow which may worsen the condition further. Cancer could be treated softly with immune modulating agents targeting specific key regulators through the cell cycle e.g. COX2, PI3K, uPA, Hsp90, MIF, mTOR, IKK-b...etc. if cancer be a syndrom of immune disorder rather than a real disease, so treatment of the syndrom will not cure the disorder which may explain the reason of inappropriateness of cancer classical therapies. The new strategy depends on considering cancer as a chronic immune disorder that is started with inflammation followed by progression of cancer as a syndrom. Only treatment the cause will relapse the whole sequence and will cease the progress of the disease. Dealing with cancer as a chronic inflammatory disease will change the view and decline the use of destructive classical cancer remedies. Furthermore, this strategy will reduce the suffer of the cancer patient and uphold the immune system which is the first selective barrier on further progression of cancer.

**Keywords:** Cancer, Anti-inflammatory, NSAIDs, Propolis, Immunomodulator, Curcumin, Vitamin D3

### INTRODUCTION

#### 1. Nonsteroidal anti-inflammatory drugs as anticancer agents

A growing body of research is showing that people who take a daily dose of aspirin (1) (figure 1) may be lowering their risk of a variety of seemingly unrelated cancers, including colon, breast, esophagus and skin cancer. Now a study published in the Journal of the National Cancer Institute found that women who took a daily dose of aspirin cut their risk of ovarian cancer by as much as 20 percent. That study, combined with earlier research, is prompting patients and doctors to wonder if more people would benefit from taking a low dose of aspirin and possibly other nonsteroid anti-inflammatory drugs. Another study revealed that women who took aspirin every other day may be reducing their colon cancer risk by 20 percent. In another study, published in 2012 in the British medical journal Lancet, participants who took aspirin reduced their risk of colon, lung or prostate cancer by 36 percent. Stanford research published last year showed that women who took aspirin had up to a 30 percent reduced risk of developing melanoma, the most deadly form of skin cancer. The findings are spurring research into the mechanisms of how aspirin and other nonsteroid anti-inflammatory drugs, such as ibuprofen (Motrin) (2), naproxen (Aleve) (3) and celecoxib (Celebrex) (4) (figure 1) appear to blunt the proliferation of cancer cells. Researchers are also trying to determine what the optimal dosage might be and which non-aspirin nonsteroid anti-inflammatory drugs are most effective in preventing cancer or possibly warding off the potential of recurrence in patients who have the disease. The over-the-counter pain killers are in a class of medications known as NSAIDs and are "a relatively safe drug compared to other interventions, and we are excited about this," said Carlo Maley, director of UCSF's Center for Evolution and Cancer and an author of a study published in June that found potentially dramatic benefits from aspirin (1) among patients with a condition called Barrett's esophagus, which can turn into esophageal cancer [1].

For that study, researchers analyzed tissue samples of some 350 patients with the precancerous condition and, over a 10-year period, found that NSAID users had a 30 to 79 percent reduction in developing esophageal cancer. "Cancers are evolutionary processes, and NSAIDs look like a way of lowering mutation rate and slowing down the process of tissues developing into cancer," Maley said. "Many cancers are facilitated by chronic inflammation." Maley, who specializes in how cancer adapts over time to survive, theorizes that this chronic inflammation may arise from the fact that our immune systems are more "jacked up" than they should be because we have far fewer infectious diseases to contend with than our ancestors had [1].

From Thun *et al*, numerous experimental, epidemiologic, and clinical studies suggest that nonsteroidal anti-inflammatory drugs (NSAIDs), particularly the highly selective cyclooxygenase (COX)-2 inhibitors, have promise as anticancer agents. NSAIDs restore normal apoptosis in human adenomatous colorectal polyps and in various cancer cell lines that have lost adenomatous polyposis coli gene function. NSAIDs also inhibit angiogenesis in cell culture and rodent models of angiogenesis. Many epidemiologic studies have found that long-term use of NSAIDs is associated with a lower risk of colorectal cancer, adenomatous polyps, and, to some extent, other cancers. Two NSAIDs, sulindac (5) and celecoxib (4), have been found to inhibit the growth of adenomatous polyps and cause regression of existing polyps in randomized trials of patients with familial adenomatous polyposis (FAP). However, unresolved questions about the safety, efficacy, optimal treatment regimen, and mechanism of action of NSAIDs currently limit their clinical application to the prevention of polyposis in FAP patients. Moreover, the development of safe and effective drugs for chemoprevention is complicated by the potential of even rare, serious toxicity to offset the benefit of treatment, particularly when the drug is administered to healthy people who have low annual risk of developing the disease for which treatment is intended. Thun *et al*, suggested research opportunities that may help to accelerate the future clinical application of NSAIDs for cancer prevention and treatment [2].

## 2. Natural Anti-inflammatory phytochemicals with anticancer properties

The Mediterranean diet and more specifically certain meats, fruits, vegetables, and olive oil found in certain parts of the Mediterranean region have been associated with a decreased cardiovascular and diabetes risk. More recently, several population based studies have observed with these lifestyle choices have reported an overall reduced risk for several cancers. One study in particular observed an inverse relationship between consumption of Mediterranean herbs such as rosemary, sage, parsley, and oregano with lung cancer. In light of these findings there is a need to explore and identify the anti-cancer properties of these medicinal herbs and to identify the phytochemicals therein. From Johnson *et al*, one agent in particular, carnosol (6), has been evaluated for anti-cancer property in prostate, breast, skin, leukemia, and colon cancer with promising results. These studies have provided evidence that carnosol (6) targets multiple deregulated pathways associated with inflammation and cancer that include nuclear factor kappa  $\beta$  (NF $\kappa$ - $\beta$ ), apoptotic related proteins, phosphatidylinositol-3-kinase (PI<sub>3</sub>K)/Akt, androgen and estrogen receptors, as well as molecular targets. In addition, carnosol (6) appears to be well tolerated in that it has a selective toxicity towards cancer cells versus non-tumorigenic cells and is well tolerated when administered to animals. This review focus on the link between anti-inflammatory and anticancer properties for carnosol (6) (Figure 1) which has high efficacy, and safety/tolerability properties as anti-cancer agent [3]. From Rayburn *et al*, Inflammation is closely linked to cancer, and many anti-cancer agents are also used to treat inflammatory diseases, such as rheumatoid arthritis. Moreover, chronic inflammation increases the risk for various cancers, indicating that eliminating inflammation may represent a valid strategy for cancer prevention and therapy. Since monotherapy is generally insufficient for treating cancer, the use of anti-inflammatory agents instead of conventional cancer therapy is also a focal point in discussion as postulated by Johnson *et al* [4].

Over the centuries, plant extracts have been used to treat various diseases. Until now, natural products have played an important role in anticancer therapy as there are more than 500 compounds from terrestrial and marine plants or microorganisms, which have antioxidant, antiproliferative, or antiangiogenic properties and are therefore able to reduce tumor growth. The recent discovery of new natural products has been accelerated by novel technologies (high throughput screening of natural products in plants, animals, marine organisms, and microorganisms). Vincristine (7), irinotecan (8), etoposide (9), and paclitaxel (10) (figure 1) are examples of compounds derived from plants that are used in cancer treatment. Similarly, actinomycin D (11), mitomycin C (12), bleomycin (13) and doxorubicin (14), (figure 1) are drugs derived from microorganisms. The molecular mechanisms of natural compounds with anti-inflammatory and anticancer activities are evidence as proposed by Orlikova *et al* [5].

Moreover, propolis, a waxy substance produced by the honeybee, has been adopted as a form of folk medicine since ancient times. It has a wide spectrum of alleged applications including potential anti-infection and anticancer effects. Many of the therapeutic effects can be attributed to its immunomodulatory functions. The composition of propolis can vary according to the geographic locations from where the bees obtained the ingredients. Two main immunopotent chemicals have been identified as caffeic acid phenethyl ester (CAPE) (15) and artemillin C. (16) Propolis, CAPE (15), and artemillin C (16) have been shown to exert cumulative immunosuppressive function on T

lymphocyte subsets but paradoxically activate macrophage function. On the other hand, they also have potential antitumor properties by different postulated mechanisms such as suppressing cancer cells proliferation via its anti-inflammatory effects, decreasing the cancer stem cell populations, blocking specific oncogene signaling pathways, exerting antiangiogenic effects, and modulating the tumor microenvironment. The good bioavailability by the oral route and good historical safety profile makes propolis an ideal adjuvant agent for future immunomodulatory or anticancer regimens. However, standardized quality controls and clinical trials are essential before either propolis or its active ingredients can be approved as a drug as reported by Chan *et al* [6].

### 3. Cyclooxygenase (COX) inhibitors as anticancer agents

As reported by Piazza *et al*, there is compelling evidence that nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 selective inhibitors have antineoplastic activity, but toxicity from cyclooxygenase (COX) inhibition and the suppression of physiologically important prostaglandins limits their use for cancer chemoprevention. Previous studies [7] suggest that the mechanism for their anticancer properties does not require COX inhibition, but instead involves an off-target effect. In support of this possibility, recent molecular modeling studies have shown that the NSAID sulindac (**5**) (figure 1) can be chemically modified to selectively design out its COX-1 and COX-2 inhibitory activity. Unexpectedly, certain derivatives that were synthesized based on *in silico* modeling displayed increased potency to inhibit tumor cell growth. Other experiments have shown that sulindac (**5**) can inhibit phosphodiesterase to increase intracellular cyclic GMP levels and that this activity is closely associated with its ability to selectively induce apoptosis of tumor cells. Together, these studies suggest that COX-independent mechanisms can be targeted to develop safer and more efficacious drugs for cancer chemoprevention [7].

Furthermore, numerous studies have shown that cyclooxygenase enzymes are overexpressed and prostaglandin levels are increased in various tumor types. These observations support the commonly held view that inflammation plays an important role in tumorigenesis and that suppression of prostaglandin synthesis is responsible for the chemopreventive activity of NSAIDs. However, there is opposing evidence to suggest that a COX-independent mechanism is either responsible for or contributes to the antineoplastic properties of NSAIDs. The COX-2 isozyme is inducible and expressed in inflammatory cells and cancer cells and was considered to be an ideal drug target for inhibiting inflammation and tumorigenesis [8-12].

NSAIDs and COX-2 selective inhibitors can suppress the growth of tumor cells that do not express COX-2, while supplementation with exogenous prostaglandins does not reverse the growth inhibitory activity of NSAIDs. Additionally, the rank order potency among NSAIDs to inhibit prostaglandin synthesis does not match the potency to inhibit tumor cell growth. In general, appreciably higher dosages of NSAIDs are required to inhibit tumor cell growth compared to anti-inflammatory dosages. For example, a series of chemically diverse NSAIDs, celecoxib (**4**), Sulindac (**5**), Diclofenac (**17**), Indomethacin (**18**), Piroxicam (**19**), Ibuprofen (**2**), Flurbiprofen (**20**) and Aspirin (**1**) are shown in table 1 and figure 1 with IC<sub>50</sub> values for growth inhibition on various cancerous cell lines. Moreover, the concentration range required to inhibit tumor cell growth exceeds the concentration in blood that can be achieved in humans with standard dosages. Still, NSAIDs show evidence of chemopreventive efficacy in long term studies, which may be the consequence of chronic administration. As highlighted, aspirin (**1**) may be unique among other NSAIDs given its ability to irreversibly bind COX, which may provide a sustained anti-inflammatory benefit [13-16].

### 4. Phospho-nonsteroidal anti-inflammatory drugs, a new class of anticancer compounds

From Huang *et al*, despite nonsteroidal anti-inflammatory drugs (NSAID) exhibit antineoplastic properties, but conventional NSAIDs do not fully meet safety and efficacy criteria for use as anticancer agents. The chemotherapeutic efficacy of 5 novel phospho-NSAIDs, phospho-aspirin (PA, MDC-118) (**21**), Phospho-sulindac (PS, OXT-328) (**22**), phospho-ibuprofen (PI, MDC-917) (**23**), phospho-flurbiprofen (PF) (**24**), phospho-desoxy-sulindac (PDS, OXT-922) (**25**) are proved, each of which includes in addition to the NSAID moiety a diethylphosphate linked through a butane moiety. All 5 compounds (**21-25**) inhibited the growth of human breast, colon, and pancreatic cancer cell lines with micromolar potency. *In vivo* investigations confirmed the antitumor activity of phospho-aspirin (PA) (**21**) and phospho-sulindac (PS) (**22**) in inhibiting tumor growth in established human xenograft models, in which cell proliferation was suppressed and apoptosis enhanced in the absence of detectable animal toxicity. Notably, all of the phospho-NSAIDs tested induced reactive oxygen and nitrogen species in cultured cells, with PA (**21**) and PS (**22**) inducing detectable levels of oxidative stress *in vivo* that were associated positively with apoptosis and negatively with proliferation. Potentially explaining these effects, all of the phospho-NSAIDs (**21-25**) tested also inhibited the thioredoxin system and the redox sensitive transcription factor NF- $\kappa$ B. Taken together, the strong anticancer efficacy and promising safety of phospho-NSAIDs in preclinical models of breast, colon, and pancreatic cancer, suggesting further evaluation as anticancer agents [17].

As mentioned earlier that aspirin (**1**) is chemopreventive against colon and probably other cancers, but this effect is relatively weak and its chronic administration to humans is associated with significant side effects. Because of these limitations, extensive effort has been exerted to improve the pharmacological properties of aspirin (**1**). It is found that novel para positional isomer of phosphoaspirin (**26**) [P-ASA, MDC-43, 4-((diethoxyphosphoryloxy)methyl)phenyl 2-acetoxybenzoate] inhibited the growth of 10 human cancer cell lines originating from colon, lung, liver, pancreas and breast, at least 18- to 144-fold more potently than conventional aspirin (**1**). P-ASA (**26**) achieved this effect by modulating cell kinetics, compared with controls, P-ASA (**26**) reduced cell proliferation by up to 68%, increased apoptosis 5.5-fold and blocked cell cycle progression in the G2/M phase. P-ASA (**26**) increased intracellular levels of reactive oxygen species (ROS), depleted glutathione levels and modulated cell signaling predominantly through the mitogen-activated protein kinase (p38 and c-jun N-terminal kinase), cyclooxygenase (COX) and nuclear factor-kappa B pathways. P-ASA (**26**) targeted the mitochondria, increasing mitochondrial superoxide anion levels, this effect on ROS led to collapsed mitochondrial membrane potential and triggered the intrinsic apoptotic pathway. The antioxidant N-acetyl cysteine abrogated the cell growth inhibitory and signaling effects of P-ASA (**26**), underscoring the centrality of ROS in its mechanism of action. P-ASA (**26**) is established as a potent inhibitor of the growth of several human cancer cell lines, suggest that it may possess broad anticancer properties. The novel P-ASA (**26**) is a promising anticancer agent, which merits further evaluation as suggested by Zhao *et al* [18]. Moreover, Huang *et al* mentioned that non-steroidal anti-inflammatory drugs such as sulindac (**5**) are promising chemoprevention agents against colon cancer, but their weak potency and side effects limit their use for both chemoprevention and chemotherapy. New sulindac derivative, phospho- desoxy-sulindac (**25**) or OXT-922, was tested on the growth of human cancer cell lines. OXT-922 (**25**) inhibited the growth of human cancer cell lines originating from colon, pancreas and breast ~11- to 30-fold more potently than sulindac (**5**). This effect was mediated by a strong cytotoxic effect. Compared with control, OXT-922 (**25**) inhibited cell proliferation by up to 67%, induced apoptosis 4.1-fold over control and blocked the G(1) to S cell cycle phase transition. OXT-922 (**25**) suppressed the levels of cell cycle regulating proteins, including cyclins D(1) and D(3) and Cyclin-dependent kinases (CDK) 4 and 6. The levels of intracellular reactive oxygen species (ROS), especially those of mitochondrial O<sub>2</sub><sup>-</sup>, were markedly elevated (5.5-fold) in response to OXT-922 (**25**). ROS collapsed the mitochondrial membrane potential and triggered apoptosis, which was largely abrogated by antioxidants. OXT-922 (**25**) suppressed nuclear factor-kappa B activation and down-regulated thioredoxin-1 expression. It also suppressed the production of prostaglandin E(2) and decreased cyclooxygenase-1 expression. Similar to sulindac (**5**), OXT-922 (**25**) enhanced spermidine/spermine N(1)-acetyltransferase activity, reduced the cellular polyamine content and synergized with difluoro-methyl-ornithine (**27**) to inhibit cancer cell proliferation and induce apoptosis. OXT-922 (**25**) possesses promising anticancer properties and deserves further evaluation [19].

### 5. Potential of resveratrol and curcumin in anticancer and anti-inflammatory therapy

Resveratrol (**28**) is a stilbene-type aromatic phytoalexin predominantly found in grapes, peanuts, berries, turmeric, and other food products. Resveratrol (**28**) has been reported by Udenigwe *et al*, to exhibit several physiological activities including anticancer and anti-inflammatory activities *in vitro* and in experimental animal models, as well as in humans. Anticancer activity of this compound is mainly due to induction of apoptosis via several pathways, as well as alteration of gene expressions, all leading to a decrease in tumor initiation, promotion, and progression. Resveratrol (**28**) exhibits anti-inflammatory activity through modulation of enzymes and pathways that produce mediators of inflammation and also induction of programmed cell death in activated immune cells. Resveratrol (**28**) has been shown to produce no adverse effects, even when consumed at high concentrations. Hence, resveratrol (**28**) possesses good potential to be used as an adjunctive or alternative therapy for cancer and inflammatory diseases [20].

Curcumin (diferuloylmethane) (**29**) is a polyphenol derived from the *Curcuma longa* plant, commonly known as turmeric. Curcumin (**29**) has been used extensively in ayurvedic medicine for centuries, as it is nontoxic and has a variety of therapeutic properties including anti-oxidant, analgesic, anti-inflammatory and antiseptic activity. More recently curcumin (**29**) has been found to possess anti-cancer activities via its effect on a variety of biological pathways involved in mutagenesis, oncogene expression, cell cycle regulation, apoptosis, tumor genesis and metastasis. From Wilken *et al*, curcumin (**29**) has shown anti-proliferative effect in multiple cancers, and is an inhibitor of the transcription factor NF-kB and downstream gene products (including c-myc, Bcl-2, COX-2, NOS, Cyclin D1, TNF-alpha, interleukins and MMP-9). In addition, curcumin affects a variety of growth factor receptors and cell adhesion molecules involved in tumor growth, angiogenesis and metastasis. Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide and treatment protocols include disfiguring surgery, platinum-based chemotherapy and radiation, all of which may result in tremendous patient morbidity. As a result, there is significant interest in developing adjuvant chemotherapies to augment currently available treatment protocols, which may allow decreased side effects and toxicity without compromising therapeutic efficacy. Curcumin (**29**) is a potential candidate, and can be an adjuvant chemotherapeutic agent [21].

### 6. The role of vitamin D in cancer prevention and treatment

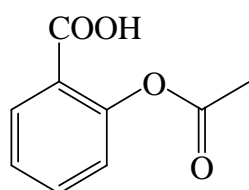
As reported by Vanoirbeek *et al*, various epidemiological studies have shown an etiological link between vitamin D deficiency and cancer incidence. The active metabolite of vitamin D, 1, 25-dihydroxyvitamin D<sub>3</sub> (**30**), has potent anti-cancer activities both *in vitro* and *in vivo*. These anti-cancer effects are attained by regulating the transcription of numerous genes that are involved in different pathways to reduce tumor genesis and are dependent on the cancer cell type. Besides reducing cell growth and inducing apoptosis, 1,25-(OH)<sub>2</sub>D<sub>3</sub> (**30**) also inhibits angiogenesis and metastasis. Moreover, its potency to inhibit inflammation also contributes to its anti-tumoral activity. 1,25-(OH)<sub>2</sub>D<sub>3</sub> (**30**) interferes with the malignant processes that are activated in cancer cells [22]. Calcitriol (**30**), the hormonally active form of vitamin D, is being evaluated in clinical trials as an anti-cancer agent. Calcitriol (**30**) exerts multiple anti-proliferative, pro-apoptotic, and pro-differentiating actions on various malignant cells and retards tumor growth in animal models of cancer. Calcitriol (**30**) also exhibits several anti-inflammatory effects including suppression of prostaglandin (PG) action, inhibition of p38 stress kinase signaling, and the subsequent production of pro-inflammatory cytokines and inhibition of NF-κB signaling. Calcitriol (**30**) also decreases the expression of aromatase, the enzyme that catalyzes estrogen synthesis in breast cancer, both by a direct transcriptional repression and indirectly by reducing PGs, which are major stimulators of aromatase transcription. Other important effects include the suppression of tumor angiogenesis, invasion, and metastasis. The calcitriol (**30**) action provides a basis for its potential use in cancer therapy and chemoprevention as concluded by Krishnan *et al* [23, 24].

From the previous studies, as shown in table 1 and figure 1, miscellaneous anti-inflammatory agents (**1-30**) have a potential anti-cancer effect; growth inhibition with IC<sub>50</sub> values ranged from nanomolar to micromolar on different cell lines indicates the strong relationship between inflammation and carcinogenesis [3,13,17,18,25-38].

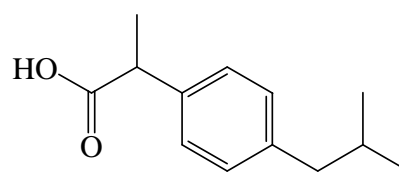
**Table 1** Growth inhibition of anti-inflammatory compounds using different cell lines

Hits	Name	(IC <sub>50</sub> ) μM	Growth Inhibition*	Reference
1	Aspirin	5000		13
2	Ibuprofen	975		13
3	Naproxen	2800		25
4	Celecoxib	50		13
5	Sulindac	60		13
6	Carnesol	82		3
7	Vincristine	0.042		26
8	Irinotecan	1.0		27
9	Etoposide	0.6		28
10	Paclitaxel	0.018		29
11	Actinomycin D	0.0004		30
12	Mitomycin C	2.34		31
13	Bleomycin	11.85		31
14	Doxorubicin	0.1		32
15	Caffeic acid phenethyl ester	130		33
16	Artepillin C	150		34
17	Diclofenac	160		13
18	Indomethacin	180		13
19	Piroxicam	900		13
20	Flurbiprofen	1800		13
21	PA, MDC-118	32		17
22	Phospho-sulindac	62		17
23	Phospho-ibuprofen	79		17
24	Phospho-flurbiprofen	65		17
25	Phospho-desoxy-sulindac	38		17
26	Phosphoaspirin, MDC-43	42.6		18
27	Difluoromethylornithine	600		35
28	Resveratrol	131-187		36
29	Curcumin	10.2-13.3		37
30	Calcitriol(Vitamin D3)	5.0		38

\*Different cell lines are tested, the figures are used to indicate the potential of anticancer activity.



Aspirin (1)



Ibuprofen (2)

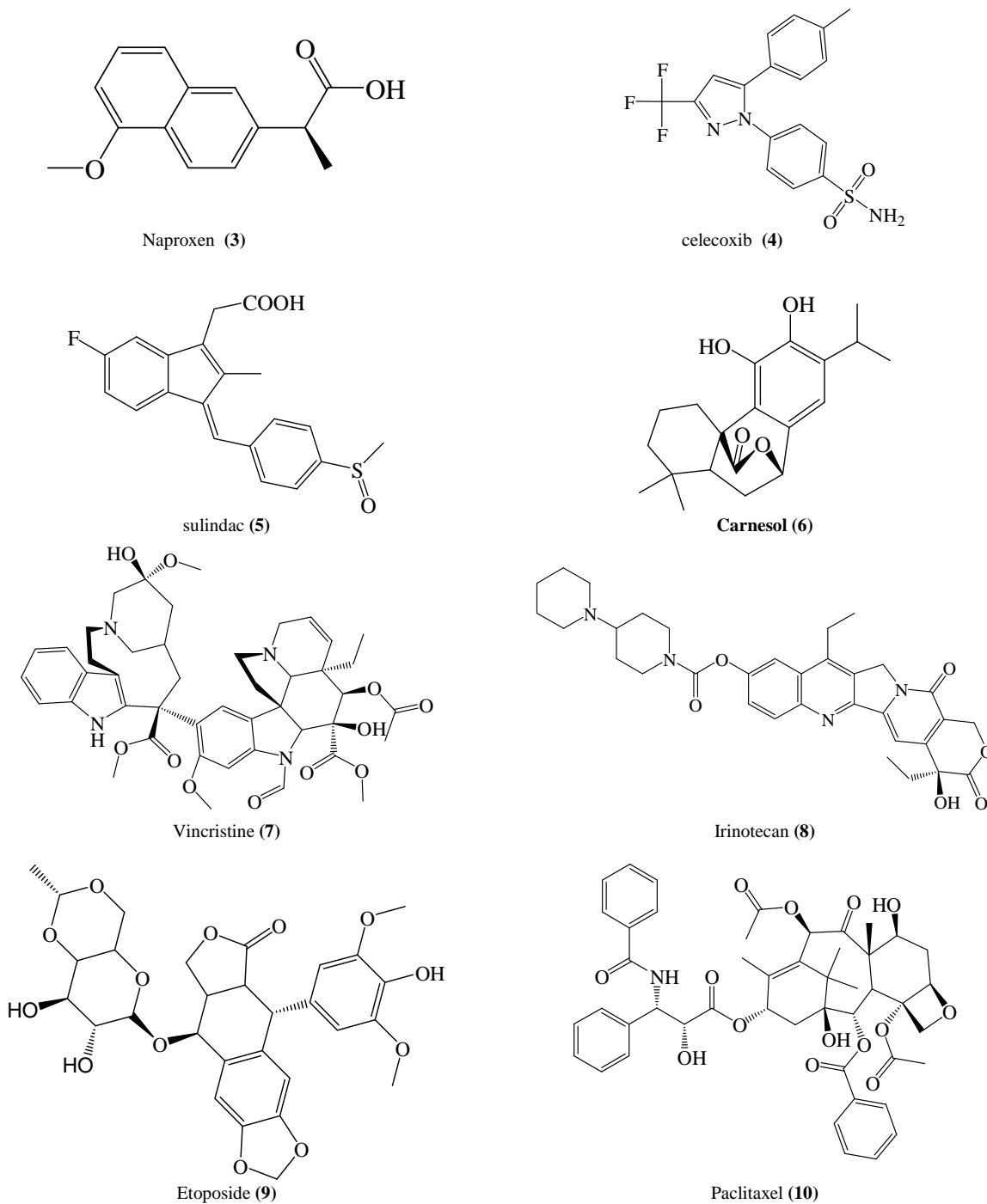
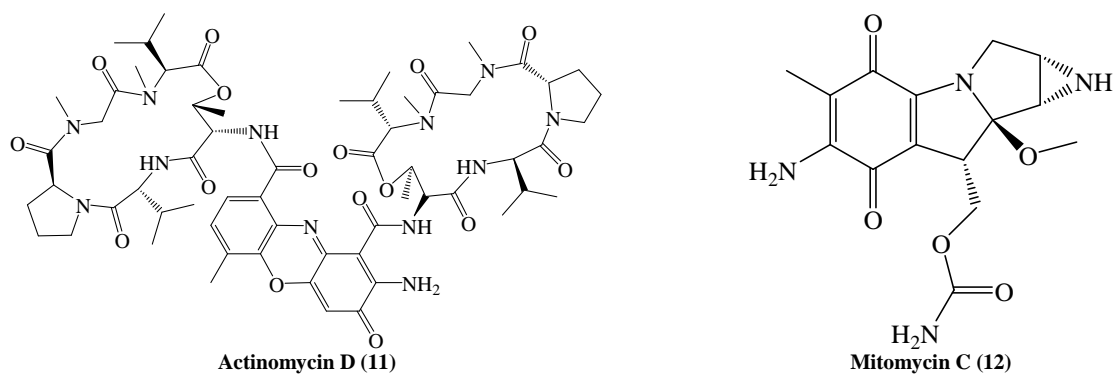


Figure 1: Chemical structure of miscellaneous anti-inflammatory, immunomodulators that exert variable anticancer effect



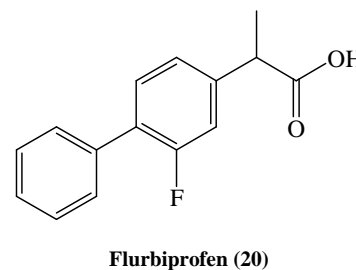
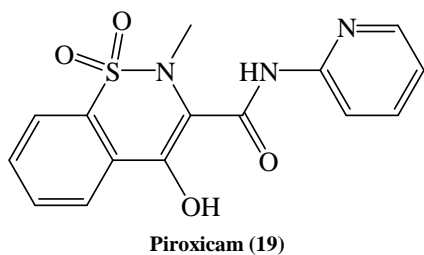
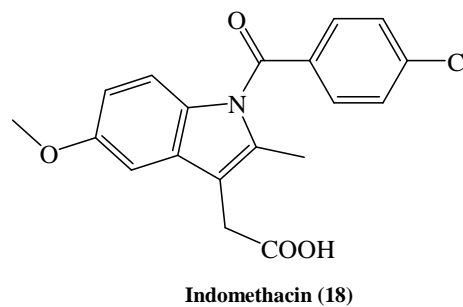
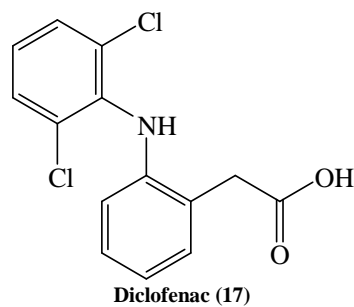
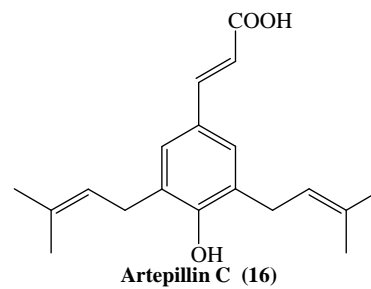
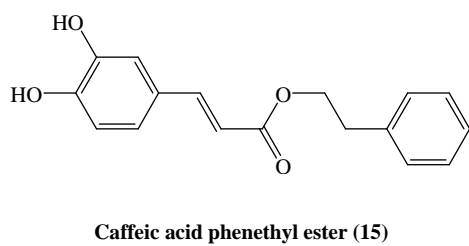
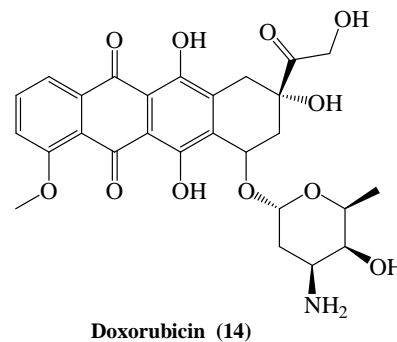
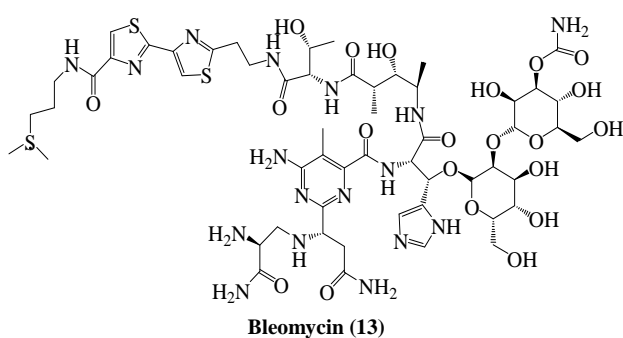
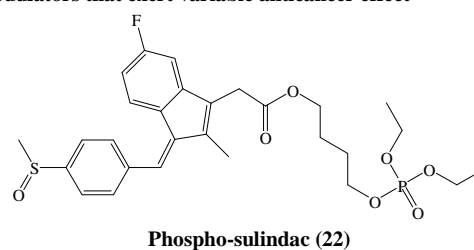
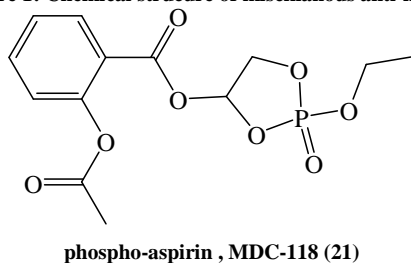


Figure 1: Chemical structure of miscillanous anti-inflammatory and immunomodulators that exert variable anticancer effect



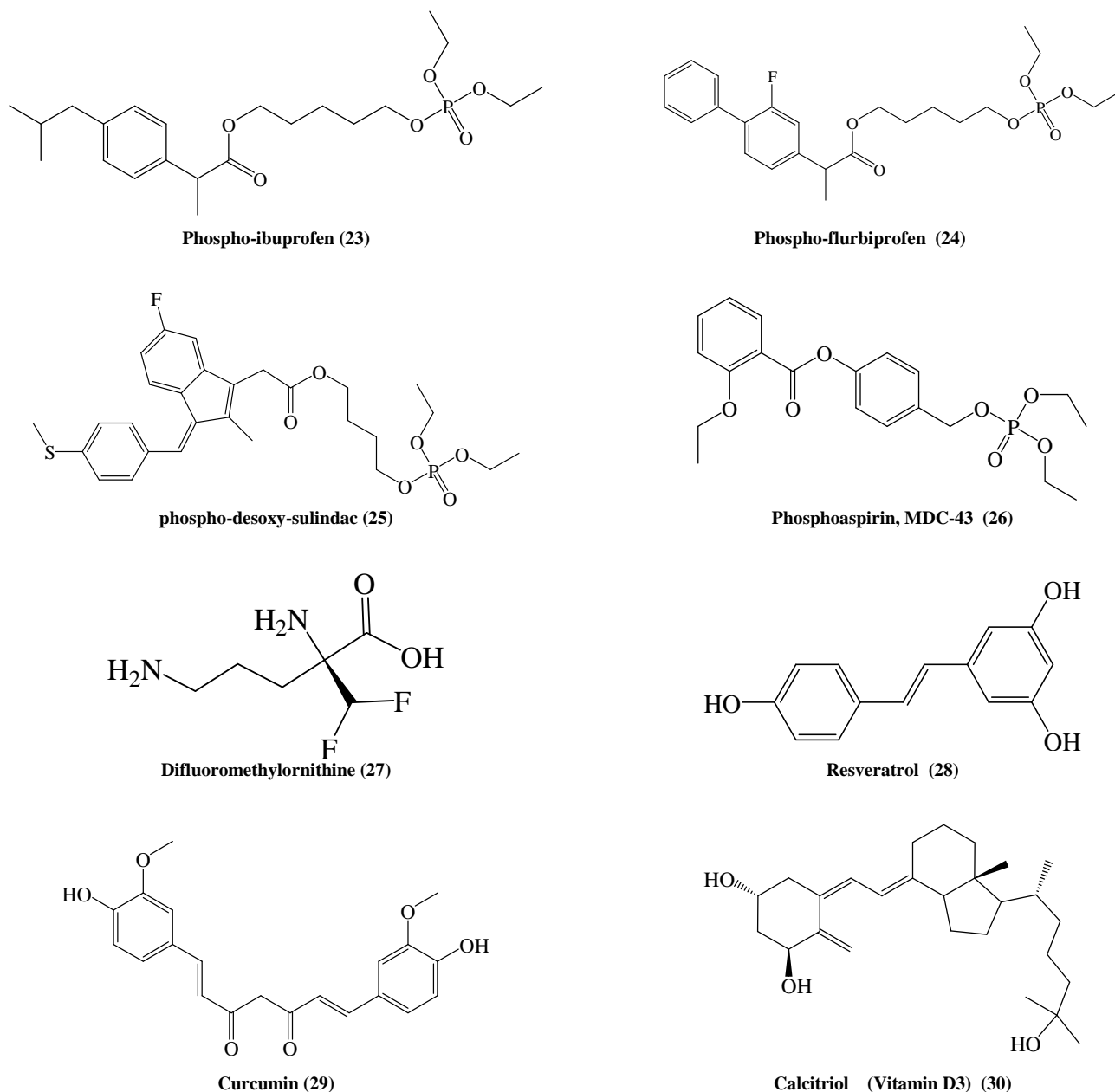


Figure 1: Chemical structure of miscellaneous anti-inflammatory and immunomodulators that exert variable anticancer effect

## CONCLUSION

Despite the miscellaneous diverse chemistry and targets, it is clear from the previous studies the tie between anti-inflammatory and anticancer properties; however the deal with cancer as a chronic inflammatory disease rather than a serious malignant disease will change the whole policies in treatment of cancer and will be a revolution in cancer therapy.

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