Life Science Informatics Publications

Research Journal of Life Sciences, Bioinformatics, Pharmaceutical and Chemical Sciences

Journal Home page http://www.rjlbpcs.com/

RJLBPCS

ISSN 2454-6348

Original Review Article **DOI: 10.26479/2022.0801.03**

PREVENTIVE PHYTOCHEMICALS OF CANCER, AS SPEED BREAKERS IN INFLAMMATORY SIGNALING

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ABSTRACT: A causal association between inflammation and cancer has long been suspected. Multiple evidences from clinical, epidemiologic and laboratory studies support that inflammation plays a critical role in the promotion and progression stages of carcinogenesis. Recent progress in our understanding of the molecular biology of cancer highlights the intracellular signal transduction network, including that involved in mediating the inflammatory response, which often functions abnormally during carcinogenesis. Cyclooxygenase-2 (COX-2) is one of the key players in inflammatory signaling. In various precancerous and malignant tissues, aberrant upregulation of COX-2 is frequently observed. This review highlights the cancer preventive effects of some anti-inflammatory phytochemicals derived from edible plants, and their fundamental molecular mechanisms with a concentration on representative transcription factors and upstream kinases responsible for COX-2 induction.

Keywords: Cancer**,** Cyclooxygenases (COXs)**,** Inflammation**,** Phytochemicals.

Article History: Received: Jan 08, 2022; Revised: Jan 25, 2022; Accepted: Jan 28, 2022.

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1. INTRODUCTION

Cancer is a group of diseases which involves abnormal cell growth with the potential to invade or spread to different parts of the body [1]. Cancers are different from benign tumors, which do not spread. Possible signs and symptoms of cancer include a lump, abnormal bleeding, prolonged

cough, weight loss, and a change in bowel movement. Cancers comprise an ample family of diseases that involve abnormal cell growth with the potential to invade or spread to other parts of the body. They form a subset of neoplasms (a neoplasm or otherwise called tumor is a group of cells that have undergone unregulated growth and it often form a mass or lump, but may be distributed diffusely).

1.1. Hallmark of Cancer

The characteristics required to produce a malignant tumor are known as the hallmarks of cancer. They include [2]:

1. Growth signal autonomy: Cancer cells can divide without the external signals normally required to stimulate division.
2. Insensitivity to growth inhibitory signals: Cancer cells are unaffected by external signals that inhibit division of normal cells.
3. Evasion of apoptosis: When excessive Deoxyribonucleic acid (DNA) damage and other abnormalities are detected, apoptosis (a type of programmed cell death) is induced in normal cells, but not in cancer cells.
4. Sustained angiogenesis: The growth of new blood vessels into the tumor is required by most cancers. Normal angiogenesis is regulated by both inhibitory and stimulatory signals not required in cancer cells.
5. Tissue invasion and metastasis: Generally, normal cells do not migrate (except in the development of embryo). Cancer cells invade other tissues including vital organs.
6. Deregulated metabolic pathways: Cancer cells use an abnormal metabolism to satisfy a high demand for energy and nutrients.
7. Evasion of the immune system: Cancer cells are able to evade the immune system.
8. Severe chromosomal instability.
9. Inflammation: Local chronic inflammation is associated with many types of cancer.

The sequence from normal cells to cells that can form a detectable mass to outright cancer involves multiple steps known as malignant progression [2, 3].

The use of tobacco is the cause of about 22% of cancer deaths. Another 10% are due to obesity, poor diet, and lack of physical activity or excessive drinking of alcohol [4]. Other factors include exposure to ionizing radiation, environmental pollutants and certain infections [5]. In the developing world, 15% of cancers are due to infections such as *Helicobacter pylori*, hepatitis B, hepatitis C, Human Papillomavirus infection, Epstein-Barr virus and Human Immunodeficiency Virus (HIV). These factors act, at least partly, by changing the genes of a cell. Typically, many genetic changes are required before cancer develops. Approximately 5–10% of cancers are due to inherited genetic defects. Cancer can be detected by certain signs and symptoms or screening tests. It is then typically further investigated by medical imaging and confirmed by biopsy. The risk of developing

certain cancers can be reduced by not smoking, maintaining a healthy weight, limiting alcohol intake, eating plenty of vegetables, fruits, and whole grains, vaccination against certain infectious diseases, limiting consumption of processed meat and red meat, and limiting exposure to direct sunlight [6, 7]. Early detection through screening is essential for colorectal and cervical cancer. The importance of screening in breast cancer are contentious [8]. Cancer is often treated with some combination of radiation therapy, surgery, chemotherapy and targeted therapy. Palliative care is particularly important in people with advanced disease [1]. The type of cancer and extent of disease at the start of treatment determines the chance of survival. In children under 15 at diagnosis, the five-year survival rate in the developed world is on average 80%. For cancer in the United States, the average five-year survival rate is 66%. About 90.5 million people had cancer in 2015. As of 2019, about 18 million new cases occur annually [9]. Annually, it caused about 8.8 million deaths (15.7% of deaths). The most common types of cancer in males are lung cancer, prostate cancer, colorectal cancer and stomach cancer. In females, the most common types are cervical cancer, breast cancer, lung cancer and colorectal cancers. If skin cancer other than melanoma were included in total new cancer cases each year, it would account for around 40% of cases [10, 11]. Brain tumors and acute lymphoblastic are most common in children, except in Africa, where non-Hodgkin lymphoma occurs more often. About 165,000 children under 15 years of age were diagnosed with cancer in 2012. The risk of cancer increases significantly with age, and many cancers occur more commonly in developed countries. Rates are increasing as more people live to an old age as lifestyle changes occur in the developing world [12]. The financial costs of cancer were estimated at 1.16 trillion USD per year as of 2010. 90-95% of cancers are due to genetic mutations from environmental and lifestyle factors, the remaining 5-10% are due to inherited genetics [5]. Environmental refers to any cause that is not inherited, such as lifestyle, economic and behavioral factors and not merely pollution [13]. Common environmental factors that contribute to cancer death include tobacco use (25–30%), diet and obesity (30–35%), infections (15–20%), radiation (both ionizing and non-ionizing, up to 10%), lack of physical activity, and pollution [5, 14]. Psychological stress does not appear to be a risk factor for the onset of cancer [15, 16], though it may worsen outcomes in those who already have cancer [15]. It is not generally possible to prove what caused a particular cancer because the various causes do not have specific fingerprints. For example, if a person who uses tobacco heavily develops lung cancer, then it was probably caused by the tobacco use, but since everyone has a small chance of developing lung cancer as a result of air pollution or radiation, the cancer may have developed for one of those reasons. Excepting the rare transmissions that occur with pregnancies and occasional organ donors, cancer is generally not a transmissible disease [17].

1.2. Statistics at a Glance: The Burden of Cancer Worldwide

Cancer is among the leading causes of death worldwide. There were 18.1 million new cases of cancer and 9.5 million cancer-related deaths worldwide in 2018.

By 2040, the number of new cancer cases per year is expected to rise to 29.5 million and the number of cancer-related deaths to 16.4 million. Generally, cancer rates are highest in countries whose populations have the highest life expectancy, education level, and standard of living. But for some cancer types, such as cervical cancer, the reverse is true, and the incidence rate is highest in countries in which the population ranks low on these measures (International Agency for Research on Cancer).

Uterine Cervical Cancer

Carcinoma of the cervix uteri is among the most preventable malignancies worldwide [18], however it remains the first leading cause of cancer deaths in African women. Human Papillomavirus (HPV) types 16 and 18 are the most common etiological factors for the pathogenesis of cervical cancer in Africa [19]. The reported prevalence rate of HPV was 97.0% in Malawi [20], 92.1% in South Africa [21], 90.7% in Ibadan Nigeria [22], and 69.8% in Maiduguri Nigeria [19]. In fact, the HPV infection is usually cleared in the immunocompetent women [23]. However, in women with underlying human immuno-deficiency virus (HIV) infection; as a common situation in Africa, there is an increasing risk of developing cancer cervix rather than in women without HIV infection, with the annual detection rates are 1.4 *versus* 0.4 per 100 persons per year; respectively [24-26].

Breast Cancer

Breast cancer (BC) is the most commonly diagnosed cancer in the African females, and it also represents the second leading cause of cancer- related deaths following cancer cervix in sub-Saharan Africa (SSA) [27]. Its incidence had been increased in the last six years by more than 23% (from 1.7 million new patients in 2012 to 2.1 million in 2018) [28, 29]. In addition, its five-year survival rate is less than 40% in SSA, compared to 86% in the United States [30].

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the third leading cause of cancer related death in Africa, and a major health problem all over the world [31]. It was recorded that 80% of HCC cases occurred in eastern Asia and in the SSA according to Cancer Today, which is an international agency for research and cancer [28]. The prevalence of HCC is heterogeneous because it has variable risk factors, since hepatitis B (HBV) and aflatoxin exposure are the major risk factors for HCC in SSA, whereas hepatitis C (HCV) is the major risk factor for HCC in Europe, Japan and USA [27].

Lung Cancer

In the United States, Lung cancer remains the first leading cause of cancer- related deaths [31], with the highest lung cancer mortality rate being detected in the African-American population [32, 33].

1.3. Stages of Cancer

Cancer is typically labeled in stages from I to IV, with IV being the most serious. Those broad groups are based on a much more detailed system that includes specific information about the tumor and how it affects the rest of your body. Most cancers that involves a tumor are staged into five

broad groups. These are usually referred to with Roman numerals. Other kinds, like lymphoma, brain cancer and blood cancers, have their own staging systems, but all the staging system tells how advanced the cancer is.

- Stage 0 means there is no cancer, only abnormal cells with the potential to become cancer are present. This is also called carcinoma in situ.
- Stage I means the cancer is small and present only in one area. This is also called early stage cancer.
- Stage II and III mean the cancer has become larger and has grown into nearby tissues or lymph nodes.
- Stage IV means the cancer has spread to other parts of the body. It's also called metastatic cancer [34].

Tumor-Node-Metastasis (TNM) System

Another factor that probably can be used to determine overall cancer stage is the TNM system, short for tumor, node, and metastasis.

- Tumor (T): "T" followed by a number from 0-4 tells how large the tumor is and sometimes where it's located. T0 means the tumor is immeasurable. The higher the number, the bigger the tumor.
- Node (N): "N" followed by a number from 0-3 tells if the cancer has spread to the lymph nodes, which are glands that filter things like viruses and bacteria before they can infect other parts of your body. N0 means lymph nodes are not involved. A higher number means the cancer is in more lymph nodes, farther away from the original tumor.
- Metastasis (M): "M" is followed by either 0 or 1. It says if the cancer has spread to organs and tissues in other parts of your body. A 0 means it hasn't, and a 1 means it has [34].

Metastasis is the spread of cancer to other parts in the body. The dispersed tumors are called metastatic tumors, while the original is called the primary tumor. Almost all cancers can metastasize. Most cancer deaths are due to cancer that has metastasized.

In the late stages of cancer, metastasis is common and it can occur via the blood or the lymphatic system or both. The typical steps in metastasis are local invasion, intravasation into the blood or lymph, circulation through the body, extravasation into the new tissue, proliferation and angiogenesis. Different types of cancers tend to metastasize to particular organs, but overall the most common places for metastases to occur are the lungs, liver, brain and the bones.

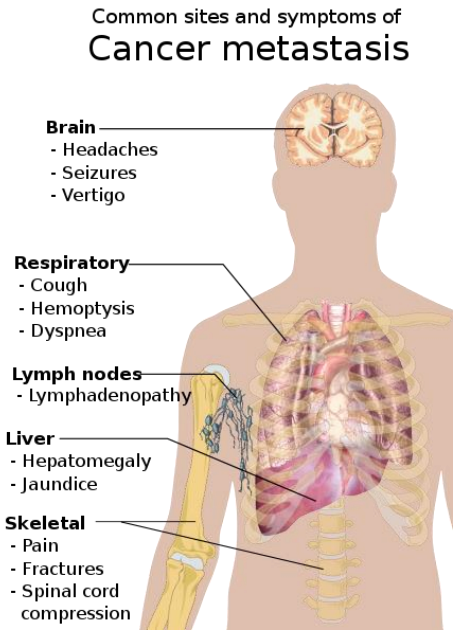

Figure 1: Symptoms of cancer metastasis depend on the location of the tumor

2. INFLAMMATION AND CANCER

2.1. Mechanisms for the association between Inflammation and Cancer

Chronic inflammation is characterized by sustained tissue damage, damage-induced cellular proliferation and tissue repair. Cell proliferation in this context is usually correlated with "metaplasia," a reversible change in cell type. "Dysplasia," a disorder of cellular proliferation leading to atypical cell production, and is regarded as the previous event of carcinoma because it was usually found adjacent to the site of neoplasm [35].

2.2. Key Molecular Players in Linking Inflammation to Cancer

To address the details of transition from inflammation to cancers and the further development of inflammation-associated cancers, it is necessary to investigate specific roles of key regulatory molecules involved in this process.

Pro-inflammatory cytokines

The cytokine network of several common tumors is rich in growth factors, chemokines and inflammatory cytokines but generally lacks cytokines which is involved in sustained and specific immune responses [36].

There is now evidence that inflammatory cytokines and chemokines, which can be produced by the tumor cells and/or tumor-associated leukocytes and platelets, may contribute directly to malignant progression. Many cytokines and chemokines are inducible by hypoxia, which is a major physiological difference between tumor and normal tissue. Examples are TNF, IL-1 and IL-6, and chemokines. The immune response to tumors is constituted by cytokines produced by tumor cells as well as host stromal cells. Tumor-derived cytokines, such as Fas ligand, vascular endothelial growth factor (VEGF), and transforming growth factor-h, may facilitate the suppression of immune

response to tumors. Moreover, inflammatory cytokines have also been reported to facilitate the spectrum of tumor development [37].

Tumor necrosis factor

TNF is a multifunctional cytokine that plays important roles in diverse cellular events such as cell survival, proliferation, differentiation, and death. TNF is a pro-inflammatory cytokine, which is secreted by inflammatory cells, which may be involved in inflammation-associated carcinogenesis. TNF exerts its biological functions through activating distinct signaling pathways such as nuclear factor-κB (NF-κB) and c-Jun N-terminal kinase (JNK). NF-κB is a major cell survival signal that is antiapoptotic while sustained JNK activation contributes to cell death. The crosstalk between the NF-κB and JNK is involved in determining cellular outcomes in response to TNF. TNF is a double-edged sword that could be either pro- or antitumorigenic. TNF could be an endogenous tumor promoter because TNF stimulates cancer cells' growth, proliferation, invasion and metastasis, and tumor angiogenesis. And as well, TNF could be a cancer killer. The property of TNF in inducing cancer cell death renders it a potential cancer therapeutic [38]. TNF can be detected in malignant and/or stromal cells in human ovarian, breast, bladder, colorectal, prostate cancer, leukemias, and lymphomas, often in association with ILs-1 and 6 and macrophage colony-stimulating factor [39].

Interleukins 1 and Interleukins 6 in cancer regulation

IL-6 is a pleiotropic cytokine that plays important roles in immune response, inflammation, and hematopoiesis. It is produced by a variety of normal cells including monocytes and macrophages but is also expressed by multiple tumor tissue types, such as breast, prostate, colorectal, and ovarian cancer. IL-6 may also play an important role in various aspects of tumor behavior, including apoptosis, tumor growth cell proliferation, migration and invasion, angiogenesis, and metastasis [40]. IL-10, initially termed “cytokine synthesis inhibitor” or “cytokine inhibitory factor” due to its inhibitory action on cytokine production by T helper cells, is produced by almost all leukocytes, as well as numerous human tumor cells including breast, kidney, colon, pancreas, malignant melanomas, and neuroblastomas. IL-10 is essential to suppress tumor-promoting inflammation mediators, thereby facilitating tumor growth and metastasis. Specifically, TAMs produce IL-10 and are also associated with in-tumor immunosuppression, thereby providing a suitable microenvironment for cancer growth [41]. In mouse models of metastasis, treatment with an IL-1 receptor antagonist (which inhibits the action of IL-1) significantly decreased tumor development, suggesting that local production of this cytokine aids the development of metastasis. Moreover, mice deficient in IL-1 were resistant to the development of experimental metastasis [42].

Chemokines

Inflammatory cytokines are major inducers of a family of chemoattractant cytokines called chemokines that play a central role in leukocyte recruitment to sites of inflammation. Most tumors produce chemokines of the two major groups α (or CXC) and β. Typically, CXC chemokines are

active on neutrophils and lymphocytes, whereas CC chemokines act on several leukocyte subsets including monocytes, eosinophils, dendritic cells, lymphocytes, and natural killer cells but not neutrophils [43]. Human and murine tumors also frequently secrete CXC chemokines such as IL-8. These chemokines are potent neutrophil attractants, yet neutrophils are rare in tumors. However, both IL-8 and a related chemokine called "gro" induce proliferation and migration of melanoma cell.

2.3. Implications for Prevention and Treatment

Tumor Necrosis Factor (TNF) blockade

Tumor Necrosis Factor (TNF) antagonists (etanercept [Enbrel] and infliximab [Remicade]) have been licensed for a clinical trial in the treatment of rheumatoid arthritis and Crohn's disease, with over 70,000 patients now treated. Thalidomide inhibits the processing of mRNA for TNF and VEGF, and continuous low-dose thalidomide has shown activity in patients with advanced myeloma. The role of etanercept in ameliorating the adverse effects of other cancer therapies is also being evaluated. There are also ongoing and planned clinical trials with infliximab. As with other "biological" approaches to cancer treatment, anti-TNF therapy may be optimal in an adjuvant setting with minimal disease [44].

Chemokine antagonism

Chemokine receptors belong to a family of receptors (transmembrane G-protein-coupled receptors) which is already a target of pharmacological interest. Tumors driven by chemokines and those where chemokines are implicated in metastasis (e.g. seeding to lymph nodes) may be an appropriate target for chemokine antagonists now under development [45]. IL-6 is a major growth factor for myeloma cells. In progressive disease, there is an excess of IL-6 production, and raised serum concentrations are associated with plasmablastic proliferative activity and short survival.

Nonsteroidal anti-inflammatory agents

Nonsteroidal anti-inflammatory drugs (NSAIDs) are nonselective or selective COX-1/2 inhibitors, which are wildly prescribed for pain killing, fever reduction, and even anti-inflammation. Patients on NSAIDs are at reduced risk of colon cancer. This may also be true for cancers of the esophagus, stomach, and rectum, and in rodent experimental bladder, breast, and colon cancer. Colon cancer is reduced when NSAIDs are administered concurrently with carcinogens. NSAIDs inhibit cyclooxygenase enzymes and angiogenesis [46]. The mechanisms involved in the association between NSAIDs and distant metastasis inhibition remain incompletely investigated. One possible explanation is that NSAIDs inhibit COX2. Abnormally high COX2 expression is observed in multicancers. Disordered COX2/PGE pathway is involved in multicancer processes, including carcinogenesis, proliferation, and metastatic spread; in addition, inhibition of COX2/PGE pathway with NSAIDs can restrain cancer cell lines. Another possible underlying mechanism is mutual promotion relationship between cancer metastasis and cancer-associated thrombosis. One key

regulator of hemostasis, which is, abnormally high constitutive level of tissue factor (TF), is expressed by metastatic cancer cells, cancer microparticles, and cancer-associated monocytes and macrophages. TNF can promote thrombosis formation by activating the extrinsic pathway of coagulation cascade. Furthermore, inflammation induced by thrombosis could result in endothelial damage that results in the vascular leak, facilitating the escape of cancer cells from blood vessels. Consequently, NSAIDs may disrupt the relationship between cancer metastasis and cancer-associated thrombosis via the suppression of platelet function, which is detrimental for the disseminated cancer cells in the bloodstream [47].

3. Chemopreventive Compounds

One of the most impressive findings in the field of chemoprevention is the large number of compounds that have been demonstrated to prevent the occurrence of cancer. Compounds belonging to over 20 different classes of chemicals have been shown to have chemopreventive capacities (Tables 1 and 2). The great chemical diversity is a positive feature in that it indicates the likelihood that a variety of approaches can be made to prevention and that the options for selecting optimal compounds will be large. Some of these inhibitors are naturally occurring constituents of food (Table 1). Chemopreventive agents can be placed into 2 broad categories. The first category includes compounds that are effective against complete carcinogens. The second includes compounds effective against tumor promoters. Some compounds fall into both categories.

3.1. Inhibitors Effective against Complete Carcinogens

The mechanisms of action of most inhibitors of carcinogenesis, both synthetic and naturally occurring, are poorly understood. This lack of information makes it difficult to organize them into a cohesive pattern. One means of providing an organizational framework is to classify inhibitors according to the time in the carcinogenic process at which they are effective. Utilizing this framework, inhibitors of carcinogenesis can be divided into 3 categories (Chart 1). The first consists of compounds that prevent the formation of carcinogens from precursor substances. The second are compounds that inhibit carcinogenesis by preventing carcinogenic compounds from reaching or reacting with critical target sites in the tissues. These inhibitors are called “Blocking agents”, which describes the mechanism of action. They exert a barrier function. A third category of inhibitors acts subsequent to exposures to carcinogenic agents. These inhibitors are termed “Suppressing agents”, they function by suppressing the expression of neoplasia in cells previously exposed to doses of a carcinogenic agent that will cause cancer.

Compounds inhibiting the formation of carcinogens.

A major focus of this group of inhibitors has been on prevention of formation of nitroso carcinogens from the reactions of precursor amines or amides with nitrite. Ascorbic acid is effective in inhibiting formation of these carcinogens both *in vitro* and *in vivo* [48, 49]. Animals that are given appropriate

precursor compounds form nitroso carcinogens *in vivo* and afterwards develop neoplasms. Under these conditions, addition of ascorbic acid to the diet will prevent formation of the nitroso compounds and the occurrence of neoplasia. α-Tocopherol and phenols also have the capacity to inhibit formation of nitroso compounds (Table 1).

Table 1: Inhibitors of carcinogen-induced neoplasia

Category of inhibitor	Chemical class	Inhibitory compounds	Refs
Compounds preventing formation of carcinogen from precursor compounds	Reductive acids	Ascorbic acid	48, 49
	Tocopherols	α-Tocopherol, γ-Tocopherol	50
	Phenols	caffeic acid, ferulic acid, Gallic acid, Propyl gallate	51
Blocking agents	Phenols	2(3)-tert-Butylhydroxyanisole, butylated hydroxytoluene,hydroxyanisole,ellagic acid, caffeic acid, ferulic acid, ρ-hydroxycinnamic acid, and others	52, 53
	Indoles	Indole-3-acetonitrile, indole-3-carbinol, 3,3'-diindolymethane	54
	Aromatic isothiocyanates	Benzyl isothiocyanate, phenethyl isothiocyanate, and phenyl isothiocyanate	55
	Coumarins		56
	Flavones	Coumarin, limettin	
	Dithiothiones	β -Naphthoflavone, α-naphthoflavone, quercetin pentamethyl ether	
	Diterpenees	5-(2-pyrazinyl)-4-methyl-1,2-dithiol-3-thione, 3-(ρ-methoxyphenyl)-1,2-dithiol-3-thione	57
	Dithiocarbamates	Kahweol palmitate	54
		Tetraethylthiuram disulfide (disulfiram), sodium diethyldithiocarbbamate, bis(ethylxanthogen)	
	Phenothiazines	Phenothiazine	
	Barbiturates	Phenobarbital	58, 59
	Trimethylquinolines	6-Ethoxy-1,2-dihydro-2,2,4-trimethylquinoline (ethoxyquin)	60 58
Suppressing agents	Retinoids and carotenoids	Retinyl palmitate, retinyl acetate, 13-cis-retinoic acid, ethyl retinamide, 2-	61

		hydroxyethylretinamide, retinyl methyl ether, n-(4-hydroxyphenyl)retinamide, other synthetic retinoids, β-carotene	62
	Selenium salts	Sodium selenite, selenium dioxide, seleniuos acid, sodium selenide	63
	Protease inhibitors	Leupeptin, antupain, soybean protease inhibitors	
	Inhibitors of arachidonic acid metabolism	Indomethacin, aspirin	
	Cyanates and isothiocyanates	Sodium cyanate, tert-butyl isocyanate, benzyl isothiocyanate	64
	Phenols	2(3)-tert-Butylhydroxyanisole	65
	Plant sterols	β -Sitosterol	15
	Methylated xanthines	Caffeine	66
	Others	Dehydroepiandrosterone, fumaric acid	67

Blocking Agents.

Blocking agents prevent carcinogens from reacting with critical target sites. A large and diverse group of compounds (both naturally occurring and synthetic) falls into this category of inhibitors (Table 1). An understanding of their mechanisms of action is based on the contributions of the Millers and others to the field of chemical carcinogenesis [48, 68]. A vast amount of information has been accumulated which demonstrates that chemical carcinogens act via common mechanisms. The most extreme carcinogenic forms of carcinogens are positively charged electrophilic species. Some carcinogens, termed “direct acting”, exist in this form or assume it in solution. Others require metabolic activation. Blocking agents can be placed into 3 groups based on the mechanism of action. One group acts simply by inhibiting the activation of a carcinogen to its ultimate carcinogenic form. Inhibitors in this group are effective only against carcinogens requiring activation. A second group of blocking agents is effective by virtue of inducing increases in activity of enzyme systems having the capacity to enhance carcinogen detoxification. The inhibitors in this group are of particular interest because they have the capacity to inhibit a wide range of carcinogens. The third group of blocking agents has the capacity to act by scavenging the reactive forms of carcinogens. Glutathione, which is a physiological nucleophiles, such as glutathione, fall into this group. Recently, xenobiotic compounds present in plant constituents of the diet have been shown to scavenge the ultimate carcinogenic form of benzo(a)pyrene. Ellagic acid has been shown to be highly potent in this regard [69]. Among compounds that can scavenge carcinogens, one group is potentially of considerable interest, namely, those that would be effective in inhibiting

gastrointestinal neoplasia.

Suppressing Agents.

Suppressing agents are compounds that inhibit carcinogenesis when administered subsequent to a course of carcinogen administrations that would result in the occurrence of cancer. The number of classes of compounds that act as suppressing agents is smaller than that of blocking agents. Unlike the situation existing for blocking agents, there are no generic short-term test systems indicating the likelihood that a compound is a suppressing agent. Thus, they are more difficult to identify. The most extensively studied suppressing agents are the retinoids [70, 71]. There are several salient points that should be made concerning the retinoids: they can be highly effective as suppressing agents; individual retinoids target to specific tissues rather than on all tissues (some tissues such as the large bowel appear to be particularly refractory); in general, the effects of the retinoids are reversible; the compounds have toxic properties; and their mechanisms of suppressing action have not been clearly elucidated. Selenium salts are an exceedingly interesting group of suppressing agents. These compounds have been found to inhibit a considerable variety of experimental neoplastic systems. Included are the inhibition of virus-induced neoplasia of the mammary gland in mice as well as carcinogenesis resulting from administration of chemical carcinogens to both mice and rats [72, 73]. Epidemiological data have been interpreted by some investigators as indicating that a low selenium consumption may increase the occurrence of neoplasia in certain human populations. There are two insistent problems in the available information concerning selenium inhibition of neoplasia. The first has to do with the mechanism(s) by which selenium acts. Unfortunately, very little information exits on the mechanism(s) by which selenium inhibits the occurrence of neoplasia. The second problem, which is related, concerns the relationships between dose, species and effectiveness of selenium as an inhibitor. Good information on the relationships of dose to protection against neoplasia is not available for different species of experimental animals and likewise for the human. Since selenium can have toxic effects, a major defect in currently available information is the inability to predict the dose level in the human that would give maximum protection without producing toxicity. Dehydroepiandrosterone is an interesting inhibitor in that it has been shown to suppress neoplasia in several experimental systems [74]. The mechanism of this suppression is not known. The number of investigators who have carried out experiments with this and related compounds as inhibitors of carcinogenesis has been very small. The use of protease inhibitors and inhibitors of arachidonic acid metabolism as inhibitors of carcinogenesis is under investigation by several groups of workers.

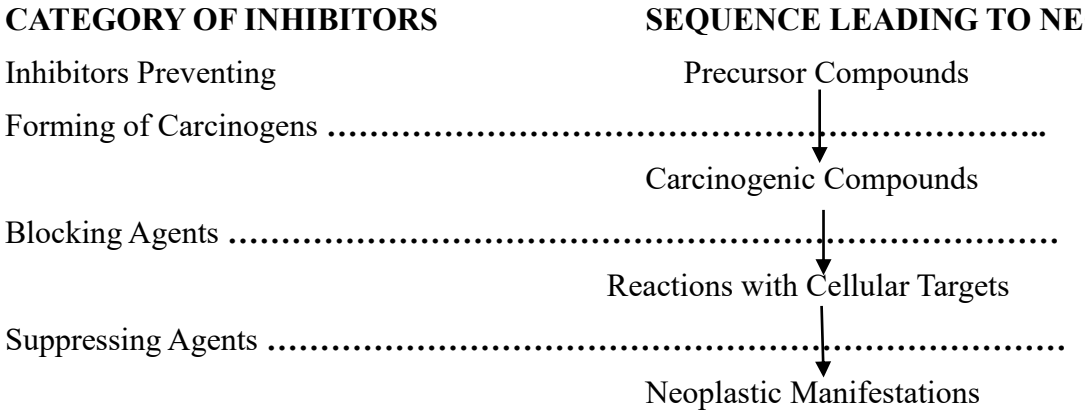

Chart 1: Classification of chemopreventive agents on the basis of the time at which they exert their protective effects.

3.2. Compounds Inhibiting Tumor Promotion

In Table 2, 9 classes of compounds that inhibit tumor promotion are listed. In some instances, a class contains a sizable number of inhibitors; and in others, there is only one inhibitor. The vast majority of these studies have focused on inhibition of promotion of epidermal neoplasia in mouse as a result of topical administration of TPA (12-O-tetradecanoylphorbol-13-acetate). A few studies have used other tumor promoters, of particular interest is an experiment in which the tumor promoter used was benzoyl peroxide. A major hypothesis concerning tumor promotion has been that attack by oxygen radicals may play a role in its causation [75, 76]. In accord with this hypothesis has been the demonstration of oxygen radical formation in the mouse epidermis following application of TPA. Several groups of inhibitors that overall prevent attack by oxygen radicals inhibit tumor promotion. Phenolic antioxidants inhibit tumor promotion by benzoyl peroxide [75]. Protease inhibitors prevent formation of oxygen radicals by TPA and inhibit tumor promotion [76]. A synthetic compound with superoxide dismutase activity, i.e., copper (II) 3, 5-disopropylsalicylic acid, inhibits tumor promotion [77, 78]. Thus, there is a body of evidence indicating the possibility that one mechanism of inhibition of tumor promotion may reside in a “blocking action” in which the tissues are protected from attack by oxygen radicals. A comparison of compounds listed in Tables 1 and 2 show that members of 3 major groups, i.e., retinoids, protease inhibitors, and inhibitors of arachidonic acid metabolism, which have the capacity to act as suppressing agents.

Table 2: Inhibitors of tumor promotion of the mouse skin

Class of inhibitor	Compound	Refs
Retinoids	All-trans-retinoic acid, 13-cis-retinoic acid, ethyl-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-trans-2,4,6,8-nonatetraenoate	79, 80
Protease inhibitors	Tosyl lysine chloromethyl ketone Tosyl arginine methyl ester Tosyl phenylalanine chloromethyl ketone Leupeptin	76, 81 63
Inhibitors of arachidonic acid metabolism	Dexamethasone 5,8,11,14-Eicosatraynoic acid Fluocinolone acetonide Fluocinonide Fluciorolone acetonide Indomethacin Nordihydroguaiaretic acid 1-Phenyl—3-pyrazoledinone ρ-Bromophenacyl bromide Dibromoacetophenone	79 82 83 84 85 82 85 82
Phenols	ρ-Methoxyphenol 2-tert-Butylhydroxyanisole 3-tert-Butylhydroxyanisole	75
Synthetic compound with superoxide dismutase activity	Copper(II) 3,5-diisopropylsalicyclic acid	77
Cyclic nucleotides or inhibitors of phosphodiesterase activity	Cyclic AMP 3-Isobutyl-1-methylxanthene	86
Polyamines	Putrescine	87
Modulation of calcium metabolism	1α,25-Dihydroxyvitamin D_3	88
Benzodiazepines	Diazepam	89
Others	Quercetin, α-difluoromethylornithine	90, 91

3.3. Role of Phytochemicals in Cancer Prevention

Capsaicin

Capsaicin (trans-8-methyl-*N*-vanilly l-6-nonenamide) is a pungent alkaloid and active component of chili pepper belonging to the plant genus called *Capsicum* [92, 93]. Capsaicin has been reported as a chemopreventive, tumor suppressing, radio-sensitizing, and anticancer agent in various cancer models [94, 95]. Topical application of capsaicin is used to reduce pain or may represent an effective treatment to alleviate the symptoms of osteoarthritis when oral non-steroidal anti-inflammatory drugs are not used due to side effects [96]. Capsaicin inhibits the activity of carcinogens, through numerous pathways, and induces apoptosis in several cancer cell lines in vitro and in rodents [93, 97, 98], and thus may be considered for cancer therapy.

Lycopene

Lycopene is a member of the carotenoid family, which is mainly found in tomatoes and other food products such as pink grapefruit, papaya, watermelons, red carrot and pink guava [99, 100]. It is a naturally occurring pigment that contributes to the red color in these food products. Lycopene is a potent dietary antioxidant and because of its antioxidant effect, it is known to have a protective effect on several diseases such as cardiovascular diseases, neurodegenerative diseases, hypertension, osteoporosis, diabetes, and cancer [101, 102].

Cucurbitacin B

Cucurbitacins are tetracyclic triterpenoids that are found in traditional Chinese medicinal plants belonging to the cucurbitaceae family. Among eight different types of Cucurbitacins, Curcubitacin B (CuB) is the most active component against cancer and showed promise in various cancer models [103]. The effective concentrations of CuB in vitro range from 20 nM–5 μM and in vivo therapeutic doses range from 0.1–2 mg/kg [104]. Several studies have shown that CuB inhibits STAT3 signaling in various cancer models such as colorectal cancer [105], lung cancer [106], neuroblastoma [107], acute myeloid leukemia [108], pancreatic cancer [109] and breast cancer [110].

Benzyl Isothiocyanate (BITC)

Isothiocyanates (ITCs) are natural compounds of high medicinal value that are present in cruciferous vegetables such as broccoli, watercress, Brussels sprouts, cabbage, cauliflower and Japanese radish [111]. They are present as conjugates in the genus *Brassica* of cruciferous vegetables. ITCs are well-known for their chemo-preventive activity and mediate anti-carcinogenic activity by suppressing the activation of carcinogens and increasing their detoxification [111]. The high content of glucosinolates, which store ITCs in cruciferous vegetables confer anti-cancerous effects. ITCs suppresses tumor growth by induction of oxidative stress mediated apoptosis, inducing cell cycle arrest, inhibiting angiogenesis and metastasis [111].

Phenethyl Isothiocyanate

Phenethyl isothiocyanate (PEITC) is another isothiocyanate mainly present in cruciferous plants.

PEITC is one of the active ingredients of cruciferous vegetables that have been extensively studied for its anti-cancer effects in glioblastoma, prostate cancer, breast cancer and leukemia [112]. Several studies have indicated that consumption of cruciferous vegetables such as broccoli, watercress, and garden cress leads to chemoprevention in various rodent models [113].

Piperlongumine

Piperlongumine or Piplartine (5,6-dihydro-1-[(2E)-1-oxo-3-(3,4,5-trimethoxyphenyl)-2-propenyl]-2(1H)-pyridinone) is a phytochemical alkaloid extracted from the roots of long pepper Piper longum L., a member of the Piperaceae family. Piperlongumine was used to treat various diseases such as malaria, cancer, bronchitis, melanogenesis, and viral hepatitis [114]. The key therapeutic features of piperlongumine are its anti-inflammatory, anti-bacterial, anti-nociceptive, anti-diabetic, anti-fungal, anti-depressant, and anti-tumor properties [115]. Overall, piperlongumine has significant chemotherapeutic and chemopreventive potential making it an effective treatment option for cancer. Piperlongumine has been found to be effective against several cancers such as multiple myeloma [116], melanoma [117], pancreatic cancer [118], colon cancer [3, 119] oral squamous cell carcinoma [120], non-small-cell lung cancer [121], gastric cancer [109], biliary cancer [120], and prostate cancer [77].

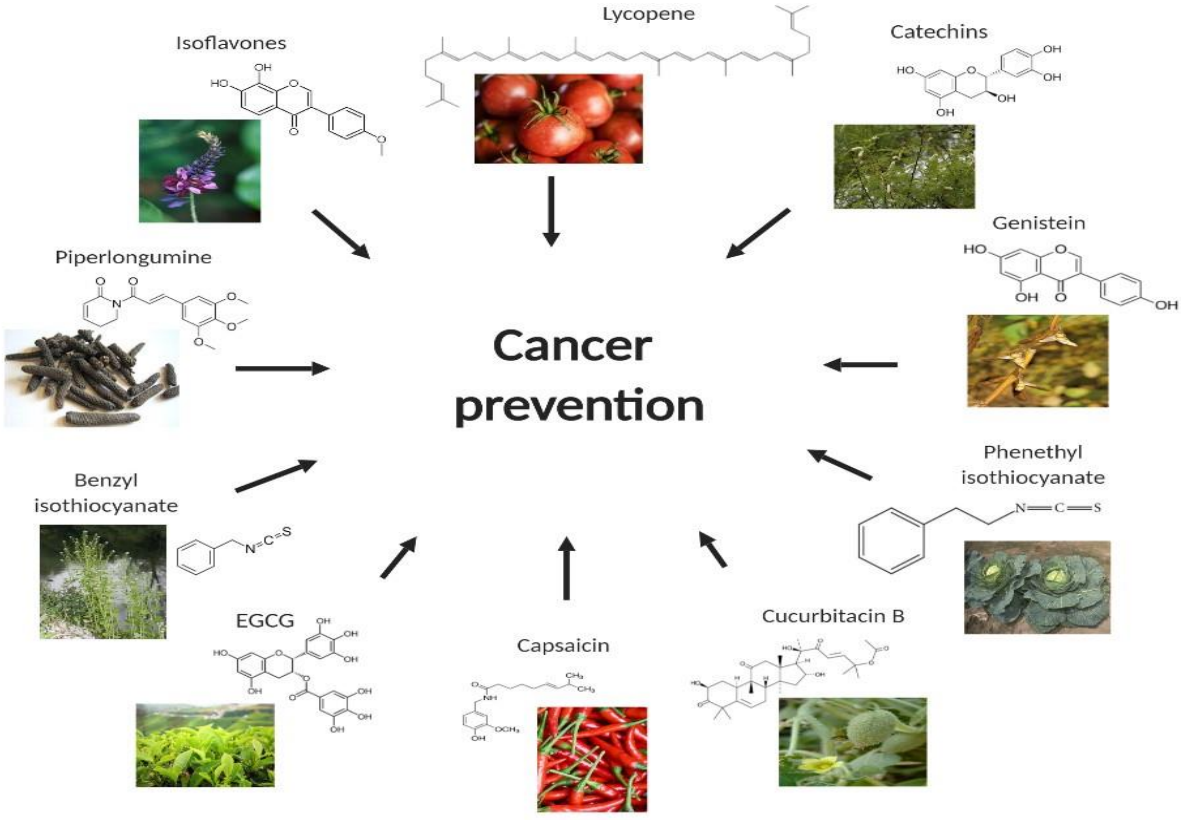

Figure 2: Phytochemicals in Cancer Chemoprevention

4. METABOLISM PATHWAYS OF ARACHIDONIC ACID

4.1. Overview of Arachidonic Acid Metabolism

The ω-6 polyunsaturated fatty acid (PUFA), arachidonic acid (AA), and its metabolites have attracted a lot of attention in cardiovascular and cancer biology, particularly in relation to inflammatory processes and disease [86, 123 – 127]. The importance of AA in biology lies in the fact that it can be metabolized by three distinct enzyme systems, i.e., cyclooxygenases (COXs, also referred to as PGG/H synthases), lipoxygenases (LOXs), and cytochrome P450 (CYP) enzymes (ω-hydroxylases and epoxygenases) to generate an impressive spectrum of biologically active fatty acid mediators (Fig. 3). The COXs, which generate prostanoids, i.e., prostaglandins (PGs) and thromboxane A2 (TXA2), were the first enzymes reported to metabolize AA. This requires the release of the lipid from the plasma membrane by phospholipases and subsequent metabolism by the COX enzymes to PGG2 and PGH2. The latter are then metabolized to PGs by specific PG synthases. There are two distinct COX isoforms; COX-1, which is constitutively expressed in most cells, is the dominant source of prostanoids that subserve housekeeping functions.7 COX-2 (also known as PTGS2), on the other hand, is induced by inflammatory stimuli, hormones, and growth factors, is generally assumed to be the more important source of prostanoid formation in inflammation and in proliferative diseases, such as cancer [128]. However, the situation is not black and white as both enzymes contribute to the generation of autoregulatory and homeostatic prostanoids, and both can contribute to prostanoid released during inflammation.

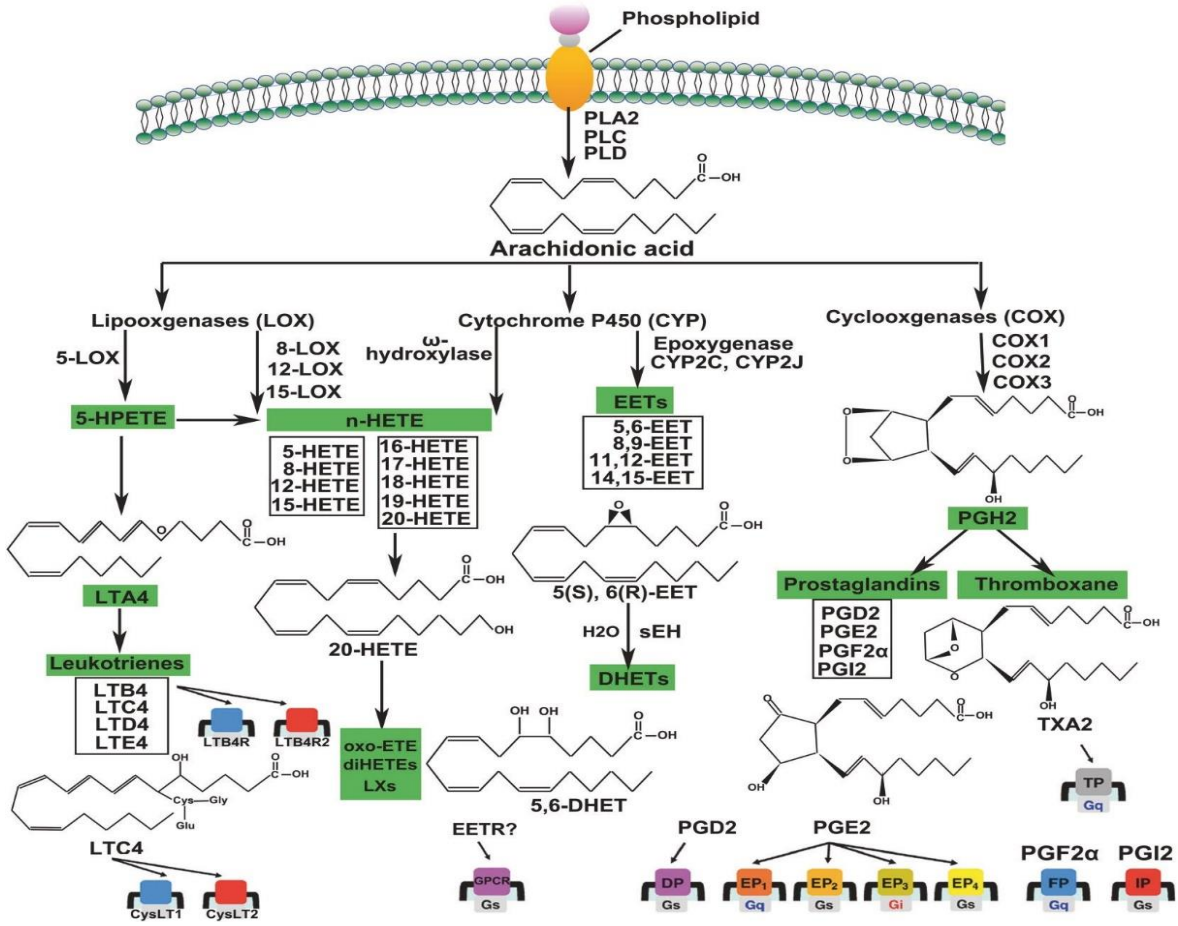

Figure 3: Overview of the arachidonic acid (AA) metabolism pathways. Three major phospholipase enzymes (PLA2, PLC and PLD) are responsible for releasing AA from membrane-bound phospholipids by catalyzing the red arrow indicated covalent bonds, respectively. The PGHSs (COXs) metabolize AA to protanoids, prostacyclin, and thromboxane. The LOXs metabolize AA to leukotrienes and HETEs. The P450 epoxygenases metabolize AA to midchain HETEs and four EET regioisomers. All EETs are then further metabolized to less active dihydroxyeicosatrienoic acids (DHETs) by sEH

4.2. Roles of COXs and their metabolites in cancer

Chronic inflammation is clearly associated with an increase in the risk of cancer [72]. One of the strongest associations between chronic inflammation and cancer is the increased risk in individuals with inflammatory bowel diseases. Inflammation also appears to have an important role in the development of other cancers, for example, prostate, bladder, and pancreatic cancers. Chronic inflammation causes the up-regulation of a number of inflammatory cytokines including Interleukin-1β (IL-1β), Interferon-γ (IFNγ), and Tumor necrosis factor-alpha (TNFα). The Nuclear factor kappa B (NF-κB) pathway is activated in many chronic inflammatory states, and evidence directly links the NF-κB pathway to increased tumor formation and inflammation in experimental mouse models

of intestinal cancer [123, 126]. Because NF-κB plays a role in COX-2 regulation at the transcriptional level, prostaglandin H synthase or COX-2 expression is increased, and higher levels of inflammatory PGs are formed [129]. Diminished expression of 15-prostaglandin dehydrogenase (15-PGDH), a prostaglandin degradation enzyme also contributes to the elevated PG levels in cancer [123, 130]. Numerous epidemiological, clinical, laboratory, and animal and cell culture studies confirm that the use of COX inhibitors or nonsteroidal NSAIDs is effective at inhibiting the incidence and mortality of colorectal cancer [131, 132]. In addition to colorectal cancer, NSAIDs have also been associated with a reduced risk of breast, esophageal, stomach, bladder, ovary, and lung cancers [133-135]. Despite the extensive studies on the effectiveness of NSAIDs as chemopreventive agents, the molecular mechanisms underlying their chemopreventive effects are not well understood. While it was initially presumed that the anti-cancer activity of the NSAIDs could be attributed to the inhibition of COX-1/COX-2, this concept has been challenged by the fact that very high doses of COX inhibitors are frequently required to exhibit tumor inhibitory effects but only low doses are required to prevent PG generation [123, 136]. Therefore, COX-independent effects may contribute to the chemopreventive activity of NSAIDs [136].

2. CONCLUSION

COX enzymes, and its metabolites of Arachidonic Acid play important roles in the initiation and development of human diseases, especially cardiovascular and cancer.

Chemoprevention is a relatively safe and cost effective approach because cancer can be prevented by changing dietary habits. This approach has gained momentum after the approval of tamoxifen and raloxifen by US Food and Drug Administration for breast cancer risk reduction [137].

Drug associated toxicity is a significant barrier for currently available chemotherapeutic drugs, however, use of natural compounds for cancer prevention may mitigate associated toxicity. Bioavailability is the biggest problem with most of the naturally occurring chemopreventive agents. Overall, this review summarizes natural compounds targeting different signaling pathways involved in cancer progression, suggesting their potential to be successful anti-cancer agents.

LIST OF ABBREVIATIONS

COX	Cyclooxygenase
IL	Interleukin
NSAIDs	Nonsteroidal anti-inflammatory drugs
PG	Prostaglandins
TNM	Tumor-Node-Metastasis
TNF	Tumor Necrosis Factor
TPA	12-O-tetradecanoylphorbol-13-acetate
TXA2	Thromboxane A2

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The author confirms that the data supporting the findings of this research are available within the article.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article

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