# CHEMOPREVENTION OF CANCER

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*Abstract:*
*Cancer chemo prevention refers to the use of agents for the inhibition, delay, or reversal of carcinogens before invasion. In the present review, agents examined in the context of cancer chemo prevention are classified in four major categories—hormonal, medications, diet-related agents, and vaccines—and the main representatives of each category are presented. Although there are serious constraints in the documentation of effectiveness of chemo preventive agents, mainly stemming from the long latency of the condition they are Addressing and the frequent lack of intermediate biomarkers, there is little disagreement about the role of aspirin, whereas a diet rich in vegetables and fruits appears to convey more protection than individual micro nutrients. Among categories of cancer chemo preventive agents, hormonal ones and vaccines might hold more promise for the future. Also, the identification of individuals who would benefit most from chemo preventive interventions on the basis of their genetic profiles could open new prospects for cancer chemo prevention.*

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## INTRODUCTION:

Epigenetic modification can be caused by DNA methylation, histone modification and m RNA. The cellular micro-environment has become another concern during cancer development. Inappropriate inflammatory responses can be critical at various cancer stages. Proinflammatory macrophages (M1)accelerate development of tumor initiation into the promotion and progression stages while anti-inflammatory macrophages (M2) are found to promote tumor growth, angiogenesis and metastasis. Also, the byproducts of metabolism are undeniably another important influence on the cellular micro environment. However, there are several factors that affect each other, including the metabolic state of the host, gut microbiota composition and the circadian clock. *In terms of single targeting, although it is suggested that single hits are more than sufficient for certain cancers such as leukemia's and sarcomas, most cancers require two or more hits, and three hits or more are prescribed in colorectal cancer. Therefore, recent cancer prevention strategies are often described as multi-stage targeting including the initiation, promotion and progression stages. In fact, there are two-stage model or expanded/multi-stages models being introduced that have successfully described features in cancer development . While discussing multistage diseases like cancer, it is crucial to understanding the effect of environmental carcinogens as initiators or/and acting as promotional agents . Carcinogens can cause tumor initiation genetically and/or epigenetically, i.e., based on changes in gene expression with or without involvement of changes in cellular DNA sequences; both may lead to promotion in expression of oncogenes and/or repression of tumor-suppressing genes. Mutations can be the result of a number of causes, such as DNA damage from infections, UV induced tissue damage and reactive oxygen species, and DNA abducts can occur as a consequence of over expression of phase I enzyme and/or down-regulation of phase II enzyme.*

According to the latest global cancer data released by International Agency for Research on Cancer (IARC), the estimated global cancer burden has risen to 18.1 million, and there have been up to 9.6 million deaths in year 2018. In terms of incidence, the major cancer types as surveyed in 2018 are lung cancer, colorectal cancer and female breast cancer, which are ranked at first, second and fifth, respectively, in terms of mortality. Cancer is a leading cause of death in less economically developed countries as well as high-income countries and constitutes an enormous burden on

societies and can Cancer is known as a multi-stage disease that conceptually can be divided into the initiation, promotion, conversion, progression, and lastly, invasion and metastasis stages. Most chemotherapeutic stages target advanced-stage cases, but there are several shortcomings of advanced chemotherapeutic drugs including side effects, price and single-target mechanisms. It has been reported that circadian misalignment may lead to spontaneous metabolic disease and re- composition of gut microbiota. Meanwhile, the aftermath of metabolic disorder syndromes like hyperinsulinemia and hyperglycemia can accelerate tumor growth in an insulin- or glucose-rich microenvironment. Furthermore, metabolic issues like fatty liver and cholestasis may lead to circadian rhythm disruption of peripheral tissue, greatly increasing the incidence of carcinogenesis. For the purpose of cancer therapy or prevention of cancer progression, cancer drug development has shown it importance to be done imperatively. Preventive strategies have gained interest in spite of some problems with follow- up control and treatment of cancer it has been demonstrated that carcinogenic pathways can be more successfully disrupted in the early stages of cancer treatment. However, cancer drug development is a costly and time consuming process that may not promise the efficacy without side effects. Phyto- chemicals have exhibited their potential to be a part or substituent of cancer drugs , at the same time reduced the cost and the avoided adverse side effects moreover different phyto-chemical may play ameliorative role different or multiple stages during cancer development.

## Cancer Chemo preventive Agents:

Cancer chemo preventive agents can be classified in four major categories
Hormonal
Medications
Diet-related agents
Vaccines
Medicinal Plant

## Hormones:

Anti estrogens Selective estrogen receptor modulators. Selective estrogen receptor modulators (SERMs) form a diverse group of compounds that exhibit a varying level of tissue-specific estrogen receptor (ER) activity that can be antagonistic but also agonistic depending on the target tissue More specifically, SERMs exert an antagonistic activity on breast tissue and an agonist activity on skeletal system. Some SERMs have been reported to with estrogen. During the last decade, strong evidence ductal carcinoma in situ (for all, except raloxifene).

Strengthening the evidence from the abovementioned meta-analysis, a recently updated analysis from the International Breast Cancer Intervention Study I (IBIS-I) provided evidence for a long term protective effect of tamoxifen after its cessation, for at least 20 years after use. Risks associated with tamoxifen are increased occurrence of thromboembolic events, endometrial cancer, and all - cause mortality. Raloxifene has been associated mainly with an increase in thrombo-embolic events The risk-to-benefit ratio of treatment with tamoxifen orA Report on Chemoprevention of Cancer raloxifenedepends on age, race, breast cancer risk, and history of hysterectomy. Over the course of a 5-year period, postmenopausal women with an intact uterus have been reported to have a better risk-to-benefit ratio for raloxifene compared with tamoxifen, whereas for postmenopausal women without a uterus the risk-to- benefit ratio was similar for the two compounds. Notwithstanding the reported results on cancer incidence, overall breast cancer mortality has not been shown to decrease in chemoprevention trials with SERMs conducted so far, and consequently some are questioning their role in reducing the overall burden of breast cancer.

Antiandrogens Both testosterone and dihydrotestosterone (DHT) are essential for normal growth and functioning of the prostate. The role of antiandrogens in prostate cancer prevention relies on the hypothesis that androgens may be implicated in the etiology of prostate cancer and that suppressing DHT synthesis may inhibit carcinogens is. 5-alpha-reductase is the enzyme that converts testosterone to the more active intracellular androgen DHT; the antiandrogens 5-alpha-reductase inhibitors (5-ARIs) block the process by inhibiting this enzyme. Two 5-ARIs, finasteride and dutasteride, have been tested as chemo preventive agents for prostate cancer. Two large randomized placebo-controlled trials, the Prostate Cancer Prevention Trial with finasteride and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE), have reported a decreased incidence of F1000Research 2015, 4(F1000Faculty Rev):916 Last updated: 29 SEP 2015 low-grade prostate cancer; in both, however, an absolute increase in high-grade prostate cancer has also been observed23–25.A meta-analysis of randomized clinical trials reported that 5-ARIs reduce the risk of prostate cancer among men who are screened regularly by using prostate-specific antigen (PSA) level26. The beneficial effects, however, were confined to men with PSA levels of less than 4.0 ng/mL. Evidence was insufficient with respect to the optimal age to initiate treatment or duration of chemoprevention. Uncertainty was also expressed with respect to the

impact of 5- ARIs on tumors with the greatest lethal potential, including those with Gleason scores of 8 to 10. In 2010, the US Food and Drug Administration (FDA) evaluated the results of trials and supported the conclusion drawn by the Oncologic Drugs Advisory Committee that finasteride and dutasteride do not have a favorable risk-to-benefit profile in order to be proposed for chemoprevention of prostate cancer among healthy men25.

**Medications:**
In the past, only aspirin and other anti-inflammatory drugs would have been classified under this category of chemo preventive agents. More recently, however, interest has emerged about a potential cancer chemo preventive role of statins and metformin. Aspirin and other anti inflammatory drugs Inflammation is linked to carcinogenesis and hence it is reasonable to assume that agents with anti- inflammatory effects, like the nonsteroidal anti- inflammatory drugs(NSAIDs), could have cancer chemo preventive properties. The main representative of NSAIDs is aspirin, but other compounds like indomethacin and piroxicam are included in this class of medications. Various hypotheses have been invoked to explain the chemo preventive properties of NSAIDs5,27. Most prominent among them is the hypothesis about cyclooxygenase (COX)inhibition. COX-1 and -2 are enzymes necessary for the synthesis of inflammatory prostaglandins from arachidonic acid, and NSAIDs inhibit these enzymes. COX2 is believed to be overexpressed in the early stages of colon carcinogenesis. Selective COX-2 inhibitors have also been developed. A large body of evidence, from both randomized trials and observational epidemiological studies, has strengthened the hypothesis that regular prophylactic aspirin use reduces incidence of and mortality from colorectal cancer in the general population. A favorable effect of aspirin has also been reported with respect to recurrence of adenomatous polyps as well as polyp load in individuals with hereditary colon cancer. Although data are less extensive, studies have shown reductions in incidence of and mortality from esophageal, stomach, and other gastrointestinal cancers as well as inverse, though small in magnitude, associations with breast, prostate, and
lung cancers. Issues that remain to be clarified are the optimal dose and duration of use and appropriate ages for use in average-risk individuals.

Reduced incidence and mortality have been seen for all daily doses of above 75 mg, but there is no

clearindication of a greater reduction with increasingdose32. In a recent systematic review, the authors concluded that prophylactic aspirin use for at least 5 years at daily doses ranging from 75 to 325 mg, starting between ages 50 and 65, has a favorable risk- to-benefit profile for cancer prevention in the average- risk general population inthe developed world for both sexes. Larger benefits were observed for 10-year use, whereas longer use still seems beneficial Nevertheless, benefits need to be balanced against harms. The side effects of aspirin and NSAIDs, attributed to inhibition of COX-1 activity in platelets, include gastrointestinal track bleeding and intracranial or extra cranial hemorrhage, but serious incidents are not common at ages of less than 70 years 27,34.Overall, it seems important for evidence- based recommendations regarding the use of aspirin in chemoprevention to be integrated with those for cardiovascular disease prevention. This Photo by Unknown Author is licensed under CC BY-SA- NC

## Statins:

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are used as cholesterol lowering drugs but have also drawn attention as potential cancer chemopreventiveagents35– 37. Reduction of mevalonate synthesis by inhibiting 3-hydroxy-3- methylglutarylcoenzyme A reductase has been invoked as a possible mechanism for a statin-induced suppression of tumor growth, induction of apoptosis, and inhibition of angiogenesis38,39.In a meta-analysisof 40 studies, a modest decrease in colorectal cancer risk with statin use was observed, which, however, was statistically significant among observational studies but notamong randomized controlled trials40. Reports for reduction of risk with respect to other cancer sites, such as prostate and gastric cancer as well as esophageal cancer (especially adenocarcinoma among patients with Barrett's esophagus), have also appeared in theliterature. Overall, however, there is currently noconclusive evidence for a cancer chemo preventive effect of statins. Of note, statin use among cancer patients before diagnosis has been associated with reduced total and site-specific mortality 13.

## Metformin:

Metformin is a commonly prescribed drug for type 2 diabetes and belongs in the biguanide class.The crucial role of energy metabolism in cell growth and proliferation implies that antidiabetic or metabolism-altering drugs may hold preventive and therapeutic value, and, in this context, mechanisms for a potential cancer preventive effect of metformin have been proposed. Epidemiologic studies indicate that diabetics treated with metformin have a decreased cancer risk compared with those on other antidiabetic medications. Although evidence of a cancer chemo preventive effect of metformin among diabetics is accumulating, the question remains asto whether metformin can exert similar beneficial effects in nondiabetics.

## Diet-related agents:

Several micronutrients have attracted the attention of the scientific community as potential cancer-preventive agents. Among them, diet-derived antioxidants have been studied intensively on account of the protection they convey against oxidative stress. Current evidence on chemo preventive effects of antioxidants and other micronutrients is summarized below.Page 3 of 10 F1000Research 2015, 4(F1000 Faculty Rev):916 Last updated: 29 SEP 2015.

## Carotenoids:

Carotenoids are fat-soluble red/orange pigments with antioxidant properties and comprise more than 600 compounds. Of the approximately 50 found in human diets, only about half can be absorbed. Carotenoids are found in vegetables and include xanthophylls (e.g.,lutein) and carotenes (e.g., beta-carotene and lycopene). Beta carotene and other carotenoids can be converted to retinol and therefore are referred to by some as "pro-vitamin A"50.Beta-carotene isone of the most studied carotenoids. Observational Epidemiologic studies have shown a beneficial effect of beta carotene dietary intake on cancer prevention, but large clinical trials conducted during the 1990s did not confirm these findings; on the contrary, they demonstrated a detrimental effect. Thus, in the Alpha- Tocopherol Beta-Carotene (ATBC) Cancer Prevention Study, beta-carotene supplementation was associated with an increase in lung cancer risk as well as in risk of other cancers, notably prostate and stomach31. Similarly, in the BetaCarotene and Retinol Efficacy Trial (CARET), beta-carotene and retinol supplementation were found to increase lung cancer risk. Overall, the evidence about a protective effect of foods rich in carotenoids against cancers of the mouth, lung, pharynx, and larynx as well as about a protective effect of foods rich in beta-carotene against esophageal cancer is evaluated as probable; there is, however, strong evidence that beta carotene supplements are associated with lung cancer in current smokers. which has been classified as "convincing" in the secondexpert report of the World Cancer Research Fund and the American Institute for

CancerResearch50. Among other carotenoids, dietarylycopene (mainly found in tomatoes) has been inversely associated with prostate cancer risk, butthe level of evidence has been downgraded from probable.

**Vitamin A and retinoids:**
Vitamin A or retinol is the best known retinoids. Retinoids are required for the maintenance of normal cell growth and differentiation; together with their dietary precursor (beta-carotene), they were some of the first agents to be tested in large population-based trials55. The CARET trial in the United States studied beta-carotene along with retinol among smokers and did not show benefit from retinol (nor for beta- carotene) supplementation. Both the ATBC and the CARE Ttrials found a significant increase in lung cancer incidence in the retinol/beta carotene- containing Arms.

**Folic acid:**
Folic acid or folate, a water-soluble vitamin B, is an important cofactor in one-carbon metabolism. Folate appears to possess dual modulatory effects on colorectal carcinogenesis depending on timing and dosage. In normal colorectal mucosa folate deficiency appears toenhance neoplastic transformation, modest levels of folic acid supplementation appear tosuppress, whereas high supplemental doses appear to enhance the development of cancer. Ofnote, folate deficiency appears also to inhibit whereas folate supplementation has a promoting effect on the progression of established colorectal neoplasms57. On the basis of a lack of compelling supportive evidence from studies in humans and its potential tumor-promoting effect, folic acid supplementation cannot currently be recommended for colorectal cancer chemoprevention. The evidence concerning the inverse association of dietary folate intake with pancreatic cancer has been downgraded from probable to limited.

**Vitamin C:**
Vitamin C is a water-soluble antioxidant and enzyme cofactor. Humans do not have the ability to synthesizeit and must obtain it through diet. Vitamin C has two chemical forms, one reduced (ascorbic acid) and one oxidized (dehydroascorbic acid) form. In 1997, expertpanels at the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research had concluded that dietary vitamin C could reduce therisk of the stomach (probably) as well as mouth, pharynx, esophagus, lung, pancreas, and cervical cancers (possibly), but in their updated report in 2007, only the evidence with respect to esophagealcancer was considered probable and there was no evidence that vitamin C supplementation modifies therisk of cancer.

Recently, in a large-scale clinical trial in men, vitamin C supplementation had no immediate or long-term effects on the risk of prostate or other site-specific cancers or total60.

**Vitamin D:**
Vitamin D plays an important role in calcium metabolism but also exerts various other physiological functions. Experimental studies have shown that manycell types, including colorectal cells, express vitamin D receptors, and activation of these receptors by 1,25(OH)2 D(1,25-dihydroxycholecalciferol or calcitriol) has been reported to exert antitumor effects. In 2008, the International Agency for Research on Cancer (IARC) Working Group on Vitamin D, having examined the evidence on various cancer sites, concluded that evidence from observational studies for an inverse association between serum 25-hydroxyvitamin D levels and the incidence of colorectal cancer and sporadic colorectal adenomas was consistent and persuasive, but there was only limited evidence of a causal association and this was due to possible confounding by other dietary or lifestyle factors. Results from randomized trials to thatdate had not demonstrated an effect of vitamin D supplementation on colorectal cancer risk butcould not be judged as contradictory to the evidence from observational studies.

**Vitamin E:**
Vitamin E is a fat-soluble vitamin with antioxidant activity. It refers to a group of compounds that include both tocotrienols and tocopherols, among which α- tocopherol is the most biologically active. In the ATBC trial, an inverse association between vitamin Esupplementation and prostate cancer was reported but it disappeared post interventionally. Null results forvitamin E supplementation were also reported in the Physicians' Health Study with respect to prostate aswell as overall cancer. In the Selenium and Vitamin ECancer Prevention Trial(SELECT) in men, vitamin E, alone or in combination with selenium, was not associated with areduction in prostate cancer risk; a subsequent report even noted an increase in the risk of prostate cancer among those who received vitamin E65,66.Hence, current evidence does not support the use of vitamin E for cancer prevention.

**Calcium:**

Calcium is an essential nutrient and plays an important role in muscular contraction, cellular growth, cell adhesion, and bone formation. Page 4 of 10 F1000Research 2015, 4(F1000 Faculty Rev):916 Last updated: 29 SEP 2015 Results from large observational studies support a relatively consistent inverse association of calcium in take with colorectal adenomas and colorectal cancer. This effect is thought to be exerted by binding to toxic secondary bile acids and ionized fatty acids to form insoluble soaps in the lumen of the colon or by directly reducing proliferation, stimulating differentiation, and inducing apoptosis in the colonicmucosa. In a systematic review and meta-analysis, supplemental calcium was reported to be effective for the Prevention of adenoma recurrence in populations with a history of adenomas, but no association was found for colorectalcancer. There is some concern that a high calcium intake may increase prostate cancer incidence. The evidence on diets high in calcium or dairy products is considered as limited but suggestive, whereas the evidence on calcium supplements has been downgraded from probable to limited, on the basis of which no conclusions can be drawn .

**Selenium:**

Selenium is an essential cofactor for the major antioxidant enzyme glutathione peroxidase, which protects against oxidative damageto lipids, lipoproteins, and DNA. The results of the SELECT clinical trial did not provide encouragingdata for prostate cancer prevention65. Also,a more recent phase III study of selenium versus placebo inpatients with high-grade prostatic intra epithelial neoplasia found no benefit in the prevention of progression to prostate cancer and even suggested thathigher intake might increase the risk of cancer22. In its updated report of2014 on prostate cancer, the WCRF concluded that there is limited suggestive evidence that low plasma concentrations of selenium are associated with increased prostate cancer risk, butno conclusions can be drawn on the basis of the existing evidence for selenium supplementation 4.

**Flavonoids:**

Flavonoids are polyphenolic compounds that inhibit carcinogen activating enzymes and possess various antioxidant properties. More than 5,000 individual flavonoids have been identified and have been classified into sub classes on the basis of their range and structural complexity. Fruits and vegetables, alongwith tea and wine, are the main dietary sources of flavonoids. Epidemiologic data, though not conclusive, suggest a protective role of flavonoids on particularcancer types, such as lung, breast, colon, and prostate. In a meta-analysis of observational studies, flavonol and flavone intake, but not other flavonoid subclass or total flavonoid intake, were associated with a decreased breast cancer risk, especially among post-menopausalwomen79. With respect to colorectal cancer, evidence on the role of flavonoid intake was judgedto be insufficient and conflicting. Evidence on a potential chemo preventive role of various polyphenols, such as isoflavones, on prostate cancer risk has also been reported8183.Multivitamin/multimineral supplements. Specifically for cancer, though the statement recognized a potential benefit among persons with poor nutritional status orsub optimal antioxidant intake, it concluded that use of multivitamin supplements by the general population was not supported by the existing scientific evidence84. In 2013, a meta-analysis of randomized controlled trials concluded that multivitamin/multimineral use had no effect on cancer prevention85. Of note, the expert panels of the WCRF report concluded that the evidence from its review of trials did not show that micro nutrient supplements have any benefits in cancer survivors, whereas high-dose supplements may even be harmful.

**Green tea polyphenol:**

Green tea polyphenols next to water, tea is the most widely consumed beverage in the world. Itwas estimated that mean consumption of tea per day is around 120 ml per person [15]. Greentea, always popular in China, Japan and India, now has gained popularity in many other countries. Black, oolong and green tea is derived from the same plant, Camellia sinensis, which is exposed to different processing methods before consumption. To obtain black tea the leaves of Camellia sinensis are fermented for a long period of time, which leads to formation of polymeric compounds, i.e.the a flavins and the arubigins. Oolong tea, often called half fermented, due to shorter fermentation time, contains polymeric as well as monomeric polyphenols. Nonfermented green tea ismade from fresh tea leaves exposed to steaming and drying (to eliminate the oxidation process by inactivating the polyphenol oxidase) and contains an abundance of polyphenols naturally occurring in Camellia sinensis [14, 15]

Green tea contains proteins(including enzymes), amino acids, carbohydrates, lipids, vitamins (B, C, E) and minerals (i.e. Ca, Mg, Cr, Fe, Zn, F,K) [13].Green tea has been found to exert a beneficial effect on the human organism and,although results

are mixed, a number of studies have revealed a correlation with a reduction ofchronic disease risk, including cancer (e.g. breast, esophageal, lung, colorectal, stomach, bladder,kidney, prostate, skin, pancreatic, ovarian) [13,16–18], cardiovascular heart disease (coronaryheart disease, hypertension, atherosclerosis) [19], Parkinson disease [20], and Alzheimer disease[21]. Green tea can also promote oral health [22, 23] and bone health [24].Consumption of this beverage is also being linked with anti-ageing processes, mainly due to itsantioxidant properties.

**Vaccines for cancer prevention:**
Several infections have been linked to increased cancer risk; however, only two vaccines against infectious agents are currently used in clinical practice for the prevention of cancer: the vaccine against the hepatitis B virus (HBV) and the vaccine against human papilloma virus (HPV)86,87.The HBV vaccine was developed in thelate 1960s. The first commercial vaccine wascirculatedin the early 1980s; genetically engineered vaccines were developed in the late 1980s and these vaccines are the ones currently used. Chronic HBVinfection is a major cause of hepatocellular carcinoma, and by preventing the infection and chronic carriagestate, the HBV vaccine provides protection againsthepato cellular carcinoma88.

HPV vaccination was introduced much later than HBV vaccination. The first HPV vaccine was approved by the FDA in the mid-2000s. Thereare more than 40 HPV types that infect human mucosal surfaces, but most infections are asymptomatic and transient. However, certain oncogenic types that persist can cause cervicalcancer and other, less common, cancers, including cancers of the anus, penis, vulva, vagina, and oropharynx. Other, non-oncologic HPV types can cause genital warts89,90. Two preventive HPV vaccines, one quadrivalent (which protects against types 16, 18, 6, and 11) and one bivalent(which protects against types 16 and 18), arecurrently used, but research for new vaccines that will protect against more oncogenic types of the virus is ongoing91. Although history of use ofthis vaccine is not long, current evidence suggests that it is both effective and safe.

**Medicinal Plants and Cancer:**
The anticancer properties of plants have been recognized for centuries. Isolation of podophyllotoxin and several other compounds (known as lignans) from the common may apple (Podophyllum peltatum) ultimately led to the development of drugs used to treat testicular and small cell lung cancer [23]. The National Cancer Institute (NCI) has screened approximately35,000 plant species for potential anticancer activities. Among them, about 3,000 plant specieshave demonstrated reproducible anticanceractivity (data available athttp://www.arsgrin.gov/duke/). Many studies have focused on the chemoprotective properties of plants such as anticarcinogenic properties of Abrus precatorius on Yoshida sarcoma in rats, fibrosarcoma in mice and ascites tumor cells [24]. Similarly, Dharetal. have examined the anticancer properties of Albizzia lebbeck on sarcoma in mice and Alstonia scholaries on benzo[a]pyrene induced forestomach carcinoma in humans [25]. Other plants that have Desaietal. Page 2Curr Drug Metab. Author manuscript; available in PMC 2014 September 11.NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript shown anticarcinoma genic properties include Anacardium occidentale in hepatoma, Asparagus racemose in human epidermoid carcinoma, Boswellia serrata in human epidermal carcinoma of then asopharynx, Erthyrina suberosa in sarcoma, Euphorbia hirta in Freund virus leukemia, Gynandropis pentaphylla in hepatoma, Nigella sativa in Lewis lung carcinoma. Peaderia foetida in human epidermoid carcinoma of thenasopharynx, Picrorrhiza kurroa in hepatic cancers, and Withania somnifera in various tumors[25]. The anticancer characteristics of a number of plants are still being actively researched andsome have shown promising results. Some plants and plant products that have shown promise asanticancer agents are discussed in detail in thefollowing sections.

**Tinospora cordifolia (Wild) Miers:**
Tinospora cordifolia, also known as guduchi in Sanskrit, giloya in Hindi and heart leaf moonseed plant in English, is a bulky, smooth, climbing deciduous shrub lacking bristles (Fig. 1). Themost commonly used part of the shrub is the stem, but roots are also known to contain importantalkaloids. This shrub is commonly found in India, Myanmar, Sri Lanka and China.According to ancient Ayurvedic lexicons, T. cordifolia is also referred to as "amrita". The term"amrita" is ascribed to this plant due to its ability to impart youthfulness, vitality and longevity.
The stem of T. cordifolia is used for general debility, dyspepsia, fever, urinary disease, andjaundice [26]. The extract of its stem is used in treating skin diseases[27].

There are certain curative properties of theroot of T.

cordifolia which allow for its use as antidotein snake bite, in combination with otherdrugs [28, 29]. T. cordifolia is well known in modern medicine for its adapto genic, immunomodulatory and anti-oxidant activities [27, 30–33]. T. cordifolia is also known to haveanti-inflammatory, anti-arthritic, anti-allergic properties [28, 34, 35]. This plant is also useful intreating skin diseases, vomiting, anemia, piles, chronic fever, and emaciation [16]. The methanolextract of Tinospora contains phenylpropanoids, norditerpene furan glycosides, diterpene furanglycosides and phytoecdysones [27].

The roots of T. cordifolia are also reported to contain other alkaloids like choline, tinosporin, columbin, isocolumbin, palmatine, tetrahydropalmatine and magnoflorine [28–30] T. cordifolia effectively kills HeLa cells in vitro, suggesting its potentialas an anticancer agent. A dose-dependent increase in cell death was observed in HeLa cellstreated with T. cordifolia extract as compared to the controls [31].

The anticancer activity of dichloromethane extract of T. cordifolia in the mice transplanted with Ehrlich ascites carcinoma has been demonstrated. T. cordifolia extract showed a dose-dependent increase in Desai etal. Page 3 CurrDrug Metab. Author manuscript; available in PMC 2014 September 11.NIH-PA Author Manuscript NIH-PA Author Manuscript NIH- PA Author Manuscript tumor-free survival with highest number of survivors observed at 50 mg/kg dose [12]. Chemical structures of some of the active constituents of T. cordifolia are given below Curcuma longa Linn Curcuma longa is popularly known as turmeric in English, haridra in Sanskrit and haldi in Hindi. The rhizome of the plant is traditionally used in cooking. The active ingredient of this plant is curcumin (diferuloylmethane), chemical structure shown below), a polyphenol derived from the rhizome of the plant [29]. Turmeric is used for both cancer prevention and treatment [30]. The anticancer potential of curcumin is associated with its ability to inhibit proliferation in a wide variety of tumor cell types. The antiproliferative properties of curcuminmay be related to its ability to down-regulate the expression of a number of genes, including NF-kappaA Report on Chemoprevention of Cancer B, Activator Protein 1 (AP-1), Epidermal growth receptor 1 (EGR- 1), cyclooxygenase 2 (COX2), lysyl oxidase (LOX), nitric oxide synthase (NOS), matrix metallopeptidase 9 (MMP9), and tumor necrosis factor (TNF) [21–23]. Moreover, turmeric reduces the expression of various chemokines, cell surface adhesion molecules, cyclins and growth factor receptors, including epidermal

growth factor receptor (EGFR), and human epidermal growth factor receptor 2 (HER2) [31]. In addition to its effects on gene expression, turmeric inhibits the activity of c-Jun N terminal kinase, protein tyrosine kinases and protein serine/threonine kinases [21] Turmeric has also been shown to inhibit tumor cell invasion and metastasis in vitro by reducing MMP-2 activity and by inhibiting HEp2 (epidermoid carcinoma cell line) cell invasion [14].A number of studies have shown that curcumin induces apoptosis, inhibits proliferation and interferes with cell cycle progression .Curcumin is suggested to exert its antiproliferative and apoptotic effects by inhibition of protein tyrosine kinase activity, inhibition of protein kinase C activity, suppression of c-myc mRNA levels and up-regulation of B-cell lymphoma 2 (Bcl-2) mRNA expression. Curcumin has been shown to cause apoptosis in vitro by bringing about a rapid decrease in mitochondrial membrane potential, release of cytochrome c, activation of caspases 3 and 9, and downregulation of antiapoptotic proteins Bcl-XL and Inhibitor of Apoptosis Protein (IAP).

## CONCLUSIONS:
Based on various studies out lined in this review report-in a broad spectrum of naturally occurring compounds with chemo preventive activity, intense consideration of the mas potential therapeutics is quite intelligible. Some of the may be already found as extract so pure substancesavailable for daily supplementation, medicinal plant and anti-inflammatory drug are becoming acommon dietary habit. However,providing a well-balanced diet containing an abundance ofbiologically active compounds should become a daily habit.

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