International Journal of Pharmacological Research
ISSN: 2277-3312 (Online)
Journal DOI: https://doi.org/10.7439/ijpr **Review Article**

Casuarinin effects on cancer chemoprevention: Progress, potential and promise

Jawaria Khan* and Muhammad Imran Qadir

Institute of Molecular Biology & Biotechnology, Bahauddin Zakariya University, Multan, Pakistan

QR Code

***Correspondence Info:**
Jawaria Khan,
Institute of Molecular Biology & Biotechnology,
Bahauddin Zakariya University, Multan, Pakistan

***Article History:**
Received: 22/08/2017
Revised: 22/09/2017
Accepted: 27/09/2017
DOI: https://doi.org/10.7439/ijpr.v7i9.4352

Abstract

Casuarinin is tannin with many medicinal properties. It has antiproliferative, antioxidant, Anti herpes simplex virus (HSV) activity and anticancer activity. Anticancer activity of Casuarinin has been proven in breast cancer, non-small lung cancer, oral tumor and leukemia by different experiments. However further work is required to establish how this tannin system can be best manipulated for therapeutic benefit. This review focuses on the use of this tannin as a medicine for cancer treatment.

Keywords: Cancer chemoprevention, tannins, polyphenols, Casuarinin.

1. Introduction

Cancer is a disease in which cells in some specific tissues escape the growth mechanism of body that controls division, survival, proliferation and death and start dividing independently. As a result of this uncontrolled proliferation, cells start accumulating inside tissue causing inflammation and cellular damages. There are more than 200 different types of cancer.

Cancer is a major public health issue even in developed countries like United States causing approximately 7 million deaths every year worldwide. More than 11 million people are diagnosed with cancer every year and it is estimated that there will be 16 million new cases per year by 2020 [1]. In the United States alone, a total of 1,399,790 new cancer cases and 564,830 deaths are expected to be reported in the year 2006 [2]. Approximately, 1 in every 2 men and 1 in every 3 American women will have some type of cancer at some point during their lifetime. Mortality rates have decreased by 1.5% per year since 1992 among men, but stabilized from 1998 through 2000 among women. Cancer death rates have continued to decrease from the three major cancer types in men (lungs, colorectal, and prostate) and from breast and colorectal cancers in women.

Uncontrolled cell division results in two types of growths called tumors. If a tumor has specific number of cells and its non-invasive it's called benign tumor and if a tumor has unlimited number of cells, still dividing and its invasive too then that type of tumor is called malignant tumor. Only malignant tumors are called cancers not benign. By definition, cancer is the uncontrolled growth and spread of malignant cells which are invasive and that may affect different tissue of the body. Most cancers are named according to the type of cell or organ in which they started. If a cancer spreads by metastasis, the new tumor will have the same name as the original (primary) tumor. Globally the most common cancers for both men and women are cancers of the lung, colon/rectum and stomach. Among men, lung, colorectal and prostate cancer are the most common cancers worldwide. In women, the most common cancers besides lung and colorectal are breast and cervical cancer.[3]

Overall survival rate for cancer patients is increasing in the past 3 decades. 5-year relative survival rate for all types of cancers has increased 20 percentage points among whites and 24 percentage points among blacks. Survival rate has increased more among patients aged 50 to 64 years than among those aged older than 65 years. Due to improvements in treatment protocols, including the discovery of targeted therapies, progress has

been most rapid for hematopoietic and lymphoid malignancies. For example, comparing patients diagnosed in the mid-1970s with those diagnosed during 2006 to 2012, the 5-year relative survival rate has increased from 41% to 71% for acute lymphocytic leukemia and from 22% to 66% for chronic myeloid leukemia[4]. Based on a recent review of clinical trial data, most patients with chronic myeloid leukemia who are treated with tyrosine kinase inhibitors, experience near normal life expectancy, particularly those diagnosed before age 65 years[5]. Although historical groupings of lymphoid malignancies are still used to track progress but World Health Organization classification system is better[6].

Although data show that survival rate for different types of cancers has increased but it's not true for lung and pancreatic cancer, for which the 5-year relative survival is currently 18% and 8%, respectively. These low rates are mainly due late diagnosis of these cancers by which time it has already spread, for which the 5-year survival is 4% and 3%, respectively. by the use of screening with low-dose computed tomography, lung cancer can be diagnosed at early stages which has been shown to reduce lung cancer mortality by up to 20% among current and former smokers with a smoking history of 30 or more pack-years[7]. However, only 2% to 4% of the 8.7 million Americans have tried a computed tomography scan of the chest to check for lung cancer in 2010[8].

Survival rate and quality of life has been majorly increased in past three decades due to availability of improved techniques and better treatments. Major treatment methods used for cancer now a day's include chemotherapy, surgery and radiation therapy [9]. In recent years immunotherapy has also been tested for the management of cancer [10]. Chemotherapy is one of the most effective treatments available for cancer. New drugs that are less invasive and therapeutic strategies are continuously being researched and developed, but the current status of chemotherapy is not satisfactory at all[11]. The effect of chemotherapy is limited and drugs used have a lot of harmful side effects. It is considered that if chemotherapy is carried out for longer periods it weakens the immunological defence system of patient's body which may result in him being in danger of more diseases and infections by making his body susceptible to them. Surgery is the least harmful method of cancer treatment but not all cancers cannot be cured by surgery[12]. Radiation therapy is another treatment option for cancer, but has a number of potentially harmful side effects including weakened resistance to other diseases and may also cause cancer itself by radiations [12]. Therefore, there is an urgent need to develop mechanism-based approaches for the management of cancer. The goals of this method should be to decrease the chances of invasive cancer and deaths from cancer at an early age by pharmacological interventions based on prevention rather than cure. Such an intervention is known as Chemoprevention[13].

Chemoprevention is a rapidly growing area of oncology which deals with the prevention of cancer using naturally occurring or synthetic agents [13]. Method depends on the identification of healthy individuals who are at a higher risk of developing cancer. In addition to inhibiting or delaying the onset of neoplasia by blocking neoplastic inception, chemoprevention plays a role in prevention of the development of invasive and metastatic properties in present neoplasms [14]. Chemoprevention of cancer is different from cancer treatment as its goal is to lower the rate of cancer. The cancer inhibitory effects of a variety of nutrients derived from plants as well as of non-nutritive plant-derived constituents (phytochemicals) have been confirmed in a variety of cell culture systems and animal tumor models[15]. Generally, cancer chemoprevention involves pharmacologic intervention with synthetic or naturally occurring compounds to prevent, inhibit or reverse carcinogenesis or prevent the development of invasive cancer [16]. Researches show that diet also affects this phenomenon. diets with abundance of fruits and vegetables and other plant-derived agents can protect against different diseases including epithelial cancers [17]. Epidemiological studies, including a number of case-control and cohort studies, have provided data that overwhelmingly support that people with large intake of fruits and vegetables have less risk of cancer[18]. These nutritional practices can be effective in cancer prevention. Many components found in fruits and vegetables may contribute to their effectiveness in reducing the risk of cancer e.g. micronutrients, dietary fiber and various polyphenolic agents [19].

An estimated 600,920 Americans will die from cancer in 2017, corresponding to about 1,650 deaths per day The most common causes of cancer death are cancers of the lung and bronchus, colorectum, and prostate in men and lung and bronchus, breast, and colorectum in women These 4 cancers account for 46% of all cancer deaths, with more than one-quarter (26%) due to lung cancer.[20]

2. Casuarinin- natural plant tannin:

Among plants secondary products, phenolic compounds are the most widely distributed. They are found in many plants used as foods and feeds. Phenolic compounds have the ability to serve as antioxidants[21], having benefits of ingesting plant phenolics. The ability of small phenolics including flavonoids and phenolic acids to act as antioxidants has been extensively investigated[22], but the high molecular weight phenolics known as tannins

have been largely neglected. Tannins are found in grains and legumes [23],[24], herbs [25], and in beverages derived from plants. The average human consumption of tannins in U.S. is estimated to be at least 1 g/day [26], so they could be a significant source of dietary antioxidants.

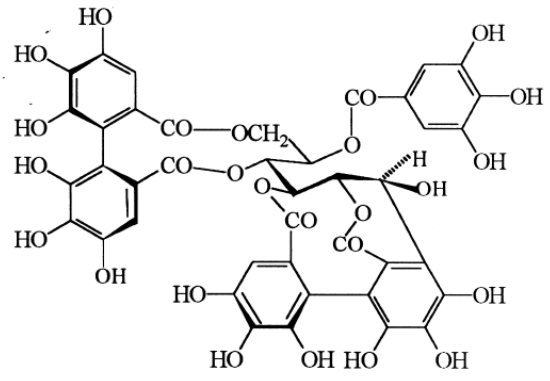
Tannins are naturally occurring phenolic compounds which have protein precipitates. In general, tannins are high molecular weight (M_r > 500) and have many phenolic groups[27]. There is significant chemical heterogeneity among the tannins, as illustrated by the representative compounds. There are three types of tannins, the condensed tannins (proanthocyanidins), the hydrolyzable tannins, and the phlorotannins. Casuarinin is tannin extracted from bark of plant *Terminalia arjuna*. *Terminalia arjuna* is a plant with vast medicinal uses.

2.1 Chemical structure and properties of Casuarinin:

Casuarinin is a tanin extracted from bark of plant *Terminalia arjuna*. *Terminalia arjuna* is a plant having vast medicinal uses. It is being used for more than 100 years for treatment of different diseases. The tannins extracted from this plant have anticancer and anti herpes simplex virus effect. The bark of T. arjuna is rich in polyphenols (60–70%) including flavones, flavanols and tannins. The high content of tannins and polyphenols are mainly responsible for anticancer activity. Casuarinin is an ellagitannin. It is also found in the pericarp of pomegranates (*Punica granatum*) and in Casuarina and Stachyurus species and in *Alnus sieboldiana*. It is an isomer of casuarictin. It is a highly active carbonic anhydrase inhibitor.

2.2 Biosynthesis

In some plants including oak and chestnut, the ellagitannins are formed from 1,2,3,4,6-pentagalloyl-glucose and further elaborated via oxidative dehydrogenation (tellimagrandin II and casuarictin formation). After conversion of casuarictin to pedunculagin, the pyranose ring of the glucose opens and the family of compounds including casuariin, Casuarinin, castalagin, and castlin, vescalagin and vescalin forms.



Casuarinin

Molecular formula: $C_{41}H_{28}O_{26}$

2.3 Chemical and Physical Properties

2.3.1 Computed Properties

Casuarinin's covalently bonded unit is 1. Its undefined bond stereocentre count is 0 and defined bond stereocentre count is also 0. Undefined atom stereocentre count and defined atom stereocentre count is also 5. Isotope atom count is 0. Complexity of Casuarinin molecule is 1880 with 0 formal charges. Its heavy atom count is 67 with tropical polar surface area of 455 A^2. Its Monoisotopic mass and exact mass is 936.087 g/mol. Rotatable bond count is 4 and hydrogen bond acceptor count is 26 and hydrogen bond donor count is 16. Molecular weight of Casuarinin is 936.649 g/mol. It's XLogP3=1.2

2.4 Casuarinin and cancer

Cancer is a disease which causes the most amounts of deaths in men and women, claiming over 6 million lives each year in the world. To date, many anticancer drugs have been developed and applied by clinical doctors. Recently, resistance to anticancer drugs was discovered. Therefore, the research and development of new and safe drugs have become necessary by the pharmaceutical industry. In phytochemicals studies of natural products, the pharmacological properties of polyphenols have been found to include various biological activities, such as host-mediated antitumor activity, antioxidant, anti-inflammatory, inhibition of lipid peroxidation and antiviral activities. In a previous report on serial studies of antitumor natural products in our institute, macrocyclic hydrolysable tannins were found to be potential antitumor drugs. The tannin fraction isolated from T. arjuna has antimutagenic effect against NPD in TA98, Sodium azide in TA100 and 2AF (S-9 dependent) a promutagen in both TA98 and TA100 tester strains of Salmonella typhimurium tested on Ames assay. The fraction inhibited the mutagenicity of 2AF very significantly in both strains while the revertant colonies induced by NPD and sodium azides were reduced moderately [28].

2.4.1 Anticancer activity in breast cancer

Casuarinin, a hydrolysable tannin isolated from the bark of T. arjuna possesses antiproliferative activity in human breast adenocarcinoma MCF-7 cells. Casuarinin inhibited the proliferation of MCF-7 by blocking cell cycle progression in the G0/G1 phase and inducing apophasis. Enzyme linked immunosorbent assay (ELISA) showed that Casuarinin increases the expression of p21/WAF1 concomitantly as the MCF-7 cells underwent G0/G1 arrest. The enhancement in Fas/APO-1 and its two forms of ligands, membrane bound Fas ligands and soluble Fas ligands might be responsible for the apoptotic effect induced by Casuarinin.

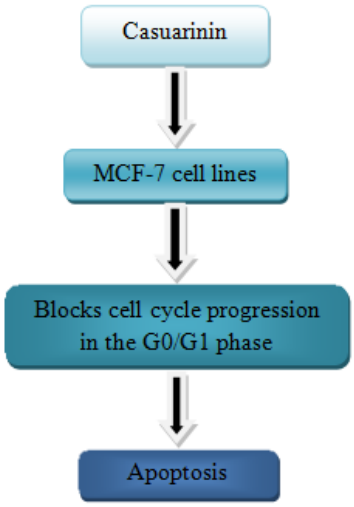


Figure 1: Casuarinin mechanism of action on MCF-7 cell lines

Ito *et al* [29] in his study to find natural carcinogens among various screening tests for the discovery of such active substances he also performed convenient primary in vitro assay, estimating the inhibitory effect on Epstein Barr virus early antigen (EBV-EA) activation induced by a well known tumor-promoter, 12- O-tetradecanoylphorbol-13-acetate (TPA). It was found that Casuarinin exhibited remarkable inhibitory effects on EBV-EA activation. Shalini *et al* [30] also studied T.arjuna plant and used its extract against MCF-7 cell lines by converting them into phytosomes for improved tropical and oral absorption and found that compounds like Casuarinin are active antiproliferative agents against breast cancer.

2.4.2 Anticancer activity in lung cancer

Casuarinin, a hydrolyzable tannin isolated from the bark of *Terminalia arjuna* Linn. (Combretaceae) inhibits human non-small cell lung cancer A549 cells by blocking cell cycle progression in the G0/G1 phase and inducing apoptosis. Enzyme-linked immunosorbent assay showed that the G0/G1 phase arrest is due to p53-dependent induction of p21/WAF1. An enhancement in Fas/APO-1 and the two forms of Fas ligand (FasL), membrane-bound FasL and soluble FasL, might be responsible for the apoptotic effect induced by casuarinin. Our study reports here for the first time that the induction of p53 and the activity of the Fas/FasL apoptotic system may participate in the antiproliferative activity of casuarinin in A549 cells as shown in Figure 2. This study suggests that the induction of p53 and activity of the Fas/FasL apoptotic system may take part in the antiproliferative activity of Casuarinin in A549 cells and its clearly demonstrated that Casuarinin may be a promising chemopreventive agent to treat lung cancer.

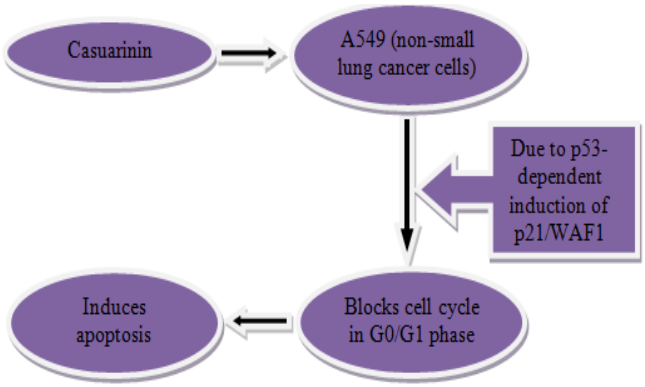


Figure 2: Casuarinin mechanism of action on non-small lung cancer cells

2.4.3 Casuarinin effect on human leukemia cells:

Casuarinin was examined for its antiproliferative effects on human promyelocytic leukemia (HL-60) and liver adenocarcinoma (SK-HEP-1). The HL-60 cells were particularly susceptible to Casuarinin and the IC_{50} were 10.8 and 12.5 mM, respectively. In addition, normal Chang liver cells were also treated with these compounds. Cytotoxic activities of these compounds were substantially lower towards normal Chang liver cells and human lymphocytes; and both compounds exerted at least 3-fold higher antiproliferative activity toward the cancer cell line than toward the normal cell line. After HL-60 cells were treated with Casuarinin for 48 h, the microscopic observations demonstrated the apoptotic characters. The preponderance of apoptotic nuclei was most likely blocked at the G2/M interface, which is in agreement with the DNA fluorescence flow cytometry pro®les. It was also noted DNA fragment ladder formation, a characteristic gel electrophoretic band pattern associated with apoptosis. The Cytotoxic mechanism of Casuarinin might induce apoptosis in HL-60 cells. So it suggested that Casuarinin could be a candidate for developing low-toxicity antitumor agents.

2.4.4 Casuarinin activity against human oral tumor:

Sakagami *et al*[31] studied cytotoxic activity of hydrolyzable tannins against human oral tumor cell lines. It was found that hydrolysable tannins showed higher Cytotoxic activities against human oral squamous cell carcinoma and slivary glandtumor cell lines than against normal human gingival fibroblasts. Casuarinin's cytotoxic activity was also tested as a monomeric hydrolysable tannin. The cytotoxic activity of dimeric hydrolysable tannins against the human oral squamous cell lines HSC-2 was generally higher than those of monomeric hydrolysable tannins like Casuarinin. The results showed that among the monomers Casuarinin showed higher cytotoxic activity than agalloylglucose suggesting the importance of HHDP group.

These observations suggested that antitumor activity of Casuarinin against human oral tumor might be explained by its apoptosis inducing ability.

2.5 Anti herpes simplex virus (HSV) activity of Casuarinin

Casuarinin also shows antiviral activity on herpes simplex type 2 viruses in vitro. IC50 value of Casuarinin in Sodium 30-[1-(phenylamino-carbonyl)-3,4-tetrazolium]-bis (4-methoxy-6 nitro)benzene sulfonic acid (XTT) and plaque reduction assays was found to be 3.6 ± 0.9 and 1.5 ± 1.0 lm. The selectivity index (SI: Ratio of CC50 to IC50) was 25 and 59 for XTT and plaque reduction assay. Casuarinin continued to exhibit antiviral activity even when added 12 h after infection. Casuarinin was also shown to prevent the attachment of HSV-2 to cells. It also exhibited an actively inhibited viral penetration. It was virucidal at a concentration of 25 lm, reducing viral titers up to 100,000-fold .

2.6 Antioxidant effect

Casuarinin shows antioxidant properties in different extracellular experiments. Chen *et al* studied cultured Madin Darby canine kidney (MDCK) cells against H_2O_2 mediated oxidative stress and also compared it with Trolox (hydro soluble Vitamin E analog). Casuarinin attenuates H_2O_2 induced oxidative stress, decreased DNA oxidative damage and prevented the depletion of intracellular Glutathione (GSH) in MDCK cells which is due to reduction in intracellular H_2O_2 levels. It suggests that Casuarinin can be used as potent antioxidant to protect tissues against oxidative damages related to increased H_2O_2 production.

2.7 Casuarinin against inflammatory skin diseases

Kwon *et al*[32] studied Casuarinin activity against inflammatory skin diseases and found that Casuarinin suppressed TNF-α/IFN-γ-induced expression of TARC and MDC mRNA and protein in HaCaT cells. Casuarinin significantly inhibited TNF-α/IFN-γ-induced activation of NF-κB, STAT1, and p38 MAPK. Furthermore, we observed that p38 MAPK contributes to inhibition of TNF-α/IFN-γ-induced TARC and MDC production by blocking NF-κB and STAT1 activation in HaCaT cells. Taken together, these results suggest that Casuarinin may exert anti-inflammatory responses by suppressing TNF-α/IFN-γ-induced expression of TARC and MDC via blockage of p38 MAPK activation and subsequent activation of NF-κB and STAT1. We propose that it could therefore be used as a therapeutic agent against inflammatory skin diseases.

3. Conclusions

There is considerable evidence that plant tannins and polyphenols may provide important health benefits. The development of diet derived chemo preventive strategies requires a thoughtful and structured approach. The most rationale approach for agent development is to test new agents on specific molecular and cellular targets in an appropriate animal model to determine the efficacy and bioavailability of the agents before initiation of clinical trials. Much information can be garnered from epidemiological studies, which can provide valuable suggestions for the development of chemo preventive agents. However, it is critically important to confirm the resultant hypothesis with experimental data, in cell culture and appropriate animal models before initiation of clinical trials. Casuarinin is a common non-mutagenic plant tannins abundantly present in fruits and plants that has shown remarkable promise as a potent chemo preventive agent. Many mechanisms of action have been identified for Casuarinin-mediated cancer prevention and therapy, including estrogenic/anti-estrogenic activity, anti-proliferative activity, induction of cell-cycle arrest and apoptosis, prevention of oxidation, induction of detoxification enzymes, regulation of the host immune system, and changes in cellular signaling.

Recent progress has been made in testing the efficacy of Casuarinin in pre-clinical models of cancer. Continued efforts are needed, focusing on additional pre-clinical studies of various animal models of cancer that closely simulate human cancers, which may be subsequently validated in clinical trials. A large body of accumulated evidence suggests that Casuarinin possesses enormous potential for development as a promising cancer chemo preventive agent in the near future.

Conflict of interest: There is no conflict of interest between the authors of this study.

References

[1]. Health WHOR, Diseases WHOC, Promotion H. Comprehensive cervical cancer control: a guide to essential practice: World Health Organization; 2006.

[2]. Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, *et al*. Cancer statistics, 2005. *CA: A Cancer Journal for Clinicians*. 2005; 55(1):10-30.

[3]. Patel D, Shukla S, Gupta S. Apigenin and cancer chemoprevention: progress, potential and promise (review). *International Journal of Oncology*. 2007; 30(1): 233-46.

[4]. Howlader N, Noone A-M, Krapcho M, Garshell J, Miller D, Altekruse S, *et al*. SEER Cancer Statistics Review, 1975-2010, National Cancer Institute. Bethesda, MD. 2013.

[5]. Sasaki K, Strom SS, O'Brien S, Jabbour E, Ravandi F, Konopleva M, *et al*. Relative survival in patients with chronic-phase chronic myeloid leukaemia in the tyrosine-kinase inhibitor era: analysis of patient data

from six prospective clinical trials. *The Lancet Haematology*. 2015; 2(5):e186-e93.

[6]. Teras LR, DeSantis CE, Cerhan JR, Morton LM, Jemal A, Flowers CR. 2016 US lymphoid malignancy statistics by World Health Organization subtypes. *CA: A Cancer Journal for Clinicians*. 2016; 66(6):443-59.

[7]. Team NLSTR. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011; 2011(365):395-409.

[8]. Rose VPD, White MC, Klabunde C, Nadel M, Richards TB, McNeel TS, *et al*. Use of lung cancer screening tests in the United States: results from the 2010 National Health Interview Survey. Cancer Epidemiology and Prevention Biomarkers. 2012: cebp. 0343.2012.

[9]. Jhanwar YS, Divgi C. Current status of therapy of solid tumors. *Journal of Nuclear Medicine*. 2005; 46(1 suppl):141S-50S.

[10]. Antonia S, Mulé JJ, Weber JS. Current developments of immunotherapy in the clinic. *Current opinion in immunology*. 2004; 16(2):130-6.

[11]. Caponigro F, Basile M, de Rosa V, Normanno N. New drugs in cancer therapy, National Tumor Institute, Naples, 17–18 June 2004. LWW; 2005.

[12]. Miner TJ. Palliative surgery for advanced cancer: lessons learned in patient selection and outcome assessment. *American Journal of Clinical Oncology*. 2005; 28(4):411-4.

[13]. Smith JJ, Tully P, Padberg RM, editors. Chemoprevention: a primary cancer prevention strategy. Seminars in oncology nursing; 2005: Elsevier.

[14]. Sporn MB, Liby KT. Cancer chemoprevention: scientific promise, clinical uncertainty. *Nature Clinical Practice Oncology*. 2005; 2(10):518-25.

[15]. Shukla S, Gupta S. Dietary agents in the chemoprevention of prostate cancer. *Nutrition and cancer*. 2005; 53(1):18-32.

[16]. Kim ES, Hong WK. An apple a day… does it really keep the doctor away? The current state of cancer chemoprevention. Oxford University Press; 2005.

[17]. Birt DF, Hendrich S, Wang W. Dietary agents in cancer prevention: flavonoids and isoflavonoids. *Pharmacology & Therapeutics.* 2001; 90(2):157-77.

[18]. Genkinger JM, Platz EA, Hoffman SC, Comstock GW, Helzlsouer KJ. Fruit, vegetable, and antioxidant intake and all-cause, cancer, and cardiovascular disease mortality in a community-dwelling population in Washington County, Maryland. *American Journal of Epidemiology*. 2004; 160(12):1223-33.

[19]. Crowell JA. The chemopreventive agent development research program in the Division of Cancer Prevention of the US National Cancer Institute: an overview. European Journal of Cancer. 2005; 41(13):1889-910.

[20]. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA: A Cancer Journal for Clinicians*. 2017; 67(1):7-30.

[21]. Decker EA. The role of phenolics, conjugated linoleic acid, carnosine, and pyrroloquinoline quinone as nonessential dietary antioxidants. *Nutrition Reviews.* 1995; 53(3):49-58.

[22]. Rice-Evans C, Miller NJ. Total antioxidant status in plasma and body fluids. *Methods in enzymology.* 1994; 234:279-93.

[23]. Kadam S, Salunkhe D, Chavan J. Dietary tannins: consequences and remedies. Boca Raton: CRC Press; 1990.

[24]. Foo LY, Porter LJ. The structure of tannins of some edible fruits. *Journal of the Science of Food and Agriculture*. 1981; 32(7):711-6.

[25]. Haslam E, Lilley T, Cai Y, Martin R, Mangnolato D. Traditional herbal medicines-the role of polyphenols. *Planta Medica.* 1989; 55(01):1-8.

[26]. Pierpoint W. Flavonoids in human food and animal feedstuffs: amounts and consequences. Flavonoids in biology and medicine III *Current issues in flavonoids research*. 1990.

[27]. Hagerman AE, Zhao Y, Johnson S. Methods for determination of condensed and hydrolyzable tannins. ACS Publications; 1997.

[28]. Kaur C, Kapoor HC. Antioxidants in fruits and vegetables–the millennium's health. *International Journal of Food Science & Technology*. 2001; 36(7):703-25.

[29]. Ito H, Miyake M, Nishitani E, Mori K, Hatano T, Okuda T, *et al*. Anti-tumor promoting activity of polyphenols from *Cowania mexicana* and *Coleogyne ramosissima*. *Cancer letters.* 1999; 143(1):5-13.

[30]. Shalini S, Kumar RR, Birendra S. *Terminalia Arjuna* bark on Human Breast Cancer Cell Lines (MCF-7). *Int J Drug Dev & Res.* 2015; 7(1):0975-9344.

[31]. Sakagami H, Jiang Y, Kusama K, Atsumi T, Ueha T, Toguchi M, *et al*. Cytotoxic activity of hydrolyzable tannins against human oral tumor cell lines—a possible mechanism. *Phytomedicine*. 2000; 7(1):39-47.

[32]. Kwon D-J, Bae Y-S, Ju SM, Goh AR, Youn GS, Choi SY, *et al*. Casuarinin suppresses TARC/CCL17 and MDC/CCL22 production via blockade of NF-κB and STAT1 activation in HaCaT cells. *Biochemical and biophysical research communications.* 2012; 417(4):1254-9.