**Plant based polyphenols in chemo-prevention and chemo-therapy of cancer**

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**ABSTRACT**

Cancer is the second leading cause of death worldwide. The presently available state-of-the-art chemotherapeutic drugs although have improved the mortality rate of the cancer patients but these drugs are associated with several toxic side effects. The toxic side effects of these anti-cancer drugs along with the high cost associated with the use of those drugs have thus necessitated the development of less toxic as well as cost effective chemotherapeutic as well as chemopreventive strategies to combat the deadly disease. Epidemiological studies suggest phytochemicals, the bioactive molecules found in fruits, vegetables and grains, are able to reduce the risk of various chronic illnesses and have thus received increased attention as candidate chemo-therapeutic as well as chemopreventive anti-cancer agent. Much of the chemopreventive efficacies of these phytochemicals and their derivatives have been attributed to polyphenols and have been proved in experimental models of cancer models. The therapeutic potential of these polyphenols either as single agent or in combination with other therapy have been reported to modulate the progression of cancer. Although these polyphenols have been reported to modulate carcinogens, reduce inflammation, induce cell cycle arrest and apoptosis in mammalian cancer models; the precise cellular and molecular mechanism by which these polyphenols exert their anti-cancer efficacy still needs to be investigated. Despite promising preliminary experimental results, the development of these polyphenols in prevention of progression of cancer and treatment of the same requires extensive research to develop them into potential candidate chemotherapeutic drugs. To bring these phytochemicals from bench to bedside, extensive studies regarding interaction of these polyphenols with cancer cells, their pharmacokinetics, ideal dosages and their long-term safety are needed.

**INTRODUCTION**

Cancer, a major public health concern worldwide and is only second to cardiovascular diseases in terms of number of deaths in United States (Siegel *et al*., 2022). The development as well as the progression of this genetic disease cancer is a multi-step process (Renan *et al*., 1993). The genetically altered cells usually gain replicative immortality as they can evade growth suppressing signals and become self-sufficient to growth signals, and thus can ultimately evade apoptosis (Hanahan *et al*., 2000). These genetically altered cells usually exhibit angiogenesis, thereby, activating invasion to destroy adjacent cells and metastasize (Hanahan *et al*., 200 Hanahan et. al 2011). Apart from these six hallmarks, genetically altered cancer cells have known to develop genomic instability that generates genetic diversity and ultimately tumor promoting inflammation (Hanahan et. al, 2011). Presently, the cancer patients are treated by surgery, radiotherapy and systemic therapy that includes chemotherapy, targeted biological therapy, hormonal therapy etc or a combination of all these according to WHO guidelines. The appropriate use of a chemotherapeutic drug depends mainly on the knowledge of its mechanism of action at the molecular, cellular as well as tissue and/or organ level and successful chemotherapy can only be achieved by targeting a wide array of cellular as well molecular processes. The presently used chemotherapeutic drugs target a combination of diverse mechanisms involving molecular association with carcinogen, exhibit anti-inflammatory, anti-oxidant effect, induction of cell cycle arrest, and/or apoptosis, induction of cellular differentiation, immunomodulatory effect, may be anti-angiogenic etc. (Kakizoe, 2003). Few commonly used chemotherapeutic agents function as DNA intercalators (cisplatin, doxorubicin), anti-metabolites (methotrexate), inhibits tubulin by binding to it (taxanes), hormones and molecular targeting agents (Nussbaumer *et al*., 2011). However, use of these chemotherapeutic agents is associated with several side effects such as gastrointestinal lesions, cardiac problems, neurological problems, suppression of immune system, hair loss and last but not the least drug resistance (Nussbaumer *et al*., 2011, Monsuez *et al*., 2010; Dropcho, 2011). These toxic side-effects along with the high cost associated with present day chemotherapeutic drugs, therefore, have necessitated the development of cost-effective anti-cancer chemopreventive and/or chemotherapeutic drugs.

Epidemiological evidence suggests that consumption of diet rich in vegetables and fruits reduces the risk of occurrence of a large number of cancers such as lung, stomach, colon, prostate and breast cancer (Block *et al*., 1992; Reddy *et al*., 2003; Benetou *et al*., 2008; Steinmetz *et al*., 1996). Hence, development of phytochemicals, i.e., the active ingredients of natural fruits and vegetables to prevent, suppress and reverse the initial phase of carcinogenesis is the need of the hour. Increased understanding of the biology of cancer, cancer markers have led to an increase in chemopreventive research (Ranjan *et al*, 2019). Moreover, understanding cancer at the molecular level helps researchers with the development of chemopreventive and/or chemotherapeutic drug development and hence, the active dietary ingredients are being tested regularly for their anti-cancer efficacy.

**PHTOCHEMICALS**

 Medicinal plants have been known to have protective or disease-preventive properties and have been traditionally used world-wide since ages. Although, herbal medicine was being used, it was not until 19th century that scientists all around the globe started searching for the active ingredient of such herbal medicine. Most studies reported the presence of bioactive compounds in fruits, vegetables and grains and were identified as phytochemicals (Wattenburg, 1992; Stavric, 1994). Epidemiological studies revealed a relationship between consumption of few of these phytochemicals with lower risk cardio-vascular disease as well as cancer. Although, more than thousand phytochemicals are known till date, only a few have received attention and are being developed as potential chemo-preventive and therapeutic anti-cancer drugs. (Mehta *et al*., 2010, Holban *et al*., 2018). There are three major classes of phytochemicals: 1. polyphenols 2. terpenoids and 3. thiols (Waladkhani *et al*.,1998, Thomas *et al*., 2015).

Polyphenols, the naturally occurring phenols are structurally diverse secondary metabolites found in various fruits and vegetables. While some polyphenols are found in a particular food (isoflavones in soya, flavanones in citrus fruits), others like quercetin are found in various plant products such as fruits, vegetables, tea etc. There are more than 500 naturally occurring polyphenols which can further be classified into four categories: 1. flavonoids, 2. phenolic acid, 3. Stilbenes and 4. Lignans depending on their chemical structure (**TABLE 1).**

**TABLE 1. Different categories of polyphenols and their sources.**

|  |  |  |  |
| --- | --- | --- | --- |
| **POLYPHENOL CLASS** | **POLYPHENOL SUB CLASS**  | **NAME OF****POLYPHENOL** | **FOOD SOURCE** |
| Flavanoids |  Flavanol  | Quercitin, Kaemferol | Red grapes, tea, apple, brocolli |
|  | Flavones | Apigenin, Luteolin | Celery, Capsicum, Herbs |
|  | Isoflavones | Genistin | Soyabean, alfaalfa |
|  | Flavanone | Hesperitin | Citrus fruits |
|  | Anthocyanidins |  | Red grapes and berries |
|  | Flavan-3-ols (tannins) | Catechin, Epicatechins, Gallate  | Tea, Chocolate, Grapes |
|  | Hydrbenzoic acid | Gallic acid, Ellagic acid | Grapeseed, Pomegranate, Tea |
| Phenolic Acids | Dihydrochalcones | Aspalathin | Apples |
| Non-flavanoid polyphenol | Curcuminoids | Curcumin | Turmeric |
|  | Lignans | Cinnamic acid, Resverartol | Grapes, Wine, Blueberries |
|  | Stilbenes | Sesamine, Enterolactone | Sesameseeds, Flax seeds, Grains |

Polyphenols have been reported to be associated with numerous health benefits since ages which may be related to their antioxidant property (Eichholzer *et. al.,* 2014) There is also evidence that polyphenols are associated with lowering the inflammation in animals (2014). The anti-oxidant and anti-inflammatory property of polyphenols play an important therapeutic role in certain diseases disease like cancer. A huge number of polyphenols have been studied successfully against a wide variety of cancer types to develop them as chemo preventive / chemotherapeutic agent (**TABLE 2**).

**TABLE 2: Some important polyphenols and their role as anti-cancer agent.**

|  |  |  |
| --- | --- | --- |
| **NAME OF POLYPHENOL** | **TYPE OF CANCER IT’S REPORTED TO CURE** |  **REFERENCES** |
| Quercitin | Ovarian | Vafadar *et. al*., 2020 |
| Kaemferol | Lung, kidney, prostate, stomach | Imran *et. al*., 2019 |
| Apigenin | Breast, lung, liver, skin, blood, colon, prostate, pancreatic, cervical, oral, and stomach | Imran *et al*., 2020 |
| Luteolin | Lung, breast,[glioblastoma](https://www.sciencedirect.com/topics/medicine-and-dentistry/glioblastoma), [prostate, colon and pancreatic](https://www.sciencedirect.com/topics/medicine-and-dentistry/prostate-cancer)  | Imran *et al*., 2019 |
| Genistin | Colon | Tuli *et al*., 2019 |
| Hesperitin | Lung and breast | Wolfram *et al*., 2016; Palit *et al*., 2015 |
| Catechin | Breast, liver, prostate, colorectal, gastric, lung | Cheng *et al*., 2020 |
| Epicatechins | Pancreas | Elbaz *et al*., 2014 |
| Gallic acid | Leukemia | Sourani *et al*., 2016 |
| Ellagic acid | Breast, Colon, Prostate | Ceci *et al*., 2018 |
| Aspalathin | Prostate | Huang *et al*., 2020 |
| Curcumin | Breast, prostate, cervical, gastric | Giordano *et al*., 2019 |
| Cinnamic acid | Colon, cervical | Anantharaju *et al*., 2017 |
| Resveratrol | Breast, prostate, skin, lungs, pancreas | Ko *et al*., 2017 |
| Enterolactone | Breast | Mali *et al*., 2017 |

**ANTI-CANCER EFFECTS OF POLYPHENOLS**

Evidence suggest that initiation and progression of cancer is primarily due to either prolonged exposure to genotoxic carcinogens, inflammation, disruption of cell cycle or evasion of apoptosis or all of these together. Experimental evidence suggest that anti-cancer potential of these polyphenols may be either chemo-preventive or chemotherapeutic.

**Chemo-preventive potential of polyophenols:**

Prolonged exposure to genotoxic carcinogens has been linked to formation of DNA adducts resulting in genetic mutation beyond repair thereby inducing cancer. The detoxification or inactivation of carcinogen and excretion of those products is of utmost importance for chemoprevention. The process of inactivation of procarcinogen or detoxification of carcinogen is primarily achieved by phase I (cytochrome P450) and phase II metabolic enzymes in the gut, liver and other tissues (Nelson *et al*., 1993). Polyphenols like EGCG (epigallocatechin gallate), flavonoid from green tea have been reported to induce phase II enzymes and help in chemo-prevention. The chemo-preventive potential of these many bio-active compounds have also been known to be either directly via neutralization of free radical or by induction of anti-oxidants like glutathione, superoxide dismutase (SOD) and or catalase (Kim *et al*., 2003). Inflammation is considered as one of the major risk factors for development and progression of certain cancer (Balkwill *et al.*, 2001). Experimental evidence suggests that polyphenols like quercitin, curcumin etc. exert their chemo-preventive effect by inhibiting NF-κB signal cascade thereby reducing inflammation (Thomas *et al*., 2015).

**Chemo-therapeutic potential of polyphenols:**

1. **Induction of cell cycle arrest and apoptosis**

The disruption of cellular cycle plays a pivotal role in initiation and progression of cancer (Hanahan); therefore, chemotherapeutic potential of any anti-cancer drug is dependent on its ability to induce cell cycle arrest and apoptosis. Epidemiological studies have suggested the efficacy of plant based polyphenols in inducing cell cycle arrest and apoptosis in certain mammalian cell lines (Sporn *et al*., 2002; Surh, 2003; [D'Incalci](http://www.ncbi.nlm.nih.gov/pubmed?term=D%27Incalci%20M%5BAuthor%5D&cauthor=true&cauthor_uid=16257798) *et al*., 2005). Polyphenols such as genistein have been reported to enhance p53 activity and thereby induce a G0-G1 arrest and inhibit cellular proliferation at (Katdare *et al*., 1998). Many phytochemicals inhibit the expression of cyclin D1 and E along with CDK4/6 and CDK2 activities thereby arresting cellular proliferation (Ahmad *et al*., 1997; Zi *et al*., 1998; Agarwal *et al*., 2000). Experimental data suggests that EGCG can modulate E2F or E2F thereby inducing cell cycle arrest the at G1 phase (Tyagi *et al*., 2002). Curcumin from turmeric have also been reported to modulate cellular proliferation by arresting cancer cells at G2-M checkpoint (Knowlees *et al*., 2001; Moragoda *et al*., 2001; Wang *et al*., 2012). Cancer cells are known to evade apoptosis by either overexpression of anti-apoptotic proteins and/or by downregulation of the pro-apoptotic proteins. Therefore, a key strategy to inhibit the progression of carcinogenesis and to remove genetically altered cells is by inducing apoptosis. Studies suggest that polyphenols can regulate the key components of both intrinsic as well as extrinsic apoptotic pathways. Reseveratrol from grapes and EGCG from green tea have been reported to augment the expression of Fas receptor, CD-95 signaling and induce extrinsic apoptotic pathway in prostate carcinoma cells (Clement *et al*., 1998; Brusselmans *et al*., 2003). EGCG and curcumin from turmeric has also been reported to upregulate Bax via p53 and thereby induce intrinsic apoptotic pathway in human prostate and breast cancer (Choudhuri *et al*., 2002; Hastak *et al*., 2005; Mori *et al*., 2006). Moreover, experimental studies suggest pre-treatment with curcumin from turmeric, EGCG, resveratrol, luteolin etc to sensitize cancer cells to apoptosis (Gao *et al*., 2005; Fulda *et al*., 2004; Nishikawa *et al*., 2005; Horinaka *et al*., 2005).

1. **Inhibition of angiogenesis and metastasis**

In the latter stage of disease progression, cancer cells almost always develop new blood vessels (angiogenesis) and metastasize to distant sites of the body and develop secondary tumor. Epigallocatechin has also been reported to inhibit angiogenesis in addition to apoptosis induction (Yang *et al*., 2002). Green tea polyphenols have anti-proliferative as well as anti-metastatic potential both in *in vivo* and *in vitro* mouse mammary carcinoma cells (Balinga *et al*., 2005). Green tea extract in combination with tamoxifen (a potent anti-cancer drug) has been reported to induce apoptosis in tumor tissue in mice with breast cancer xenografts (Sartippour *et al*., 2006).

1. **Modulation of signaling cascades**

Many of these polyphenols like hesperetin, a flavanone from citrus fruits have been shown to modulate the signalling cascades involved in growth of breast cancer cells (Palit *et al*., 2015) and ellagic acid, a polyphenol from pomegranate has been reported to inhibit metastasis of breast cancer cells (Lansky *et al.,* 2005). Epigallocatechin regulates cellular proliferation and induces apoptosis in prostate cancer cell by epigenetic modification (Park *et al*., 2015). Some phytochemicals catechins from green tea are able to exhibit anti-proferative effect in neuroblastoma, breast and prostate cancer by modulating the PI3K/Akt/ mTOR signaling pathway (Tsai et al, Srivastav et al, 2019). Phytoestrogens such as isoflavone from soyabean is known to weakly bind to the estrogen receptor thereby preventing the binding of estrogen reducing cellular proliferation (Thomas *et al*., 2015).

Chemopreventive as well as therapeutic potential of many of these polyphenols and their derivatives have been proved in experimental models of colon, prostate, lung, skin, pancreas and mammary gland cancer (**TABLE 2**). Polyphenols like other biomolecules interact with various cellular components and few of them successfully inhibit the development and progression of cancer; few of them even leading to reversion of cancer (**FIGURE 1**). The precise molecular mechanisms by which these polyphenols exert their anti-cancer effects still needs to be explored as their mode of action is wide-range and complex. (Thomas *et al*., 2015).



**FIGURE 1.** Schematic representation of probable interactions occurring between polyphenols with various events associated with development and progression of cancer.

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**FUTURE PROSPECTS**

Inspite of all the epidemiological as well as pre-clinical experimental evidence of the anti-cancer efficacies of these polyphenols, cancer chemoprevention using them has not been adopted in clinical practice. One of the major drawbacks in this field of phytochemical based cancer therapeutic research is the lack of knowledge of the optimum doses of many of these polyphenols. Many of these polyphenols are water insoluble and have poor bioavailability. Another reason for their poor translational efficacy may be due to their poor penetration and rapid uptake by normal tissues and therefore are difficult to develop as current cancer therapeutics. All these limitations can be overcome by nanoparticle-based delivery of these polyphenols thereby, enhancing their aqueous solubility, bioavailability and specific targeting of the cancerous tissue.

**CONCLUSION**

 The toxic side effects of the presently available chemotherapeutic agents as well as acquired resistance to them has necessitated the development of effective as well as less toxic therapeutic strategies to combat this deadly disease. Dietary phytochemicals are therefore being developed as potential chemo-preventive and therapeutic agents due to their multifarious roles in preventing the progression of the disease. Based on our literature survey we have come to know that only a few phytochemicals especially polyphenols have the potential to be candidate anti-cancer agents. The anti-proliferative effect of the polyphenols may be due to their ability to arrest cell cycle progression as well as induction of apoptosis in a wide variety of cancer models. The therapeutic potential of many these polyphenols is also due to their anti-angiogenic and anti-metastatic property in *in vivo* models of several cancers. Despite promising preliminary *in vitro* as well as *in vivo* experimental evidence of their therapeutic potential, poor bioavailability and low potency of these polyphenols pose a limitation. The development of these polyphenols as potential candidate therapeutic agent therefore requires extensive research regarding interaction of these bioactive compounds with cancer cells, pharmacokinetics, ideal dosages and their long term safety. The chemopreventive and therapeutic potential of these polyphenols may result either from their use in monotherapy or as adjuvant chemotherapy. These compounds being less toxic and easily available, using them in adjuvant chemotherapy may bring down the optimal dose of the presently used toxic chemotherapeutic agents and thereby reduce the cost and side effects of chemotherapy.

**REFERENCES:**

1. [Agarwal C](http://www.ncbi.nlm.nih.gov/pubmed?term=Agarwal%20C%5BAuthor%5D&cauthor=true&cauthor_uid=10942529)., [Sharma Y](http://www.ncbi.nlm.nih.gov/pubmed?term=Sharma%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=10942529), [Agarwal R](http://www.ncbi.nlm.nih.gov/pubmed?term=Agarwal%20R%5BAuthor%5D&cauthor=true&cauthor_uid=10942529). 2000. Anticarcinogenic effect of a polyphenolic fraction isolated from grape seeds in human prostate carcinoma DU145 cells: modulation of mitogenic signaling and cell-cycle regulators and induction of G1 arrest and apoptosis. [*Mol Carcinog*.](http://www.ncbi.nlm.nih.gov/pubmed/10942529) 28:129-138.
2. [Ahmad N](http://www.ncbi.nlm.nih.gov/pubmed?term=Ahmad%20N%5BAuthor%5D&cauthor=true&cauthor_uid=9414176)., [Feyes DK](http://www.ncbi.nlm.nih.gov/pubmed?term=Feyes%20DK%5BAuthor%5D&cauthor=true&cauthor_uid=9414176), [Nieminen AL](http://www.ncbi.nlm.nih.gov/pubmed?term=Nieminen%20AL%5BAuthor%5D&cauthor=true&cauthor_uid=9414176), [Agarwal R](http://www.ncbi.nlm.nih.gov/pubmed?term=Agarwal%20R%5BAuthor%5D&cauthor=true&cauthor_uid=9414176), [Mukhtar H](http://www.ncbi.nlm.nih.gov/pubmed?term=Mukhtar%20H%5BAuthor%5D&cauthor=true&cauthor_uid=9414176). 1997. Green tea constituent epigallocatechin-3-gallate and induction of apoptosis and cell cycle arrest in human carcinoma cells*.* [*J Natl Cancer Inst.*](http://www.ncbi.nlm.nih.gov/pubmed/9414176) 89:1881-1886.
3. Anantharaju PG., Reddy DB., Mahesh A. Padukudru MA., Chitturi CMK., Vimalambike MG., Madhunapantula SV. 2017. Induction of colon and cervical cancer cell death by cinnamic acid derivatives is mediated through the inhibition of Histone Deacetylases (HDAC). *Plos One.* 12(11): e0186208.
4. [Baliga MS](http://www.ncbi.nlm.nih.gov/pubmed?term=Baliga%20MS%5BAuthor%5D&cauthor=true&cauthor_uid=15756018)., [Meleth S](http://www.ncbi.nlm.nih.gov/pubmed?term=Meleth%20S%5BAuthor%5D&cauthor=true&cauthor_uid=15756018), [Katiyar SK](http://www.ncbi.nlm.nih.gov/pubmed?term=Katiyar%20SK%5BAuthor%5D&cauthor=true&cauthor_uid=15756018). 2005. Growth inhibitory and antimetastatic effect of green tea polyphenols on metastasis-specific mouse mammary carcinoma 4T1 cells in vitro and in vivo systems. [*Clin Cancer Res.*](http://www.ncbi.nlm.nih.gov/pubmed/?term=Clin.+Cancer+Res%2C+11%2C+1918-27)11:1918-1927.
5. Balkwill F., Mantovani A. (2001) Inflammation and cancer: back to Virchow? *Lancet* 357, 539–545.
6. Bat-Chen W., Golan T., Peri I., Ludmer Z., Schwartz B. 2010. Allicin purified from fresh garlic cloves induces apoptosis in colon cancer cells via *Nrf2.* *Nutr Cancer.* 62(7):947-57
7. [Benetou V](http://www.ncbi.nlm.nih.gov/pubmed?term=Benetou%20V%5BAuthor%5D&cauthor=true&cauthor_uid=18268122)., [Orfanos P](http://www.ncbi.nlm.nih.gov/pubmed?term=Orfanos%20P%5BAuthor%5D&cauthor=true&cauthor_uid=18268122), [Lagiou P](http://www.ncbi.nlm.nih.gov/pubmed?term=Lagiou%20P%5BAuthor%5D&cauthor=true&cauthor_uid=18268122), [Trichopoulos D](http://www.ncbi.nlm.nih.gov/pubmed?term=Trichopoulos%20D%5BAuthor%5D&cauthor=true&cauthor_uid=18268122), [Boffetta P](http://www.ncbi.nlm.nih.gov/pubmed?term=Boffetta%20P%5BAuthor%5D&cauthor=true&cauthor_uid=18268122), [Trichopoulou A](http://www.ncbi.nlm.nih.gov/pubmed?term=Trichopoulou%20A%5BAuthor%5D&cauthor=true&cauthor_uid=18268122). 2008. Vegetables and fruits in relation to cancer risk: evidence from the Greek EPIC cohort study*.* [*Cancer Epidemiol Biomarkers Prev.*](http://www.ncbi.nlm.nih.gov/pubmed/18268122)17:387-392.
8. [Block G](http://www.ncbi.nlm.nih.gov/pubmed?term=Block%20G%5BAuthor%5D&cauthor=true&cauthor_uid=1408943)., [Patterson B](http://www.ncbi.nlm.nih.gov/pubmed?term=Patterson%20B%5BAuthor%5D&cauthor=true&cauthor_uid=1408943), [Subar A](http://www.ncbi.nlm.nih.gov/pubmed?term=Subar%20A%5BAuthor%5D&cauthor=true&cauthor_uid=1408943). 1992. Fruit, vegetables, and cancer prevention: a review of the epidemiological evidence. [*Nutr Cancer.*](http://www.ncbi.nlm.nih.gov/pubmed/1408943) 18:1-29.
9. [Brusselmans K](http://www.ncbi.nlm.nih.gov/pubmed?term=Brusselmans%20K%5BAuthor%5D&cauthor=true&cauthor_uid=12918062)., [De Schrijver E](http://www.ncbi.nlm.nih.gov/pubmed?term=De%20Schrijver%20E%5BAuthor%5D&cauthor=true&cauthor_uid=12918062), [Heyns W](http://www.ncbi.nlm.nih.gov/pubmed?term=Heyns%20W%5BAuthor%5D&cauthor=true&cauthor_uid=12918062), [Verhoeven G](http://www.ncbi.nlm.nih.gov/pubmed?term=Verhoeven%20G%5BAuthor%5D&cauthor=true&cauthor_uid=12918062), [Swinnen JV](http://www.ncbi.nlm.nih.gov/pubmed?term=Swinnen%20JV%5BAuthor%5D&cauthor=true&cauthor_uid=12918062). 2003. Epigallocatechin-3-gallate is a potent natural inhibitor of fatty acid synthase in intact cells and selectively induces apoptosis in prostate cancer cells. [*Int J Cancer.*](http://www.ncbi.nlm.nih.gov/pubmed/12918062)106:856-862.
10. Ceci C., Lacal PM., Tentori L., Martino MGD., Miano R., Graziani G. 2018. Experimental evidence of the antitumor, antimetastatic and antiangiogenic activity of ellagic acid. *Nutrients.* 10(11): 1756.
11. Cheng Z., Zhang Z., Han Y., Wang J., Wang Y., Chen X., Shao Y., Cheng Y., Zhou W., Lu X., Wu Z. 2020. A review on anti-cancer effect of green tea catechins. *Journal of Functional Foods.* 74: 104172.
12. Chou FP., Chu YC., Hsu JD., Chiang HC., Wang CJ. (2000) Specific induction of glutathione S-transferase GSTM2 subunit expression by epigallocatechin gallate in rat liver. *Biochemi. Pharmacol.* 60, 643–650.
13. [Choudhuri T](http://www.ncbi.nlm.nih.gov/pubmed?term=Choudhuri%20T%5BAuthor%5D&cauthor=true&cauthor_uid=11852106)., [Pal S](http://www.ncbi.nlm.nih.gov/pubmed?term=Pal%20S%5BAuthor%5D&cauthor=true&cauthor_uid=11852106), [Agwarwal ML](http://www.ncbi.nlm.nih.gov/pubmed?term=Agwarwal%20ML%5BAuthor%5D&cauthor=true&cauthor_uid=11852106), [Das T](http://www.ncbi.nlm.nih.gov/pubmed?term=Das%20T%5BAuthor%5D&cauthor=true&cauthor_uid=11852106), [Sa G](http://www.ncbi.nlm.nih.gov/pubmed?term=Sa%20G%5BAuthor%5D&cauthor=true&cauthor_uid=11852106). 2002. Curcumin induces apoptosis in human breast cancer cells through p53-dependent Bax induction*.* [*FEBS Lett.*](http://www.ncbi.nlm.nih.gov/pubmed/?term=Choudhuri+T+2002) 512:334-340.
14. [Clément MV](http://www.ncbi.nlm.nih.gov/pubmed?term=Cl%C3%A9ment%20MV%5BAuthor%5D&cauthor=true&cauthor_uid=9680369)., [Hirpara JL](http://www.ncbi.nlm.nih.gov/pubmed?term=Hirpara%20JL%5BAuthor%5D&cauthor=true&cauthor_uid=9680369), [Chawdhury SH](http://www.ncbi.nlm.nih.gov/pubmed?term=Chawdhury%20SH%5BAuthor%5D&cauthor=true&cauthor_uid=9680369), [Pervaiz S](http://www.ncbi.nlm.nih.gov/pubmed?term=Pervaiz%20S%5BAuthor%5D&cauthor=true&cauthor_uid=9680369). 1998. Chemopreventive agent resveratrol, a natural product derived from grapes, triggers CD95 signaling-dependent apoptosis in human tumor cells. [*Blood.*](http://www.ncbi.nlm.nih.gov/pubmed/9680369)92:996-1002.
15. [D'Incalci M](http://www.ncbi.nlm.nih.gov/pubmed?term=D%27Incalci%20M%5BAuthor%5D&cauthor=true&cauthor_uid=16257798)., [Steward WP](http://www.ncbi.nlm.nih.gov/pubmed?term=Steward%20WP%5BAuthor%5D&cauthor=true&cauthor_uid=16257798), [Gescher AJ](http://www.ncbi.nlm.nih.gov/pubmed?term=Gescher%20AJ%5BAuthor%5D&cauthor=true&cauthor_uid=16257798). 2005. Use of cancer chemopreventive phytochemicals as antineoplastic agents. [*Lancet Oncol*.](http://www.ncbi.nlm.nih.gov/pubmed/16257798)6:899-904.
16. Dropcho EJ. 2011. The neurologic side effects of chemotherapeutic agents. *Continuum (Minneap Minn).* 17: 95-112.
17. [Elbaz](https://pubmed.ncbi.nlm.nih.gov/?term=Elbaz+HA&cauthor_id=24516636)HA., [Antwih](https://pubmed.ncbi.nlm.nih.gov/?term=Antwih+DA&cauthor_id=24516636)DA.,  [Liu](https://pubmed.ncbi.nlm.nih.gov/?term=Liu+J&cauthor_id=24516636)J.,  [Hüttemann](https://pubmed.ncbi.nlm.nih.gov/?term=H%C3%BCttemann+M&cauthor_id=24516636) M., [Zielske](https://pubmed.ncbi.nlm.nih.gov/?term=Zielske+SP&cauthor_id=24516636) SP. 2014. Stimulates Mitochondrial Activity and Selectively Sensitizes Cancer Cells to Radiation. 2014. *Plos One.* 9(2): e88322.
18. [Eichholzer](https://pubmed.ncbi.nlm.nih.gov/?term=Eichholzer%20M%5BAuthor%5D) M., [Richard](https://pubmed.ncbi.nlm.nih.gov/?term=Richard%20A%5BAuthor%5D) A., [Nicastro](https://pubmed.ncbi.nlm.nih.gov/?term=Nicastro%20HL%5BAuthor%5D) HL.,  [Elizabeth A](https://pubmed.ncbi.nlm.nih.gov/?term=Platz%20EA%5BAuthor%5D)P., [Linseisen](https://pubmed.ncbi.nlm.nih.gov/?term=Linseisen%20J%5BAuthor%5D), and  [Rohrmann](https://pubmed.ncbi.nlm.nih.gov/?term=Rohrmann%20S%5BAuthor%5D) S. 2014. Urinary lignans and inflammatory markers in the US National Health and Nutrition Examination Survey (NHANES) 1999–2004 and 2005–2008. [Cancer Causes Control. 25(3): 395–403.](https://www.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&retmode=ref&cmd=prlinks&id=24463788)
19. [Fulda S](http://www.ncbi.nlm.nih.gov/pubmed?term=Fulda%20S%5BAuthor%5D&cauthor=true&cauthor_uid=15273734)., [Debatin KM](http://www.ncbi.nlm.nih.gov/pubmed?term=Debatin%20KM%5BAuthor%5D&cauthor=true&cauthor_uid=15273734). 2004. Sensitization for anticancer drug-induced apoptosis by the chemopreventive agent resveratrol. [*Oncogene*.](http://www.ncbi.nlm.nih.gov/pubmed/15273734)23:6702-6711.
20. [Gao X](http://www.ncbi.nlm.nih.gov/pubmed?term=Gao%20X%5BAuthor%5D&cauthor=true&cauthor_uid=16416600)., [Deeb D](http://www.ncbi.nlm.nih.gov/pubmed?term=Deeb%20D%5BAuthor%5D&cauthor=true&cauthor_uid=16416600), [Jiang H](http://www.ncbi.nlm.nih.gov/pubmed?term=Jiang%20H%5BAuthor%5D&cauthor=true&cauthor_uid=16416600), [Liu YB](http://www.ncbi.nlm.nih.gov/pubmed?term=Liu%20YB%5BAuthor%5D&cauthor=true&cauthor_uid=16416600), [Dulchavsky SA](http://www.ncbi.nlm.nih.gov/pubmed?term=Dulchavsky%20SA%5BAuthor%5D&cauthor=true&cauthor_uid=16416600), [Gautam SC](http://www.ncbi.nlm.nih.gov/pubmed?term=Gautam%20SC%5BAuthor%5D&cauthor=true&cauthor_uid=16416600). 2005. Curcumin differentially sensitizes malignant glioma cells to TRAIL/Apo2L-mediated apoptosis through activation of procaspases and release of cytochrome c from mitochondria. [*J Exp Ther Oncol.*](http://www.ncbi.nlm.nih.gov/pubmed/16416600)5:39-48.
21. Giordano A., Tommonaro G. 2019. Curcumin and cancer. *Nutrients.* 11(10): 2376.
22. Hanahan D., Weinberg RA. 2000. The hallmarks of cancer. *Cell.* 100:57-70
23. [Hantz HL](http://www.ncbi.nlm.nih.gov/pubmed?term=Hantz%20HL%5BAuthor%5D&cauthor=true&cauthor_uid=15734720)., [Young LF](http://www.ncbi.nlm.nih.gov/pubmed?term=Young%20LF%5BAuthor%5D&cauthor=true&cauthor_uid=15734720), [Martin KR](http://www.ncbi.nlm.nih.gov/pubmed?term=Martin%20KR%5BAuthor%5D&cauthor=true&cauthor_uid=15734720). 2005. Physiologically attainable concentrations of lycopene induce mitochondrial apoptosis in LNCaP human prostate cancer cells. [*Exp Biol Med (Maywood).*](http://www.ncbi.nlm.nih.gov/pubmed/15734720)230:171-179.
24. [Hastak K](http://www.ncbi.nlm.nih.gov/pubmed?term=Hastak%20K%5BAuthor%5D&cauthor=true&cauthor_uid=15764647)., [Agarwal MK](http://www.ncbi.nlm.nih.gov/pubmed?term=Agarwal%20MK%5BAuthor%5D&cauthor=true&cauthor_uid=15764647), [Mukhtar H](http://www.ncbi.nlm.nih.gov/pubmed?term=Mukhtar%20H%5BAuthor%5D&cauthor=true&cauthor_uid=15764647), [Agarwal ML](http://www.ncbi.nlm.nih.gov/pubmed?term=Agarwal%20ML%5BAuthor%5D&cauthor=true&cauthor_uid=15764647). 2005. Ablation of either p21 or Bax prevents p53-dependent apoptosis induced by green tea polyphenol epigallocatechin-3-gallate. [*FASEB J.*](http://www.ncbi.nlm.nih.gov/pubmed/?term=Hastak+K+2005)19:789-791.
25. Holban AM., Grumezescu AM. 2018. Therapeutic Foods. Handbook of Food Bioengineering. Chapter 13. 397-427.
26. [Horinaka M](http://www.ncbi.nlm.nih.gov/pubmed?term=Horinaka%20M%5BAuthor%5D&cauthor=true&cauthor_uid=16007131)., [Yoshida T](http://www.ncbi.nlm.nih.gov/pubmed?term=Yoshida%20T%5BAuthor%5D&cauthor=true&cauthor_uid=16007131), [Shiraishi T](http://www.ncbi.nlm.nih.gov/pubmed?term=Shiraishi%20T%5BAuthor%5D&cauthor=true&cauthor_uid=16007131), [Nakata S](http://www.ncbi.nlm.nih.gov/pubmed?term=Nakata%20S%5BAuthor%5D&cauthor=true&cauthor_uid=16007131), [Wakada M](http://www.ncbi.nlm.nih.gov/pubmed?term=Wakada%20M%5BAuthor%5D&cauthor=true&cauthor_uid=16007131), [Nakanishi R](http://www.ncbi.nlm.nih.gov/pubmed?term=Nakanishi%20R%5BAuthor%5D&cauthor=true&cauthor_uid=16007131), [Nishino H](http://www.ncbi.nlm.nih.gov/pubmed?term=Nishino%20H%5BAuthor%5D&cauthor=true&cauthor_uid=16007131), [Matsui H](http://www.ncbi.nlm.nih.gov/pubmed?term=Matsui%20H%5BAuthor%5D&cauthor=true&cauthor_uid=16007131), [Sakai T](http://www.ncbi.nlm.nih.gov/pubmed?term=Sakai%20T%5BAuthor%5D&cauthor=true&cauthor_uid=16007131). 2005. Luteolin induces apoptosis via death receptor 5 upregulation in human malignant tumor cells. [*Oncogene*.](http://www.ncbi.nlm.nih.gov/pubmed/16007131) 24:7180-7189
27. Huang SH., Kao Y., Muller CJF., Joubert E., Chuu C. 2020. Aspalathin-rich green Aspalathus linearis extract suppresses migration and invasion of human castration-resistant prostate cancer cells via inhibition of YAP signalling. *Phytomedicine.* [69](https://www.sciencedirect.com/science/journal/09447113/69/supp/C):153210.
28. Imran M., Salehi B., Sharifi-Rad J., Gondal TA., Saeed F., Imran A., Shahbaz M., Fokou PVT., Arshad MU., Khan H., Guerreiro SG., Martins N., Estevinho LM. 2019. Kaempferol: A Key Emphasis to Its Anticancer Potential. *Molecules.*24, 2277.
29. Imran M., Rauf A, Abu-Izneid T., Nadeem M., Shariati MA., Khan IA., Imran A., Orhan IE., Rizwan M., Atif M., Gondal TA., Mubarak MS. 2019. Luteolin, a flavonoid, as an anticancer agent: A review. *Biomed. Pharmacother.* 116: 109084.
30. Imran M., Gondal TA., Muhammad A., Muhammad S., Qaisarani TB., Mughal MH., Salehi B., Martorell M., Sharifi-Rad J. 2020. Apigenin as an anticancer agent. *Phytother. Res.* 34: 1812-1828.
31. [Kakizoe T](http://www.ncbi.nlm.nih.gov/pubmed?term=Kakizoe%20T%5BAuthor%5D&cauthor=true&cauthor_uid=14594936). 2003. Chemoprevention of cancer--focusing on clinical trials. [*Jpn J Clin Oncol.*](http://www.ncbi.nlm.nih.gov/pubmed/?term=chemoprevention+of+cancer+focussing+on+clinical+trials+kakizoe) 33:421-442.
32. [Katdare M](http://www.ncbi.nlm.nih.gov/pubmed?term=Katdare%20M%5BAuthor%5D&cauthor=true&cauthor_uid=9468547)., [Osborne MP](http://www.ncbi.nlm.nih.gov/pubmed?term=Osborne%20MP%5BAuthor%5D&cauthor=true&cauthor_uid=9468547), [Telang NT](http://www.ncbi.nlm.nih.gov/pubmed?term=Telang%20NT%5BAuthor%5D&cauthor=true&cauthor_uid=9468547). 1998. Inhibition of aberrant proliferation and induction of apoptosis in pre-neoplastic human mammary epithelial cells by natural phytochemicals. [*Oncol Rep*.](http://www.ncbi.nlm.nih.gov/pubmed/9468547) 5:311-315.
33. Kim HY., Kim OH., Sung MK. 2003. Effects of phenol-depleted and phenol-rich diets on blood markers of oxidative stress, and urinary excretion of quercetin and kaempferol in healthy volunteers. *J Am. Coll. Nutr.* (3):217-23.
34. [Ko](https://www.ncbi.nlm.nih.gov/pubmed/?term=Ko%20JH%5BAuthor%5D&cauthor=true&cauthor_uid=29194365) J., [Sethi](https://www.ncbi.nlm.nih.gov/pubmed/?term=Sethi%20G%5BAuthor%5D&cauthor=true&cauthor_uid=29194365) G., [Um](https://www.ncbi.nlm.nih.gov/pubmed/?term=Um%20JY%5BAuthor%5D&cauthor=true&cauthor_uid=29194365) J., [Shanmugam](https://www.ncbi.nlm.nih.gov/pubmed/?term=Shanmugam%20MK%5BAuthor%5D&cauthor=true&cauthor_uid=29194365) MK., [Arfuso](https://www.ncbi.nlm.nih.gov/pubmed/?term=Arfuso%20F%5BAuthor%5D&cauthor=true&cauthor_uid=29194365) F., [Kumar](https://www.ncbi.nlm.nih.gov/pubmed/?term=Kumar%20AP%5BAuthor%5D&cauthor=true&cauthor_uid=29194365) AP., [Bishayee](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bishayee%20A%5BAuthor%5D&cauthor=true&cauthor_uid=29194365) A., [Ahn](https://www.ncbi.nlm.nih.gov/pubmed/?term=Ahn%20KS%5BAuthor%5D&cauthor=true&cauthor_uid=29194365) KS. 2017. The Role of Resveratrol in Cancer Therapy. [*Int J Mol Sci*](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5751192/)*.* 18(12): 2589.
35. [Liang YC](http://www.ncbi.nlm.nih.gov/pubmed?term=Liang%20YC%5BAuthor%5D&cauthor=true&cauthor_uid=10462699)., [Lin-Shiau SY](http://www.ncbi.nlm.nih.gov/pubmed?term=Lin-Shiau%20SY%5BAuthor%5D&cauthor=true&cauthor_uid=10462699), [Chen CF](http://www.ncbi.nlm.nih.gov/pubmed?term=Chen%20CF%5BAuthor%5D&cauthor=true&cauthor_uid=10462699), [Lin JK](http://www.ncbi.nlm.nih.gov/pubmed?term=Lin%20JK%5BAuthor%5D&cauthor=true&cauthor_uid=10462699). 1999. Inhibition of cyclin-dependent kinases 2 and 4 activities as well as induction of Cdk inhibitors p21 and p27 during growth arrest of human breast carcinoma cells by (-)-epigallocatechin-3-gallate. [*J Cell Biochem.*](http://www.ncbi.nlm.nih.gov/pubmed/10462699) 75:1-12.
36. Mali A., Joshi A., Hedge M., Kadam S. 2017. Enterolactone Suppresses Proliferation, Migration and Metastasis of MDA-MB-231 Breast Cancer Cells Through Inhibition of uPA Induced Plasmin Activation and MMPs-Mediated ECM Remodeling. *Asian Pac. J. Cancer Prev.* 18 (4): 905-915.
37. [Mehta RG](http://www.ncbi.nlm.nih.gov/pubmed?term=Mehta%20RG%5BAuthor%5D&cauthor=true&cauthor_uid=20238150). , [Murillo G](http://www.ncbi.nlm.nih.gov/pubmed?term=Murillo%20G%5BAuthor%5D&cauthor=true&cauthor_uid=20238150), [Naithani R](http://www.ncbi.nlm.nih.gov/pubmed?term=Naithani%20R%5BAuthor%5D&cauthor=true&cauthor_uid=20238150), [Peng X](http://www.ncbi.nlm.nih.gov/pubmed?term=Peng%20X%5BAuthor%5D&cauthor=true&cauthor_uid=20238150). 2010. Cancer chemoprevention by natural products: how far have we come? [*Pharm Res*.](http://www.ncbi.nlm.nih.gov/pubmed/?term=19.%09Mehta+RG%2C+Murillo+G%2C+Naithani+R+and+Peng+X.+%282010%29.+Pharm+Res+27%3A950-961.) 27:950-961.
38. Monsuez J., Charniot JC., Vignat N., Artigou JY. 2010. Cardiac side-effects of cancer chemotherapy. *Inter J Cardiol*. 144: 3–15.
39. [Moragoda L](http://www.ncbi.nlm.nih.gov/pubmed?term=Moragoda%20L%5BAuthor%5D&cauthor=true&cauthor_uid=11396178)., [Jaszewski R](http://www.ncbi.nlm.nih.gov/pubmed?term=Jaszewski%20R%5BAuthor%5D&cauthor=true&cauthor_uid=11396178), [Majumdar AP](http://www.ncbi.nlm.nih.gov/pubmed?term=Majumdar%20AP%5BAuthor%5D&cauthor=true&cauthor_uid=11396178). 2001. Curcumin induced modulation of cell cycle and apoptosis in gastric and colon cancer cells. [*Anticancer Res*.](http://www.ncbi.nlm.nih.gov/pubmed/11396178) 21:873-878.
40. [Naithani R](http://www.ncbi.nlm.nih.gov/pubmed?term=Naithani%20R%5BAuthor%5D&cauthor=true&cauthor_uid=18473802)., [Huma LC](http://www.ncbi.nlm.nih.gov/pubmed?term=Huma%20LC%5BAuthor%5D&cauthor=true&cauthor_uid=18473802), [Moriarty RM](http://www.ncbi.nlm.nih.gov/pubmed?term=Moriarty%20RM%5BAuthor%5D&cauthor=true&cauthor_uid=18473802), [McCormick DL](http://www.ncbi.nlm.nih.gov/pubmed?term=McCormick%20DL%5BAuthor%5D&cauthor=true&cauthor_uid=18473802), [Mehta RG](http://www.ncbi.nlm.nih.gov/pubmed?term=Mehta%20RG%5BAuthor%5D&cauthor=true&cauthor_uid=18473802). 2008. Comprehensive review of cancer chemopreventive agents evaluated in experimental carcinogenesis models and clinical trials*.* [*Curr Med Chem.*](http://www.ncbi.nlm.nih.gov/pubmed/18473802) 15:1044-1071.
41. Nelson DR., Kamataki T., Waxman DJ., Guengerich FP., Estabrook RW., Feyereisen R *et al*. (1993) The P450 superfamily: update on new sequences, gene mapping, accession numbers, early trivial names of enzymes, and nomenclature. *DNA Cell Biol.* 12: 1–51.
42. [Nishikawa T](http://www.ncbi.nlm.nih.gov/pubmed?term=Nishikawa%20T%5BAuthor%5D&cauthor=true&cauthor_uid=16481065)., [Nakajima T](http://www.ncbi.nlm.nih.gov/pubmed?term=Nakajima%20T%5BAuthor%5D&cauthor=true&cauthor_uid=16481065), [Moriguchi M](http://www.ncbi.nlm.nih.gov/pubmed?term=Moriguchi%20M%5BAuthor%5D&cauthor=true&cauthor_uid=16481065), [Jo M](http://www.ncbi.nlm.nih.gov/pubmed?term=Jo%20M%5BAuthor%5D&cauthor=true&cauthor_uid=16481065), [Sekoguchi S](http://www.ncbi.nlm.nih.gov/pubmed?term=Sekoguchi%20S%5BAuthor%5D&cauthor=true&cauthor_uid=16481065), [Ishii M](http://www.ncbi.nlm.nih.gov/pubmed?term=Ishii%20M%5BAuthor%5D&cauthor=true&cauthor_uid=16481065), [Takashima H](http://www.ncbi.nlm.nih.gov/pubmed?term=Takashima%20H%5BAuthor%5D&cauthor=true&cauthor_uid=16481065), [Katagishi T](http://www.ncbi.nlm.nih.gov/pubmed?term=Katagishi%20T%5BAuthor%5D&cauthor=true&cauthor_uid=16481065), [Kimura H](http://www.ncbi.nlm.nih.gov/pubmed?term=Kimura%20H%5BAuthor%5D&cauthor=true&cauthor_uid=16481065), [Minami M](http://www.ncbi.nlm.nih.gov/pubmed?term=Minami%20M%5BAuthor%5D&cauthor=true&cauthor_uid=16481065), [Itoh Y](http://www.ncbi.nlm.nih.gov/pubmed?term=Itoh%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=16481065), [Kagawa K](http://www.ncbi.nlm.nih.gov/pubmed?term=Kagawa%20K%5BAuthor%5D&cauthor=true&cauthor_uid=16481065), [Okanoue T](http://www.ncbi.nlm.nih.gov/pubmed?term=Okanoue%20T%5BAuthor%5D&cauthor=true&cauthor_uid=16481065). 2006. A green tea polyphenol, epigalocatechin-3-gallate, induces apoptosis of human hepatocellular carcinoma, possibly through inhibition of Bcl-2 family proteins. [*J Hepatol.*](http://www.ncbi.nlm.nih.gov/pubmed/?term=Nishikawa+T+2006++J.+Hepatol) 44:1074-1082.
43. Nussbaumer S., Bonnabry P., Veuthey JL., Sandrine F. 2011. Analysis of anticancer drugs: A review. *Talanta*. 85: 2265-2289.
44. Palit S., Kar S., Sharma G., Das PK. 2015. Hesperetin Induces Apoptosis in Breast Carcinoma by Triggering Accumulation of ROS and Activation of ASK1/JNK Pathway. *J Cell Physiol.* 230(8):1729-39.
45. Park EJ., John M., Pezzuto JM. 2015. The pharmacology pf resveratrol animals and humans. *Biochim. Biophys. Acta Mol. Basis Dis.*1852 (6): 1071-1113.
46. [Ranjan](https://pubmed.ncbi.nlm.nih.gov/?term=Ranjan%20A%5BAuthor%5D) A.,  [Ramachandran](https://pubmed.ncbi.nlm.nih.gov/?term=Ramachandran%20S%5BAuthor%5D) S.,  [Gupta](https://pubmed.ncbi.nlm.nih.gov/?term=Gupta%20N%5BAuthor%5D) N.,  [Kaushik](https://pubmed.ncbi.nlm.nih.gov/?term=Kaushik%20I%5BAuthor%5D) I.,  [Wright](https://pubmed.ncbi.nlm.nih.gov/?term=Wright%20S%5BAuthor%5D) S.,  [Srivastava](https://pubmed.ncbi.nlm.nih.gov/?term=Srivastava%20S%5BAuthor%5D) S., [Hiranmoy Das](https://pubmed.ncbi.nlm.nih.gov/?term=Das%20H%5BAuthor%5D) H., [Srivastava](https://pubmed.ncbi.nlm.nih.gov/?term=Srivastava%20S%5BAuthor%5D) S.,  [Prasad](https://pubmed.ncbi.nlm.nih.gov/?term=Prasad%20S%5BAuthor%5D) S., [Sanjay K. Srivastava](https://pubmed.ncbi.nlm.nih.gov/?term=Srivastava%20SK%5BAuthor%5D) SK., 2019. Role of Phytochemicals in Cancer Prevention. *Int J Mol Sci*. 20(20):4981.
47. [Reddy L](http://www.ncbi.nlm.nih.gov/pubmed?term=Reddy%20L%5BAuthor%5D&cauthor=true&cauthor_uid=12804695)., [Odhav B](http://www.ncbi.nlm.nih.gov/pubmed?term=Odhav%20B%5BAuthor%5D&cauthor=true&cauthor_uid=12804695), [Bhoola KD](http://www.ncbi.nlm.nih.gov/pubmed?term=Bhoola%20KD%5BAuthor%5D&cauthor=true&cauthor_uid=12804695). 2003.Natural products for cancer prevention: a global perspective. [*Pharmacol Ther*.](http://www.ncbi.nlm.nih.gov/pubmed/12804695) 99:1-13.
48. [Sartippour MR](http://www.ncbi.nlm.nih.gov/pubmed?term=Sartippour%20MR%5BAuthor%5D&cauthor=true&cauthor_uid=16785249)., [Pietras R](http://www.ncbi.nlm.nih.gov/pubmed?term=Pietras%20R%5BAuthor%5D&cauthor=true&cauthor_uid=16785249), [Marquez-Garban DC](http://www.ncbi.nlm.nih.gov/pubmed?term=Marquez-Garban%20DC%5BAuthor%5D&cauthor=true&cauthor_uid=16785249), [Chen HW](http://www.ncbi.nlm.nih.gov/pubmed?term=Chen%20HW%5BAuthor%5D&cauthor=true&cauthor_uid=16785249), [Heber D](http://www.ncbi.nlm.nih.gov/pubmed?term=Heber%20D%5BAuthor%5D&cauthor=true&cauthor_uid=16785249), [Henning SM](http://www.ncbi.nlm.nih.gov/pubmed?term=Henning%20SM%5BAuthor%5D&cauthor=true&cauthor_uid=16785249), [Sartippour G](http://www.ncbi.nlm.nih.gov/pubmed?term=Sartippour%20G%5BAuthor%5D&cauthor=true&cauthor_uid=16785249), [Zhang L](http://www.ncbi.nlm.nih.gov/pubmed?term=Zhang%20L%5BAuthor%5D&cauthor=true&cauthor_uid=16785249), [Lu M](http://www.ncbi.nlm.nih.gov/pubmed?term=Lu%20M%5BAuthor%5D&cauthor=true&cauthor_uid=16785249), [Weinberg O](http://www.ncbi.nlm.nih.gov/pubmed?term=Weinberg%20O%5BAuthor%5D&cauthor=true&cauthor_uid=16785249), [Rao JY](http://www.ncbi.nlm.nih.gov/pubmed?term=Rao%20JY%5BAuthor%5D&cauthor=true&cauthor_uid=16785249), [Brooks MN](http://www.ncbi.nlm.nih.gov/pubmed?term=Brooks%20MN%5BAuthor%5D&cauthor=true&cauthor_uid=16785249). 2006. The combination of green tea and tamoxifen is effective against breast cancer. [*Carcinogenesis.*](http://www.ncbi.nlm.nih.gov/pubmed/16785249) 27:2424-433.
49. Siegel R., Miller K., Jemal A. 2020. Cancer statistics, 2020. *CA Cancer J Clin* 70: 7-30.
50. Sourani Z., Pourgheysari B., Beshkar P., Shirzad H., Shirzad M. 2016. Gallic Acid Inhibits Proliferation and Induces Apoptosis in Lymphoblastic Leukemia Cell Line (C121) [*Iran J Med Sci*](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5106568/)*.* 41(6): 525–530.
51. [Sporn MB](http://www.ncbi.nlm.nih.gov/pubmed?term=Sporn%20MB%5BAuthor%5D&cauthor=true&cauthor_uid=10688873)., [Suh N](http://www.ncbi.nlm.nih.gov/pubmed?term=Suh%20N%5BAuthor%5D&cauthor=true&cauthor_uid=10688873). 2000. Chemoprevention of cancer. [*Carcinogenesis*.](http://www.ncbi.nlm.nih.gov/pubmed/10688873) 21:525-530.
52. [Stavric B](http://www.ncbi.nlm.nih.gov/pubmed?term=Stavric%20B%5BAuthor%5D&cauthor=true&cauthor_uid=7867212). 1994. Role of chemopreventers in human diet. [*Clin Biochem*.](http://www.ncbi.nlm.nih.gov/pubmed/?term=Role+of+chemopreventors+in+human+diet) 27:319-332.
53. [Steinmetz KA](http://www.ncbi.nlm.nih.gov/pubmed?term=Steinmetz%20KA%5BAuthor%5D&cauthor=true&cauthor_uid=8841165)., [Potter JD](http://www.ncbi.nlm.nih.gov/pubmed?term=Potter%20JD%5BAuthor%5D&cauthor=true&cauthor_uid=8841165). 1996. Vegetables, fruit, and cancer prevention: a review*.* [*J Am Diet Assoc.*](http://www.ncbi.nlm.nih.gov/pubmed/8841165) 96:1027-10.
54. [Surh YJ](http://www.ncbi.nlm.nih.gov/pubmed?term=Surh%20YJ%5BAuthor%5D&cauthor=true&cauthor_uid=14570043). 2003. Cancer chemoprevention with dietary phytochemicals. [*Nat Rev Cancer.*](http://www.ncbi.nlm.nih.gov/pubmed/14570043)3:768-780.
55. Thomas R., Butler E., Macchi F., Williams M. 2015. Phytochemicals in cancer prevention and management? *Br. J. of Med. Pract.* 8(2).
56. [Tuli](https://www.ncbi.nlm.nih.gov/pubmed/?term=Tuli%20HS%5BAuthor%5D&cauthor=true&cauthor_uid=31866857) HS.,[Tuorkey](https://www.ncbi.nlm.nih.gov/pubmed/?term=Tuorkey%20MJ%5BAuthor%5D&cauthor=true&cauthor_uid=31866857) MJ., [Thakral](https://www.ncbi.nlm.nih.gov/pubmed/?term=Thakral%20F%5BAuthor%5D&cauthor=true&cauthor_uid=31866857) F.,  [Sak](https://www.ncbi.nlm.nih.gov/pubmed/?term=Sak%20K%5BAuthor%5D&cauthor=true&cauthor_uid=31866857) K.,[Kumar](https://www.ncbi.nlm.nih.gov/pubmed/?term=Kumar%20M%5BAuthor%5D&cauthor=true&cauthor_uid=31866857) M., [Sharma](https://www.ncbi.nlm.nih.gov/pubmed/?term=Sharma%20AK%5BAuthor%5D&cauthor=true&cauthor_uid=31866857) AK., [Sharma](https://www.ncbi.nlm.nih.gov/pubmed/?term=Sharma%20U%5BAuthor%5D&cauthor=true&cauthor_uid=31866857) U., [Jain](https://www.ncbi.nlm.nih.gov/pubmed/?term=Jain%20A%5BAuthor%5D&cauthor=true&cauthor_uid=31866857) A., [Aggarwal](https://www.ncbi.nlm.nih.gov/pubmed/?term=Aggarwal%20V%5BAuthor%5D&cauthor=true&cauthor_uid=31866857) V.,[Bishayee](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bishayee%20A%5BAuthor%5D&cauthor=true&cauthor_uid=31866857) A. 2019. Molecular Mechanisms of Action of Genistein in Cancer: Recent Advances. [*Front Pharmacol*](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6910185/)*.* 10: 1336.
57. Vafadar A., [Shabaninejad](https://www.ncbi.nlm.nih.gov/pubmed/?term=Shabaninejad%20Z%5BAuthor%5D&cauthor=true&cauthor_uid=32175075) Z., [Movahedpour](https://www.ncbi.nlm.nih.gov/pubmed/?term=Movahedpour%20A%5BAuthor%5D&cauthor=true&cauthor_uid=32175075) A., [Fallahi](https://www.ncbi.nlm.nih.gov/pubmed/?term=Fallahi%20F%5BAuthor%5D&cauthor=true&cauthor_uid=32175075) F.,[Taghavipour](https://www.ncbi.nlm.nih.gov/pubmed/?term=Taghavipour%20M%5BAuthor%5D&cauthor=true&cauthor_uid=32175075) M., [Ghasemi](https://www.ncbi.nlm.nih.gov/pubmed/?term=Ghasemi%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=32175075) Y.,[Akbari](https://www.ncbi.nlm.nih.gov/pubmed/?term=Akbari%20M%5BAuthor%5D&cauthor=true&cauthor_uid=32175075) M., [Shafiee](https://www.ncbi.nlm.nih.gov/pubmed/?term=Shafiee%20A%5BAuthor%5D&cauthor=true&cauthor_uid=32175075) A.,[Hajighadimi](https://www.ncbi.nlm.nih.gov/pubmed/?term=Hajighadimi%20S%5BAuthor%5D&cauthor=true&cauthor_uid=32175075) S., [Moradizarmehri](https://www.ncbi.nlm.nih.gov/pubmed/?term=Moradizarmehri%20S%5BAuthor%5D&cauthor=true&cauthor_uid=32175075) S., Razi E., [Savardashtaki](https://www.ncbi.nlm.nih.gov/pubmed/?term=Savardashtaki%20A%5BAuthor%5D&cauthor=true&cauthor_uid=32175075) A., Mirzaei H. 2020. Quercetin and cancer: new insights into its therapeutic effects on ovarian cancer cells. *Cell Biosci.* 10: 32.
58. [Waladkhani AR](http://www.ncbi.nlm.nih.gov/pubmed?term=Waladkhani%20AR%5BAuthor%5D&cauthor=true&cauthor_uid=9852292)., [Clemens MR](http://www.ncbi.nlm.nih.gov/pubmed?term=Clemens%20MR%5BAuthor%5D&cauthor=true&cauthor_uid=9852292). 1998. Effect of dietary phytochemicals on cancer development (review). [*Int J Mol Med.*](http://www.ncbi.nlm.nih.gov/pubmed/9852292)1:747-753.
59. [Wattenberg LW](http://www.ncbi.nlm.nih.gov/pubmed?term=Wattenberg%20LW%5BAuthor%5D&cauthor=true&cauthor_uid=1544145). 1992. Inhibition of carcinogenesis by minor dietary constituents. [*Cancer Res.*](http://www.ncbi.nlm.nih.gov/pubmed/1544145) 52:2085s-2091s.
60. [Wolfram](https://www.ncbi.nlm.nih.gov/pubmed/?term=Wolfram%20J%5BAuthor%5D&cauthor=true&cauthor_uid=26502889) J.,[Scott](https://www.ncbi.nlm.nih.gov/pubmed/?term=Scott%20B%5BAuthor%5D&cauthor=true&cauthor_uid=26502889) B.,[Boom](https://www.ncbi.nlm.nih.gov/pubmed/?term=Boom%20K%5BAuthor%5D&cauthor=true&cauthor_uid=26502889) K.,[Shen](https://www.ncbi.nlm.nih.gov/pubmed/?term=Shen%20J%5BAuthor%5D&cauthor=true&cauthor_uid=26502889) J., [Borsoi](https://www.ncbi.nlm.nih.gov/pubmed/?term=Borsoi%20C%5BAuthor%5D&cauthor=true&cauthor_uid=26502889) C., [Sur K.](https://www.ncbi.nlm.nih.gov/pubmed/?term=Suri%20K%5BAuthor%5D&cauthor=true&cauthor_uid=26502889), [Grande](https://www.ncbi.nlm.nih.gov/pubmed/?term=Grande%20R%5BAuthor%5D&cauthor=true&cauthor_uid=26502889) R.,[Fresta](https://www.ncbi.nlm.nih.gov/pubmed/?term=Fresta%20M%5BAuthor%5D&cauthor=true&cauthor_uid=26502889) M., [Celia](https://www.ncbi.nlm.nih.gov/pubmed/?term=Celia%20C%5BAuthor%5D&cauthor=true&cauthor_uid=26502889) C., [Zhao](https://www.ncbi.nlm.nih.gov/pubmed/?term=Zhao%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=26502889) Y., [Shen](https://www.ncbi.nlm.nih.gov/pubmed/?term=Shen%20H%5BAuthor%5D&cauthor=true&cauthor_uid=26502889) H., [Ferrari](https://www.ncbi.nlm.nih.gov/pubmed/?term=Ferrari%20M%5BAuthor%5D&cauthor=true&cauthor_uid=26502889) M. 2016. Hesperetin liposomes for cancer therapy. *Curr Drug Deliv*.13(5): 711–719.
61. Yang CS., Maliakal P., meng X. 2002. Inhibition of carcinogenesis by tea. *Annu. Rev. Pharmacol. Toxicol.*42: 25-54.
62. [Zi X](http://www.ncbi.nlm.nih.gov/pubmed?term=Zi%20X%5BAuthor%5D&cauthor=true&cauthor_uid=9581834)., [Grasso AW](http://www.ncbi.nlm.nih.gov/pubmed?term=Grasso%20AW%5BAuthor%5D&cauthor=true&cauthor_uid=9581834), [Kung HJ](http://www.ncbi.nlm.nih.gov/pubmed?term=Kung%20HJ%5BAuthor%5D&cauthor=true&cauthor_uid=9581834), [Agarwal R](http://www.ncbi.nlm.nih.gov/pubmed?term=Agarwal%20R%5BAuthor%5D&cauthor=true&cauthor_uid=9581834). 1998. A flavonoid antioxidant, silymarin, inhibits activation of erbB1 signaling and induces cyclin-dependent kinase inhibitors, G1 arrest, and anticarcinogenic effects in human prostate carcinoma DU145 cells. [*Cancer Res*.](http://www.ncbi.nlm.nih.gov/pubmed/9581834) 58:1920-1929.
63. Tsai Y.J., Chen B.H. 2016. Preparation of catechin extracts and nanoemulsions from green tea leaf waste and their inhibition effect on prostate cancer cell PC-3. *Int. J. Nanomed.* 11:1907–1926. doi: 10.2147/IJN.S103759.