

PLANT BASED POLYPHENOLS IN CHEMO-PREVENTION AND CHEMO-THERAPY OF CANCER

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.

Keywords: Cancer, Phytochemicals, Polyphenols, Chemoprevention, Chemotherapy.

Author

Shreyasi Palit

Department of Biochemistry

Sarsuna College

Kolkata, India.

mail2shreyasi@gmail.com

I. 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.*, 2000; 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.

II. 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	Quercetin, 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	Sesame seeds, 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
Quercetin	Ovarian	Vafadar <i>et al.</i> , 2020
Kaemferol	Lung, kidney, prostate, stomach	Imran <i>et al.</i> , 2019
Apigenin	Breast, lung, liver, skin, blood, colon, prostate, pancreatic, cervical, oral, and stomach	Imran <i>et al.</i> , 2020
Luteolin	Lung, breast, glioblastoma, prostate, colon and pancreatic	Imran <i>et al.</i> , 2019
Genistin	Colon	Tuli <i>et al.</i> , 2019
Hesperitin	Lung and breast	Wolfram <i>et al.</i> , 2016; Palit <i>et al.</i> , 2015
Catechin	Breast, liver, prostate, colorectal, gastric, lung	Cheng <i>et al.</i> , 2020
Epicatechins	Pancreas	Elbaz <i>et al.</i> , 2014
Gallic acid	Leukemia	Sourani <i>et al.</i> , 2016
Ellagic acid	Breast, Colon, Prostate	Ceci <i>et al.</i> , 2018
Aspalathin	Prostate	Huang <i>et al.</i> , 2020
Curcumin	Breast, prostate, cervical, gastric	Giordano <i>et al.</i> , 2019
Cinnamic acid	Colon, cervical	Anantharaju <i>et al.</i> , 2017
Resveratrol	Breast, prostate, skin, lungs, pancreas	Ko <i>et al.</i> , 2017
Enterolactone	Breast	Mali <i>et al.</i> , 2017

III. 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.

1. Chemo-preventive Potential of Polyphenols: 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 quercetin, curcumin etc. exert their chemo-

preventive effect by inhibiting NF- κ B signal cascade thereby reducing inflammation (Thomas *et al.*, 2015).

2. Chemo-therapeutic Potential of Polyphenols:

- **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 *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).
- **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).
- **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-proliferative 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).

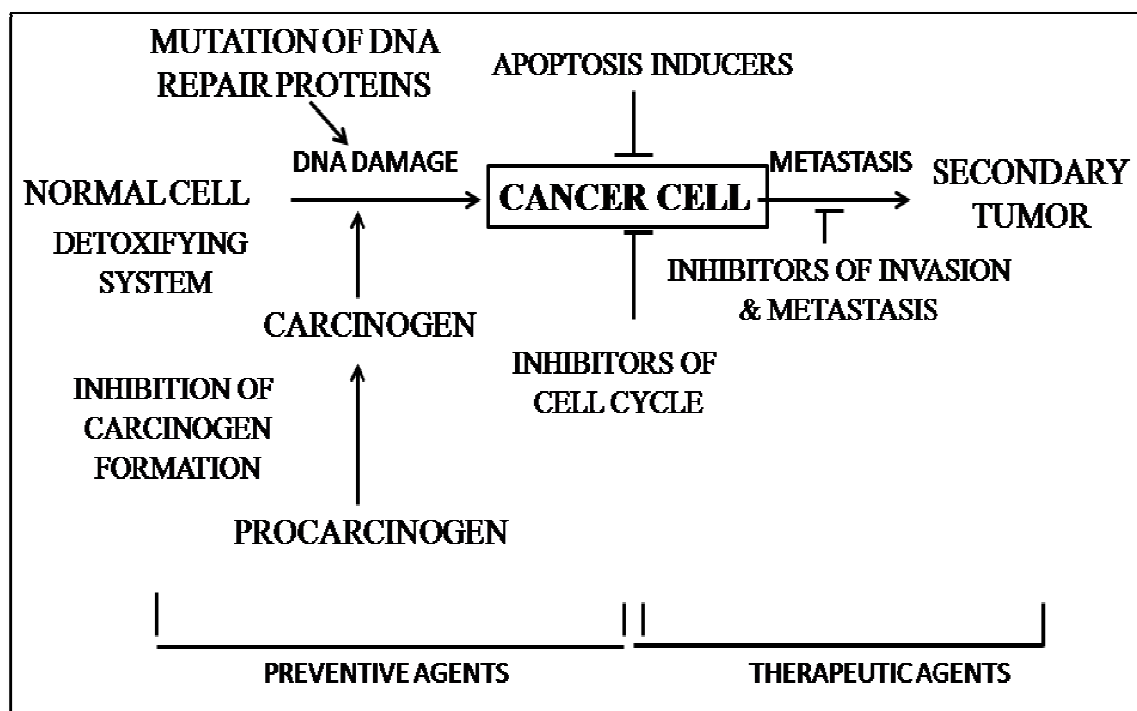


Figure 1: Schematic representation of probable interactions occurring between polyphenols with various events associated with development and progression of cancer.

IV. FUTURE PROSPECTS

In spite 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.

V. 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.

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