Catechin: Molecular Mechanism of Anti-Cancer Effect

Katekin: Mekanisme Molekular Efek Antikanker

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Abstract

Over the recent decade, attention have been focused on the pathologic role of free radicals in a variety of diseases, which are most related to carcinogenesis process. Carcinogenesis is a multi-step process that is induced primarily by carcinogens leading to the development of cancer. Extensive research in the last few years has revealed that regular consumption of certain fruits and vegetables can reduce the risk of acquiring specific cancers. Catechins are phytochemical compounds found in high concentrations in a variety of plant-based foods and beverages. Studies with cell lines have demonstrated that catechins affect signal transduction pathways, inhibit cell proliferation and induce apoptosis. More mechanistic studies in these areas will help us to understand the inhibitory action of catechin against carcinogenesis and provide background for evaluating the effects of catechin on human carcinogenesis.

Keywords: Catechin, Carcinogenesis, Cancer prevention

INTRODUCTION

Tumorigenesis is a multistep process that begins with cellular transformation, progresses to hyperproliferation and culminates in the acquisition of invasive potential, angiogenic properties and establishment of metastatic lesions. This process can be activated by any one of the various environmental carcinogens (such as cigarette smoke, industrial emissions, gasoline vapours), inflammatory agents (such as tumour necrosis factor and H2O2), tumour promoters (such as phorbol esters and okadaic acid). This multistep process of carcinogenesis consists of three phases: tumour initiation, promotion, and progression phases.1 Carcinogenesis is characterized by uncontrolled cell growth and acquisition of metastatic properties. In most cases, activation of oncogenes and/or deactivation of tumour suppressor genes lead to uncontrolled cell cycle progression and inactivation of apoptotic mechanisms.2

Chemoprevention, especially through the use of naturally occurring phytochemicals capable of impeding the process of carcinogenesis at one or more steps, is an ideal approach for cancer management.3 Cancer chemoprevention, by the use of natural, dietary or synthetic agents that can reverse, suppress or prevent carcinogenic progression, has become an appealing strategy to combat the dogma associated
with increasing cases of cancers worldwide. Extensive research in the last few years has revealed that regular consumption of certain fruits and vegetables can reduce the risk of acquiring specific cancers. Phytochemicals derived from such fruits and vegetables, referred to as chemopreventive agents include genistein, resveratrol, diallyl sulfide, S-allyl cysteine, alllicin, lycopene, capsaicin, curcumin, 6-gingerol, ellagic acid, ursolic acid, silymarin, catechins, and eugenol. One of the phytochemical compounds that currently have an important role as an antioxidant is catechins. Catechins are a group of polyphenolic compounds belonging to flavonoid class present in high concentrations in a variety of plant-based fruits, vegetables, and beverages. Many research articles have established that in vitro studies of catechins have the potential to impact a variety of human diseases. The beneficial effect of catechins is reported in the treatment of cancer, cardiovascular diseases, diabetes, neurodegenerative diseases, and liver diseases. Apparently, catechins have function not only as powerful antioxidant, preventing oxidative damage in healthy cells, but also as an antiangiogenic, antitumor agent, and a modulator of tumor cell response to chemotherapy. It can induce apoptosis by increasing caspas and promotes cell growth arrest by altering the expression of cell cycle regulatory proteins. This review describes the molecular mechanism of catechins as a non-toxic natural agent in preventing the tumour progression and/or treatment of human malignancies. Sources and structure of catechins Polyphenols are the most abundant antioxidants in our diets. The main classes of polyphenols are phenolic acids (mainly caffeic acid) and flavonoids (the most abundant in the diet are flavanols (catechins plus proanthocyanidins), anthocyanins and their oxidation products), which account for one- and two-thirds, respectively. Catechins are the main flavanols, which are very abundant in tea. Young shoots contain 200–340 mg of catechin, gallicatechins and their galloylated derivatives per gram of dry leaves. Frequent consumption of tea, an important source of both flavonoids and flavonols, has been correlated with a lower incidence of cancer of the breast, prostate, bladder, lung, pancreas, colon, stomach, oesophagus, and oral cavity. The term catechins are commonly used to refer the family of flavonoids and the subgroup flavan-3-ols or simply, flavanol. Catechins are differentiated from the ketone-containing flavonoids such as quercetin and rutin, which are called flavonols. High concentrations of catechin can be found in fresh tea leaves, red wine, broad beans, black grapes, apricots, and strawberries. Green tea has attracted significant attention recently, both in the scientific and in consumer communities for its health benefits for a variety of disorders, ranging from cancer to weight loss. The beneficial effects of green tea are attributed to the polyphenolic compounds present in green tea, particularly the catechins, which make up 30% of the dry weight of green tea leaves. Also, epicatechin concentrations are high in apples, blackberries, broad beans, cherries, black grapes, pears, raspberries, and chocolate (Table 1).

<table>
<thead>
<tr>
<th>Food</th>
<th>Catechins (mg/100g)</th>
<th>Catechins (mg/serving)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apple</td>
<td>10-45</td>
<td>20-86</td>
</tr>
<tr>
<td>Apricot</td>
<td>10-25</td>
<td>20-50</td>
</tr>
<tr>
<td>Beans</td>
<td>35-55</td>
<td>70-110</td>
</tr>
<tr>
<td>Black tea</td>
<td>6-50</td>
<td>12-100</td>
</tr>
<tr>
<td>Blackberry</td>
<td>9-11</td>
<td>9-11</td>
</tr>
<tr>
<td>Cherry</td>
<td>5-22</td>
<td>10-44</td>
</tr>
<tr>
<td>Chocolate</td>
<td>46-61</td>
<td>23-30</td>
</tr>
<tr>
<td>Cider</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Grape</td>
<td>3-17.5</td>
<td>6-35</td>
</tr>
<tr>
<td>Green tea</td>
<td>10-80</td>
<td>20-160</td>
</tr>
<tr>
<td>Peach</td>
<td>5-14</td>
<td>10-28</td>
</tr>
<tr>
<td>Red raspberry</td>
<td>2-48</td>
<td>2-48</td>
</tr>
<tr>
<td>Red wine</td>
<td>8-30</td>
<td>8-30</td>
</tr>
<tr>
<td>Strawberry</td>
<td>2-50</td>
<td>2-50</td>
</tr>
</tbody>
</table>

Table 1. Sources of catechin widely distributed in food

Apples contain a variety of polyphenols including quercetin, catechin, chlorogenic acid, all of which are strong antioxidants. Strawberries were found to contain the most complex mixture of catechins, comprising catechin (75% of total catechins), (−) epicatechin-3-gallate (ECG) 18% of total catechins, (−) epigallocatechin (EGC) 5% of total catechins, and (+) gallatechin (GC) 3% of total catechins. There are many vegetables, which are good sources of catechins. Catechins and type B proanthocyanidins have not been found in leafy greens or root vegetables but have been detected in legumes such as broad and green beans. The beneficial effects of green tea are attributed to the polyphenolic compounds present in green tea, particularly the catechins, which make up 30% of the dry weight of green tea leaves. Catechins are the major building blocks of tannins when they join, they are also known as proanthocyanidins. These compounds are most common in the seeds and skins of grapes that have not fully ripened. There are several polyphenolic catechins in green tea, viz. (−) epicatechin (EC), EGC, EGC, (−) epigallocatechin-3-gallate (EGCG), (+) catechin, and GC (Figure 1). EGCG, the most abundant catechin in green tea, accounts for 65% of the total catechin content. A cup of green tea may...
contain 100–200 mg of EGCG. Catechin and gallo-
catechin are present in trace amounts. Most of the
medicinal properties of green tea are associated with
the epicatechins (2R, 3R) rather than the catechins
(2S, 3R).

Figure 1. Structures of the major polyphenolic catechins present in green tea.6

It is well known that oncogene mutation and re-
active oxygen species (ROS) play important roles in
the cancer initiation stage. Oncogene mutation leads
to procarcinogen activation by activating some phase
I enzymes such as the cytochrome P450s. ROS ac-
tively participate in the metabolic activation of pro-
carcinogens. EGCG can neutralize these procarci-
nogens by inhibiting the activity of cytochrome
P450 enzymes and modulating ROS. Initiation pha-
se, catechins are able to neutralize the procarci-
nogens by inhibiting the activity of cytochrome
P450 enzyme and modulating free radicals.21 Wang
et al. proved that catechins were able to inhibit the
activity of Nicotinamide adenine dinucleotide phos-
phate (NADPH)-cytochrome c reductase. Mukhtar
et al. also claimed that EGCG could interact with he-
patic cytochrome P450 and inhibit the P450-dependent
mixed-function oxidase enzymes in skin and liver.22 The epicatechin derivative structure is capa-
bile in inhibiting microsomal enzyme system derived
from the catechin hydroxyl group.23 The pyrogallol
structure causes catechin molecules to have a strong
metal-chelating ability that can bind to metal transition
ions and act as preventive antioxidants. Its high
affinity for the two layers of lipid cell membrane
makes it easier for catechin molecules to enter the
nucleus of cancer cells.25

The initiation and progression of cancer are related
to epigenetic alterations, including aberrant DNA
methylation and acetylation. Cancer is modulated by
both genetic and epigenetic events. Epigenetic
events could alter gene expression without changing
the primary DNA sequence, and epigenetic mechani-
isms include DNA methylation and histone ace-
tylation. These epigenetic changes are involved in
the alteration of gene function and expression, lea-
ding to a malignant cellular formation. Among vari-
ous epigenetic modifications, DNA methylation is
most extensively studied in mammals.24 Hyperme-
thylation on the DNA molecule limits the binding of
transcription factors to promoters, resulting in the
recruitment of additional silencing-associated proteins
and gene silencing. This methylation is mediated by
DNA methyltransferase (DNMT).25 EGCG has been
known as an inhibitor of DNMT by direct inhibitory
interaction with the catalytic site of DNMT. The
EGCG increases levels of acetylation on lysine of
histone H3 and histone H4, leading to the up regu-
lation of tumor-suppressor genes p16INK4a, and
Cip1/p21 in skin carcinoma cells.25

ROSs are critical signalling molecules that modu-
late anticancer effects. First, EGCG could directly
scavenge ROS. The antioxidant activity of EGCG
results from the transfer of hydrogen atom or single-
electron transfer reactions, involving hydroxyl
groups of the B and/or D rings. The antioxidant
effect of EGCG is related to anticancer function. The
EGCG reduces cell proliferation and induces apop-
tosis in low-dose H2O2 (10M)-treated colon carci-
nomacells and down regulates 12-O-tetradecanoyl-
phorbol-13-acetate-mediated oxidative stress in
cervical carcinomacells.26

The cancer promotion stage is a reversible and a
long-term process, in which some intracellular sig-
alling pathways and proteins associated with cell
cycle are involved. EGCG exerts its anticancer effect
by interfering with many signalling pathways and
modulating cell cycle. The inhibitory mechanism of
the promotion stage is divided into three process,
namely the intervention of intracellular signalling
pathways, increases the caspase activity, and cell
cycle modulation. Yamamoto et al. showed that ca-
techins inhibit phosphorylation of extracellular signal-regulated protein kinases (ERK)-1 and 2 and suppress the activity of p38MAPKs in human fibrosarcoma cells. The ERK enzymes are important transducers of proliferation signals. Alshawti evaluated the role of catechin hydrate (CH) in suppressing proliferation of MCF-7 cells through TP53/caspase mediated apoptosis. CH exhibits anticaner effects by blocking the proliferation of MCF7 cells and inducing apoptosis in part by modulating expression levels of caspase-3, -8, and -9 and p53. The induction of apoptosis by CH is affected by its ability to regulate the expression of pro-apoptotic genes such as caspase-3, -8, and -9 and p53. Nakazato et al. found that EGCG induced apoptosis in human multiple myeloma cells. Most anticancer agents have been reported to kill tumour cells by inducing apoptosis via the mitochondrial apoptotic pathway, or via the death receptors. Apoptosis has been known as a key strategy for the elimination of cancer cells. The ratio between anti-apoptotic Bcl-2 families (Bcl-2 and Bcl-xL) and pro-apoptotic Bcl-2 families (Bax and Bak) decides the cellular susceptibility against anticancer drugs in cancer cells. Furthermore, BH3-only proteins (PUMA, Noxa, and Bim) bind with anti-Bcl-2 proteins to inhibit their functions, resulting in induction of apoptosis. EGCG induces apoptosis by the down-regulation of Bcl-2 and/or up-regulation of Bax expression in nasopharyngeal carcinoma cells. However, another research found that catechin, particularly EGCG, did not modulate the apoptotic pathway, but predominantly induced caspase-independent cell death in accordance with the necrotic morphology. The EGCG induced necrotic cell death via a caspase-independent mechanism in chronic myelogenous leukemia (CML) cell lines, without influencing any of the apoptotic pathway. Katunuma et al. reported that the tea catechin derivatives are shown to inhibit activities of caspases-3, 2 and 7 in vitro, and prevented experimentally alapoptosis at the cell and animal levels. Epigallocatechin-gallates showed the strongest inhibition to these caspases, but cysteine cathepsins and caspase-8 were not inhibited.

Catechins can also inhibit the cell cycle. The cell cycle is controlled by numerous mechanisms ensuring correct cell division. The mechanisms are regulation of cyclin-dependent kinases (CDK) by cyclins, CDK inhibitors and phosphorylating events. Cell-cycle dysregulation is a hallmark of tumor cells. The ability of normal cells to undergo cell-cycle arrest after damage to DNA is crucial for the maintenance of genomic integrity. The biochemical pathways that stop the cell cycle in response to cellular stressors are called checkpoints. Defective checkpoint function results in genetic modifications that contribute to tumorigenesis. The regulation of checkpoint signalling also has important clinical implications because the abrogation of checkpoint function can alter the sensitivity of tumour cells to chemotherapeutics. Mayr et al. evaluated the cytotoxic effect of EGCG alone or in combination with cisplatin on eight BTC cell lines. The EGCG reduced the mRNA levels of various cell cycle-related genes while increasing the expression of cell cycle inhibitor p21 and the apoptosis-related death receptor 5. This observation was accompanied by an increase in caspase activity and cells in the sub-G1 phase of the cell cycle, indicating induction of apoptosis. EGCG also induced a down-regulation of expression of stem cell-related genes and genes that are associated with an aggressive clinical character of the tumour, such as CD133 and ABCG2. The function of catechin is also related to cell cycle modulation in the cancer cell. Nihal et al. showed that catechins can inhibit Cdk1 and Cdk2 activities as well as CK1 initiation such as p16, p21, and p27 in melanoma. Kavanagh et al. found that p27 capable of stopping cell cycle arrest was induced by catechins in breast cancer. Another study reported by Hastak et al. showed that catechins were able to block the cell cycle, especially in the dependent p53 pathway which involved the function of p21 and Bax in prostate carcinoma cells. Mayr et al. reported a reduction in regulatory genes triggering cell cycle such as cCNA2, cCNA1, cENDL, and e2F1 due to catechin administration, whereas p21 expression which was a cell cycle inhibitor and also dr5 gene associated with apoptosis increased. This condition affected mRNA expression followed by increased activity caspase, subG1 population (an indication of apoptosis), decrease in population G2/M (an indication of cell cycle arrest) in bladder cancer cells. Carcinogenesis involves uncontrolled cell growth, which follows the activation of oncogenes and/or the deactivation of tumour suppression genes. Metastasis requires down-regulation of cell adhesion receptors necessary for tissue-specific, cell-cell attachment, as well as up-regulation of receptors that enhance cell motility. Inhibition of migration and invasion of tumor cells could be a target of anticancer therapy. Catechin resistance at the stage of cancer progression is its role in inhibiting MMP. This enzyme is a protease that can degrade almost all com-
ponents of the extracellular matrix. Catechins are able to inhibit MMP-2 and MMP-9 in endothelial cells.\textsuperscript{38} MMP-2 and MMP-9 secretion is elevated in several types of human cancers and their elevated expression has been associated with poor prognosis. Expression of MMPs is highly regulated by cytokines and signal transduction pathways, including those activated by phorbol 12-myristate 13-acetate (PMA).\textsuperscript{38}

Angiogenesis, the development of new capillaries from pre-existing blood vessels, is required in physiological processes such as wound healing and pathological conditions including tumour growth and metastases. Tumour angiogenesis is a complex process that consists of several steps including the secretion of angiogenic factors by tumour and host cells, activation of proteolytic enzymes, endothelial cell migration, invasion, endothelial cell proliferation, and capillary formation. Vascular endothelial growth factor (VEGF) and its receptors have been known as the important angiogenic factors and are commonly over expressed in several types of human cancers. Catechins especially EGCG is proved to inhibit tumour growth and angiogenesis by the down-regulation of VEGF expression in serum-deprived HT29 human colon cancer cells.\textsuperscript{39} Leong et al. also found that green tea extract inhibits angiogenesis partly through the disruption of STAT3-mediated transcription of genes, including VEGF.\textsuperscript{40} Several members of the signal transducers and activators of transcription (STAT) family play a role in tumorigenesis. The STAT3 activity is commonly up-regulated in breast cancer and regulates the expression of angiogenic genes including VEGF and MMP-9.\textsuperscript{40}

CONCLUSION

This review presents evidence that catechins can be used not just to prevent cancer but also to treat cancer because of their effects in the initiation, promotion, and progression stages. Catechins, especially EGCG promotes anticancer effects by modulation of multiple processes, including inhibition of carcinogen activity, tumorigenesis, proliferation, apoptosis induction, cell cycle arrest, metastasis, and angiogenesis. Based on the molecular mechanisms of the EGCG-induced anti-cancer effect, further studies are needed to define the use of catechins in clinical treatment.

Conflict of interest

The author declares no conflicts of interest.

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