Mini Review: Antitumor promotion as the best strategy for chemoprevention

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Abstract: Transformation of normal cell to cancer cell is known to be a multiple step process known as carcinogenesis. A lot of chemopreventive agents have been isolated from plant derived phyto compound reported to exhibit potent anticancer activity in many cancer models in vitro and in vivo as they can inhibit the crucial process during carcinogenesis. Carcinogenesis comprises of three stages, namely initiation, promotion and progression. Due to multistep process of carcinogenesis, opportunities exist for intervention at any stages including promotion. Targeting promotion stage during carcinogenesis has become a promising approach in chemoprevention by inhibition of main events involved in this stage such as sustain cell proliferation and altered gene expression.

Keywords: Anticancer, carcinogenesis, chemoprevention, proliferation, promotion.

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I. Introduction

The huge impact on health, social and economic due to cancer has led the attention of experts to develop cancer prevention strategies, including dietary control, lifestyle changes, new anticancer drugs and also chemoprevention. Currently, experts believe that the method of chemoprevention is one of the most promising approaches, although there is still a controversy about the effectiveness of the supplements or drugs with anticancer effects among clinicians. This review briefly focuses on the carcinogenesis, chemoprevention, promotion stage of carcinogenesis and the strategy of targeting promotion stage for chemoprevention, well as the most common models used in antitumor-promotion study. The objective(s) of this review is to justify the beneficial strategy of targeting tumor promotion stage to fight cancer development and progression and to identify the mode of action of several plant-based antitumor agents that have been studied on antitumor-promotion in vitro or in vivo.

II. Basic Of Carcinogenesis

Cancer is a cellular pathological condition, which is characterized by uncontrolled growth and cell division of abnormal cell. It affects all groups of age, gender, social class, race and ethnicity[1]. Cancer can be developed in any part of the body and in any organ or tissues. In normal cell, cell division is tightly controlled by expression and activation of multiple series of protein regulators. Changes in these processes will result in an abnormal function of cell cycle. Cells that undergo these changes will transform and lose their normal functions. This will eventually be followed by the abnormal cell rising in number faster than the normal cell, thus leads to the development of tumor [2].

The unregulated tumor growth is characterized by DNA damage, which results in mutation of genes that are responsible for encoding proteins that control cell division. These mutations can be caused by external exposure to chemical agents, radiations or by certain viruses, and by internal factors such as inherited mutation, hormones and immune status. Mutation occurs spontaneously, and may be passed down from one generation to the next generation as a result of mutations within germ lines [2].

Transformation of normal cell to cancer cell is known to be a multiple step process known as carcinogenesis. Carcinogenesis comprises of three stages, namely initiation, promotion and progression. The process begins when cells are initiated by carcinogenic/mutagenic agents, which apparently cause genetic mutations in genes. It is ubiquitously known that genes play a role in the process of cell growth. This stage is irreversible and the cell with altered genes is at higher risk of neoplastic transformation. However, initiation alone is insufficient for tumor formation [3]. In promotion, the subsequent changes of an initiated cell leading to neoplastic changes may require repeated and prolong exposure to promoting stimuli such as oxidative stress and, inflammation together with accumulation of genetic alteration. In contrast to initiation, the promotion phase is reversible. It will lead to clonal expansion of initiated cell [4]. The term progression refers to the stepwise transformation of pre-neoplastic cell into cell with higher malignancy. The mechanism of tumor progression is
poorly understood, however, accumulation of gene mutations and chromosomal aberrations are thought to be involved \cite{5}. At this stage, tumor is characterized by rapid clonality, anaplasia, invasion, metastasis and coupled with alteration in the biochemistry and morphology of the cell\cite{5-6}.

**III. Chemoprevention**

Over decades of research have shown that cancer is easier to prevent than cured \cite{7}. The areas of chemoprevention research have developed to the point where it is now considered to be a tremendously promising method for the prevention of cancer. Cancer prevention approaches by using chemopreventive agents have the potential to make a significant contribution to the decreasing incidence of cancer morbidity and mortality through early intervention for individuals who are at high risk. The important concept that must be emphasized is early intervention, which is, before transformation or before carcinogenesis progresses to invasive form, when it can still be arrested, slowed, or reversed.

Chemoprevention is defined as the use of non-cytotoxic nutrients or pharmacologic compounds that delay, inhibit or reverse the development and progression of mutant clones of malignant cells \cite{8}. Due to multistep nature of carcinogenesis, opportunities exist for intervention at an early stage as well as later stages of the process (Fig. 1). Chemopreventive agents are diverse with respect to source, chemical structure and pharmacological effects that include micronutrients such as vitamin and minerals, natural products, and synthetic compounds \cite{8}. Chemopreventive agents that can target a single or multiple tumorigenesis stages are of advantage to be discovered.

Some agents have been found to act as both blocking and suppressing agents \cite{9}. Chemopreventive agents make target tissue less vulnerable to neoplastic transformation by producing cellular maturation, decreasing the function of target cells and by decreasing cell proliferation \cite{10-11}. Natural, synthetics or micronutrients, that exhibit any or a combination of these biological activities qualify as a chemopreventive agents. Chemopreventive agents can be very competent if they are able to significantly delay the tumor onset, reduce tumor incidence and prevent tumor progression \cite{12}.

The use of medicinal plant to manage or arrest carcinogenesis has provided an alternative to the use of conventional therapy. Many herbs have been evidenced in experimental and/or clinical trials to exhibit antitumoral properties against various cancers \cite{13}. Citrus peel for instance, has been described to possess potential chemopreventive properties. Ethanolic extract of *C. reticulata* peel is able to reduce N-Ras expression in DMBA-induced liver cell and suppress c-Myc expression *in vivo*. Meanwhile, *C. aurantiifolia* showed positive inhibition of carcinogenesis in DMBA-induced mammary glands in Sprague dawley rats via induction of apoptosis and inhibition of cell proliferation \cite{14}. The peels of *C. aurantiifolia* contain a number of flavonoids like naringin, hesperidin, naringenin, hesperitin, rutin, nobiletin and tangretin\cite{14-15}.

![Illustration of stepwise neoplastic transformation and potential targets for chemopreventive agents to inhibit carcinogenesis.](image)
Genistein is a phytocompound found in a wide variety of food, mostly soy. Genistein particularly from soy acts as an anti-estrogen and shows antiproliferative effects against breast cancer cells [16]. Soy consumption has been correlated with reduced risk of breast cancer in numerous epidemiological studies [17]. Genistein acts as an anti-carcinogen in estrogen receptor α-breast cancer predominantly at dose 10μM [18]. In regards to prostate cancer, genistein through soy intake has been implicated in epidemiological studies to be associated with reduced risk of prostate cancer. In vitro results suggested that genistein inhibits nuclear factor-κB (NF-κB) in various cells and suppresses metalloproteins that are associated with cancer [19]. Other possible mechanisms of action include prevention of an up-regulation in 5α-reductase activity in the prostate from high-fat diet [20]. These results have been applied to animal models showing genistein intervention possesses anti-carcinogenic activity through reducing the risk of metastasis [21].

Resveratrol is a polyphenol compound presents in grapes. Resveratrol is formed in two isomeric structures, i.e. trans-resveratrol and cis-resveratrol. Trans-resveratrol is commonly known as an active form of resveratrol in which its actions include modulation of inflammation and antiproliferative activity in selected cancer cells [22, 23]. In addition, resveratrol is also able to suppress genes that are induced by NF-κB in response to inflammation and halt cancer progression in some experimental models [24]. Resveratrol may also suppress cell-cycle related proteins like Cyclin D1, Cyclin E and Cyclin-dependent kinase (CDK), which can block the Protein Kinase B (AKT) pathway in rat smooth muscle cells, bladder and liver cancer cells [25-27].

Curcumin is the yellow color substance associated with the spice turmeric, scientifically known as *Curcuma longa*. It exerts potent anti-inflammation effects, and this anti-inflammatory effect appears to be a protective factor against progression in a number of cancer cells [28]. Curcumin has been shown to impede multiple cell signaling pathways including apoptosis, proliferation, cell cycle, angiogenesis, invasion and metastasis [29-31]. Low dose of curcumin fed rats were able to prevent formation of DNA adducts in DMBA-induced hepatic and colonic cells [32, 33]. Curcumin treatment in vitro has been shown to induce bladder and B-cell chronic lymphocytic leukemia cancer cells death [34, 35]. Moreover, curcumin has been shown to have large safety threshold in which no toxicity effect could be seen, even cells that were exposed at high doses [36]. In spite of low toxicity, curcumin is also known for its low bioavailability. Intravenous administration, as well as nanoformulation has been shown to increase curcumin bioavailability compared to unformulated and oral route respectively [37-38].

Quercetin is a flavonoid found in vegetables and fruits and abundantly found in onions and apples. Similar to many other flavonoids, quercetin has anticancer, antioxidant and anti-atherogenic properties [39,41]. A number of its actions make it a promising anticancer agent, such as inhibition of tyrosine kinase, cell cycle regulation and overcoming anti-apoptotic mutation in drug resistant human tumors [42]. Quercetin is also reported to inhibit the androgen receptor expression at the transcriptional level, and downregulate the androgen-inducible genes such as PSA, hK2, NKK3.1 and ODC, which play crucial roles in growth and progression of prostate cancer [43]. Apart from that, it was also reported to induce MCF-7 cells apoptosis by inducing G0/ G1 phase arrest and regulating the expression of survivin in MCF-7 cells, which may be the essential mechanism in its anticancer effect [44].

Annonaceousacetogenin is a group of bioactive compounds isolated from the plant of Annonaceae family. Acetogenins consist of C35/C37 long chain fatty acids derived from the polyketide pathway. Biogenetically, annonaceousacetogenin is derived from C32/C34 fatty acids combine with a 2-propanol unit at C-2 to form methyl-substituted α,β-unsaturated γ-lactone [45]. Several oxygenated functional groups, such as epoxide, ketone, hydroxyl, tetrahydropyran (THP) and tetrahydrofuran (THF) may be present, as well as double and triple bonds. Majority of annonaceousacetogenins showed potent cytotoxicity against various cancer models in vitro and in vivo through inhibition oxidative phosphorylation and cytosolic ATP production. Hence lead to deprivation of cancer cells for ATP resulting in apoptosis of the cancer cell [46, 47]. The other most popular reported chemopreventive agents and their mechanism of action in carcinogenesis of various experimental models are shown in Table 1.

Therefore, there are a growing number of evidences regarding plant phytocompounds that exhibit antitumor properties with low and/or negligible toxicity. Further exploration on plants and plant-derived phytocompounds in suppressing carcinogenesis may result in the discovery of potent anticancer agents.

**Table 1** Selected chemopreventive agents and their effects reported in various experimental models.

<table>
<thead>
<tr>
<th>Number</th>
<th>Phytochemicals</th>
<th>Source</th>
<th>Mechanism of actions</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tangeretin</td>
<td>Key lime</td>
<td>Induce apoptosis, inhibit cell proliferation, inhibit growth and invasion</td>
<td>Meiyanoto et al., 2011 [44]; Kandaswami et al., 1991 [40]</td>
</tr>
<tr>
<td>2</td>
<td>Genistein</td>
<td>Soy</td>
<td>Inhibition of carcinogen activation and inflammation</td>
<td>Wei et al., 1998 [42]</td>
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- homeostasis and thus activate ERK1/2, AKT and NF

- inhibition of endogenous antioxidant enzymes such as GSH

- and MAPK/ERK -

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- reports of pharmacological studies we have r

- of sustained cell proliferation have been marked as an important cellular process during this stage. From the 40 reports of pharmacological studies we have reviewed for this article, more than 50% of chemopreventive agents act on promotion stage showed inhibition of cell proliferation followed by 35% for induction of apoptosis. In comparison to the initiation stage which is an irreversible process, the promotion stage occurs over to an extended period of time that may be reversible during the tumorigenesisprocess [59, 60]. Upon induction by the tumor promoter such as TPA, a number of key events have been recognized in tumor promotion including severe hyperplasia, sustained cell proliferation, inflammation, and oxidative stress [4, 61]. The aforementioned events were occurred due to activation of protein kinase C (PKC) signal transduction, increased in ornithine decarboxylase (ODC) activity and accumulation of polyamines in tumor cells [62, 63]. Moreover, PKC has also been shown to activate the Ras/Raf/PI3K and MAPK/ERK pathwaysthat eventually mediatethe cell proliferation [64, 65].

- It has been shown that during carcinogenesis, single and multiple applications of tumor promoter upregulate the expression of TGFα and IGF-1 [66-68]. High expression level of TGFα and IGF-1 leads to the activation of the RAS/RAF/PI3K/AKT/MTOR pathways [69, 70]. The upregulation of ERK, AKT and MTOR has been implicated in tumorogenesis by acceleration of cell proliferation and avoidance of apoptosis [71]. Since sustained cell proliferation is a hallmark for tumor promotion, the crosstalk between the two signaling pathways, RAS/RAF/PI3K/AKT and PI3K/AKT/MTOR play an important role in many human carcinogenesis due to mutation, gene amplification and receptor upregulation [4, 72].

- It is widely known that there is a strong association between inflammation and carcinogenesis [73, 74]. In fact, tumor promoting inflammation has been identified as one the hallmark of cancer [2]. There is a large body of growing evidence showing that inflammation can eventually lead to carcinogenesis in different organs such as skin, stomach, prostate, colon, breast and pancreas [2, 73, 75,77]. Two major transcription factors namely, NF-kBand TNF-α play an essential role in inflammation as well as in immunity [73]. Deregulation of its function was later identified to be responsible for the various steps in cancer initiation and progression [78]. Besides, another inflammation biomarker, COX-2-derived prostaglandins, also act as endogenous tissues tumor promoters via induction of inflammation, angiogenesis, cell proliferation and anti-apoptosis [75, 76].

- A great number of evidences have shown an association of excess free radicals with carcinogenesis. Potentially, tumor promoter stimulates theproduction of free radicals in inflammatory cells and keratinocyte and inhibits the activity of endogenous antioxidant enzymes such as GSH-Px, catalase and superoxide dismutase [79, 80]. Oxidative stress can also affect the intracellular signaling via substrates that are sensitive to redox homeostasis and thus activate ERK1/2, AKT and NF-xB [4, 71, 81]. Signaling pathways that promote cell survival as well as activation of JNK, p38, and p53 could result in cell cycle arrest and induction of apoptosis [4, 81]. Besides that, AKT and its anti-apoptotic pathways can also be activated by inhibition of PTEN due to oxidation of its active site [82].
V. Anti-Promotion As A Promising Approach For Chemoprevention

Since the carcinogenesis is a multistage and slow process researchers believes that the primary target of chemoprevention is to reduce the number of initiated cells, inhibit the promotion of initiated cells and reverse the promotion process at an early stage. There are many strategies that may be beneficial for chemoprevention. The selection of antipromotion is based on the reasoning that it is possibly a better approach to prevent cancer at the promotion stage since: (i) the promotion stage of multistage carcinogenesis is a long process and reversible at an early stage, thus there will be a sufficient time for chemopreventive agent to inhibit, suppress or reverse the promotion process; (ii) the initiation stage of multistage carcinogenesis is irreversible and possibly inevitable due to continuous exposure to carcinogenic physical and chemical agents \[^{[83, 84]}\]; (iii) since progression/metastasis is the most challenging part related to cancer treatment and is the major cause of cancer-related death, targeting latest stage of carcinogenesis will be less relevant to the chemoprevention objectives that to reduce cancer mortality and morbidity; (iv) among the diverse pathways, main mechanisms contributing to anticancer activity involves the inhibition of signal transduction pathways that disturb the effects of tumor promoters \[^{[4, 7, 85]}\]. It is important to highlight that carcinogenesis is a multistep process in experimental models and possibly in human cancer induction, development and progression \[^{[83, 84]}\]. Human malignancies, however, also appear to involve a gradual accumulation of genetic changes and frequent events of altered expression occurred in various genes over a period of years predominantly at promotion stage\[^{[84, 86]}\] (Table 2). Therefore, the inhibition of tumor promotion is expected to be an effective approach in controlling cancer growth.

In general, antitumor agents can be classified into two categories depending on their targeted point(s) during carcinogenesis \[^{[96]}\]. The first category is known as tumor-blocking agent and acts on initiation stage of carcinogenesis. This agent aims to protect the normal cell from exposure of negative effect of carcinogen. This eventually will prevent or inhibit the cells from cellular damage and mutation \[^{[97]}\]. Number of mechanism exerted by tumor-blocking agents include inhibition of carcinogen activation, modulation of carcinogen-induced genotoxicity, carcinogen detoxification, scavenging of excess free radicals, induce DNA repair mechanism and halt the inflammation process \[^{[1, 7, 10, 98-100]}\].

On the other hand, the second category is known as tumor-suppressing agent. This agent affects the later stages of carcinogenesis, promotion and progression by decreasing the capability of cell proliferation of initiated cells due to carcinogen exposure \[^{[101]}\]. The mechanisms reported by previous study by tumor-suppressing agents include inhibition of cellular signal transduction such as EGFR, PKC/MAPK and NF-κB \[^{[54, 70, 88]}\]. Besides that, tumor-suppressing agent also showed its antitumor-promoting activities via suppression of tumor growth, induction of apoptosis, modulation of the immune system, inhibition of ODC and inhibition of cell proliferation \[^{[1, 7, 10, 96, 98-102]}\]. However, this classification is not absolute, because the mechanism of action of chemoprevention can take place in a continuous manner and interrelated between stages in the whole process of cancer cell development.

<table>
<thead>
<tr>
<th>Number</th>
<th>Mechanisms</th>
<th>Molecular targets</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Inflammation</td>
<td>COX-2, p38, TNF-α</td>
<td>Patel et al., 2008[^{[87]}]; Afaq et al., 2004[^{[90]}]; Khan et al., 2012[^{[91]}]</td>
</tr>
<tr>
<td>2</td>
<td>Sustained cell proliferation</td>
<td>ODC, p27, p21, Cyclin D</td>
<td>Afaq et al., 2010[^{[92]}]; Khan et al., 2012[^{[93]}]</td>
</tr>
<tr>
<td>3</td>
<td>Inhibition of apoptosis</td>
<td>Bax, Bcl-2, Caspases</td>
<td>Roy et al., 2008[^{[94]}]; Nigam et al., 2009[^{[95]}]; Narayanapilai et al., 2012[^{[96]}]</td>
</tr>
<tr>
<td>4</td>
<td>Modulation of cellular signals transduction/ altered gene expression</td>
<td>NF-κB, EGFR, PKC, AP-1, Raf/MEK/ERK, PI3K/PTEN/Akt/mTOR</td>
<td>Patel et al., 2008[^{[97]}]; Milosevic et al., 2014[^{[98]}]; Khan et al., 2012[^{[99]}]</td>
</tr>
<tr>
<td>5</td>
<td>Cell survival</td>
<td>Akt, FJRK</td>
<td>Roy et al., 2008[^{[100]}]; Saleem et al., 2004[^{[101]}]</td>
</tr>
<tr>
<td>6</td>
<td>Oxidative stress</td>
<td>PKC, p53, ERK, JNK, PTEN</td>
<td>Patel et al., 2008[^{[102]}]; Roy et al., 2008[^{[103]}]; Chen et al., 2013[^{[104]}]</td>
</tr>
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VI. Antitumor-promotion models

Numbers of bioassay methods are available in the literature for the screening of potential chemopreventive agents. Assays for screening chemopreventive agent can be divided into in vitro and in vivo primary screening assays, in vivo assay as well as mechanism-based in vitro assay. There are only two methods used in primary screening assay in vitro which are inhibition of EBV-EA activation induced by 12-O-tetradecanoyl-phorbol-13-acetate (TPA) and anti-mutagen assay (AM) \[^{[105]}\]. As for in vivo primary screening assay, there are only three methods commonly used, i.e. inhibition of croton oil induced ear edema, inhibition of TPA induced ear edema and inhibition of teleosidin induced ear edema. To date there are 21 methods available...

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6.1 In vitro model: inhibition of Epstein-Barr virus early antigen (EBV-EA) activation assay

Epstein-Barr virus-Early antigen (EBV-EA) assay model is an established method that was first developed by Ito and his group. They designed a short-term in vitro assay for detecting tumor promoters by utilizing the activation of Epstein-Barr virus (EBV) expression in Epstein-Barr virus genome-carrying human lymphoblastoid cells i.e. Raji cells. This system is composed of EBV-non-producer Raji cells as the indicator, n-butylate as the EBV-inducer, and the test substance. This assay system allows for a rapid detection of the activity of the tumor promoter such as 12-O-tetradecanoyl-phorbol-13-acetate (TPA). After the reaction, the treated cells are subjected to EBV- positive sera staining from nasopharyngeal carcinoma (NPC) patients and fluorescein isothiocyanate (FITC)-labeled antihuman IgG as primary and secondary antibody respectively. EBV-EA positive cell are counted using fluorescence microscope. Intensity of this fluorescence signal is proportional to EBV-EA activation. Any test substances that inhibits EBV-EA activation could be considered as potential antitumor promoters. Numerous studies have validated that the inhibition of EBV-EA is correlated with antitumor promoting effects in in vivo model of carcinogenesis.

6.2 In vivo model: chemical induced two-stage mouse skin carcinogenesis

There are various animal models used in experimental carcinogenesis studies. One of the models is the two-stage tumorigenesis mouse model, which utilizes tumor initiator (DMBA), followed by repeated applications of tumor promoter (TPA) on the mouse dorsal skin for a certain period. This model is frequently used since skin is proven to be a unique target in differentiating between the effect of a test substance as either an anti-initiator or an anti-promoter under appropriate experimental conditions. In addition, this model can be used to evaluate both new skin cancer prevention strategies and the effect of genetic background and genetic manipulation on three stages of carcinogenesis.

Studies have shown poly-aromatic hydrocarbon (PAH) such as DMBA can be used to determine the process of carcinogenesis in a two-stage mouse skin carcinogenesis. The H-Ras1 mutation appears to be a critical event in the initiation process. Carcinogenic activation begins with biotransformation of DMBA by cytochrome P450 to form proximate carcinogen. Proximate carcinogen is an intermediate metabolite which will undergo further metabolism to the ultimate carcinogen (DMBA epoxides). This epoxide compound covalently binds to the exocyclic amino groups, deoxyadenosine (da) or deoxyguanosine (dg) on DNA. This interaction (DNA adducts) can induce mutations in genes that eventually causes cancer initiation. This DNA adducts are capable of controlling the cell cycle, thus promoting cancer cell division.

Repeated exposures of the tumor promoter, such as croton oil, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and TPA are crucial in order to create genetic alterations that facilitate the progression of malignancy. TPA application promotes cell signaling, increases production of growth factors, generates oxidative stress as well as tissue inflammation. Papillomas generated during two-stage skin carcinogenesis protocol may progress to malignant form of squamous cell carcinoma as early as 20 weeks since treatment begins. This conversion is highly dependent on different mouse strains as follows; (SENCAR> DBA/2≥ CD-1> C3H/He> C57BL/6), as well as dose of initiator and promoter and duration period of treatment (>20 weeks).

VII. Conclusion

In conclusion, tumor promotion results from continuous and persistent activation of multiples signaling pathway that lead to cell proliferation and avoidance of apoptosis. These events can be induced directly by tumor promoter through activation of mitotic pathway, chronic inflammation, excess free radical production and continuous activation of signaling pathway. Thus, it is clear that inhibition of signaling pathway and numbers of molecular mechanisms involved in promotion stage, suggested to be the best target in carcinogenesis. Because most of human cancer development is through a multi-stage process and share a common feature of tumor promoter effect, sustained cell proliferation, as in the mouse skin models. Elucidating the molecular mechanism involved in promotion stage of carcinogenesis should lead to better approaches of human cancer prevention.

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