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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 phytocompound 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 [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[5-6].

III. Chemoprevention

Over decades of research have shown that cancer is easier to prevent than cured [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 [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 [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 [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 [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 [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 [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 [14]. The peels of *C. aurantiifolia* contain a number of flavonoids like naringin, hesperidin, naringenin, hesperitin, rutin, nobiletin and tangretin[14-15].

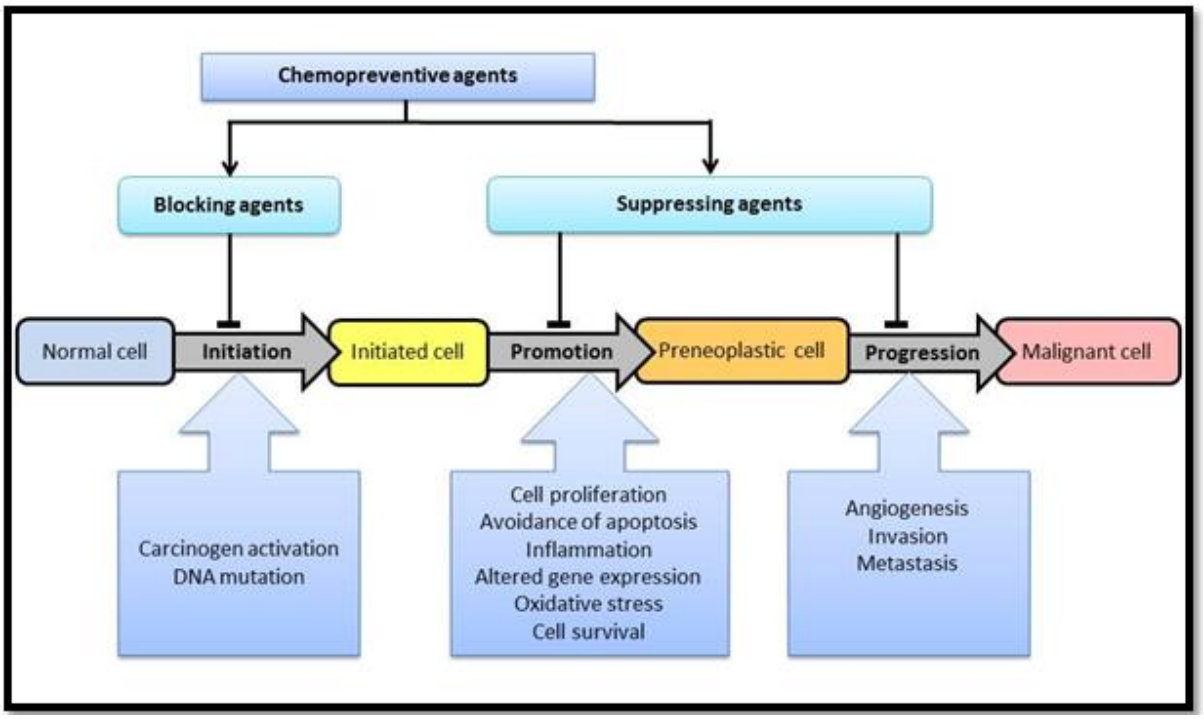

Fig.1 Illustration of stepwise neoplastic transformation and potential targets for chemopreventive agents to inhibit carcinogenesis.

Genistein is a phytocompound found in a wide variety of food, mostly soy. Genistein particularly from soy acts as an anti-estrogen and showsantiproliferative 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-kB) 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-kB 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-inflammatory effect, 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[30]. In spite of low toxicity, curcumin is also known for its low bioavailability. Intravenous administration, as well as nano-formulation has been shown to increase curcumin bioavailability compared to unformulated and oral route respectively [36-38].

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, NKX3.1 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 antitumor 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 annonaceousacetogeninsshowed potent cytoxicity 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 phytochemicals 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.

Number	Phytochcompounds	Source	Mechanism of actions	References
1	Tangeretin	Key lime	Induce apoptosis, inhibit cell proliferation, inhibit growth and invasion	Meiyanto et al., 2011[14]; Kandaswami et al., 1991[48]
2	Genistein	Soy	Inhibition of carcinogen activation and inflammation	Wei et al., 1998[49]

3	Resveratrol	Grapes	Induction of apoptosis	Roy et al., 2009[50]
4	Curcumin	Tumeric	Inhibition of inflammation and cell proliferation, prevent DNA adduct formation, and induction of apoptosis	Anand et al., 2008[28]; Mukundan et al., 1993[32]; Chadalapaka et al., 2008[34]
5	Quercetin	Apple	Induction of apoptosis, inhibition of growth and progression	Xing et al., 2001[43]; Zheng et al., 2013[44]
6	Annonaceousacetogenin	Soursop	Induction of apoptosis	Oberlies et al., 1997[46]; Alali et al., 1999[47]
7	Beta carotene	Carrot	Supressed cell proliferation	Garewal et al., 1995[51]
8	Vitamin E	Palm oil	Supressed cell proliferation	Garewal et al., 1995[51]
9	Ferullic acid	Seed of apple, peanut, orange	Free radical scavenging activity	Thakkar et al., 2015[52]
10	Retinoids	Broccoli	Regressing formation of premalignant lessions	Bukhari et al., 2007[53]
11	Polyphenols	Black tea	Supressed cell proliferation	Patel et al., 2008[54]
12	Vitamin D	Mushrooms	Delayed tumor formation	Mier et al., 2007[55]
13	[6]-gingerol	Ginger	Inhibition of cell proliferation	Park et al., 1998[56]
14	Euglobal-G1	Rose gum	Inhibition of cell proliferation	Takasaki et al., 2000[57]
15	Lycopene	Tomato	Inhibition of cell proliferation and free radical scavenging activity	Bhuvaneswari et al., 2001[58]

IV. Promotion Stage In Carcinogenesis

One of the main events in carcinogenesis is promotion. Induction of cell proliferation and maintenance 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/MAPK 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/MAPK/ERK and PI3K/AKT/MTOR pathways [69, 70]. The upregulation of ERK, AKT and MTOR has been implicated in tumorigenesis 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/MAPK/ERK 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-κBand 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-κB[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 primarytarget 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 antitumor promotion 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 genesover 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, antitumoragents 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 andNF-κB[54, 70, 88].Besides that, tumor-suppressing agentsalso 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 2 Major mechanism and its molecular targets involved in promotion stage of carcinogenesis.

Number	Mechanisms	Molecular targets	References
1	Inflammation	COX-2, p38, TNF-α	Patel et al., 2008 [54]; Afaq et al., 2004[87]; Khan et al., 2012[88]
2	Sustained cell proliferation	ODC, p27, p21, Cyclin D	Afaq et al., 2010[89]; Khan et al., 2012[90]
3	Inhibition of apoptosis	Bax, Bcl-2, Caspases	Roy et al., 2008[91]; Nigam et al., 2009[94]; Narayanapilai et al., 2012[95]
4	Modulation of cellular signals transduction/ altered gene expression	NF-κB, EGFR, PKC, AP-1, Raf/MEK/ERK, PI3K/PTEN/Akt/mTOR	Patel et al., 2008[54]; Milosevic et al., 2014[70]; Khan et al., 2012[90]
5	Cell survival	Akt, PI3K	Roy et al., 2008[91];Saleem et al., 2004[93]
6	Oxidative stress	PKC, p53, ERK, JNK,PTEN	Patel et al., 2008[54]; Roy et al., 2008[91]; Chen et al., 2013[92]

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) [103]. 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

for *in vivo* assay[104]. These assays employ several animal models with different cancer tissues induced with different initiator and promoter. Other than that, mechanism-based *in vitro* assays have also been used in chemoprevention study to elucidate which mechanisms are involved in anticancer activity such as inflammation, apoptosis, cellular proliferation, cellular differentiation as well as other mechanisms [103, 104].

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 [105]. 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-butyrate 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 promoter [106]. Numerous studies have validated that the inhibition of EBV-EA is correlated with antitumor promoting effects in *in vivo* model of carcinogenesis[107-109].

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 [84]. 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 [110]. 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 [84].

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[107-109]. The *H-Ras1* mutation appears to be a critical event in the initiation process [84]. 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 [111].

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 [112]. 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) [59, 112, 113].

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 ofcarcinogenesis should lead to better approaches of human cancer prevention.

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References

[1] S. Manoharan, R.B. Singh, and S. Balakrishnan, Chemopreventive Mechanisms of Natural Products in Oral, Mammary and Skin Carcinogenesis: An Overview, *The Open Nutraceuticals Journal*, *2*(*1*), 2009, 52-63.

[2] D. Hanahan, and R.A. Weinberg, Hallmark of cancer, in J.K David et al, (Ed.), *Oxford Textbook of Oncology* 3, (Kettering, UK: Oxford University Press, 2016) 3-10.

[3] J.M. Cullen, R. Page, and W. Misdorp, in J.M. Donald, *An Overview of Cancer Pathogenesis, Diagnosis, and Management*, (Iowa: Iowa State Press, 2008) 1-44.

[4] J.E. Rundhaug, and S.M. Fischer, Molecular Mechanisms of Mouse Skin Tumor Promotion. *Cancers*, *2*(*2*), 2010, 436-482.

[5] B. Alberts, A. Johnson, J. Lewis, M. Raff, K. Roberts, and P. Walter, *Molecular biology of the cell*. (New York: Garland Science, 2002).

[6] P. Duesberg, and R. Li, Multistep Carcinogenesis: A Chain Reaction of Aneuploidizations. *Cell Cycle*, *2*(*3*), 2003, 201-209.

[7] Y.N. Gholse, and S.R. Yadav, Developement in nutraceuticals for chemoprevention: a review. *International Journal of Pharmacy & Technology*, *4*(*1*), 2012, 1950-1973.

[8] P. Greenwald, G. Kelloff, C.B. Whitman, and B.S. Kramer, Chemoprevention. *Cancer Journal of Clinicians*, *45*(*1*), 1995, 31-49.

[9] L.W. Wattenberg, Inhibition of Carcinogenesis by minor Anutrient Constituents of the Diet. *Proceedings of the Nutrition Society*, *49*(*2*), 1990, 173-183.

[10] M. Levi, R. Borne, J. Williamson, A Review of Cancer Chemopreventive Agents. *Current Medicinal Chemistry*, *8*(*11*), 2001, 1349-1362.

[11] I.A. Siddiqui, V. Sanna, N. Ahmad, M. Sechi, and H. Mukhtar, Resveratrol nano-formulation for cancer prevention and therapy. *Annals of the New York Academy of Science*, *1348*(*1*), 2015, 20-31.

[12] A. S. Tsao, E.S. Kim, and W.K. Hong, Chemoprevention of cancer. *Cancer Journal of Clinicians*, *54*(*1*), 2004, 150-180.

[13] A. Desai, G. Qazi, R. Ganju, M. El-Tamer, J. Singh, A. Saxena, Y.S. Bedi, S.C. Taneja, and H. Bhat, Medicinal Plants and Cancer Chemoprevention. *Current Drug Metabolism*, *9*(*7*), 2008, 581-591.

[14] E. Meiyanto, A. Hermawan, and A. Anindyajati, Natural Products for Cancer-Targeted Therapy: Citrus Flavonoids as Potent Chemopreventive Agents. *Asian Pacific Journal of Cancer Prevention*, *13*(*2*), 2011, 427-436.

[15] S. Choi, H. Ko, S. Ko, J. Hwang, J. Park, S. Kang, S.H. Han, S.H. Yun, and S.J. Kim, Correlation between Flavonoid Content and the NO Production Inhibitory Activity of Peel Extracts from Various Citrus Fruits. *Biological and Pharmaceutical Bull*etin, *30*(*4*), 2007, 772-778.

[16] G.G. Kuiper, J.G. Lemmen, B. Carlsson, J.C. Corton, J. C.,S.H. Safe, P.T. Van der Saag, B. van der Burg, and J.A. Gustafsson, Interaction of Estrogenic Chemicals and Phytoestrogens with Estrogen Receptor β. *Endocrinology*, *139*(*10*), 1998, 4252-4263.

[17] K.B. Bouker, and L. Hilakivi-Clarke, Genistein: Does It Prevent or Promote Breast Cancer? *Environmental Health Perspectives*, *108*(*8*), 2000, 701-708.

[18] T.T. Wang, N. Sathyamoorthy, and J.M. Phang, Molecular effects of genistein on estrogen receptor mediated pathways. *Carcinogenesis*, *17*(*2*), 1996, 271-275.

[19] Y. Li, Inactivation of Nuclear Factor B by Soy IsoflavoneGenistein Contributes to Increased Apoptosis Induced by Chemotherapeutic Agents in Human Cancer Cells. *Cancer Research*, *65*(*15*), 2005, 6934-6942.

[20] L. Cai, J. Cai, W. Wu, and Y Zhu, 17α-Estradiol and Genistein Inhibit High Fat Diet Induced Prostate Gene Expression and Prostate Growth in the Rat. *The Journal of Urology*, *186*(*4*), 2011, 1489-1496.

[21] J. Wang, I. Eltoum, and C. A. Lamartiniere, Genistein chemoprevention of prostate cancer in TRAMP mice. *Journal of Carcinogenesis*, *6*(*1*), 2007, 1-10.

[22] M. Athar, J. Back, X. Tang, K. Kim, L. Kopelovich, D. Bickers, and A. Kim, Resveratrol: A review of preclinical studies for human cancer prevention. *Toxicology and Applied Pharmacology*, *224*(*3*), 2007, 274-283.

[23] C. Rius, M. Abu-Taha, C. Hermenegildo, L. Piqueras, J. Cerda-Nicolas,et al, Trans- but Not Cis-Resveratrol Impairs Angiotensin-II-Mediated Vascular Inflammation through Inhibition of NF- B Activation and Peroxisome Proliferator-Activated Receptor-Upregulation. *The Journal of Immunology*, *185*(6), 2010, 3718-3727.

[24] C. saki, A. Mobasheri, and M. Shakibaei, Synergistic chondroprotective effects of curcumin and resveratrol in human articular chondrocytes: inhibition of IL-1β-induced NF-κB-mediated inflammation and apoptosis. *Arthritis Research Therapy*, *11*(*6*), 2009, R165.

[25] E. Park, Y. Lim, J. Hong, H. Yoo, C. Lee, M. Pyo, and Y, Yun, Pterostilbene, a natural dimethylatedanalog of resveratrol, inhibits rat aortic vascular smooth muscle cell proliferation by blocking Akt-dependent pathway. *Vascular Pharmacology*, *53*(*1-2*), 2010, 61-67.

[26] Y. Bai, Q. Mao, J. Qin, X. Zheng, Y. Wang, K. Yang, et al, Resveratrol induces apoptosis and cell cycle arrest of human T24 bladder cancer cells in vitro and inhibits tumor growth in vivo. *Cancer Science*, *101*(*2*), 2010, 488-493.

[27] P. Parekh, L. Motiwale, N. Naik, and K. Rao, Downregulation of cyclin D1 is associated with decreased levels of p38 MAP kinases, Akt/PKB and Pak1 during chemopreventive effects of resveratrol in liver cancer cells. *Experimental and Toxicologic Pathology*, *63*(*1-2*), 2011, 167-173.

[28] P. Anand, C. Sundaram, S. Jhurani, A.B. Kunnumakkara, and B.B. Aggarwal, Curcumin and cancer: An "old-age" disease with an "age-old" solution. *Cancer Letters*,*267*(*1*), 2008, 133-164.

[29] D. Deeb, H. Jiang, X. Gao, S. Al-Holou, A.L. Danyluk, S.A. Dulchavsky, and S.C. Gautam, Curcumin [1,7-Bis(4-hydroxy-3-methoxyphenyl)-1-6-heptadine-3,5-dione; C21H20O6] Sensitizes Human Prostate Cancer Cells to Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand/Apo2L-Induced Apoptosis by Suppressing Nuclear Factor- B via Inhibition of the ProsurvivalAktSignaling Pathway. *Journal of Pharmacology and Experimental Therapeutics*, *321*(*2*), 2007, 616-625.

[30] V. Pongrakhananon, and Y. Rojanasakul, in HalaGali-Muhtasib (Ed.), Anticancer Properties of Curcumin. *Advances in Cancer Therapy*, (China: InTech 2011) 345-368.

[31] P.H. Killian, E. Kronski, K.M. Michalik, O. Barbieri, S. Astigiano, C.P. Sommerhoff et al, Curcumin inhibits prostate cancer metastasis *in vivo* by targeting the inflammatory cytokines CXCL1 and -2. *Carcinogenesis*, *33*(*12*), 2012, 2507-2519.

[32] M. Mukundan, M. Chacko, V. Annapurna, and K. Krishnaswamy, Effect of turmeric and curcumin on BP-DNA adducts. *Carcinogenesis*, *14*(*3*), 1993, 493-496.

[33] S. Oetari, M. Sudibyo, J.N. Commandeur, R. Samhoedi and N.P. Vermeulen, Effects of curcumin on cytochrome P450 and glutathione S-transferase activities in rat liver. *Biochemical Pharmacology*, *51*(*1*), 1996, 39-45.

[34] G. Chadalapaka, I, Jutooru, S. Chintharlapalli, S. Papineni, R. Smith, X. Li, and S. Safe, Curcumin Decreases Specificity Protein Expression in Bladder Cancer Cells. *Cancer Research*, *68*(*13*), 2008, 5345-5354.

[35] P.C. Everett, J.A. Meyers, A. Makkinje, M. Rabbi, and A. Lerner, Preclinical assessment of curcumin as a potential therapy for B-CLL. *American Journal of Hematology*, *82*(*1*), 2007, 23-30.

[36] K.K Cheng, C.F. Yeung, S.W. Ho, S.F. Chow, A.H. Chow, and L. Baum, Highly Stabilized Curcumin Nanoparticles Tested in an *In Vitro* Blood–Brain Barrier Model and in Alzheimer's Disease Tg2576 Mice. *American Association of Pharmaceutical Scientist Journal*, *15*(*2*), 2012, 324-336.

[37] J. Sun, C. Bi, H.M. Chan, S. Sun, Q. Zhang, and Y. Zheng, Curcumin-loaded solid lipid nanoparticles have prolonged in vitro antitumour activity, cellular uptake and improved in vivo bioavailability. *Colloids and Surfaces B: Biointerfaces*, *111*, 2012, 367-375.

[38] S. Prasad, A.K. Tyagi, and B.B Aggarwal, Recent Developments in Delivery, Bioavailability, Absorption and Metabolism of Curcumin: the Golden Pigment from Golden Spice. *Cancer Research Treatment. 46*(*1*), 2014, 2-18.

[39] J. Lee, J. Kim, J. Park, G. Chung, and Y. Jang, The antioxidant, rather than prooxidant, activities of quercetin on normal cells: quercetin protects mouse thymocytes from glucose oxidase-mediated apoptosis. *Experimental Cell Research*, *291*(*2*), 2003, 386-397.

[40] Y. Lee, J. Hwang, D.Y. Kwon, Y. Surh, and O.J. Park, Induction of apoptosis by quercetin is mediated through AMPKα1/ASK1/p38 pathway. *Cancer Letters*, *292*(*2*), 2010, 228-236.

[41] S. Hrelia and C. Angeloni, Quercetin and Its Metabolites in Heart Health, in R.W. Ronald et al, *Bioactive Food as Dietary Interventions for Cardiovascular Disease*, (San Diego, USA: Academic Press, 2013) 217-228.

[42] A. Murakami, H. Ashida, and J. Terao, Multitargeted cancer prevention by quercetin. *Cancer Letters*, *269*(*2*), 2008, 315-325.

[43] N. Xing, Y. Chen,S.H. Mitchell, and Y.F. Young, Quercetin inhibits the expression and function of the androgen receptor in LNCaP prostate cancer cells. *Carcinogenesis*, *22*(*3*), 2001, 409-414.

[44] F,J. Zheng, H.Y. Song, Y.F. Zhou, and G.Y. Yuan, Effects of quercetin on the proliferation of breast cancer cells and expression of survivin*in vitro*. *Experimental and Therapeutic Medicine*, 6(*5*), 2013, 1155-1158.

[45] L. Zeng, Q. Ye, N.H. Oberlies, G. Shi, Z. Gu, K. He, and J.L. McLaughlin, Recent advances in annonaceousacetogenins. *Natural Product Rep*orts. *13*(*4*), 1996, 275-306.

[46] N.H. Oberlies, C. Chang, and J.L. McLaughlin, Structure−Activity Relationships of Diverse AnnonaceousAcetogenins against Multidrug Resistant Human Mammary Adenocarcinoma (MCF-7/Adr) Cells. *Journal of Medicinal Chemistry*, *40*(*13*), 1997, 2102-2106.

[47] F.Q. Alali, X. Liu, and J.L. McLaughlin, AnnonaceousAcetogenins: Recent Progress. *Journal of Natural Products,62*(*3*), 1999, 504-540.

[48] C. Kandaswami, E. Perkins, D. Soloniuk, G. Drzewiecki, and E. Middleton, Antitproliferative effects of citrus flavonoids on a human squamous cell carcinoma in vitro. *Cancer Letters*, *56*(*2*), 1991, 147-152.

[49] H. Wei, R. Bowen, X. Zhang, and M. Lebwohl, Isoflavonegenistein inhibits the initiation and promotion of two-stage skin carcinogenesis in mice. *Carcinogenesis*, *19*(*8*), 1998, 1509-1514.

[50] P. Roy, N. Kalra, S. Prasad, J. George, and Y. Shukla, Chemopreventive Potential of Resveratrol in Mouse Skin Tumors Through Regulation of Mitochondrial and PI3K/AKT Signaling Pathways. *Pharmaceutical Research*, *26*(*1*), 2008, 211-217.

[51] H. Garewal, Beta-carotene and Antioxidant Nutrients in Oral Cancer Prevention, in K.N. Prasad et al. (Ed.), *Nutrients in Cancer Prevention and Treatment*, (Totowa: Humana Press Inc., 1995) 235-247.

[52] A. Thakkar, S. Chenreddy, J. Wang, and S. Prabhu, Ferulic acid combined with aspirin demonstrates chemopreventive potential towards pancreatic cancer when delivered using chitosan-coated solid-lipid nanoparticles. *Cell & Bioscience*, *5*(*1*), 2015, 46-51.

[53] M.H. Bukhari, S.S. Qureshi, S. Niazi, M. Asef, M. Naheed, S.A. Khan, et al, Chemotherapeutic/chemopreventive role of retinoids in chemically induced skin carcinogenesis in albino mice. *International Journal of Dermatology*, *46*(*11*), 2007, 1160-1165.

[54] R. Patel, R. Krishnan, A. Ramchandani, and G. Maru, Polymeric black tea polyphenols inhibit mouse skin chemical carcinogenesis by decreasing cell proliferation. *Cell Proliferation*, *41*(*3*), 2008, 532-553.

[55] J.D. Meier, D.J. Enepekides, B. Poirier, C.A. Bradley, J.S Albala, and D.G. Farwell, Treatment With 1-Alpha,25-Dihydroxyvitamin D3 (Vitamin D3) to Inhibit Carcinogenesis in the Hamster Buccal Pouch Model. *Archives of Otolaryngology–Head & Neck Surgery*, *133*(*11*), 2007, 1149.

[56] K. Park, K. Chun, J. Lee, S.S. Lee, and Y. Surh, Inhibitory effects of [6]-gingerol, a major pungent principle of ginger, on phorbol ester-induced inflammation, epidermal ornithine decarboxylase activity and skin tumor promotion in ICR mice. *Cancer Letters*, *129*(*2*), 1998, 139-144.

[57] M. Takasaki, T. Konoshima, H. Etoh, I. Pal Singh, H. Tokuda, and H. Nishino, Cancer chemopreventive activity of euglobal-G1 from leaves of Eucalyptus grandis. *Cancer Letters*, *155*(*1*), 2000, 61-65.

[58] V. Bhuvaneswari, B. Velmurugan, S. Balasenthil, C.R. Ramachandran, S. Nagini, Chemopreventive efficacy of lycopene on 7,12-dimethylbenz[a]anthracene-induced hamster buccal pouch carcinogenesis. *Fitoterapia*, *72*(*8*), 2001, 865-874.

[59] J. DiGiovanni, Genetics of Susceptibility to Mouse Skin Tumor Promotion, in E.S. Alphonse (Ed.), The *Pathobiology of Neoplasia*, (New York, US: Springer, 1989) 247-274.

[60] J. DiGiovanni, Multistage carcinogenesis in mouse skin. *Pharmacology & Therapeutics*, *54*(*1*), 1992, 63-128.

[61] R. Sharmila, and S. Manoharan, Antitumor activity of rosmarinic acid in 7,12-dimethylbenz(a)anthracene (DMBA) induced skin carcinogenesis in Swiss albino mice. *Indian Journal of Experimental Biology*, *50*, 2012, 187-194.

[62] K.A. Droms, ans A.M. Malkinson, Phorbol Ester-Induced Tumor Promotion by Downregulation of Protein Kinase C. *Molecular Carcinogenesis*, *4*(*1*), 1991, 1-2.

[63] T. Kawamori,T. Tanaka, A. Hara. J. Yamahara, and H. Mori, Modifying effects of naturally occurring products on the development of colonic aberrant crypt foci induced by azoxymethane in F344 rats. *Cancer Research*, *55*, 1995, 1277-1282.

[64] D.C. Schönwasser, R.M. Marais, C.J. Marshall, and P.J. Parker, Activation of the Mitogen-Activated Protein Kinase/Extracellular Signal-Regulated Kinase Pathway by Conventional, Novel, and Atypical Protein Kinase C Isotypes. *Molecular and Cellular Biology*, *18*(*2*), 1998, 790-798.

[65] E.E. Cohen, M.W. Lingen, B. Zhu, H. Zhu, M.W. Straza, and C. Pierce, Protein Kinase C Mediates Epidermal Growth Factor-Induced Growth of Head and Neck Tumor Cells by Regulating Mitogen-Activated Protein Kinase. *Cancer Research*, *66*(*12*), 2006, 6296-6303.

[66] A. Imamoto, L.M. Beltrán, and J. Digiovanni, Evidence for autocrine/paracrine growth stimulation by transforming growth factor-α during the process of skin tumor promotion. *Molecular Carcinogenesis*, *4*(*1*), 1991. 52-60.

[67] K. Kiguchi, L.M. Beltrán, J, You, O. Rho, and J. Digiovanni, Elevation of transforming growth factor-α mRNA and protein expression by diverse tumor promoters in sencar mouse epidermis. *Molecular Carcinogenesis*, *12*(*4*), 1995, 225-235. doi:10.1002/mc.2940120407

[68] O. Rho, D.K. Bol, J. You, L. Beltrán, T. Rupp, and J. DiGiovanni, Altered expression of insulin-like growth factor I and its receptor during multistage carcinogenesis in mouse skin. *Molecular Carcinogenesis.17*(*2*), 1996, 62-69.

[69] L.S. Steelman, W.H. Chappell, S.L Abrams, C.R Kempf, J. Long, P. Laidler, S. Mijatovic, D. Maksimovic,-Ivanic, et al, Roles of the Raf/MEK/ERK and PI3K/PTEN/Akt/mTOR pathways in controlling growth and sensitivity to therapy-implications for cancer and aging. *Aging*, *3*(*3*), 2011, 192-222.

[70] Z. Milosevic, M. Pesic, T. Stankovic, J. Dinic, Z. Milovanovic, J. Stojsic, R. Dzodic, N. Tanic, J. Bankovic, Targeting RAS-MAPK-ERK and PI3K-AKT-mTOR signal transduction pathways to chemosensitize anaplastic thyroid carcinoma. *Translational Research*, *164*(*5*), 2014, 411-423.

[71] V. Asati, D.K. Mahapatra, S.K. Bharti, PI3K/Akt/mTOR and Ras/Raf/MEK/ERK signaling pathways inhibitors as anticancer agents: Structural and pharmacological perspectives. *European Journal of Medicinal Chemistry*, *109*, 2016, 314-341.

[72] R. Zandi, A.B. Larsen, P. Andersen, M. Stockhausen, and H.S. Poulsen, Mechanisms for oncogenic activation of the epidermal growth factor receptor. *Cellular Signalling*, *19*(*10*), 2007, 2013-2023.

[73] S. Maeda, and M. Omata, Inflammation and cancer: Role of nuclear factor-kappa B activation. *Cancer Science*, *99*(*5*), 2008, 836-842.

[74] S.M. Crusz, and F.R. Balkwill, Inflammation and cancer: advances and new agents. *Nature Reviews Clinical Oncology*, *12*(*10*), 2015, 584-596.

[75] S.M. Fischer, A. Pavone, C. Mikulec, R. Langenbach,and J.E. Rundhaug, Cyclooxygenase-2 expression is critical for chronic UV-induced murine skin carcinogenesis. *Molecular Carcinogenesis*, *46*(5), 2007, 363-371.

[76] J.K. Akunda, K. Chun, A.R. Sessoms, H. Lao, S.M. Fischer, and R. Langenbach, Cyclooxygenase-2 deficiency increases epidermal apoptosis and impairs recovery following acute UVB exposure. *Molecular Carcinog*enesis, *46*(*5*), 2007, 354-362.

[77] S. Shalapour, and M. Karin, Immunity, inflammation, and cancer: an eternal fight between good and evil. *Journal of Clinical Investigation*, *125*(*9*), 2015, 3347-3355.

[78] B. Hoesel, and J.A. Schmid, The complexity of NF-κBsignaling in inflammation and cancer. *Molecular Cancer*, *12*(*1*), 2013, 86.

[79] G.J. Kelloff, C.W. Boone, V.E. Steele, J.R. Fay, R.A. Lubet, J.A. Crowell, and C.C. Sigman, Mechanistic considerations in chemopreventive drug development. J Cell BiochemSuppl, 20, 1994, 1–24.

[80] A. Murakami, D. Takahashi, T. Kinoshita, K. Koshimizu, et al. Zerumbone, a Southeast Asian ginger sesquiterpene, markedly suppresses free radical generation, proinflammatory protein production, and cancer cell proliferation accompanied by apoptosis: the α,β-unsaturated carbonyl group is a prerequisite. *Carcinogenesis*,*23*,2002,795– 802.

[81] M.E. Goetz, and A. Luch, Reactive species: A cell damaging rout assisting to chemical carcinogens. *Cancer Letters*, *266*(*1*), 2008, 73-83.

[82] Clerkin, J., Naughton, R., Quiney, C., & Cotter, T. (2008). Mechanisms of ROS modulated cell survival during carcinogenesis. *Cancer Letters*, *266*(1), 30-36. doi:10.1016/j.canlet.2008.02.029

[83] R.B. Filler, S.J. Roberts, and M. Girardi, Cutaneous Two-Stage Chemical Carcinogenesis. *Cold Spring Harbor Protocols*, *2007*(*18*), 2007, pdb.prot4837-pdb.prot4837.

[84] E.L. Abel, J.M. Angel, K. Kiguchi, and J. DiGiovanni, Multi-stage chemical carcinogenesis in mouse skin: Fundamentals and applications. *Nature Protocols*, *4*(*9*), 2009, 1350-1362.

[85] F. Broekman, E. Giovvannetti, and G.J. Peters, Tyrosine kinase inhibitors: Multi-targeted or single-targeted? *World Journal of Clinical Oncology*, *2*(*2*), 2011, 80.

[86] M. Singh, S. Suman, and Y. Shukla, New Enlightenment of Skin Cancer Chemoprevention through Phytochemicals: *In Vitro* and *In Vivo* Studies and the Underlying Mechanisms. *BioMed Research International*, *2014*, 2014, 1-18.

[87] F. Afaq, A. Malik, D. Syed, D. Maes, M.S. Matsui, and H. Mukhtar, Pomegranate fruit extract modulates UVB-mediated phosphorylation of mitogen activated protein kinases and activation of nuclear factor kappa B in normal human epidermal keratinocytes. *Photochemistry and Photobiology*, *81*,2004, 38-45.

[88] A.Q. Khan, R. Khan, M.U. Rehman, A. Lateef, M. Tahir, F. Ali, and S. Sultana, Soy isoflavones (daidzein&genistein) inhibit 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced cutaneous inflammation via modulation of COX-2 and NF-κB in Swiss albino mice. *Toxicology*, *302*(*2-3*), 2012, 266-274.

[89] F. Afaq, N. Khan, D.N. Syed, and H. Mukhtar, Oral Feeding of Pomegranate Fruit Extract Inhibits Early Biomarkers of UVB Radiation-induced Carcinogenesis in SKH-1 Hairless Mouse Epidermis. *Photochemistry and Photobiology*, *86*(*6*), 2010, 1318-1326.

[90] N. Khan, D.N. Syed, H.C. Pal, H. Mukhtar, and F. Afaq, Pomegranate Fruit Extract Inhibits UVB-induced Inflammation and Proliferation by Modulating NF-κB and MAPK Signaling Pathways in Mouse Skin. *Photochemistry and Photobiology*, *88*(5), 2012, 1126-1134.

[91] P. Roy, N. Kalra, S. Prasad, J. George, and Y. Shukla, Chemopreventive Potential of Resveratrol in Mouse Skin Tumors Through Regulation of Mitochondrial and PI3K/AKT Signaling Pathways. *Pharmaceutical Research*, *26*(*1*), 2008, 211-217. doi:10.1007/s11095-008-9723-z

[92] A.C. Chen, G.M. Halliday, and D.L. Damian, Non-melanoma skin cancer: carcinogenesis and chemoprevention. *Pathology*, *45*(*3*), 2013, 331-341.

[93] M. Saleem, F. Afaq, V.M. Adhami, and H. Mukhtar, Lupeol modulates NF-κB and PI3K/Akt pathways and inhibits skin cancer in CD-1 mice. *Oncogene*, *23*(*30*), 2004, 5203-5214.

[94] N. Nigam, S. Prasad, J. George, and Y. Shukla, Lupeol induces p53 and cyclin-B-mediated G2/M arrest and targets apoptosis through activation of caspase in mouse skin. *Biochemical and Biophysical Research Communications*, *381*(*2*), 2009, 253-258.

[95] S. Narayanapillai, C. Agarwal, C. Tilley, and R. Agarwal, Silibinin Is a Potent Sensitizer of UVA Radiation-induced Oxidative Stress and Apoptosis in Human Keratinocyte HaCaT Cells. *Photochemistry and Photobiology*, *88*(*5*), 2012, 1135-1140.

[96] S. De Flora, and L.R. Ferguson, Overview of mechanisms of cancer chemopreventive agents. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesi*,*591(1)*, 2005, 8-15.

[97] W. Steward, and K. Brown, Cancer chemoprevention: a rapidly evolving field. *British journal of cancer*, *109(1)*, 2013, 1-7.

[98] V.E. Steele, and G.J. Kelloff, Development of cancer chemopreventive drugs based on mechanistic approaches. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, *591(1–2)*, 2005, 16-23.

[99] S.M. Lippman, S.E. Benner, and W.K. Hong, Cancer chemoprevention. *Journal of Clinical Oncology*, *12*, 1994, 851-873.

[100] V.E. Steele, Current mechanistic approaches to chemoprevention of cancer. *Journal of Biochemistry and Molecular Biology*, *36*(*1*), 2003, 78-81.

[101] L.W. Wattenberg, Inhibitors of chemical carcinogens. *Journal of environmental pathology and toxicology*, *3(4)*, 1980, 35-52.

[102] M. Karin, Nuclear factor-κB in cancer development and progression. *Nature*, *441(7092)*, 2006, 431-436.

[103] T. Akihisa, and K. Yasukawa, Antitumor-promoting and anti-inflammatory activities of triterpenoids and sterols from plants and fungi.*Bioactive Natural Products (Part F)*, 2001, 43-87.

[104] T. Akihisa, K. Yasukawa, and H. Tokuda, Potentially Cancer Chemopreventive And Anti-Inflammatory Terpenoids From Natural Sources. *Bioactive Natural Products (Part J)*, 2003, 73-126.
[105] C. Ito, M. Itoigawa, H. Furukawa, E. Ichiishi, T. Mukainaka, M. Okuda, M. Ogata, H. Tokuda, and H. Nishino, Anti-tumor-promoting effects of phenylpropanoids on Epstein–Barr virus activation and two-stage mouse skin carcinogenesis. *Cancer Letters*, *142*(*1*), 1999, 49-54.
[106] Y. Ito, S. Yanase, J. Fujita, T. Harayama, M. Takashima, and H. Imanaka, A short-term in vitro assay for promoter substances using human lymphoblastoid cells latently infected with Epstein-Barr virus. *Cancer Letters*, *13*(*1*), 1981, 29-37.
[107] G.J. Kapadia, M.A Azuine, H. Tokuda, M. Takasaki, T. Mukainaka, T. Konoshima, and H. Nishino, Chemopreventive effect of resveratrol, sesamol, sesame oil and sunflower oil in the epstein–barr virus early antigen activation assay and the mouse skin two-stage carcinogenesis. *Pharmacological Research*, *45*(*6*), 2002, 499-505.
[108] M.A. Azuine, H. Tokuda, J. Takayasu, F. Enjyo, T. Mukainaka, T. Konoshima, H. Nishishino, and G.J. Kapadia, Cancer chemopreventive effect of phenothiazines and related tri-heterocyclic analogues in the 12-O-tetradecanoylphorbol-13-acetate promoted Epstein-Barr virus early antigen activation and the mouse skin two-stage carcinogenesis models. *Pharmacological Research*, *49*(*2*), 2004, 161-169.
[109] J. Tatsuzaki, K. Nakagawa-Goto, H. Tokuda, and K. Lee, Cancer preventive agents 10. Prenylateddehydrozingeroneanalogs as potent chemopreventive agents. *Journal of Asian Natural Products Research*, *12*(*3*), 2010, 227-232.
[110] R.C. Moon, and R.G. Mehta, Chemoprevention of experimental carcinogenesis in animals. *Preventive Medicine*, *18*(*5*), 1989, 576-591.
[111] M. Miyata, G. Kudo, Y. Lee, T.J. Yang, H.V. Gelboin, P. Fernandez-Salguero, S. Kimura, and F.J. Gonzalez, Targeted Disruption of the Microsomal Epoxide Hydrolase Gene: Microsomal epoxide hydrolase is required for the carcinogenic activity of 7,12-Dimethylbenz[a]Anthracene. *Journal of Biological Chemistry*, *274*(*34*), 1999, 23963-23968.
[112] J. DiGiovanni, S. Walker, C. Aldaz, T. Slaga, T. and C. Conti, Further studies on the influence of initiation dose on papilloma growth and progression during two-stage carcinogenesis in SENCAR mice. *Carcinogenesis*, *14*(*9*), 1993, 1831-1836.
[113] M.C. Stern, F. Benavides, M. LaCava, C.J. Conti, Genetic analyses of mouse skin tumor progression susceptibility using SENCAR inbred derived strains. *Molecular Carcinog*enesis. *35*(*1*), 2002, 13-20.

Mohd Rohaizad. "Mini Review: Antitumor promotion as the best strategy for chemoprevention." IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS) 12.4 (2017): 33-42.