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Review Article

Immunomodulatory phytochemicals for chemoprevention

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ABSTRACT

Chemoprevention and chemotherapeutics with traditional and complimentary system has gained importance with increase in the relapse cases treated with modern system of medicine. The increased mortality rate due to severe toxicity is another concern. The role of phytochemicals from different class viz-dietary polyphenols and saponins in chemoprevention along with different mechanistic pathways has created remarkable progress as the toxicity issues are of lesser concern. Phytochemicals can prevent the carcinogenesis process via antioxidant or anti-inflammatory action by modulating the proteins involved in different pathways like NF-kB, Nrf-2, AP-1, MAPK, and COX-2. In this review, we have focused on the potential molecular targets and signalling pathways that provoke the tumorigenesis process and the various phytochemicals that are targeted towards these signalling pathways by chemoprevention.

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1. Introduction

Cancer is one of the major health problems around the world and the second highest major trigger, which is fatal to human next to cardiovascular diseases. Carcinogenesis is a multistep process involving initiation, promotion, and progression in analogous to various signal transduction pathways. The initiation step is comparatively shorter and is irreversible where the carcinogens provoke the process of tumorigenesis in healthy cells whereas the promotion as well as the progression process is shorter than the former one and is reversible in nature.¹ Since traditional times, medicinal plants are used across the world for cancer therapy.²

Chemoprevention is widely preferred nowadays, in which the natural agents or pharmacological agents can either suppress the progression, arrest the growth or reverse the tumorigenesis process in early phases of the cell lifecycle.³ The fundamental notion behind

chemoprevention was to either block or slow down the process of development of premalignant tumors by using these natural substances.⁴ The chemopreventive agents can act as either by blocking the initiation step of tumor metastasis or act as cancer suppressing agents. In the later process, it temporary halt the tumorigenesis process or stop the promotion and progression of precancerous cells into malignant ones. However, sometimes the agents have the ability to act on all the stages of cancer development, they may be considered as both blocking agent as well as suppressing agent.¹

The chemopreventive agents obtained from dietary compounds evoke the various cellular defense mechanisms like detoxifying and anti-oxidant enzyme system, inhibition of anti-inflammatory as well as anti-cell growth signalling pathways, confining the carcinogens from multiplying and inhibiting the nitrosation reactions and aromatase pathways.^{5,6} Phytochemicals are those chemopreventive agents which are bioactive extraneous nutrients obtained from plants.⁵ These dietary phytochemicals persuade

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programmed cell death in pre-neoplastic or neoplastic cells via different growth inhibitory mechanisms like activating the cytochrome c/caspase enzyme system and initiating the cell cycle arrest process, inhibiting the nuclear factor-kB (NF- κ B) and activating the transcription (STAT) signalling pathways which can inhibit the tumor progression.⁷ Also, these agents will be able to reverse the carcinogenesis process by modulating the intracellular signalling network molecules and arrest or invert the progression stage of cancer development process.⁸

The World Health Organization (WHO) states that cancer has close relation to dietary lifestyles; therefore, dietary phytochemicals can be used in chemoprevention. USFDA successfully launched Tamoxifen and Finasteride as chemopreventive agents. These drugs can effectively bind to specific molecular targets for cancer prevention. Phytochemicals like EGCG [(-)-epigallocatechin gallate], Resveratrol,⁶-Gingerol and many others show modulation in different molecular signal transduction pathways^{9–11} This review aims to focus on various modulating pathways, which are involved in treating cancer with the help of different phytochemicals.

2. Cancer Modulating Pathways

2.1. Antioxidant and anti-inflammatory pathway

Oxidative stress is a condition in which there is an imbalance between the production of ROS (reactive oxygen species) or RNS (reactive nitrogen species) and the anti-oxidative defense system.¹² In cancerous cells, relatively higher amounts of reactive oxygen species and predominantly H_2O_2 are produced which developed the perception of “persistent oxidative stress in cancer”.¹³ Also, Superoxide dismutase (SOD) antioxidant defense system is confined to cytosol and mitochondria and this action may alter or conjugate the ROS to change into molecules which are less toxic.¹¹

In case of inflammation, the DNA damage can be prevented chemopreventive agents via multiple mechanisms such as direct radical scavenging, chelating divalent cations which are involved in Fenton reaction¹³, modulating the enzymes like glutathione peroxidase, glutathione reductase, SOD, etc. which are related to oxidative stress.⁸ The major pathways which are seen to be involved in targeting the molecular pathways by chemopreventive agents are MAPK, transcription factor NF- κ B which are targets of antioxidants.¹⁴ The antioxidants block the ROS generation and thereby subsequently provide chemoprevention.¹⁵

Phytochemicals can act on the M1 polarized macrophages which in turn results in the elevation of pro-inflammatory cytokines and chemokines¹⁶

The H_2O_2 production during the oxidative stress in cancer cells intervene signal transduction which eventually leads to the transcriptional activation of cyclooxygenase-

2 (COX-2), matrix metalloproteinases (MMP) and cyclin B. MMP genes code for proteins which are involved in tumor invasion and metastasis whereas cyclin B1 code for proteins which are involved in cell progression via G₂/M-phase. Also binding of epidermal growth factor (EGF) to its receptor (EGFR) produce a large amount of H_2O_2 in cancer cells, which further increase the protein tyrosine kinases (PTK)-mediated phosphorylation or increase the activation of EGFR which initiates the RAS signalling cascade, initiating the mitogen-activated protein kinases (MAPK) signalling pathway. This states that higher the production of H_2O_2 in cancer cells, greater is the activity of the MAPK cascade. The overactivated MAPK causes overexpression of transcription factors like nuclear factor-kappa B and activator protein-1 which are highly redox-sensitive.⁴

2.2. NF- κ B, AP-1 and Nrf-2 activation pathways

2.2.1. NF- κ B pathway

The Nuclear transcription factor-kB found in the cytoplasm. Upon activation of this factor, it is translocated to the nucleus. Inside the nucleus, it starts gene transcription by binding to various promoter genes.¹⁷ The nuclear factor-kB regulation pathway actuates the inflammatory as well as intrinsic immune responses by its binding.¹⁸ The activation of NF- κ B is responsible for cell survival and proliferation mechanisms and thus dysregulation of this pathway causes changes which are related to changes involved in neoplastic transformation.¹⁹ The activation of NF- κ B can be due to various factors like tumor necrosis factor (TNF- α), T and B cell mitogens, bacterial lipopolysaccharide (LPS), viruses, ultraviolet (UV) light, gamma rays and oxidative stress.¹

The activation of I κ B kinase (IKK) complex by NF- κ B inducing kinase (NIK) results in the phosphorylation and degradation of I κ B α and the NF- κ B dimer is released which is then translocated into the nucleus where it activates the transcription of targeted genes which are seen to be responsible in cell survival or cell death events.¹ The phytochemicals disturbs the nuclear translocation process as well as DNA binding process of NF- κ B.¹³

2.2.2. AP-1 pathway

AP-1 transcription factor (activator protein-1) is dimeric in nature and consists of basic members of Jun, Fos and Maf proteins. A number of stimuli like growth factors, oxidative stress, pro-inflammatory cytokines, and tumor promoters regulates this pathway. The AP-1 dimer reacts with the promoter region of target genes containing TPA or cyclic AMP element. As this transcription factor is involved in events of cell proliferation, apoptosis, differentiation, and tumorigenesis, activation of this pathway plays a major role in reversing the tumor promotion and/or tumor progression stages.¹ The NF- κ B factor works in association with the AP-1 factor¹⁸ for transcription of genes by cellular

differentiation and proliferation process.¹⁹

Phenolic phytochemicals possessing anti-oxidant activity will help in reducing the signalling events by scavenging H₂O₂ and inhibiting the protein phosphorylation.^{13–21}

2.2.3. Nrf-2 pathway

The nuclear transcription factor erythroid-related factor (Nrf2) plays an important role while regulating the phase-2 anti-oxidant gene induction. Nrf2 is traced in the cytoplasm along with the inhibitory protein subunit (Keap1) in an inactive complex form.¹⁸ The chemopreventive agents generate electrophiles or ROS, which activate the mitogen-activated protein kinases (MAPKs) that can provoke the release of Nrf-2 and its translocation. Also, these agents can interact directly with the Nrf2-Keap1 complex which can cause the release of Nrf2 from the complex into the nucleus.¹

The Nrf2 that is transferred into nucleus interacts with the small Maf protein to form a heterodimer which binds to antioxidant responsive elements (ARE) or electrophilic responsive elements (EpRE), which is found to be present in the promoter/ enhancer regions of genes that encode a number of antioxidant and detoxifying enzymes. The detachment of Nrf2-Keap1 complex is provoked by mainly MAPK as shown in Figure 1. Thus, phytochemicals possessing antioxidant activity modulate the Nrf2-Keap1 complex signalling pathway by showing its antioxidant activity towards the carcinogens. Therefore, we can say that Nrf2 plays a major role in protecting the cells from oxidative stress as well as from inflammatory actions.²¹

Nrf-2 also plays a vital role in regulating the starting process of Phase II antioxidant and detoxifying enzyme genes, which help the cells in protecting themselves from the damage occurring by the oxidative and electrophilic attack. It also helps in protecting the cells from inflammation by increasing the NADPH oxidase-dependent ROS generation whereas it also helps to regulate the innate immune responses.²²

Thus, phytochemicals which are responsible in activating the inhibition of tumor initiation by Nrf2 pathway damage the DNA, detoxify the carcinogen and helps in protecting the cells from further damage, thus acting as blocking agents whereas those that are responsible to prevent tumor promotion or progression via NF-kB act as suppressing agents.^{23–25}

2.3. MAPK pathway

Mitogen-activated protein kinases (MAPKs) are involved in transferring the extracellular signals from the cell membrane into the nucleus through phosphorylation and negatively regulated by MAPK phosphatases (MKPs). Studies show that ROS can activate the MAPK signalling pathway, but still, the mechanism is unclear. MAPKs are protein-serine or threonine kinases that are divided into three subgroups in

mammalian cells-

1. ERKs (extracellular signal-regulated kinases),
2. JNKs(c-Jun N-terminal kinases),
3. p-38 MAPKs

Oxidative stress induces activation of epidermal growth factor receptor, which on activation initiates the Ras-GTPase to induce the Raf (protein kinase) which further cause activation of ERK pathway by MAP or ERK kinase as shown in Figure 2. The p-38 MAPK pathway is activated by inflammatory cytokines and by other stimuli like stress or hormones whereas other factors like cytokines, agents interfering with DNA and protein synthesis activate the JNK pathway. Antioxidants will help in preventing the ROS accumulation that will further block the MAPK activation. This MAPK inactivation will prevent the oxidative stress condition by reducing the H₂O₂ production in cancer cells that states that the ROS system will function properly by thus giving an anti-cancer effect.²⁶

2.4. COX-2 involvement in transcriptional factors

Cyclooxygenase-2 (COX-2) is an enzyme which is involved in the production of prostaglandins E₂ (PGE₂) from the substrate arachidonic acid (AA) and is found to increase the cell proliferation and VEGF production to cause angiogenesis.²⁷

COX-2 is seen to be involved at different stages of cancer development like cell proliferation, suppression of apoptosis and also enhancement of angiogenesis and invasiveness.²⁸ COX-2 is an activated isoform, which increases the production of prostaglandins in response to inflammatory stimuli, hormones, and growth factors. As COX-2 expression is linked with cell growth regulation, tissue remodeling, and carcinogenesis, it has attained more interest in the cancer research, unlike COX-1. Studies have shown that COX-2 inhibitors and NSAIDs decrease the risk of different cancerous conditions especially colon and lung cancers, thus chemopreventive agents may be helpful in preventing and inhibiting the tumor growth by downregulating the COX-2 pathway.²⁹

The pro-inflammatory stimulus like TPA is highly increased in tissues which are inflamed causing activation of upstream kinases, thus increasing the COX-2 levels by activation of different transcription factors like NF-kB, AP-1 etc. and these increased COX-2 levels affect the progression and promotion stage of cell development in cancer.³⁰

2.5. Role of epidermal growth factor receptors in cancer development

The epidermal growth factor receptors like EGFR, HER2 and HER3 are involved in cancer proliferation, programmed cell death, differentiation, metastasis, and angiogenesis by

activating various signal transduction pathways and binding to the ligand. On binding of a ligand to the EGFR monomer, homodimerization takes place with the help of second EGFR molecule or with another HER member which further leads to intracellular phosphorylation of HER receptors activating the downstream signalling pathways.³¹

Studies showed that high levels of FAS (fatty acid synthase) are involved in various human cancers. FAS is involved in the anabolic conversion of food into energy²⁷ by catalyzing the reductive synthesis of palmitate from acetyl-CoA and malonyl CoA and thus inhibiting this FAS would show a significant anti-tumor effect in the human cancer cells. HER2, a part of EGFR family²⁸, regulates the FAS expression by Akt signal transduction pathways. Diosgenin a plant steroid which can be obtained from *Solanum* and *Dioscorea*³² species shows the anti-tumor effect on cancer cells^{30–33} and also inhibits the growth of cancerous cells. Cell culture studies showed that Diosgenin can effectively inhibit FAS expression in HER2-overexpressing cancer cells. Also increased exposure of such exogenous estrogens which are obtained from dietary phytoestrogens may help in reducing the risk in case of breast cancers.³⁴ Also, it was seen that Diosgenin can show anti-tumor effects by intervening the disruption of calcium homeostasis and inhibiting the NF- κ B pathway.^{35,36}

3. Tumor Angiogenesis

Antiangiogenic therapy for cancer hypothesized by Folkman and colleagues three decades before, and after which the researches started to carry out the clinical trials of the antiangiogenic drugs for anticancer activity. Angiogenesis process forms new blood vessels from the pre-existing vasculature and this is required at each stage of cancer progression. Further phytochemicals studied extensively for their antiangiogenic activities for cancer prevention and therapy. These studies revealed that these phytochemicals would inhibit the production and release of angiogenic factors from tumor cells, which would also help in upregulation of antiangiogenic factors.

The phytochemicals would also help in inhibition of endothelial cell activation, proliferation, and migration, would directly kill the endothelial cells by apoptosis induction and can also disrupt the capillary tube formation and organization and remodeling of the extracellular matrix. Vascular endothelium growth factor (VEGF) secreted from tumor cells, stimulates tumor angiogenesis and vascular permeability. EGCG shows inhibition of receptor tyrosine kinase signalling pathway as well as secretion of VEGF in cancer cells whereas Genistein and Curcumin inhibit the TGF- β induced expression of VEGF.³⁷

Homeostasis in a normal cell is maintained by the gap-junction intercellular communication (GJIC) and this modulates the cell proliferation and differentiation.³⁸ Studies showed that inhibiting this GJIC will affect the

inflammatory process³⁹ also it is seen to be involved in tumor promotion. So if the downregulation of GJIC is prevented by various chemopreventive drugs in neoplastic cells it can give anti-cancer effect.^{38–40} Also, oxidative stress can inhibit GJIC and can give anti-cancer effect.⁴

Note: DMBA, 7,12-dimethylbenz[a]anthracene; DMAB, 3,2'-dimethyl-4-aminobiphenol; TPA, 12-O-tetradecanoylphorbol-13-acetate, DHPN, 2,2'-dihydroxy-di-n-propylnitrosamine; EHEN, N-ethyl-N-hydroxyethyl nitrosamine

Fig. 1: Mechanism of Chemopreventive agents via Nrf2 Pathway

Fig. 2: Mitogen-activated protein kinases (MAPK) Pathway

4. Phytochemicals Targeted to Wards Various Pathways

Studies show that various phytochemicals show chemopreventive action by mediating different signalling pathways.

Table 1: Different carcinogens involved in different types of cancer

Carcinogens	Cancer
DMBA	Lymphoma/leukaemia Breast cancer Oral cancer
Azoxymethane	Gastrointestinal cancer Colon cancer
Diethyl nitrosamine	Hepatic hyperplasia Liver cancer
DMAB	Prostate cancer
TPA + UV-A	Skin cancer Dermatitis Skin tumor
DHPN, EHEN	Multi-organ cancer

Table 2: Clinical trials with Curcumin reported for different types of cancer

Curcumin dose	Type of cancer	Observed results	Ref
Oral curcuma extract (36-180mg/ day for 120 days)	Colorectal cancer	Reduced the glutathione-S-transferase activity Increase in dose made to cause a dose dependent inhibition of COX-2	41
Oral administration of Curcumin (375mg, 3 times/day for 6-22 months)	Idiopathic inflammatory orbital psuedotumours	Inflammation was reduced and condition was reverted completely with no occurrence	41
Topical application of Curcumin containing ointment	External cancerous lesions at different sites (breast, vulva, oral, skin)	Reduced itching, lesion size and pain	42
Oral Curcumin dose (2-12g/day, daily)	Multiple myeloma	Inhibited the NF-kB and COX-2 activities	43
Oral Curcumin with piperine (500mg/day for 6 weeks)	Tropical pancreatitis and advanced pancreatic cancer	Increased the GSH levels and also inhibited the NF-kB and COX-2 activities	44

Fig. 3: Curcumin action ontumor inhibition

4.1. Curcumin

Curcumin (*Curcuma longa*), belonging to the family of Zingiberaceae, is seen to show strong anticancer, anti-inflammatory as well as antioxidant activities. The cyclooxygenase-2 (COX-2) expression is inhibited via inactivation of NF- κ B which progress by blocking MAPK¹⁹ and downregulation of COX-2 pathway, Curcumin acts as a chemoprotective agent against cancer by restricting the translocation of the NF- κ B in the nucleus.⁴⁵

Curcumin thus downregulating the COX-2 pathway, thereby inhibits the breakdown of arachidonic acid to prostaglandin⁴⁶ thus showing anti-inflammatory activity.⁴⁷ This effect is predominantly due to suppression of the IKK signalling complex thus interferes with the nuclear translocation of the NF- κ B and blocking its activation.⁴⁸

Also, studies show that Curcumin suppresses the tumor promotion by inhibiting the I κ B degradation by downregulating the NF- κ B-inducing kinase (NIK) and I κ B kinase (IKK) α/β thus showing anti-inflammatory activity by further inhibiting the effect on the I-kappa B kinase (IKK)-mediated phosphorylation. This effect could help in cell cycle arrest and initiate the programmed cell death by downregulating the NF- κ B genes.^{27-40,45-50}

Curcumin reduces the iNOS i.e. inducible nitric oxide synthase which is concerned with oxidative stress and ROS generation through activation of neutrophils and macrophages. Thus, through the prevention of the phosphorylation and degradation of the inhibitor $\text{I}\kappa\text{B-}\alpha$, it blocks the activation which reduces the iNOS generation.⁵¹

Curcumin is found to block the TPA-induced activation of extracellular- regulated protein kinase and the NF- κ B activation. It also induces HO-1 expression through Nrf-2 and NF- κ B which causes a decrease in the oxidative stress. Curcumin thus shows anti-inflammatory activity either by decreasing the pro-inflammatory pathways or by initiating the phase II enzymes to avoid the formation of toxic metabolites which will further prevent the tumor initiation process in carcinogenesis. Curcumin thus reduces both the

invasion as well as metastasis of cancer cells.⁴⁵

Curcumin as an anti-initiation factor disturbs the Nrf2-Keap1 complex which increases the binding of Nrf2 to ARE (antioxidant response element), increasing the nuclear translocation of Nrf2.²³

Thus, Curcumin acts on multiple molecular targets by giving chemopreventive effect either by inhibiting various pathways^{52,53} or modulating them. Curcumin can also show antioxidant activity by causing programmed cell death of cancer cells by depleting the glutathione (GSH)⁴⁶, which can increase both the production of reactive oxygen species and also the availability of peroxides in the cytosol as well as in mitochondria.⁵⁴ A study was carried out for skin cancer where Curcumin was applied topically on the mouse skin model, it was seen that the activity of GSH was enhanced.⁵⁵

Also, the anti-inflammatory activity in cancer cells can be seen due to the regulation of the MAPK signalling pathway. Studies show that Curcumin suppresses the matrix metalloproteinases (MMPs) and inhibit the TPA induced activation of ERK⁴⁷ as well as the transcriptional activation of NF- κ B in human breast cancer epithelial cells.⁴⁷ Thus, Curcumin can stop cancer either by blocking the growth of cancer cells or by putting a halt on its invasion as shown in Figure 3.^{47,48,50–56}

The structural activity relationship studies showed that substitution of ortho-methoxy group and hydrogenation of heptadiene group, both are responsible for scavenging of radicals^{57,58} to give an antioxidant effect whereas less hydrogenation of the unsaturated diketone moiety and methoxylation of the molecules are highly responsible for the anti-inflammatory and anti-tumoral effect.⁴³ Further advanced studies showed that the presence of aromatic rings is important for cytotoxic and antiandrogenic activity along⁵⁹ with substitutions of 3'-dimethoxy and 4'-dimethoxy and/or 3'-methoxy-4'-hydroxy substitutions on phenyl ring which will help in designing new Curcumin analogs.⁶⁰

The laboratory studies carried on the mouse with already grown tumors as well as in patients suffering from multiple myeloma⁶¹ or pancreatic cancer⁶² showed the inhibition of NF- κ B activation through Curcumin.⁶³ Curcumin also has the ability to suppress different carcinogens and thus help in preventing cancer, which is shown in Table 1. Studies have shown that Curcumin can decrease the occurrence of breast cancer metastasis due to suppression of NF- κ B as well as of COX-2 pathways.⁶⁴ The various clinical trials with Curcumin are reported in Table 2.

4.2. EGCG

Epigallocatechin gallate (EGCG) is a chemoprotective antioxidant polyphenol^{65,66} which inhibits the cell growth, G₀/G₁ phase arrest and induction of cell death in human epidermoid carcinoma cells.¹⁵ It shows an anti-oxidant activity by inhibiting the MAPK cascade by scavenging

H₂O₂.¹¹ It also inhibits the activation of NF- κ B and AP-1 by arresting the COX-2 induction, also showing upregulation of the antioxidant enzymes by initiating the Nrf-2 and ARE signalling pathway¹⁶

Studies show that EGCG inhibits epidermal growth factor receptor (EGFR) in case of prostate cancer cells which further inhibit the MAPK signalling cascades whereas it inhibits the production of vascular endothelial growth factor (VEGF) in colon and breast cancer cells. The TRAMP (transgenic adenocarcinoma of the mouse prostate) model was extensively used as an in vivo model for studies of EGCG with a dose of (1mg/mouse/day for 14 days), which showed that there was 80% reduction in the development of tumor by putting a stop on both androgen-dependent and independent tumors but was found to be more effective on dependent tumors.⁶⁷

It is reported that EGCG is one of the potent activators of Nrf2 among the other polyphenols because EGCG can provoke the transactivation of ARE promoter gene. Also, it has the ability to activate the Nrf2-mediated HO-1 expression which can stimulate the expression of Nrf2 dependent genes whereas it gives an inhibitory effect on the proliferation of bovine capillary endothelial cells.⁶⁸

EGCG also inhibits the translocation of NF- κ B into the nucleus^{69,70} by inhibiting the activation of IKK and phosphorylation of I- κ B α .^{44,71–73} It inhibits the oxidative stress-mediated phosphorylation of MAPK signalling pathways.⁷⁴ The galloyl and a hydroxyl group at 3' position on EGCG are found to be involved in anti-inflammatory action⁷⁵

4.3. Resveratrol

Resveratrol is a phytoalexin which is obtained from plant parts mainly from skin and seeds of red grapes and possesses anti-oxidative, anti-inflammatory as well as chemopreventive activities. Resveratrol works by triggering programmed cell death by inhibiting the cell growth and also by reducing the prevalence of carcinogen-induced carcinogenesis process.⁶⁴

The studies proved that resveratrol is effective in blocking the initiation, promotion and progression stage of tumorigenesis induced by polynuclear aromatic hydrocarbon dimethylbenz (a) anthracene (DMBA).^[74] Studies showed that resveratrol and its analogs can effectively modulate the major cell cycle mediators which will arrest the cancer cells at G₁/S phase of the cell cycle and inhibit the ERK signal transduction pathway.⁷⁶ It can also directly inhibit the DNA synthesis by diminishing ribonucleotide reductase and DNA polymerase.^{77,78} Resveratrol can also show anticancer activity by inhibiting the COX-2 pathway⁷⁹ and can block TPA-induced NF- κ B activation⁸⁰, of which hydroxylated resveratrol is more selective towards inhibition of COX-2 activity^{81,82}

Resveratrol can act by different mechanisms to inhibit the growth of cancer cells, one of which is that it can act on chemical carcinogens to undergo oxidative metabolism by Phase I enzymes which help in detoxifying the enzymes^{83,84} by converting them into polar intermediates and eliminate via conjugation with Phase II enzymes. In absence of Phase II enzymes, the active carcinogens will attack the cellular DNA which starts the tumorigenesis process whereas in presence of these enzymes resveratrol gives an antioxidant effect by two basic mechanisms.

1. Suppressing the nuclear translocation of NF- κ B further blocking the phosphorylation which will arrest the growth of cancer cells and cause programmed cell death.^{85,86}

2. By activating the Nrf2 pathway which will help to detoxify the carcinogens and prevent tumorigenesis.⁸³ Resveratrol also exhibits antitumor effect by blocking the COX-2 expression whereas it shows both anti-inflammatory⁸⁷ as well as antitumor effect⁸⁸ by downregulating the MAP kinases.^{89–93}

4.4. Genistein

Genistein, an isoflavone present in soybean enriched foods also shows inhibition of cancer growth in human cells by inhibiting the NF- κ B activation.²³ It shows anticancer activity by inhibiting the translocation of NF- κ B into the nucleus.⁷⁰ It also shows antagonizing effect via estrogen and androgen-mediated signalling pathways during the carcinogenesis process.²³ Studies showed that Genistein blocks the NF- κ B activation⁹⁴ by known inducers such as H₂O₂ and TNF- α . It inhibits this translocation of NF- κ B into the nucleus thus prevent its binding to the target DNA and causing programmed cell death. It also shows the antioxidant effect by protecting the cells against ROS^[94,95] by eliminating the free radicals and reducing the expression of stress-regulated genes.²³

4.5. Quercetin

Quercetin found in vegetables, fruits and also in red wine is a naturally occurring flavonoid which shows anticancer effect. A number of mechanisms have been put forward based on the activity of quercetin on cancer lines, one of which is that it shows the antioxidant effect by producing reactive oxygen species and prevents the cellular damage.^{41,96} Another mechanism that is hypothesized is that it inhibits the cell cycle mechanism in late G1 phase which further blocks the various signalling pathways and causing programmed cell death.^{97,98} Studies show that Quercetin increases the DNA fragmentation and the activity of caspase 3 in malignant cell lines.^{52,99}

At the molecular level, quercetin has the ability to downregulate the expression of oncogenes also it can inhibit various tyrosine and serine-threonine kinases which will further affect the MAPK and AKT pathways.⁴⁴

The phenolic hydroxyl groups at the III position are found to be responsible for the free radical scavenging activity. Quercetin binds directly to RAF and MEK protein kinases and inhibits the phosphorylation activities to cause programmed cell death.⁴²

5. Conclusion

Phytochemicals discussed above are of prime importance in chemoprevention and there has been a shift noticed towards herbal treatment owing to adverse effects associated with modern drugs. The knowledge of these modulating pathways helps in understanding the essence of a traditional medicinal system which could alleviate a number of ailments by leading to homeostasis.

6. Source of Funding

None.

7. Conflict of Interest

None.

References

- Huang WY, Cai YZ, Zhang Y. Natural phenolic compounds from medicinal herbs and dietary plants: Potential use for cancer prevention. *Nutr Cancer*. 2010;62(1):1–20. doi:10.1080/01635580903191585.
- Tan AC, Konczak I, Sze DMY, Ramzan I. Molecular Pathways for Cancer Chemoprevention by Dietary Phytochemicals. *Nutr Cancer*. 2011;63(4):495–505. doi:10.1080/01635581.2011.538953.
- Lee KW, Lee HJ. The roles of polyphenols in cancer chemoprevention. *BioFactors*. 2006;26(2):105–21. doi:10.1002/biof.5520260202.
- Huang W, Cai Y, Zhang Y, Huang W, Cai Y. Natural Phenolic Compounds From Medicinal Herbs and Dietary Plants: Potential Use for Cancer Prevention. *Nutr Cancer*. 2009;62(1):37–41.
- Singh RP, Dhanalakshmi S, Agarwal R. Phytochemicals as Cell Cycle Modulators A Less Toxic Approach in Halting Human Cancers Phytochemicals as Cell Cycle Modulators A Less Toxic Approach in Halting Human Cancers sc ie nc ot fo is tr ib ut. *Cell Cycle*. 2002;1(3):156–61.
- Lee JH, Khor TO, Shu L, Su ZY, Fuentes F, Kong AT. Dietary phytochemicals and cancer prevention: Nrf2 signaling, epigenetics, and cell death mechanisms in blocking cancer initiation and progression. *Pharm Ther*. 2013;137(2):153–71. doi:10.1016/j.pharmthera.2012.09.008.
- Ramos S. Cancer chemoprevention and chemotherapy: Dietary polyphenols and signalling pathways. *Mol Nutr Food Res*. 2008;52(5):507–26. doi:10.1002/mnfr.200700326.
- Lee KW, Bode AM, Dong Z. Molecular targets of phytochemicals for cancer prevention. *Nat Rev Cancer*. 2011;11(3):211–8. doi:10.1038/nrc3017.
- Khan N, Afaq F, Mukhtar H. Cancer Chemoprevention Through Dietary Antioxidants: Progress and Promise. *Antioxidants & Redox Signaling*. 2008;10(3):475–510. Available from: <https://dx.doi.org/10.1089/ars.2007.1740>. doi:10.1089/ars.2007.1740.
- Behl T, Kumar K, Brisc C, Rus M, Zengin G, Bustea C, et al. Exploring the multifocal role of phytochemicals as immunomodulators. *Biomed Pharm*. 2021;133:110959. doi:10.1016/j.biopha.2020.110959.
- AHaque M, Jantan I, Arshad L, Bukhari SNA. Exploring the immunomodulatory and anticancer properties of zerumbone. *Food Funct*. 2017;8(10):3410–31. doi:10.1039/c7fo00595d.

12. Loo G. Redox-sensitive mechanisms of phytochemical-mediated inhibition of cancer cell proliferation I (Review). *J Nutr Biochem*. 2003;14(2):64–73. doi:10.1016/s0955-2863(02)00251-6.
13. Zubair H, Azim S, Ahmad A, Khan M, Patel G, Singh S. Cancer Chemoprevention by Phytochemicals: Nature's Healing Touch. *Molecules*. 2017;22(3):395. doi:10.3390/molecules22030395.
14. Koh YC, Yang G, Lai CS, Weerawatanakorn M, Pan MH. Chemopreventive Effects of Phytochemicals and Medicines on M1/M2 Polarized Macrophage Role in Inflammation-Related Diseases. *Int J Mol Sci*. 2018;19(8):2208. doi:10.3390/ijms19082208.
15. Nakagawa H, Hasumi K, Woo JT, Nagai K, Wachi M. Generation of hydrogen peroxide primarily contributes to the induction of Fe(II)-dependent apoptosis in Jurkat cells by (-)-epigallocatechin gallate. *Carcinogenesis*. 2004;25(9):1567–74. doi:10.1093/carcin/bgh168.
16. Aggarwal BB, Shishodia S. Suppression of the Nuclear Factor- κ B Activation Pathway by Spice-Derived Phytochemicals: Reasoning for Seasoning. *Ann New York Acad Sci*. 2004;1030(1):434–41. doi:10.1196/annals.1329.054.
17. Hemalswarya S, Doble M. Potential synergism of natural products in the treatment of cancer. *Phytotherapy Res*. 2006;20(4):239–49. doi:10.1002/ptr.1841.
18. Surh YJ. Cancer chemoprevention with dietary phytochemicals. *Nat Rev Cancer*. 2003;3(10):768–80. doi:10.1038/nrc1189.
19. Chikara S, Nagaprashantha LD, Singhal J, Horne D, Awasthi S, Singhal SS. Oxidative stress and dietary phytochemicals: Role in cancer chemoprevention and treatment. *Cancer Lett*. 2018;413:122–34. doi:10.1016/j.canlet.2017.11.002.
20. Hun J, Oo T, Shu L, Su Z, Fuentes F, Kong AT. Pharmacology & Therapeutics Dietary phytochemicals and cancer prevention : Nrf2 signaling , epigenetics , and cell death mechanisms in blocking cancer initiation and progression. *Pharm Ther*. 2013;137(2):153–71.
21. Surh YJ, Na HK. NF- κ B and Nrf2 as prime molecular targets for chemoprevention and cytoprotection with anti-inflammatory and antioxidant phytochemicals. *Genes Nutr*. 2008;2(4):313–7. doi:10.1007/s12263-007-0063-0.
22. Oommen E, Hummel A, Allmannsberger L. IgA antibodies to myeloperoxidase in patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss). *Clin Exp Rheumatol*. 2017;103(1):98–101.
23. Itoh K, Chiba T, Takahashi S. An Nrf2/Small Maf Heterodimer Mediates the Induction of Phase II Detoxifying Enzyme Genes through Antioxidant Response Elements. *Biochem Biophys Res Commun*. 1997;236(2):313–22. doi:10.1006/bbrc.1997.6943.
24. Saw CL, Hu R. Regulation of NF-E2-related factor 2 signaling for cancer chemoprevention: antioxidant coupled with antiinflammatory. *Antioxid Redox Signal*. 2010;13(11):1679–98. doi:10.1089/ars.2010.3276.
25. Surh YJ, Kundu JK, Na HK, Lee JS. Redox-sensitive transcription factors as prime targets for chemoprevention with anti-inflammatory and antioxidative phytochemicals. *J Nutr*. 2005;135(12):2993–3001. doi:10.1093/jn/135.12.2993S.
26. Son Y, Cheong YK, Kim NH, Chung HT, Kang DG, Pae HO. Mitogen-Activated Protein Kinases and Reactive Oxygen Species: How Can ROS Activate MAPK Pathways? *J Signal Transduct*. 2011;2011:1–6. doi:10.1155/2011/792639.
27. Samec M, Liskova A, Koklesova L, Samuel SM, Murin R, Zubor P, et al. The role of plant-derived natural substances as immunomodulatory agents in carcinogenesis. *J Cancer Res Clin Oncol*. 2020;146(12):3137–54. doi:10.1007/s00432-020-03424-2.
28. Yahfoufi N, Alsadi N, Jambi M, Matar C. The Immunomodulatory and Anti-Inflammatory Role of Polyphenols. *Nutrients*. 2018;10(11):1618. doi:10.3390/nu10111618.
29. Sharma N, Dhekne HS, Senapati S. Immunomodulatory Potential of Phytochemicals: Recent Updates. In *Phytochemistry: An in-silico and in-vitro Update*. Singapore; 2019. p. 133–60.
30. Thakur VS, Deb G, Babcook MA, Gupta S. Plant phytochemicals as epigenetic modulators: role in cancer chemoprevention. The AAPS journal. *AAPS J*. 1989;16(1):151–63. doi:10.1208/s12248-013-9548-5.
31. Rilke F, Colnaghi MI, Cascinelli N, Andreola S, Baldini MT, Bufalino R, et al. Prognostic significance of her-2/neu expression in breast cancer and its relationship to other prognostic factors. *Int J Cancer*. 1991;49(1):44–9. doi:10.1002/ijc.2910490109.
32. Roman ID, Thewles A, Coleman R. Fractionation of livers following diosgenin treatment to elevate biliary cholesterol. *Biochim Biophys Acta (BBA) - Lipid Metab*. 1995;1255(1):77–81. doi:10.1016/0005-2760(94)00212-h.
33. Liu MJ, Wang Z, Ju Y, Wong RS, Wu QY. Diosgenin induces cell cycle arrest and apoptosis in human leukemia K562 cells with the disruption of Ca²⁺ homeostasis. *Cancer Chemother Pharm*. 2005;55(1):79–90. doi:10.1007/s00280-004-0849-3.
34. Peeters PHM, Boker LK, Schouw YT, Grobbee DE. Phytoestrogens and Breast Cancer Risk. *Breast Cancer Res Treat*. 2003;77(2):171–83. doi:10.1023/a:1021381101632.
35. Leger D, Liagre B, Beneytout JL. Role of MAPKs and NF- κ B in diosgenin-induced megakaryocytic differentiation and subsequent apoptosis in HEL cells. *Int J Oncol*. 2006;28(1):201–7. doi:10.3892/ijo.28.1.201.
36. Chiang CT, Way TD, Tsai SJ, Lin JK. Diosgenin, a naturally occurring steroid, suppresses fatty acid synthase expression in HER2-overexpressing breast cancer cells through modulating Akt, mTOR and JNK phosphorylation. *FEBS Lett*. 2007;581(30):5735–42. doi:10.1016/j.febslet.2007.11.021.
37. Bhat TA, Singh RP. Tumor angiogenesis - A potential target in cancer chemoprevention. *Food Chem Toxicol*. 2008;46(4):205–17. doi:10.1016/j.fct.2007.08.032.
38. Kumar NM, Gilula NB. The Gap junction Communication Channel. *Cell*. 2011;84(3):881–8. doi:10.1016/s0092-8674(00)81282-9.
39. Rosenkranz HS, Pollack N, Cunningham AR. Exploring the relationship between the inhibition of gap junctional intercellular communication and other biological phenomena. *Carcinogenesis*. 2000;21:1007–11.
40. Trosko JE. Commentary: Is the concept of 'tumor promotion'? a useful paradigm? *Mol Carcinogenesis*. 2001;30(3):131–7. doi:10.1002/mc.1021.
41. Duthie SJ, Collins AR, Duthie GG, Dobson VL. Quercetin and myricetin protect against hydrogen peroxide-induced DNA damage (strand breaks and oxidised pyrimidines) in human lymphocytes. *Mutation Res/Genet Toxicol Environ Mutagenesis*. 1997;393(3):223–31. doi:10.1016/s1383-5718(97)00107-1.
42. Murakami A, Ashida H, Terao J. Multitargeted cancer prevention by quercetin. *Cancer Lett*. 2008;269(2):315–25. doi:10.1016/j.canlet.2008.03.046.
43. Sugiyama Y, Kawakishi S, Osawa T. Involvement of the β -diketone moiety in the antioxidative Mechanism of Tetrahydrocurcumin. *Biochemical Pharm*. 1996;52(4):519–25. doi:10.1016/0006-2952(96)00302-4.
44. Khan N, Mukhtar H. Multitargeted therapy of cancer by green tea polyphenols. *Cancer Lett*. 2008;269(2):269–80. doi:10.1016/j.canlet.2008.04.014.
45. Thangapazham RL, Sharma A, Maheshwari RK. Multiple molecular targets in cancer chemoprevention by curcumin. *AAPS J*. 2006;8:443–9. doi:10.1208/aapsj080352.
46. Huang M, Lysz T, Ferraro T, Abidi T. Inhibitory effects of curcumin on in vitro lipoxygenase and cyclooxygenase activities in mouse epidermis. *Cancer Res*. 1991;51(3):813–9.
47. Goel A, Boland CR, Chauhan DP. Specific inhibition of cyclooxygenase-2 (COX-2) expression by dietary curcumin in HT-29 human colon cancer cells. *Cancer Lett*. 2001;172(2):111–8. doi:10.1016/s0304-3835(01)00655-3.
48. Zhang F, Altorki NK, Mestre JR, Subbaramaiah K, Dannenberg AJ. Curcumin inhibits cyclooxygenase-2 transcription in bile acid- and phorbol ester-treated human gastrointestinal epithelial cells. *Carcinogenesis*. 1999;20(3):445–51. doi:10.1093/carcin/20.3.445.
49. Shishodia S, Aggarwal BB. Diosgenin inhibits osteoclastogenesis, invasion, and proliferation through the downregulation of Akt, I κ B kinase activation and NF- κ B-regulated gene expression. *Oncogene*. 2006;25(10):1463–73. doi:10.1038/sj.onc.1209194.

50. Nie Y, Cao M, Wu D. KH-type splicing regulatory protein is regulated by nuclear factor- κ B signaling to mediate innate immunity in Caco-2 cells infected by *Salmonella enteritidis*. *Folia Microbiol.* 2018;63(6):669–76. doi:10.1007/s12223-018-0606-3.
51. Dhandapani KM, Mahesh VB, Brann DW. Curcumin suppresses growth and chemoresistance of human glioblastoma cells via AP-1 and NF κ B transcription factors. *J Neurochemistry.* 2007;102(2):522–38. doi:10.1111/j.1471-4159.2007.04633.x.
52. Liu J, Lin S, Carcinogenesis JL. Inhibitory effects of curcumin on protein kinase C activity induced by 12-O-tetradecanoyl-phorbol-13-acetate in NIH 3T3 cells. *Carcinogenesis.* 1993;4(5):857–861. doi:10.1093/carcin/14.5.857.
53. Huang T, Lee S. Suppression of c-Jun/AP-1 activation by an inhibitor of tumor promotion in mouse fibroblast cells; 1991. Available from: <http://www.pnas.org/content/88/12/5292.short>. Accessed September 26, 2018.
54. Bhaumik S, Anjum R, Rangaraj N, Pardhasaradhi BV, Khar A. Curcumin mediated apoptosis in AK-5 tumor cells involves the production of reactive oxygen intermediates. *FEBS Lett.* 1999;456(2):311–4. doi:10.1016/s0014-5793(99)00969-2.
55. Jagtap S, Meganathan K, Wagh V, Winkler J, Hescheler J, Sachinidis A. Chemoprotective Mechanism of the Natural Compounds, Epigallocatechin-3-O-Gallate, Quercetin and Curcumin Against Cancer and Cardiovascular Diseases. *Curr Med Chem.* 2009;16(12):1451–62. doi:10.2174/092986709787909578.
56. Shehzad A, Wahid F, Lee YS. Curcumin in Cancer Chemoprevention: Molecular Targets, Pharmacokinetics, Bioavailability, and Clinical Trials. *Arch der Pharmazie.* 2010;343(9):489–99. doi:10.1002/ardp.200900319.
57. Sandur SK, Pandey MK, Sung B, Ahn KS, Murakami A, Sethi G. Curcumin, demethoxycurcumin, bisdemethoxycurcumin, tetrahydrocurcumin and turmerones differentially regulate anti-inflammatory and anti-proliferative responses through a ROS-independent mechanism. *Carcinogenesis.* 2007;28(8):1765–73. doi:10.1093/carcin/bgm123.
58. Somporn P, Phisalaphong C, Nakornchai S, Unchern S, Morales NP. Comparative Antioxidant Activities of Curcumin and Its Demethoxy and Hydrogenated Derivatives. *Biolo Pharm Bull.* 2007;30(1):74–8. doi:10.1248/bpb.30.74.
59. Lin L, Shi Q, Nyarko AK. Antitumor agents. 250. Design and synthesis of new curcumin analogues as potential anti-prostate cancer agents. *J Med Chem.* 2006;49(13):3963–72.
60. Teiten MH, Gaascht F, Eifes S, Dicato M, Diederich M. Chemopreventive potential of curcumin in prostate cancer. *Genes Nutr.* 2010;5(1):61–74. doi:10.1007/s12263-009-0152-3.
61. Raj SV, Weber DM, Wang M. Curcumin Downregulates NF- κ B and Related Genes in Patients with Multiple Myeloma: Results of a Phase I/II Study. *Blood.* 2007;110(11):1177.
62. Dhillon N, Aggarwal BB, Newman RA, Wolff RA, Kunnumakara AB, Abbruzzese JL, et al. Phase II Trial of Curcumin in Patients with Advanced Pancreatic Cancer. *Clin Cancer Res.* 2008;14(14):4491–9. doi:10.1158/1078-0432.ccr-08-0024.
63. Kunnumakara AB, Anand P, Aggarwal BB. Curcumin inhibits proliferation, invasion, angiogenesis and metastasis of different cancers through interaction with multiple cell signaling proteins. *Cancer Lett.* 2008;269(2):199–225. doi:10.1016/j.canlet.2008.03.009.
64. Mukhopadhyay A, Ramos CB, Chatterjee D, Pantazis P, Aggarwal BB. Curcumin downregulates cell survival mechanisms in human prostate cancer cell lines. *Oncogene.* 2001;20(52):7597–609. doi:10.1038/sj.onc.1204997.
65. Shao ZM, Shen ZZ, Liu CH. Curcumin exerts multiple suppressive effects on human breast carcinoma cells. *Int J Cancer.* 2002;98(2):234–40.
66. Stuart EC, Scandlyn MJ, Rosengren RJ. Role of epigallocatechin gallate (EGCG) in the treatment of breast and prostate cancer. *Life Sci.* 2006;79(25):2329–36. doi:10.1016/j.lfs.2006.07.036.
67. Kou X, Kirberger M, Yang Y, Chen N. Natural products for cancer prevention associated with Nrf2–ARE pathway. *Food Sci Hum Wellness.* 2013;2(1):22–8. doi:10.1016/j.fshw.2013.01.001.
68. Chen C, Sun Y, Chen JJ, Chiu KT. Induced Cyclooxygenase-2 Expression in Human Lung Epithelial Cells: Involvement of the Phospholipase C-2, Protein Kinase C-, Tyrosine Kinase, NF- κ B-Inducing Kinase, and I- β Kinase 1/2 Pathway. *J Immunol.* 2000;165(5):2719–28.
69. Natarajan K, Manna SK, Chaturvedi MM, Aggarwal BB. Protein Tyrosine Kinase Inhibitors Block Tumor Necrosis Factor-Induced Activation of Nuclear Factor- κ B, Degradation of I κ B α , Nuclear Translocation of p65, and Subsequent Gene Expression. *Arch Biochem Biophys.* 1998;352(1):59–70. doi:10.1006/abbi.1998.0576.
70. Ahmad N, Gupta S, Mukhtar H. Green Tea Polyphenol Epigallocatechin-3-Gallate Differentially Modulates Nuclear Factor κ B in Cancer Cells versus Normal Cells. *Arch Biochem Biophys.* 2000;376(2):338–46. doi:10.1006/abbi.2000.1742.
71. Afaq F, Adhami VM, Ahmad N, Mukhtar H. Inhibition of ultraviolet B-mediated activation of nuclear factor κ B in normal human epidermal keratinocytes by green tea Constituent (-)-epigallocatechin-3-gallate. *Oncogene.* 2003;22(7):1035–44. doi:10.1038/sj.onc.1206206.
72. Ahmad N, Gupta S, Mukhtar H. A green tea-derived polyphenol, epigallocatechin-3-gallate, inhibits I κ B kinase activation and IL-8 gene expression in respiratory epithelium. *Arch Biochem Biophys.* 2002;26(5):233–41. doi:10.1006/abbi.2000.1742.
73. Sarkar FH, Li Y. Cell signaling pathways altered by natural chemopreventive agents. *Mutation Res/Fundamental Mol Mech Mutagenesis.* 2004;555(1-2):53–64. doi:10.1016/j.mrfmmm.2004.04.015.
74. Khan N, Afaq F, Saleem M, Ahmad N, Mukhtar H. Targeting Multiple Signaling Pathways by Green Tea Polyphenol (-)-Epigallocatechin-3-Gallate. *Cancer Res.* 2006;66(5):2500–5. doi:10.1158/0008-5472.can-05-3636.
75. Cuendet M, Othman CP, Moon RC, Pezzuto JM. Quinone Reductase Induction as a Biomarker for Cancer Chemoprevention. *J Nat Prod.* 2006;69(3):460–3. doi:10.1021/np050362q.
76. Fontecave M, Lepoivre M, Elleingand E, Gerez C, Guittet O. Resveratrol, a remarkable inhibitor of ribonucleotide reductase. *FEBS Lett.* 1998;421(3):277–9. doi:10.1016/s0014-5793(97)01572-x.
77. Sun NJ, Woo SH, Cassidy JM, Snapka RM. DNA Polymerase and Topoisomerase II Inhibitors from *Psoralea corylifolia*. *J Nat Prod.* 1998;61(3):362–6. doi:10.1021/np970488q.
78. Durgaprasad S, Pai G, Vasanthkumar C, Alvres JF, Sanjeeva N. A pilot study of the antioxidant effect of curcumin in tropical pancreatitis. *Indian J Med Res.* 2005;122(4):315–8.
79. Kundu JK, Shin YK, Kim SH, Surh YJ. Resveratrol inhibits phorbol ester-induced expression of COX-2 and activation of NF- κ B in mouse skin by blocking I κ B kinase activity. *Carcinogenesis.* 2006;27:1465–74.
80. Murias M, Handler N, Erker T, Pleban K, Ecker G, Saiko P, et al. Resveratrol analogues as selective cyclooxygenase-2 inhibitors: synthesis and structure–activity relationship. *Bioorganic Med Chem.* 2004;12(21):5571–8. doi:10.1016/j.bmc.2004.08.008.
81. Athar M, Back JH, Kopelovich L, Bickers DR, Kim AL. Multiple molecular targets of resveratrol: Anti-carcinogenic mechanisms. *Arch Biochem Biophys.* 2009;486(2):95–102. doi:10.1016/j.abbi.2009.01.018.
82. Kundu JK, Surh YJ. Molecular basis of chemoprevention by resveratrol: NF- κ B and AP-1 as potential targets. *Mutation Res/Fundamental Mol Mech Mutagenesis.* 2004;555(1-2):65–80. doi:10.1016/j.mrfmmm.2004.05.019.
83. Baur JS, Sinclair DA. Therapeutic Potential of resveratrol: the in vivo evidence. *Nat Rev Drug Discov.* 2006;5(6):493–506. doi:10.1038/nrd2060.
84. Tsai SH, Shiau SYL, Lin JK. Suppression of nitric oxide synthase and the down-regulation of the activation of NF κ B in macrophages by resveratrol. *Br J Pharm.* 1999;126(3):673–80. doi:10.1038/sj.bjp.0702357.
85. Cho DI, Koo NY, Chung WJ. Effects of resveratrol-related hydroxystilbenes on the nitric oxide production in macrophage cells: Structural requirements and mechanism of action. *Life Sci.* 2002;71(17):2071–82. doi:10.1016/s0024-3205(02)01971-9.

86. Kundu JK, Shin YK, Surh YJ. Resveratrol modulates phorbol ester-induced pro-inflammatory signal transduction pathways in mouse skin in vivo: NF- κ B and AP-1 as prime targets. *Biochem Pharm.* 2006;72(11):1506–15. doi:10.1016/j.bcp.2006.08.005.
87. Yu R, Hebbar V, Kim DW, Mandlekar S, Pezzuto JM, Kong ANT. Resveratrol Inhibits Phorbol Ester and UV-Induced Activator Protein 1 Activation by Interfering with Mitogen-Activated Protein Kinase Pathways. *Mol Pharm.* 2001;60(1):217–24. doi:10.1124/mol.60.1.217.
88. Alkhalaf M. Resveratrol-induced growth inhibition in MDA-MB-231 breast cancer cells is associated with mitogen-activated protein kinase signaling and protein translation. *Eur J Cancer Prev.* 2007;16(4):334–41. doi:10.1097/01.cej.0000228413.06471.4c.
89. Trung LQ, An DTT. Is Resveratrol a Cancer Immunomodulatory Molecule? *Front Pharm.* 2018;6(9):1255. doi:10.3389/fphar.2018.01255.
90. Kundu JK, Shin YK, Kim SH, Surh YJ. Cancer chemopreventive and therapeutic potential of resveratrol: mechanistic perspectives. *Cancer Lett.* 2006;269(2):1465–74. doi:10.1016/j.canlet.2008.03.057.
91. Dong Z. Molecular mechanism of the chemopreventive effect of resveratrol. *Mutation Research - Fundamental and Molecular Mechanisms of Mutagenesis.* 2003;p. 145–150.
92. Kundu JK, Surh YJ. Cancer chemopreventive and therapeutic potential of resveratrol: Mechanistic perspectives. *Cancer Lett.* 2008;269(2):243–61. doi:10.1016/j.canlet.2008.03.057.
93. Natarajan K, Manna SK, Chaturvedi MM, Aggarwal BB. Protein Tyrosine Kinase Inhibitors Block Tumor Necrosis Factor-Induced Activation of Nuclear Factor- κ B, Degradation of I κ B α , Nuclear Translocation of p65, and Subsequent Gene Expression. *Arch Biochem Biophys.* 1998;352(1):59–70. doi:10.1006/abbi.1998.0576.
94. Larrea MB, Mohan AR, Paganga G, Miller NJ, Bolwell GP, Evans CAR. Antioxidant Activity of Phytoestrogenic Isoflavones. *Radical Res.* 1997;26(1):63–70. doi:10.3109/10715769709097785.
95. Zhou Y, Lee AS. Mechanism for the suppression of the mammalian stress response by genistein, an anticancer phytoestrogen from soy. *J Natl Cancer Inst.* 1998;90(5):381–8. doi:10.3109/10715769709097785.
96. Gross M, Pfeiffer M, Martini M, Campbell D, Slavin J, Potter J. The quantitation of metabolites of quercetin flavonols in human urine. *Cancer Epidemiol Biomark Prev.* 1996;5(9):711–20.
97. Yoshida M, Yamamoto M, Nikaido T. Quercetin arrests human leukemic T-cells in late G1 phase of the cell cycle. *Cancer Res.* 1992;52(23):6676–81.
98. Subbaramaiah K, Chung WJ, Michaluart P, Telang N, Tanabe T, Inoue H, et al. Resveratrol Inhibits Cyclooxygenase-2 Transcription and Activity in Phorbol Ester-treated Human Mammary Epithelial Cells. *J Biol Chem.* 1998;273(34):21875–82. doi:10.1074/jbc.273.34.21875.
99. Yeap SK, Abu N, Mohamad NE, Beh BK, Ho WY, Ebrahimi S. Chemopreventive and immunomodulatory effects of *Murraya koenigii* aqueous extract on 4T1 breast cancer cell-challenged mice. *BMC Complement Altern Med.* 2015;15(1):306. doi:10.1186/s12906-015-0832-z.

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