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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.

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 hault 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- kB) 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 reaction[13], 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-kB 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 chemokines[16]

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 G_2/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-kB, AP-1 and Nrf-2 activation pathways

2.2.1. NF-kB 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-kB 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-kB 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 IkB kinase (IKK) complex by NF-kB inducing kinase (NIK) results in the phosphorylation and degradation of IkBα and the NF-kB 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-kB.[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 API-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-kB factor works in association with the AP-1 factor [18] 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 H_2O_2 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 inFigure 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 H_2O_2 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

Cycloxygenase-2 (COX-2) is an enzyme which is involved in the production of prostaglandins E_2 (PGE_2) 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 energy[27] 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 family[28], 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-kB 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 process[39] 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]nthracene; DMAB, 3,2'-dimethyl-4-aminobiphenol; TPA, 12-O-tetradecanoylphorbol-13-acetate, DHPN, 2,2'-dihydroxy-di-n-propylnitrosamine; EHEN, N-ethyl-N-hydroxyethylnitrosamine

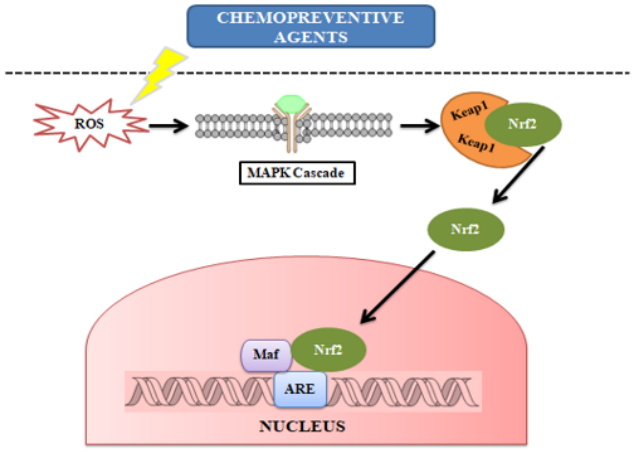

Fig. 1: Mechanism ofChemopreventive agents via Nrf2 Pathway

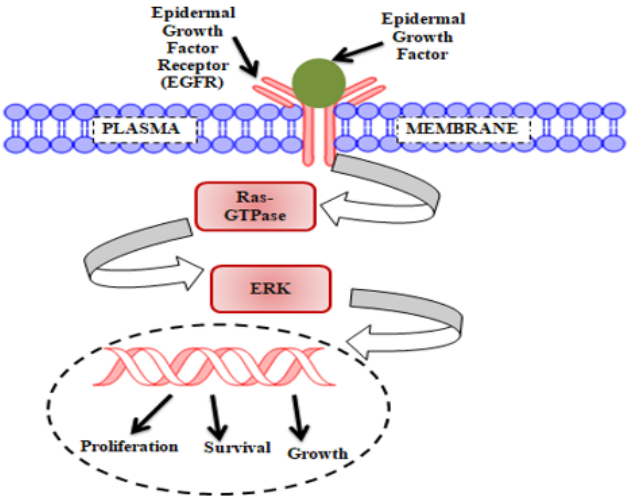

Fig. 2: Mitogen-activated protein kinases (MAPK) Pathway

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

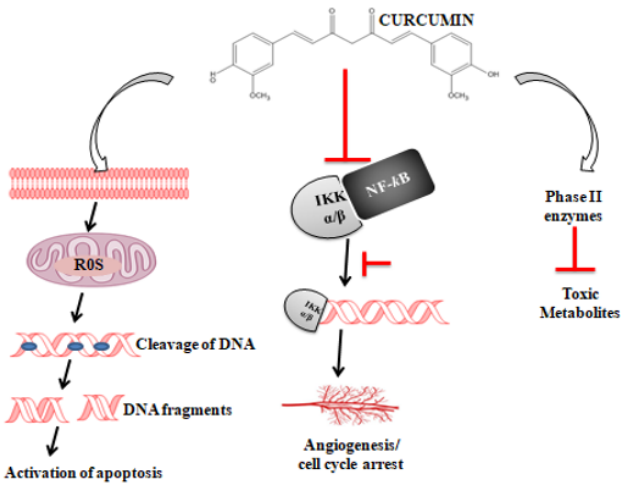

Fig. 3: Curcumin action ontumor inhibition

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-kB which progress by blocking MAPK[19] and downregulation of COX-2 pathway, Curcumin acts as a chemoprotective agent against cancer by restricting the translocation of the NF-kB in the nucleus.[45]

Curcumin thus downregulating the COX-2 pathway, thereby inhibits the breakdown of arachidonic acid to prostaglandin[46] 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-kB and blocking it activation.[48]

Also, studies show that Curcumin suppresses the tumor promotion by inhibiting the IkB degradation by downregulating the NF-kB-inducing kinase (NIK) and IkB 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- kB 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 kB-α, 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-kB activation. It also induces HO-1 expression through Nrf-2 and NF-kB 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 ERK[47] as well as the transcriptional activation of NF-kB 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 inFigure 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 along[59] 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 myeloma[61] or pancreatic cancer[62] showed the inhibition of NF-kB 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-kB 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, G_0/G_1 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 H_2O_2.[11] It also inhibits the activation of NF-kB and AP-1 by arresting the COX-2 induction, also showing upregulation of the antioxidant enzymes by initiating the Nrf-2 and ARE signalling pathway[16]

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-kB into the nucleus[69,70]by inhibiting the activation of IKK and phosphorylation of I-kappaBα.[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 action[75]

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 prooved 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 pathway[79] and can block TPA-induced NF-kB activation[80], 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-kB 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-inflammatory[87] as well as antitumor effect[88] 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-kB activation.[23] It shows anticancer activity by inhibiting the translocation of NF-kB 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-kB activation[94] by known inducers such as H_2O_2 and TNF-α. It inhibits this translocation of NF-kB 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.

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