

Phytochemicals mediated signalling pathways and their implications in cancer chemotherapy: challenges and opportunities in phytochemicals based drug development : A review

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Abstract

Cancer is considered as major leading cause for death in India and around world. Modern drug-targeted therapies have undoubtedly improved treatment to the cancer patients but also evoke severe side effects. Organ failure and immunosuppression is also a reason for death of cancer patients. However, advanced metastasized stage of cancers remained untreatable at present. So, there is need for the safer and more effective treatment for the improvement of efficiency and to lower the treatment cost to treat the disease. To readdress the above mentioned issues, phytochemical (s) based therapies are being advocated. Phytomedicine is an emerging strategy for the prevention, delaying, impeding the occurrence of cancer and curing the patients. The active herbal compounds of plants induce cytoprotective enzymes by the modulation of molecular targets of cancer while acting in co-ordination to detoxify and remove reactive substances formed by carcinogenic agents. The plant based principles have been reported to possess anti-carcinogenic, anti-proliferative and anti-mutagenic properties and hence exhibit potential to induce and stimulate cell death by genotoxic damage and reduction-oxidation imbalance in cells. These herbal compounds may inhibit or reverse multi-stages of cancer proliferation. This review summarizes an updated account of research in cancer chemoprevention and treatment strategy using phytochemical agents from medicinal plants. The underlying molecular mechanisms of actions of phytochemicals, the challenges in developing phytochemicals as effective anticancer drugs and possible solutions are also illustrated.

Keywords: Cancer, phytochemicals, anti-cancer, chemoprevention, apoptosis, mechanism

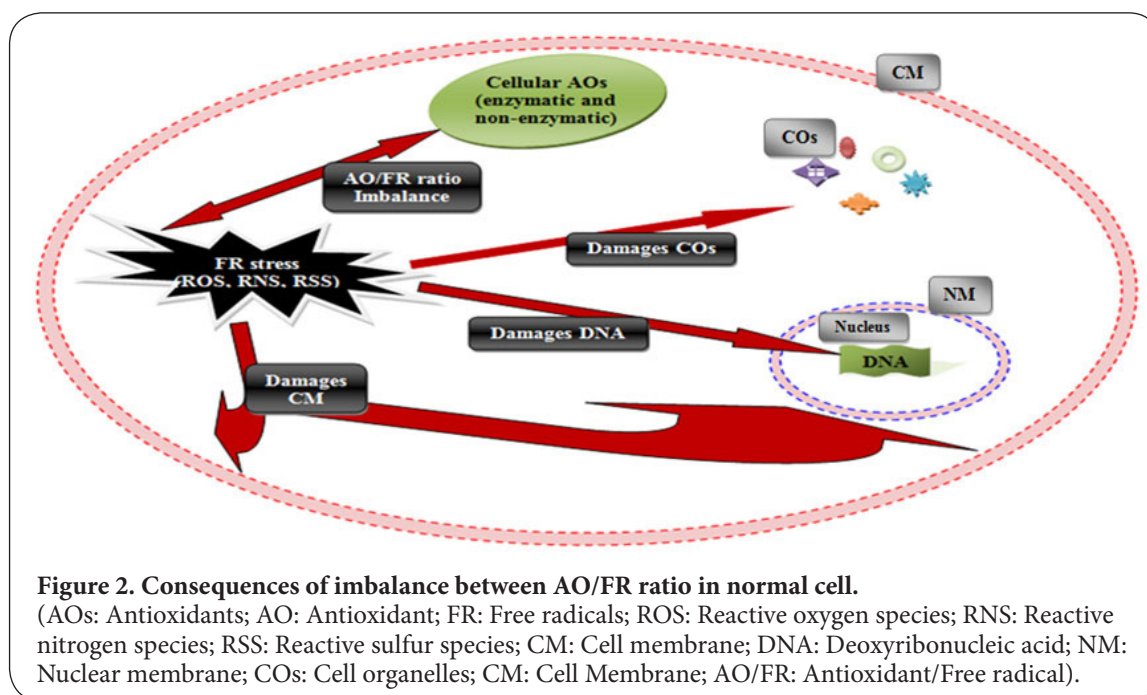
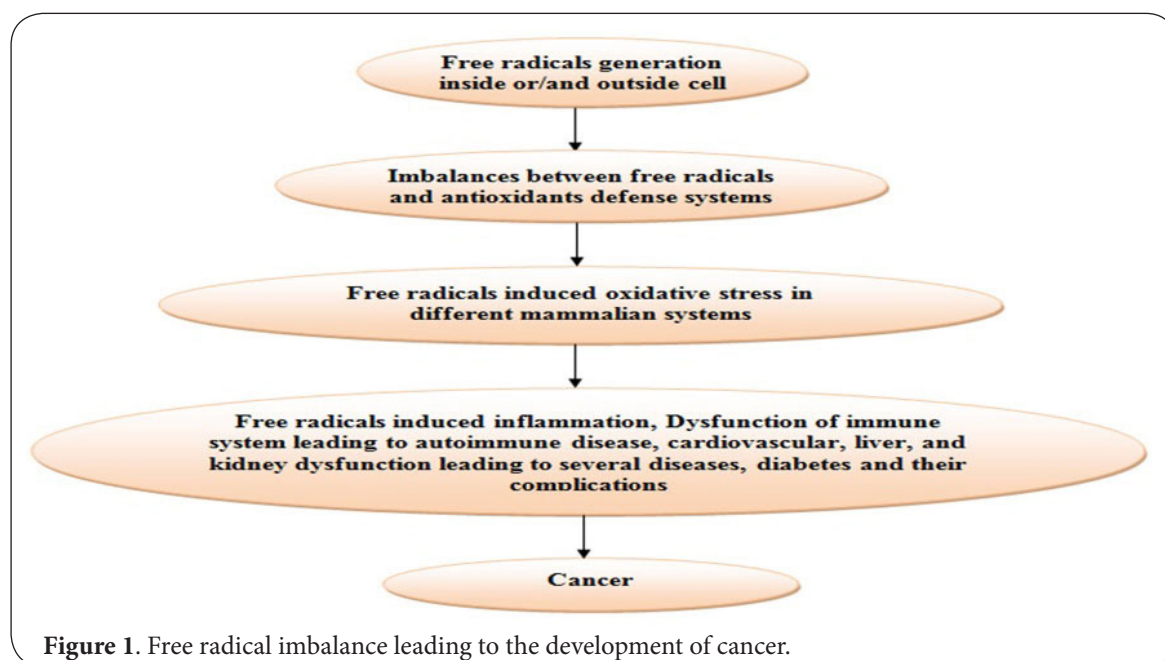
Introduction

Cancer is recognised as an abnormal growth of cells. It is originated due to lack of proper regulation in cell cycle. Cancer develops through an accumulation of genetic changes or mutations which could emerge due to different factors which could be physical (such as UV and other radiations), chemical (such as chewing and smoking of tobacco, chemical pollutants/mutagens), biological (such as viruses) and in some cases it may be hereditary. The types of damages within DNA may be induced by free radicals including strand breaks (single or double strand breaks), various forms of base damage in DNA (such as 8-hydroxyguanosine, thymine glycol, damage to deoxyribose sugar as well as DNA protein cross links) result into a heritable change in the DNA (mutations) thus causing cancer in the germ cells or malformations in fetus (somatic cells). Different types of free radicals have

been reported to react with the biomolecules by (i) electron donation and electron acceptance (ii) hydrogen abstraction, (iii) addition reactions, (iv) self-annihilation reactions and (v) by disproportionation [1], leading to the production of reactive oxygen species (ROS) and reactive nitrogen species (NOS) which are linked to onset of cancer and other severe diseases [2]. The consequences of free radical induced oxidative stress are presented in **Figures 1** and **2**.

Cancers at global and Indian context

Earlier cancers were reported only in developed countries but now developing countries are also getting affected [3]. According to World Health Organization (WHO) the percentage of diagnosed cancer cases in developing countries may increase by more than 60% in 2030 [4]. Ferlay et al. (2008) have presented a



worldwide estimate of new cancer cases and cancer deaths to be about 12.7 million and 7.6 million, respectively [4]. Several workers have reported that the cancer rates in successive generations of migrants shifts in the direction of prevailing rates in host country, suggesting that the variations in cancer rates largely reflect differences in environmental risk factors such as lifestyle and culture etc. rather than their genetic differences [5]. A list of gender based common diagnosed cancers along the world has been listed in [Table 1](#). In general,

the life style have been known to be the major factors for cancer development and as an infectious agents in developing countries. While prevalence of smoking is declining in developed countries [6], it is increasing in some developing countries which may be a main cause of increase in the burden of cancer in the developing countries [7]. However, the complete effect of these unhealthy lifestyle changes on the cancer burden in developing countries are likely to take decades to be realized [8,9].

Table 1. Commonly diagnosed cancers based on gender.

Gender diagnosed with different types of cancers and their corresponding countries			
Countries		different types of cancers	
Male	Female	Male	Female
Eastern Europe and Asia	Australia, Western Asia, North Africa, North America, and parts of South America	lung cancer	breast cancer
North America, Australia, Western and Northern Europe, and South America	Central America, parts of South America, Sub-Saharan Africa, and India	prostate cancer	cervical cancer
West Africa	Mongolia and Vietnam	liver cancer	liver cancer
central parts of Africa	China and North Korea	Kaposi sarcoma	lung cancer
East Africa	NA	Oesophagus	NA
Egypt	NA	bladder cancer	NA

Review

Prevention and treatment for cancer by phytochemicals

Prevention of a disease is always considered superior approach than its cure. A large number of medicinal herbal plants have been reported to prevent and treat various diseases for thousands of years [10]. The naturally occurring bioactive chemical components derived from plants have been reported to be exerting their beneficial effects, and have also been confirmed for their anti-cancerous activities (Table 2) [11-145]. The available experimental and epidemiological data have shown that a variety of nutritional factors including vitamin A, C, E, beta-carotene and micronutrients and different phytochemicals found in edible and non-edible plants can act as anti-cancer agents and inhibit the process of cancer development. Extensive studies on anti-cancer phytochemicals has been done by Wang et al. (2012) [10]. The name and properties of these herbal compounds are shown in Table 2.

Interaction of phytochemicals with signaling pathways involved in apoptosis of cancer cells

Many phytochemicals used as anti-inflammatory or anti-viral reagents target the apoptosis pathways in cancer [146]. Based on practical experiences of applications of traditional Chinese medicines, the involvement of apoptosis pathways was deciphered [146]. Apoptosis is the process of programmed cell death that may occur in multicellular organisms which includes blebbing, cell shrinkage, and nuclear fragmentation. The apoptosis mechanism involves several signalling pathways. Apoptotic proteins cause mitochondrial swelling and increase the permeability of the mitochondrial membrane through membrane pores and leak out the apoptotic effectors [147].

Small mitochondrial derived activators of caspases (SMACs) are released from mitochondria into cytosol. These activators bind to inhibitor of apoptosis proteins (IAPs), inactivate IAPs and prevent them from arresting the apoptotic processes. Caspases, which carry out the cell degradation and are suppressed by IAPs, proceed for cell apoptosis process [148]. Cytochrome c released from mitochondria due to the formation of mitochondrial apoptosis-induced channel

(MAC) in the outer membrane of mitochondria and binds with apoptotic protease activating factor-1 (Apaf-1) and ATP. This assembly then binds to pro-caspase-9 followed by the formation of an apoptosome and cleaves pro-caspase and release active caspase-9, which is then followed by the activation of caspase-3 [149]. Bcl-2 family proteins regulate MAC and Mitochondrial Outer Membrane Permeabilization Pore (MOMP) complex. The anti-apoptotic Bcl-2, Bcl-xL or Mcl-1 inhibits the formation of the pore [150]. When binding of Tumor Necrosis Factor (TNF), a cytokine mainly produced by activated macrophages, with its receptor takes place, the cell survival and inflammatory responses are initiated. The interaction of FasL (a trans-membrane protein of the TNF family) and Fas receptor (Apo-1 or CD95) forms Fas-associated death domain protein (FADD), caspase-8, and caspase-10 complex, also called death-inducing signaling complex (DISC) [151]. In mammalian cells, a balance between pro-apoptotic (BAX, BID, BAK, or BAD) and anti-apoptotic (Bcl-2 and Bcl-XI) proteins of the Bcl-2 family is maintained. Caspase activators (such as cytochrome c and SMAC) can be released from the mitochondrial membrane when the pro-apoptotic homodimers are formed in the outer-membrane of the mitochondrion. Inhibitor caspases (caspase 2, 8, 9 and 10) may require certain adaptor proteins. The effector caspases (caspases 3, 7 and 6) are activated by the active initiator caspase via proteolytic cleavage and degradation of intracellular proteins to promote the cell death process. Some of the cancer and phytochemicals associated apoptotic signalling mechanisms are discussed in more detail in the following sections.

Cyclooxygenases-2 (COX-2)

Cyclooxygenases are bi-functional membrane-bound enzymes [152,153]. Housekeeping function mediated by COX-1 and COX-2 is low in most cells but is constitutively elevated in colorectal and other cancers [152]. COX-2 has been reported to be associated in colorectal cancers with larger tumour size and poor survival of the cells [154] therefore the expression of COX-2 has been proposed to be a nutritional target for colon cancer [155]. COX-2 may be induced at very early

Table 2. Phytochemicals from medicinal plants, their sources and anticancer functions against cancers.

S. No.	Naturally occurring compound	Source Plant	Preventive /protective functions	Organ	References
1	Apigenin	<i>Moringa peregrina</i> Celery, Chamomile Parsley	Induced apoptosis through different signalling pathways i.e. leptin/leptin receptor pathway or by activating p38 MAPK pathway	Breast cancer cell lines, colon cancer cell line, lung adenocarcinoma cell line and B16 cells.	[11-17]
2	Berberamine	<i>Berberine amarensis</i>	Apoptosis dependent on Caspase-3	NA	[18-20]
3	Beta lapachone	<i>Tabebuia avellaneda</i>	Topoisomerase I and topoisomerase II inhibition	NA	[21-24]
4	Betulinic acid	<i>Betula alba</i>	Through mitochondrial apoptotic pathway	NA	[25-28]
5	Colchicine	<i>Colchicum autumnale</i>	Anti-mitotic	NA	[29,30]
6	Curcumin (diferuloylmethane)	<i>Curcuma longa</i>	Induce apoptosis in cancer cells without cytotoxic effects on healthy cells. modulates growth of tumor cells through regulation of multiple cell signaling pathways, down regulation of COX-2 and MMP-2 expression, suppression of gene expression of EGFR, increases AP-1-luciferase activity, inhibits NF-κB stimulator lipopolysaccharide (LPS)-induced inflammation, reduced LPS-induced IκB phosphorylation	Colon cancer, breast cancer, lung metastases, and brain tumor, human prostate cancer PC-3 cells	[31-37]
7	Crocetin	<i>Crocus sativus</i> (Saffron)	Exact mechanism of action is still not clear but it may be due to the inhibition of nucleic acid synthesis, enhancing anti-oxidative system, inducing apoptosis and hindering growth factor signaling pathways.	Hepatocellular carcinoma, human lung cancer, pancreatic cancer cell line, skin carcinoma, colorectal cancer cells, and breast cancer.	[38-45]
8	Cyanidin	Berries, plums, red cabbage and red onion.	Inhibiting cell proliferation, Inhibiting iNOS and COX-2 gene expression, blocks activation of ErbB2/cSrc/FAK pathway, induce the activation of AP-1 and NF-κB, blocked the activation of the Fyn kinase signaling pathway	Colon cancer cells, breast cancer cells, Oesophagus cell line, tumorigenic rat esophagus cell line, epidermal skin cell line	[46-50]
9	Daphnoretin	<i>Wikstroemia indica</i>	Suppressed protein and DNA synthesis	NA	[51]
10	3,3'-Diindolyl methane (DIM) +	<i>Brassica</i> sps. vegetables (broccoli, cauliflower, collard greens)	DIM Modulated the receptor tyrosine kinase/PI3K/Akt signaling pathway via aryl hydrocarbon (Ah) receptor, NF-κB/Wnt/Akt/mTOR pathways, cell cycle arrest, modulated key CYP enzymes, altering angiogenesis, invasion, metastasis and epigenetic behaviour of cancer cells.	Lung, prostate, and breast cancer	[52-58]
11	Ellipticine	<i>Ochrosia borbonica</i>	Inhibition of DNA topoisomerase II	NA	[59]
12	Epigallocatechin gallate (EGCG)	Green tea	Inhibits anti-apoptotic protein Bcl-xl, interfered with EGFR signaling, inhibited hepatocyte growth factor-induced cell proliferation, caused damage to mitochondria and JNK mediated EGCG-induced apoptotic cell death mediated by Nrf2	Brain, prostate, cervical, bladder cancers, colonic premalignant lesions in mice, human colon cancer cells	[60-66]
13	Etoposide	<i>Podophyllum peltatum</i>	Mitotic block	NA	[67]
14	Fisetin	<i>Acacia greggii</i> , <i>Acacia berlandieri</i> , (Strawberry and apple Euroasian smoketree, persimmon, grape, onion, and cucumber)	Induced the expression of Nrf2 and the phase II gene product HO-1, Inhibits PI3K/Akt and mTOR signaling, and Wnt signaling through the modulation of beta-catenin. Decreased cell viability with G1-phase arrest and disrupted Wnt/β-catenin signaling, inhibits the abilities of adhesion, migration, and invasion, and decreases the nuclear levels of NF-κB and AP-1	Human colon cancer cells, human lung cancer cells, human retinal pigment epithelial cells	[68-74]

Continuation of Table 2.

S. No.	Naturally occurring compound	Source Plant	Preventive /protective functions	Organ	References
15	Flavopiridol	<i>Amoora rohituka</i>	Inhibition of cell cycle progression	NA	[75]
16	Genistein	<i>Vicia faba</i> Soyabeans (kudzu, psoralea) <i>Flemingia vestita</i> (coffee)	Inhibition of 3A 4-mediated metabolism and oxidative metabolism antiangiogenic effects and inhibiting the growth factors, inhibiting DNA topoisomerase II.	Leukemia, colon cancer	[76-82]
17	Gingerol	<i>Zingiber officinale</i> (Zinger)	Decreases iNOS and TNF-alpha expression via suppression of IκBα phosphorylation, NF-κB nuclear translocation and Inducing apoptosis of by mitochondrial pathway.	Colon, breast, ovarian, pancreatic and leukemia cells	[83-86]
18	Harringtonine	<i>Cephalotaxus harrintonia</i>	Inhibition of protein synthesis	NA	[87]
19	4-Ipomeanol	<i>Ipomea batatas</i>	Through cytochrome P450 mediated conversion into DNA binding metabolites	NA	[88]
	Irisquinone	Iridaceaelatea pallasii	Function as chemosensitizer	NA	[89]
20	Kaempferol	Tea, broccoli, grape-fruit, Brussels sprouts, apples	Induced apoptosis through the activation of p53 in the intrinsic pathway, breast cancer resistance protein (Bcrp, Abcg2) inhibitor and may also be a Bcrp substrate.	Pancreatic cancer, lung cancer, ovarian cancer cells, oesophageal cancer and breast cancer	[90-95]
21	Lycopene	Tomato, red carrot, watermelon, and red papaya	By activating phase II detoxification enzymes, Inhibits human cancer cell proliferation, and suppress insulin-like growth factor-I stimulated growth	Prostate cancer breast cancer cells endometrial cancer cells and colon cancer cells	[96-100]
22	Pervilleines	<i>Erythroxylum pervillei</i>	As a P-glycoprotein inhibitor	NA	[101,102]
23	Phenyl isothiocyanates (PEITC)	Broccoli, cabbage (cruciferous vegetable)	Induced the activation of caspase-8, -9, and -3-dependent pathways, leading to cell cycle arrest at the G2/M phase by modulation of cyclin B1 expression, caspase-independent down regulation of Mcl-1, Akt inactivation and activation of JNK, also increase the death receptors (DR4 and DR5) expression, induced caspase-8 and truncated BID, down-regulated the ERK1/2 and MEK phosphorylation.	Breast cancer cells, cervical cancer, osteogenic sarcoma, prostate cancer, myeloma cell lines and metastatic human lung cancer cells.	[103-114]
24	Psoralidin	<i>Psorelia corylifolia</i>	Inhanced apoptosis through Tumor necrosis factor	NA	[115]
25	Resveratrol	Grapes skin and peanuts	anti-initiation activity, anti-inflammatory effects and inhibiting cyclooxygenase and hydroperoxidase functions. inhibit metastasis via reducing hypoxia inducible factor-1α and MMP-9 expression, Wnt signaling and beta-catenin localization, increased AP-1 luciferase activity and induced cell death, increased activation of LPS-induced NF-κB-luciferase activity at lower dose, but inhibited activation at higher dose, reduced LPS-induced IκB alpha phosphorylation and induced caspase-3 activation.	human promyelocytic leukemia, skin tumor, gastrointestinal tract tumor, colon cancer cell, human colon cancer cell line	[116-120]

Continuation of Table 2.

S. No.	Naturally occurring compound	Source Plant	Preventive /protective functions	Organ	References
26	Rosmarinic acid	Culinary spice and medicinal herbs (lemon balm, peppermint, sage, thyme, oregano, and rosemary)	inhibits migration, adhesion, and invasion via the NF- κ B pathway and simulates suppression of interleukin-8 (IL-8), sensitized TNF- α - induced apoptosis through the suppression of NF- κ B and reactive oxygen species (ROS) and suppressed NF- κ B activation through inhibition of phosphorylation and degradation of I κ B α , also reduced 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced COX-2 promoter activity and protein levels, repressed binding of the AP-1	human colon carcinoma cells, breast carcinoma, human leukemia cells, non-malignant breast epithelial cell line	[121-124]
27	Salvicine	<i>Salvia priontis</i>	Inhibits topoisomerase II	NA	[125]
28	Silvestrol	<i>Aglaia foveolata</i>	Triggers extrinsic pathway of programmed cell death of tumor cells through mitochondrial pathway	NA	[126]
29	Sulforaphane	cruciferous vegetables (broccoli, Brussels sprouts and cabbages)	Down regulation of Wnt/betacatenin self-renewal pathway, inhibited cancer cell growth by inducing apoptosis, cytotoxicity with deleted p53, increased Bax, Bcl-2 inhibition followed by mitochondrial release of cytochrome c and activation of apoptosis, induced JNK activity, induced Nrf2 protein expression and ARE-mediated transcription activation, retarded degradation of Nrf2 through inhibiting Keap1, and activated transcriptional expression of antioxidant enzyme HO-1, suppressed NF- κ B and NF- κ B-regulated gene expression through I κ B- α , and IKK pathway, p38 MAPK can phosphorylate Nrf2 and enhances the association between Nrf2 and Keap1 proteins, thereby potentially inhibiting Nrf2, inhibited LPS-stimulated mRNA expression, protein expression of TNF alpha, IL-1beta, COX-2 and iNOS, induced Nrf2-dependent detoxification and phase III transporters.	breast cancer stem cells, colon cancer cells, human hepatoma cells, human prostate cancer cells, liver and skin tumorigenesis in mice	[127-132]
30	Topotecan	<i>Comptotheca acuminata</i>	Inhibits DNA topoisomerase I	NA	[133]
31	Triterpenoids	wax-like coatings of fruits and medicinal herbs	Enhanced apoptosis, stimulating DR4, DR5, caspase-3/7/8, Bax, JNK, MAPK, p38, decreasing PARP cleavage, suppressing COX-2, IL-1 β , NF- κ B, IKK α / β , cyclins (D1, A, B1), ER α protein and mRNA, HER2 phosphorylation, caveolin-1, Akt, JAK1, STAT 3, Bcl2, c-Jun, c-Fos, JNK, mTOR and blocking cell cycle at G1, G1-S, G2-M.	breast cancer, pancreatic cancer	[134]
32	Vitamin D3	Mushroom	Vitamin D receptors (VDR).	breast cancer, colon cancer, ovarian cancer, prostate cancer and pancreatic cancer	[135-139]
33	Vitamin E (tocopherols)	Sunflower oil	inhibit NF- κ B, STAT3 and COX-2, inhibit AKT and ERK activation and suppress cell proliferation by suppressing the ErbB2 pathway, selectively inhibit the HMG-CoA reductase pathway through posttranslational degradation, suppress the activity of NF- κ B, reduced the activation of ERK MAP kinase and that of its downstream mediator ribosomal protein S6 kinase (RSK) and suppressing the activation of AKT.	Anti-proliferative, pro-apoptotic pancreatic cancer cell lines,	[140-143]
34	Vindesine	<i>Vinca roseus</i>	Mitotic block	NA	[144,145]
35	Vinorelbine	<i>Vinca roseus</i>	Mitotic block	NA	[145]

stage of cancer development therefore the prevention of its aberrant expression may prevent the formation of cancer [156]. COX-2 contained a number of upstream regulatory sequences specific for binding with a variety of transcription factors, such as NF- κ B, SP-1 transcription factor and activator protein-1 (AP-1) [157]. These transcription factors could be the final executors for a number of intracellular signaling pathways which make the COX-2 transcriptional regulation highly complicated.

Hedgehog signaling pathway (HSP)

Hedgehog signaling pathway (HSP) has been reported to be involved in providing the instructions to the cells for their proper development. The abnormal activation of this pathway may give rise to cancer through transformation of adult stem cells into cancer stem cells. Therefore, the researchers are looking for specific inhibitors of this pathway to devise an efficient cancer therapy [158]. In vertebrates, when sonic hedgehog (SHH) binds to the Patched-1 (PTCH1) receptor, the downstream protein Smoothened (SMO) which is inhibited by PTCH1, resulting in SHH activation leading to the activation of Gli transcription factors [159]. The accumulation of activated Gli in the nucleus controls the transcription of hedgehog target genes. Therefore the activation of hedgehog signaling pathway results into the increases of angiogenic factors and the decreases of apoptotic genes [160,161]. Hedgehog signaling pathway has been extensively reviewed as a target pathway for cancer treatment [162]. Therefore the approaches to regulate the hedgehog signaling pathway have been used to inhibit cell growth and promote apoptosis in prostate cancer by modulating SMO, PTCH and Gli3 (5E1) [163].

NF- κ B pathway

NF- κ B is a family of rapid-acting primary transcription factors. They are present in inactive state inside cells and do not require new protein synthesis to get activated which allows them to be the first responder to harmful stimuli. Free radicals such as reactive oxygen species (ROS), lipopolysaccharide (LPS), TNF alpha and IL-1 beta are some examples of NF- κ B inducers. The NF- κ B dimmers are sequestered in the cytoplasm by a family of I κ Bs. The ankyrin repeat domains of I κ Bs mask the nuclear localization signals (NLS) of NF- κ B. I κ Bs are modified by ubiquitination via I κ B kinases (IKK). NF- κ B is then free to enter in to the nucleus where it may turn on the expression of specific genes. The NF- κ B turns on expression of its own repressor, I κ B alpha, which in turn reinhibits NF- κ B, which results in oscillating levels of NF- κ B activity [164]. Blocking NF- κ B may cause tumor cells to stop proliferating, become more sensitive to the action of anti-cancer agents and to die [165].

Nrf2 pathway

Nuclear factor (erythroid-derived 2)-like 2 (Nrf2, or NFE2L2) is a transcription factor that regulates antioxidant responses

[166]. Nrf2 is a basic leucine zipper (bZIP) transcription factor and under normal condition, Nrf2 is tethered in the cytoplasm by the Kelch like-ECH-associated protein 1 (Keap1) [167]. Oxidative stress disrupts critical cysteine residues in Keap1 and releases Nrf2 to be translocated into the nucleus. There, Nrf2 heterodimerizes with small Maf proteins binds to the anti-oxidant response element (ARE) in the promoter region of many antioxidative genes and initiate their transcription [168]. The cytoprotective proteins include phase II drug metabolizing enzymes such as glutathione-S-transferase (GST), NAD(P)H-quinone oxidoreductase-1 (NQO1), heme oxygenase-1 (HO-1), UDP-glucuronosyl transferase (UGT) or phase III transporters (multidrug resistance-associated proteins (MRPs) [169-173]. Mechanism of Nrf2 pathway is summarised in **Figure 3**.

PI3K pathway

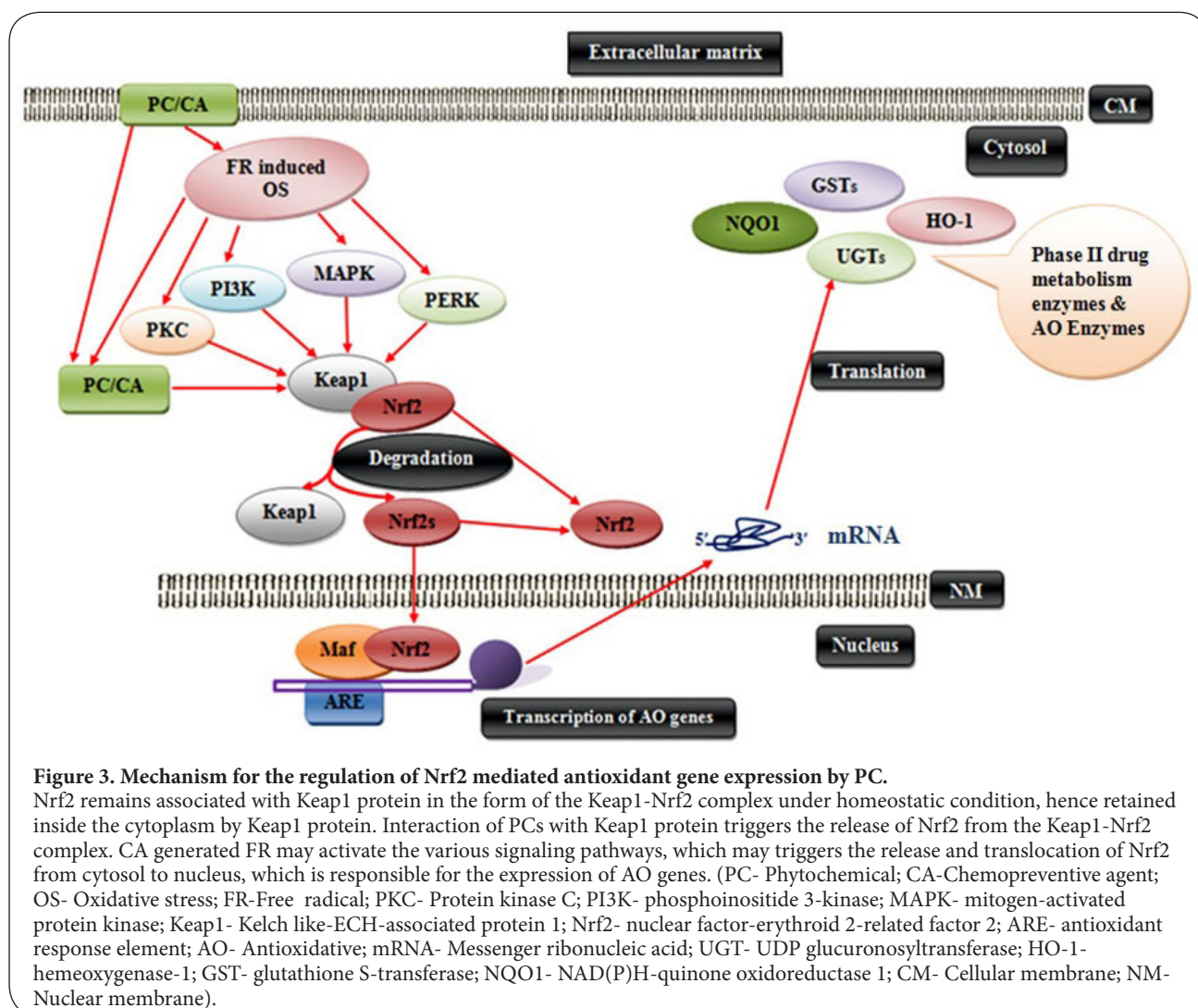
Phosphatidylinositol 3-kinases (PI3Ks) are a family of enzymes involved in cell growth, proliferation, differentiation, survival and intracellular trafficking. Activated PI3K produces Phosphatidylinositol (3,4,5)-trisphosphate (PtdIns(3,4,5)P3) and Phosphatidylinositol (3,4,5)-disphosphate (PtdIns(3,4)P2). The translocation of AKT across the plasma membrane are restricted due to that of the PtdIns(3,4,5)P3 and PtdIns(3,4)P2. The activity of PI3K may significantly contribute to the cellular transformation and the development of cancer. Inhibition of PI3K could be an important therapeutic strategy for suppressing cancer development [174].

STAT 3 pathway

STAT 3 (Signal transducer and activator of transcription 3) is a transcription factor that plays a key role in cell growth and apoptosis. STAT3 is activated through phosphorylation of tyrosine 705 and serine 727 residues in response to cytokines and growth factors then form homo- or heterodimers that translocate to the cell nucleus. The constitutive STAT3 activation has been associated with poor prognosis, anti-apoptotic and proliferative effects in cancer cells [175].

Wnt pathway

Wnt proteins are involved in normal physiological process of adult animals as well as in embryogenesis and cancers [176]. These proteins activate various pathways in the cell including canonical and noncanonical Wnt pathways and exert their effect in cell differentiation, embryonic development and generation of cell polarity [177]. In canonical pathway, the Wnt proteins bind to cell-surface receptors, causing the activation Dishevelled (DSH) family proteins and ultimately change in the amount of β -catenin that reaches into the nucleus. DSH complex inhibits axin, GSK-3 and APC complex proteins which normally promotes the proteolytic degradation of β -catenin. The inhibition of β -catenin destruction allows cytoplasmic β -catenin stabilization and entering the nucleus to interact with TCF/LEF family transcription factors to promote specific



expression of a gene. Therefore, the modifications in Wnt, APC, axin, and TCF are associated with carcinogenesis. The non-steroidal anti-inflammatory drugs (NSAIDs) that interfere with β -catenin signaling have been shown to prevent colorectal cancer [178].

Besides the mechanisms listed above, there are several other mechanisms for apoptosis such as the extra-virgin olive oil may target the human epidermal growth factor receptor (HER2) in breast cancer [179], resveratrol may reduce hypoxia-induced factor-1 α , MMP-9 expression in colon cancer, lycopene may alter mevalonate pathway and many others [180].

Pharmaceutical challenges and opportunities in developing phytochemicals based drugs in therapy for cancer

Many natural dietary phytochemicals have been studied for cancer prevention and treatment. These native phytochemicals and/or their synthetic analogues have guided continuing research to bring them into the market as anti-

cancer agents. Applying phytochemicals to cancer patients for chemoprevention encounters an immediate challenge in terms of their effects on human, as it is not feasible to design a clinical study to prove that the suppression of cancers in patient is due to the intake of phytochemicals. Though the chemical structures of some of the potential phytochemicals are well understood, but their physicochemical properties are not well documented yet and needs detailed investigation. Bioavailability of phytochemicals is another challenge that needs to be addressed. The nanotechnology, liposomes, micelles and phospholipids complexes have been applied to increase the water solubility of phytochemicals to enhance their bioavailability. Phytochemicals are generally considered as non-toxic materials but they may exert their toxicities to animals or humans at certain situation (drug-drug interaction and concentration), which may delay their application in the clinical studies and application in cancer treatment. This may be due to the synergistic effects existing in natural

compounds consumed as a whole rather than a single extracted/ purified compound. Using recently developed new technologies; some novel natural plant based compounds may be identified and developed as anticancer agents for chemoprevention of the disease. Such phytochemicals may prove to be cost effective, safe and more potential with enhanced efficacy against cancer [181]. However, a thorough study of these phytochemicals and their pharmacological effects may generate insights for their drugability as well as transition from laboratory to the patients.

Conclusion

Phytochemicals in cancer chemoprevention are considered as the cheapest option in cancer treatment. Phytochemicals have been widely used in preclinical cancer prevention and treatment studies. Phytochemical chemopreventive agents are believed to play significant roles in controlling, inhibiting, and blocking signals which can cause translation of normal cells to cancer cells. The chemoprevention of cancer using phytochemicals have been such an attractive approach therefore efforts should be made to thoroughly understand their potencies, pharmacokinetics, pharmacodynamic responses, metabolisms, toxicities, drug-drug interactions, polymorphisms, formulations dose and to explore the molecular mechanisms of phytochemicals in cancer treatment more clearly. Genomic instability provides a means for selective targeting of cancer cells over normal cells. Among the various cancers chemopreventive agents many cause changes in chromatin conformation, disrupt the intracellular redox balance and deregulate DNA repair proteins. Thus, these compounds might activate the DNA damage response in cancer cells as compared to the normal cells. It is hoped that the improved understanding of these mechanisms will provide a more rational basis for combining specific dietary compounds and radiation therapy or chemotherapy approaches. More studies should be focused on dose-dependent responses and toxicity of the phytochemicals to ascertain their safety before usage.

List of abbreviations

ADM: antioxidant defense mechanisms
AO/FR: Antioxidant/Free radical
AO: antioxidant
AP-1: Activator protein-1
Apaf-1: Apoptotic protease activating factor-1
ARE: Anti-oxidant response element
ATP: Adenosine triphosphate
bZIP: basic leucine zipper
CA: Chemopreventive agent
CHD: Chromodomain helicase
DNA-binding protein
CM: Cell membrane; Cellular membrane
COs: Cell organelles
COX-2: Cyclooxygenases-2
CpG: "—C—phosphate—G—"

CYP enzymes:
DDR : DNA damage response
DISC: death-inducing signaling complex
DME: drug metabolism enzymes
DNA: Deoxyribonucleic acid
DSH: Dishevelled
EGCG: gastrointestinal toxicities (green tea polyphenols)
FADD : Fas-associated death domain protein
FR: Free radicals
GST: glutathione S-transferase
HER2: human epidermal growth factor receptor
HO-1: hemoxygenase-1
IAPs: inhibitor of apoptosis proteins
ICMR: Indian Council of Medical Research
IKK: IκB kinases
IL: Interleukin
INO80: inositol requiring 80
Keap1: Kelch like-ECH-associated protein 1
LPS: lipopolysaccharide
MAC: mitochondrial apoptosis-induced channel
MAPK: Mitogen-activated protein kinase
MBDs: Methyl-CpG-binding domain proteins
MOMP: Mitochondrial Outer Membrane Permeabilization Pore
mRNA: Messenger ribonucleic acid
MRPs: Multidrug resistance-associated proteins
mTOR: Mechanistic target of rapamycin
NAD: Nicotinamide dinucleotide
NF-κB: Nuclear factor kappa B
NM: Nuclear membrane
NQO1: NAD(P)H-quinone oxidoreductase 1
Nrf2 or NFE2L2: Nuclear factor-erythroid 2-related factor 2
NSAIDs: Non-steroidal anti-inflammatory drugs
OS: Oxidative stress
PARP: poly(ADP-ribose) polymerase
PC: Phytochemical
PI3K: phosphoinositide 3-kinase
PKC: Protein kinase C
Plk1: Polo-like kinase 1
PTCH: Patched receptor
PTCH1: Patched-1 receptor
PtdIns(3,4)P2): Phosphatidylinositol (3,4,5)-disphosphate
PtdIns(3,4,5)P3): Phosphatidylinositol (3,4,5)-trisphosphate
RNAs: Ribonucleic acids
RNS: Reactive nitrogen species
ROS: Reactive oxygen species
RSS: Reactive sulfur species
SHH: Sonic hedgehog
SMACs: Small mitochondrial derived activators of caspases
STAT3: Signal transducer and activator of transcription 3
TNF alpha: Tumour Necrosis Factor
UV: ultra violet
WHO: world health organization

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	VKG	RS	BS
Research concept and design	✓	✓	✓
Collection and/or assembly of data	✓	✓	✓
Data analysis and interpretation	✓	✓	✓
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