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Plants Phytochemicals, Re-Covering Cancerous Cells

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Cancer is a multifactorial disease of mammoth burden of global scale and the second major cause of death worldwide where millions of new cases are diagnosed each year [1]. The cancer characteristics, such as long-term proliferative signalling, apoptotic resistance, invasion and metastasis, and immune destruction, are multifaceted therapeutic targets that cannot be adequately addressed by conventional therapeutic modalities like surgery, radiotherapy, and chemotherapy. The growing body of ethnopharmacological and molecular studies has recently shifted the focus to phytochemicals, which are secondary plant metabolites, as promising therapeutic agents in the recovery and reprogramming of cancerous cells [2].

Phytochemicals are structurally heterogeneous bioactive substances that are produced by plants as elements of their adaptive defence systems. These molecules represent only a wide chemical distribution that comprise of phenolic acids, flavonoids, stilbenes, lignans, terpenoids, alkaloids, saponins and organosulfur compounds [3]. Their anticancer action is not limited to cytotoxicity, but phytochemicals have multifaceted molecular negotiations with oncogenic signalling pathways, epigenetic modulators, and tumour microenvironment elements, which collectively tip the biological balance between a malignant and a quiescent or an apoptotic cellular state [4]. The increasing in vitro, in vivo and preclinical evidence favours the therapeutic interest of phytochemicals in a wide variety of cancers, such as breast, colorectal, lung, hepatocellular, and prostate malignancies [5].

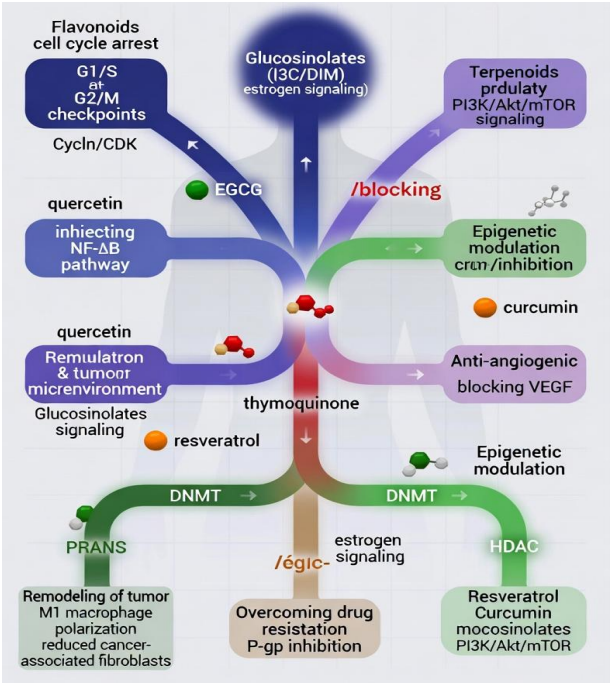

Figure 1. Phytochemicals targeting multiple hallmarks of cancer.

Flavonoids and cell cycle arrest

Flavonoids are a type of anticancer phytochemicals that are one of the best-researched classes of phytochemicals. Quercetin, kaempferol, luteolin and epigallocatechin-3-gallate (EGCG) have shown the ability to block cell cycle at the G1/S and G2/M checkpoints by regulating cyclins and cyclin-dependent kinases [6]. These polyphenolic substances induce the expression of tumour suppressor proteins like p53 and p21, which provide molecular states that are hostile to the uncontrolled cell division. The role of flavonoids in the regulation of long non-coding RNA expression that regulates proliferative gene networks in colorectal and lung cancer cells has also been explained in recent studies [7]. At the same time, flavonoids reduce the expression of antiapoptotic proteins such as Bcl-2 and Bcl-xL, and stimulate the induction of caspase-dependent apoptotic cascades. EGCG, a green tea extract, has shown specific ability to stimulate mitochondrial-pathway apoptosis in breast and prostate cancer by stimulating Bax and cytochrome c release [8]. Notably, the most recent pharmacokinetic studies have discovered nanoencapsulation methods that can enhance the oral bioavailability of quercetin and kaempferol far beyond their established clinical translation shortcoming [9].

NF-B pathway and terpenoids inhibition

Another structurally diverse phytochemical group that has been shown to have anticancer activity is terpenoids. Triterpenoid including betulinic acid and ursolic acid induce apoptosis in cancer-causing cells but not normal tissue, which provides significant therapeutic

benefit relative to traditional cytotoxic therapy [10]. Sesquiterpene lactones, such as parthenolide and synthetic analogues, have been identified to inhibit nuclear factor-kappa B (NF- kB) pathway, which is a supreme controller of tumour survival, inflammatory crosstalk, and chemotherapy resistance. A study carried out in 2021 showed that parthenolide was able to sensitise triple-negative breast cancer cells to doxorubicin by disrupting antiapoptotic signalling orchestrated by NF-KB [11]. NF-KB suppression by phytochemical therapies thus suppresses the expression of pro-survival cytokines, matrix metalloproteinases, and angiogenic factors which promote tumour growth (Figure 1). Recent in vivo models have demonstrated impaired Ras-MAP kinase signalling and lowered tumour burden in pancreatic and colorectal cancer xenografts with limonene and perillyl alcohol, monocyclic monoterpenes derived by citrus peel, supporting the mechanistic diversity of terpenoid anticancer action [12].

PI3K/Akt/mTOR signaling axis modulation.

The PI3K/Akt/mTOR pathway is a common dysregulated signalling pathway in human tumours and enhances cell survival, proliferation and reorganisation of cancerous cellular metabolism. A number of phytochemicals have been reported to be strong agonists of this pathway. Resveratrol is a stilbene present in grapes and red berries that suppresses phosphorylation of Akt and subsequent mTORC1 activation thus limiting protein production and causing autophagy-mediated death in cancer lines [13]. The main bioactive curcuminoid of Curcuma longa, curcumin, also inhibits Akt and mTOR signalling and at the same time stimulates AMP-activated protein kinase, shifting the cancer cell metabolism towards catabolic signalling pathways that cannot support malignant growth [14]. The formulation innovations such as phospholipid complexes and self-emulsifying drug delivery systems have facilitated the clinical translation of curcumin, and Phase II clinical trials have shown favourable safety profiles, as well as initial evidence of tumour marker reduction in colorectal cancer patients [15].

Phytochemicals and anti-angiogenic mechanisms

The angiogenic pathway of tumours which attracts new vascularity to meet its oxygen and nutrient needs is a key target of therapy in oncology. Genistein, epigallocatechin gallate and thymoquinone, phytochemicals have been observed to prevent vascular endothelial growth factor (VEGF) expression and receptor tyrosine kinase activity effectively starving tumours of the blood supply needed to grow and metastatically spread [16]. Nigella sativa yields thymoquinone, which has been studied with great intensity, with several papers demonstrating its ability to suppress hypoxia-inducible factor-1alpha (HIF-1 alpha), the major transcriptional regulator of VEGF in hypoxic tumour cores [17]. These antiangiogenic effects of plant bioactives are complementary to the already available anti-VEGF pharmacological agents and have been shown to add to the effect of known antiangiogenic agents in preclinical tumour models, implying future clinical protocols would be complementary with current antiangiogenic therapies [18].

Re-educating the tumour microenvironment

The tumour microenvironment (TME) is an immunosuppressive niche that comprises regulatory T cells, myeloid-derived suppressor cells, cancer-associated fibroblasts and polarised M2 macrophages and together they inhibit antitumour immune responses. Recently, phytochemicals have been identified to be regulators of the TME, with the ability to remodel immunosuppressive immune cells into cytotoxic phenotypes. Sulforaphane, an isothiocyanate of cruciferous vegetables activates M1 macrophage polarisation and increases dendritic cell maturation, and thus, rescues immunosurveillance in the tumour milieu [19]. Recent studies have shown that the berberine and luteolin inhibit the activation of cancer-associated fibroblasts and lower the release of tumour-promoting growth factors such as transforming growth factor- 20 and stromal cell-derived factor-1 [20].

Phytochemicals as epigenetic modulators

A central element of the process of carcinogenesis is epigenetic dysregulation, which entails altered DNA-methylated states, histone-altered states, and non-coding RNA. Phytochemicals also have significant epigenetic modulatory properties, which provides a mechanism of gene expression normalisation to enhance direct cytotoxicity. EGCG is a DNA methyltransferase (DNMT) inhibitor, which reactivates tumour suppressor gene silenced in colorectal and breast cancers by promoter hypermethylation. One study has shown that inhibition of DNMT3a by EGCG could restore DKK3 Wnt antagonist expression in hepatocellular carcinoma and inhibit the expansion of tumours in vivo significantly [21]. Curcumin suppresses histone deacetylases (HDACs) and increases acetylation of tumour suppressor gene loci that stimulate their transcriptional reinstatement. Moreover, resveratrol stimulates the action of Sirtuin-1 (SIRT1), a class III HDAC, which alters the acetylation levels of p53 and NF-kB and shifts their action towards tumour suppressive and not protective action [22]. Together, these epigenetic activities have indicated that phytochemicals might be especially useful at reversing oncogenic epigenomic programming which presently represents a growing clinical goal due to the emerging epigenetic cancer therapy landscape [23].

Hormonal control cancer and glucosinolates

The Glucosinolates and hydrolysis products of glucosinolates, especially the indole-3-carbinol (I3C) and 3,3'-diindolylmethane (DIM) produced by Brassica species, have proven pleiotropic anticancer properties with particular application against hormonally-driven cancer. I3C alters oestrogen receptor signalling, favours the 2-hydroxylation of estradiol to the more genotoxic 16alpha-hydroxylation pathway and suppresses the expression of the oncogene HER2/neu in breast cancer models [24]. In a 2021 clinical pilot study, DIM supplementation in women with early-stage cervical intraepithelial neoplasia had been found to achieve histological regression in a considerable proportion of participants over placebo, giving the preclinical supportive evidence on the hypothesized mechanism translational credibility [25]. These phytochemicals comprise a mechanistically dissimilar group of anticancer agents that have been specifically employed in breast, cervical, and endometrial carcinomas, in which the hormonal disturbance contributes to tumour growth. In the future, further randomised controlled trials should determine the clinical dosing and efficacy parameters of them [26].

CONCLUSION

Plant phytochemicals are scientifically sound and diverse in mechanism bioactive molecules that have considerable potential in the re-covering of cancerous cells. Phytochemicals interact with malignant cellular biology at multiple points of vulnerability concurrently, by modulating apoptotic cascades, oncogenic signaling pathways, angiogenesis, epigenetic programming, immune microenvironmental

dynamics as well as drug resistance mechanisms. The available preclinical evidence has shown persuading anticancer activities in a wide range of cancers and phytochemical families. The findings are increasingly being confirmed by translational clinical trials, but issues relating to bioavailability, standardisation, and pharmacokinetic optimization still need to be overcome. Implementation of phytochemical-based interventions into a multidisciplinary oncology care is likely to revolutionise the therapeutic outcomes, treatment-related toxicity, and survival rates in cancer patients.

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