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Anti-cancer Phytochemicals: A Broad Overview

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Abstract:
Phytochemicals, the secondary metabolites are the biologically active compounds known for their potential health benefits in the prevention of various diseases, including cancer. The present review article has been aimed to explore the therapeutic benefits of the major phytochemical constituents, in cancer treatment and prevention based on the epidemiological studies, pre-clinical and clinical trials. Despite the strong anticancer effect of many of these phytochemicals, as well as their proven efficacy in multiple epidemiological studies, there is still a great need for human studies and clinical evaluation, with due caution regarding the safety measures. This review article provides an overview of the epidemiological, pre-clinical and clinical evidence supporting the potential chemopreventive and anticancer properties of selected phytochemicals, with a focus on the need for further research in this area.

Keywords: secondary metabolite, phytochemicals, cancer, cancer prevention,

Introduction:

Phytochemicals are used as a method of preventing diseases even as severe as cancer. These naturally derived plants are used as a source for their medicinal properties due to various biological activities. Phytochemicals can regulate more than one cell signalling pathways such as PI3K/Akt, NF-κB, p53, MAPK, mTOR, Wnt/β etc. As these are sourced from naturally occurring plants, these can be deemed as almost nontoxic and safer option for treatment as compared to conventional chemotherapy medications. These tend to have zero to negligible side effects which proves to be in their favour. The availability of plant products such as fruits, vegetables, roots, leaves, herbs etc also make phytochemicals a better option for treatment of cancer. Additionally, plant-based compounds have antioxidant and anti-inflammatory properties which prove to be useful in prevention of cancer.

There are already different modes of treatment available in oncology. Surgery though useful for solid

tumours which are detected early, it often fails in case of metastatic cancer. So other methods such as radiotherapy are considered mainly in cases of brain tumour, breast cancer, cervical cancer etc. Chemotherapy is one of the most common modes of treatment performed after surgical removal of tumour. Despite of being one of the most common treatments, it has several side effects for being nonspecific and cytotoxic. Targeted molecular therapy is one of the most recent and advanced therapy using monoclonal antibodies and TKIs (Tyrosine Kinase Inhibitors). It has more specificity than other more common procedures but can be costly. Immunotherapy can be used to block immune suppression pathways, which makes it one of the most revolutionary methods in oncology. Hormone therapy is mostly used in breast and prostate cancer. Stem cell therapy is used in leukaemia, lymphoma and some myeloma. Personalized treatment by Next generation sequencing and biomarker profiling for patient specific mutations. Modern oncology leans toward combinational therapy for patients such as surgery and chemotherapy or radiotherapy, chemotherapy and radiotherapy or hormone therapy etc.

There are different unconventional procedures which are also used apart from Phytotherapy. Such as traditional Indian medical systems like Ayurveda, traditional Chinese medicine, Tibetan and Unani medicine etc which are often used when modern technologies have failed or sometimes in combination with modern treatment. Nutritional diets such as ketogenic diets, natural immunomodulatory therapies, acupuncture, hyperthermia therapy are sometimes used too for cancer treatment.

Phytochemicals with anticancer activity

Among dietary agents with chemo preventive properties, the most effective in decreasing the proliferative activity of cancer cell lines include tea polyphenol epigallocatechin-3-gallate (EGCG), curcumin, resveratrol, lycopene, pomegranate extracts, luteolin, genistein, piperine, β-carotene, and sulforaphane. These phytochemicals have been extensively researched for over thirty years. Some examples of these compounds are detailed below.

1. Artemisinin

Artemisinin and its derivatives are naturally occurring antimalarial drugs used to treat malaria by targeting the parasites that cause the disease. Artemisinin and its derivatives have shown promising anticancer activity. Artemisinin is a sesquiterpene lactone compound containing a unique 1,2,4 trioxane ring structure. The anticancer activity of Artemisinin is attributed to its strong activity against cancer cells by the endoperoxide bond present in the compound. It is activated by ferrous ions (Fe^{2+}). The activated compound has cytotoxic activity against cancer cells. It induces apoptosis by generating free radicals after interacting with iron ions present inside the cancer cell. The free radicals induce oxidative stress that disrupts the cell components and finally leads to apoptosis.

Artemisinin also disrupts the normal cell cycle by halting the cycle at the G1 phase. This halting of the cell cycle by Artemisinin inhibits cancer cell proliferation to the S phase, where DNA synthesis occurs. Artemisinin's ability to induce apoptosis and disrupt the cell cycle makes it a strong anticancer agent.[1]

2. Berberine

Berberine, an alkaloid, inhibits bcl-2 expression by activating caspase-3. This activation, along with the release of cytochrome c, boosts AMPK activity and increases ROS production. This promotes apoptosis and controls cancer progression.

Berberine is a bioactive compound extracted from the roots and rhizomes of *Berberis vulgaris* (barberry), *Berberis aquifolium, Rhizoma coptidis,* and *Tinospora cordifolia.* It has been used to manage the spread of cancers, including breast, colorectal, and prostate cancer. Berberine promotes programmed cell death, causes cell cycle arrest at the G2/M phase, inhibits anti-apoptotic proteins like Bcl-2 and c-IAP1, and activates pro-apoptotic proteins such as p53, p21, caspase-3, and caspase-9. [2]

3. Curcumin

Curcumin, derived from the rhizomes of the *Curcuma longa* plant, is the primary yellow pigment in turmeric, a widely used spice. Curcumin has been shown to disrupt the carcinogenic process by inhibiting the initiation phase or suppressing the promotion and progression stages in animal models.[3] It has also been reported to have synergistic chemo preventive effects with other diet-derived polyphenols, such as genistein, EGCG, and embelin, and to boost the efficacy of various anticancer drugs, including 5-fluorouracil, vinca alkaloid, vinorelbine, cisplatin, and gemcitabine.

Curcumin induces cell apoptosis and autophagy while suppressing the PI3K/AKT/mTOR/P70S6K pathway, leading to cell death. Curcumin demonstrates strong anticancer properties by reducing AKT expression in MDA-MB-231 cells, which leads to the inhibition of cell growth. Furthermore, curcumin hinders the mTORC1 pathway, essential for cell growth, survival, and the prevention of angiogenesis. [4]

4. Camptothecin

Camptothecin is a quinolone bioactive compound sourced from the Chinese tree *Camptotheca acuminata*. The semi-synthetic derivatives of camptothecin, irinotecan and topotecan, are approved drugs by the FDA. Camptothecin and its derivatives inhibit the topoisomerase 1 enzyme, leading to DNA damage and cell death. After its isolation and structural analysis in 1966, the naturally occurring compound CPT garnered significant interest from the clinical community due to its promising antitumor effects observed in numerous in vitro and in vivo studies. In 1985, it was found that CPT inhibited the nuclear protein Topo I through a unique mechanism, reigniting interest in CPT as a crucial lead compound. This discovery paved the way for the development of effective anticancer drugs, such as the approved TPT and CPT-11. Their clinical success and fascinating mechanism of action spurred further investigation into CPT derivatives with enhanced antitumor properties, with several derivatives currently undergoing preclinical evaluation. [5]

5. Chalcone

Chalcone is an anti-tumour flavonoid found in edible greens and fruits. It triggers various caspases and increases pro-apoptotic proteins such as Bid, Bax, and Bak. Chalcones are used to treat liver, breast, and adenocarcinoma cancers.

Chalcones, known as 1,3-diaryl-2-propen-1-ones, serve as precursors for flavonoids and isoflavonoids, which are fundamental chemical structures present in numerous natural compounds. The ease of synthesizing chalcone derivatives has led to the creation of many such compounds. Chalcones, as synthetic analogues, have garnered significant attention due to their wide range of biological activities, particularly their potential in treating various diseases, with a focus on antitumor properties. The chalcone family has shown promising in vitro and in vivo anticancer activity through various mechanisms, such as disrupting the cell cycle, regulating autophagy, inducing apoptosis, and modulating immune and inflammatory responses. Developing chalcones as new anticancer agents is a promising strategy. Furthermore,

combining chalcones with other therapies is anticipated to enhance anticancer treatment effectiveness. Chalcone compounds possess a chemical framework that can be easily modified to change their biological activity. In various screening assays, chalcones have been shown to target multiple cellular molecules, including p53, tubulin, NF-kappa B, VEGF, VEGFR-2 kinase, HIF-1, MMP-2/9, and P-gp/MRP1/BCRP. Consequently, chalcones may exert anticancer effects by inducing tumour cell apoptosis, inhibiting microtubule polymerization, and exhibiting anti-inflammatory, antiangiogenic, and multidrug resistance inhibition properties. This characteristic makes chalcones highly appealing as foundational elements for synthesizing agents that target cancer molecules. Abbreviations: MDR, multidrug resistance; MMP, matrix metalloproteinase; MRP1, multidrug resistance-associated protein 1; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; P-gp, P-glycoprotein; VEGF, vascular endothelial factor. [6]

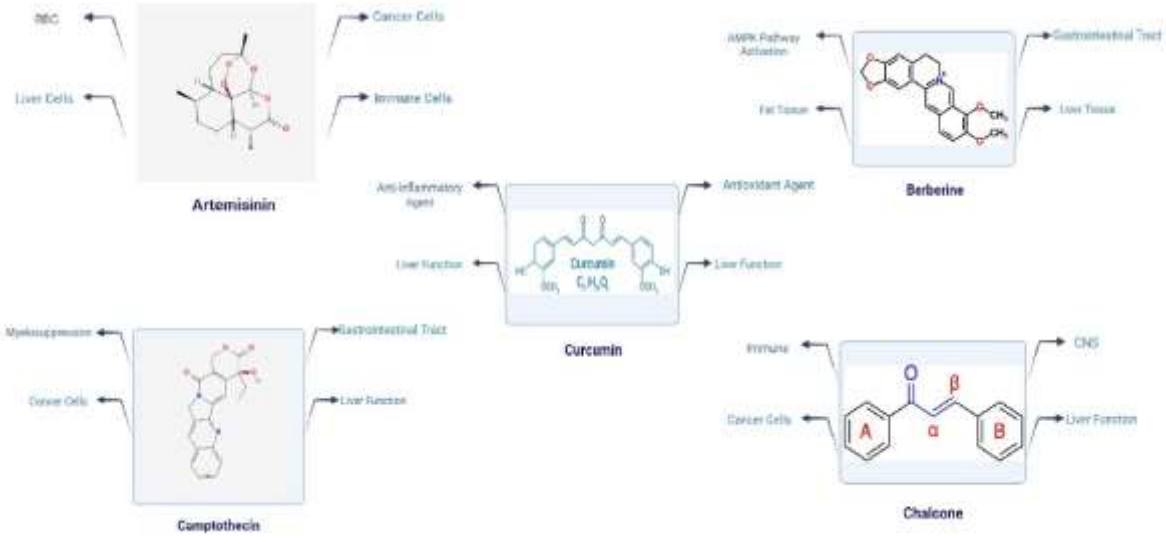

Fig 1: Phytochemicals and their major effects in the human body

6. Colchicine

Colchicine is a natural bioactive compound extracted from *Colchicum autumnale* (Colchicaceae) and is used to treat inflammatory diseases like arthritis, gout, and cirrhosis. Colchicine induces caspase-mediated cell death and targets tubulin, interrupting the cell cycle at various phases. Recently, plants like *Gloriosa superba* from tropical regions have become significant sources of colchicine.

Among the tubulin isoforms, αβI and αβIII play crucial roles in predicting how cancer cells respond to colchicine derivatives. However, because αβI tubulin is prevalent throughout the human body, targeting it could result in significant adverse effects. Therefore, αβIII tubulin is considered the primary molecular target for inhibiting microtubule polymerization, leading to cancer cell cytotoxicity. In contrast, αβI and αβII tubulin isoforms are regarded as secondary targets. [7]

7.Resveratrol

Resveratrol, a phytoalexin found in red wine and abundant in grape skin, has been shown to reduce the number and size of oesophageal, intestinal, and colon tumors when used prophylactically. It has been reported to prevent 7,12-dimethylbenz(a)anthracene-induced mammary carcinogenesis and inhibit the growth of M.D. Anderson-metastatic breast 231 (MDA-MB231) tumour cell line xenografts. Additionally,

it is believed to induce apoptosis in prostate cancer cell lines PC-3, DU145, and LNCaP and suppress prostate cancer progression in transgenic mice.

Resveratrol can be sourced from grapes (*Vitis vinifera*), berries and peanuts. By modifying apoptotic inhibition proteins and controlling cell cycle signalling cascades, resveratrol prevents photo-carcinogenesis. Resveratrol inhibits endothelial cell activation by downregulating cyclin D1/CDK4 and VEGF production. Resveratrol increased apoptosis and decreased tumour growth, metastasis, and angiogenesis via suppressing MTA1 expression.[8]

8. EGCG (Epigallocatechin-3-gallate)

EGCG, the most prevalent polyphenol in green tea, can trigger caspase 8-dependent apoptosis in tumour cell cultures and animal models. Numerous clinical trials are underway involving EGCG alone or in combination with cisplatin and oxaliplatin due to EGCG's ability to enhance the effectiveness of these conventional drugs against prostate carcinoma and colorectal cancer.

EGCG has its natural sources from cocoa and green tea (*Camellia sinensis*). EGCG modulates the 67-KDa laminin receptor, impacts JAK/STAT, MAPK, and PI3K/AKT signalling pathways, and effects estrogen and androgen receptors in breast and prostate neoplasms, respectively. By inducing apoptosis and limiting the growth of human breast cancer cells in a mouse model, it not only mitigates nitrosamine-induced lung tumour formation but also impedes tumour development and reduces tumour burden. EGCG causes apoptosis in sarcoma cells by activating p53 and BAX, suppressing BCL-2, and stopping the cell cycle at the G2/M phase [9]. BAX overexpression and caspase activation coincide with apoptosis in prostate cancer cells (Caspases 3 and 8) [10]. Together with the function of BAX, EGCG mainly initiates and encourages senescence and apoptosis via p53-mediated signalling.

9. Quercetin

Quercetin, a flavonoid polyphenol, is prevalent in various plants such as onions (*Allium cepa*) and apples (*Malus domestica*) and has garnered considerable interest due to its antioxidant, anti-inflammatory, and antitumor properties. Quercetin treatment led to a decrease in the vitality of KON cells while having a negligible impact on MRC cells. After administering quercetin, apoptosis and cell death were characterized in KON cells. The application of quercetin to KON cells resulted in an increase in ROS production. Additionally, it was found that quercetin raised the proportion of dead cells and caused cell cycle arrest in the S and G2/M phases. Furthermore, quercetin hindered the migration and invasion abilities of KON cells, affecting their stability and structure. By identifying the mechanism that induces apoptosis and inhibits metastasis, it was revealed that quercetin downregulated BCL-2/BCL-XL expression and upregulated BAX expression. TIMP-1 expression was increased, whereas MMP-2 and MMP-9 were decreased. The anticancer properties and specific mechanisms of quercetin's action on KON cells were elucidated. [11]

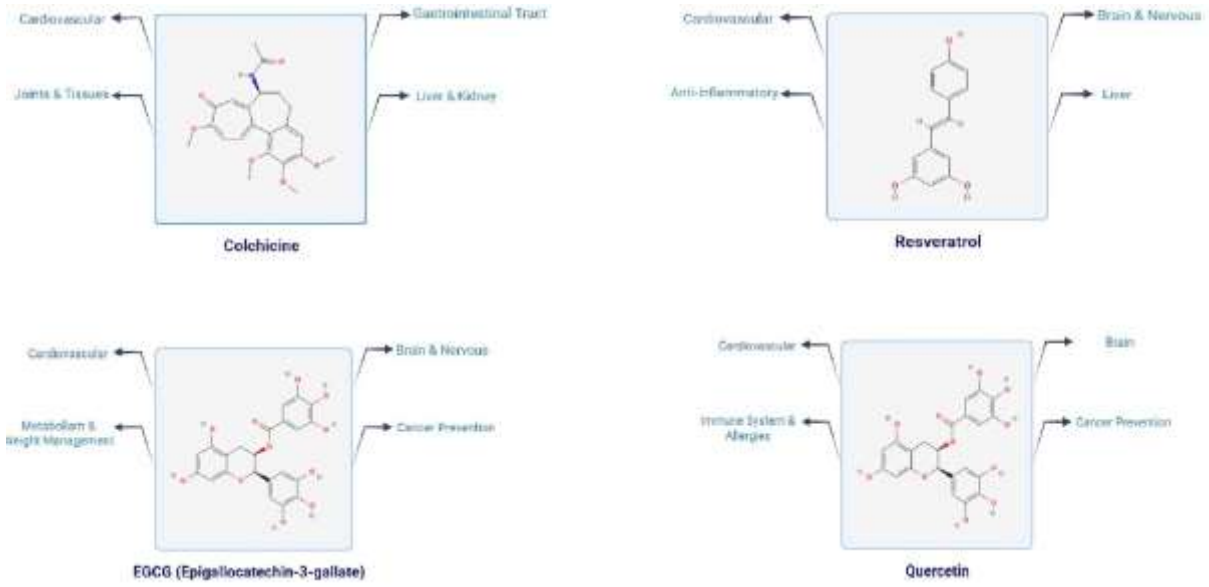

Fig 2: Phytochemicals and their major effects in the human body

10. Genistein

Genistein, a phytoestrogen found in abundance in soybeans and soy-based products, has been linked to a reduced risk of prostate, breast, and endometrial cancers. Genistein, also known as 5,7,4′-trihydroxyisoflavone, is a naturally occurring isoflavone (phytoestrogens) predominantly located in the roots and seeds of legume plants. Although genistein is not a steroidal estrogen like estradiol, estriol, and estrone, it shares structural features with them, such as aromatic rings and phenolic hydroxyl groups, which allow it to interact with estrogen receptors.

This compound has shown notable anti-inflammatory and anti-cancer properties in various types of cancer, including colorectal, bladder, breast, prostate, and non-small cell lung cancers. It curtails the release of angiogenic factors in low-oxygen environments, thus restricting tumor growth. Furthermore, genistein diminishes cancer stem cell-like traits in GC cells, reducing their ability to self-renew, resist drugs, and invade. It also boosts the effectiveness of standard chemotherapy drugs like 5-fluorouracil (5-FU) and cisplatin, and makes TRAIL-resistant GA cells more susceptible to TRAIL-induced cell death. In GA, genistein curbs cell proliferation by causing cell cycle arrest, inhibiting NF-κB activity, and increasing the levels of apoptosis-related proteins such as caspase-3, thereby inducing apoptosis in cancer cells in a dose- and time-dependent manner. [12]

11. Sulforaphane

Sulforaphane is a powerful chemo preventive agent found in *Brassica* vegetables. Sulforaphane (SF), a phytochemical abundantly found in cruciferous vegetables, has demonstrated significant anti-inflammatory, antioxidant, and antitumor properties. Recent research suggests that SF's antitumor effects are achieved by inhibiting cell proliferation and cell-cycle processes, inducing apoptosis, and preventing methylation in precancerous cells. However, its impact on cancer stem cells (CSCs) in head and neck squamous cell carcinoma (HNSCC), whether used alone or alongside traditional chemotherapy, is not well understood. Consequently, our current study aims to explore whether SF can enhance the effectiveness of

cisplatin (CIS) and 5-fluorouracil (5-FU) chemotherapy on HNSCC stem cells and to elucidate its mechanisms of action. [13]

12. Lycopene

Lycopene, a natural antioxidant responsible for the red colour of tomatoes, watermelon, and pink grapefruit, has been linked to a lower incidence of certain cancers, including those of the digestive tract, prostate, and cervix, according to epidemiological studies. Lycopene has also been found to suppress lung cancer cell growth. Lycopene exhibited its anticancer potential by decreasing NF-κB and STAT3 expression while increasing heme oxygenase 1 expression. Its anti-proliferative and anti-metastatic effects were enhanced by the downregulation of ITGB1, MMP9, ITGA5, FAK, ILK, and EMT markers, which led to decreased MAPK activity and inhibited integrin 5 protein expression. Lycopene supplementation inhibited NNK-induced pulmonary α7 nAChR and hepatic CYP2E1, which were associated with reduced mortality and fewer pulmonary and hepatic lesions. Lycopene reduced both the occurrence and number of skin tumours, as well as the tumorigenesis of normal skin cells, specifically during the promotion phase. Through an integrated method that combines bioinformatics and network pharmacology, we identified that lycopene's protective effect against skin tumours is linked to intracellular autophagy and redox balance. Lycopene promoted the activation of antioxidant enzymes and the movement of the transcription factor Nrf2 (nuclear factor erythroid 2-related factor 2), which primarily sustains intracellular redox balance. The cancer-preventive effects were facilitated by Nrf2. Additionally, lycopene increased the levels of the autophagy protein p62, leading to the breakdown of Keap1 (Kelch ECH associating protein 1), the primary protein that retains Nrf2 in the cytoplasm. In summary, our research offers preclinical evidence of lycopene's chemopreventive effects on skin tumours and uncovers the mechanistic connection between lycopene's activation of the Nrf2 signalling pathway and p62-driven degradation of Keap1 through the autophagy-lysosomal pathway.[14]

13. Luteolin

Luteolin, a flavonoid found in various green vegetables like cabbage, spinach, and peppers, exhibits anticancer effects by inducing cell cycle arrest, senescence, or apoptosis in cells of oral squamous cancer, human esophageal adenocarcinoma, lung carcinoma, human colon cancer, human hepatoma, and prostate cancer.

Superoxide induction is an initial and vital step in luteolin-induced apoptotic and nonapoptotic death in lung cancer cells. The c-Jun N-terminal kinase (JNK) was strongly activated following superoxide buildup. Inhibition of superoxide completely prevented luteolin-induced JNK activation, which was closely linked to a reduction in luteolin's cytotoxic effects. Although luteolin slightly activated the JNK-activating kinase mitogen-activated protein kinase kinase 7, this activation was not reliant on superoxide. Luteolin initiates a superoxide-dependent rapid breakdown of the JNK-inactivating phosphatase mitogen-activated protein kinase phosphatase-1 (MKP-1). Introducing a degradation-resistant MKP-1 mutant significantly reduced luteolin-induced JNK activation and cytotoxicity, indicating that the inhibition of the JNK suppressor MKP-1 is crucial in luteolin-induced lung cancer cell death. A novel pathway involving superoxide, MKP-1, and JNK is responsible for luteolin's cytotoxicity in lung cancer cells, and manipulating this pathway could be an effective strategy for using luteolin in lung cancer prevention and treatment [15, 16].

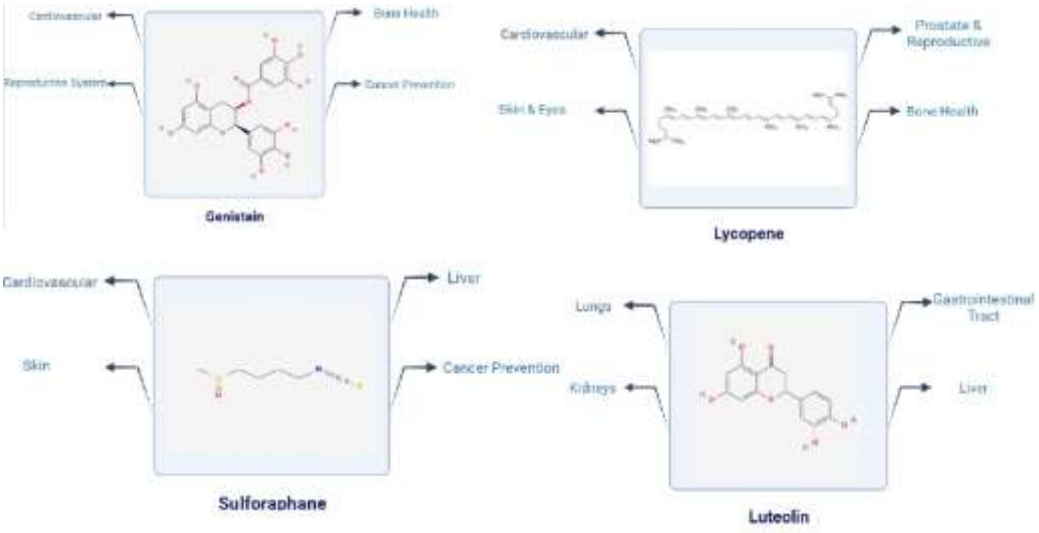

Fig 3: Phytochemicals and their major effects in the human body

14. 2-phenethylisothiocyanate (PEITC)

2-phenethylisothiocyanate (PEITC), a component found in cruciferous vegetables, can inhibit cytochrome P450 enzymes, which play a role in converting carcinogens into their active forms. PEITC is naturally found as its glucosinolate precursor, gluconasturtiin, in vegetables like cabbage, cauliflower, wintercress, and broccoli. In experimental cancer models, PEITC has demonstrated potential antioxidant and chemopreventive properties. PEITC, along with other isothiocyanates, can hinder cancer development in experimental models through various mechanisms, such as the activation of carcinogen-detoxifying phase 2 enzymes, triggering apoptosis, and halting cell cycle progression. The biological effects of PEITC are linked to the suppression of proinflammatory cytokines in the inflamed gut. A total of 21 genes associated with inflammation, apoptosis, cell cycle control, proliferation, chemokine activity, and transcriptional regulation were influenced by PEITC treatment. Given that chronic inflammation in the colon is a significant risk factor for colon cancer, we proposed that PEITC's ability to improve the functions of inflammatory and cell death mediators might explain its previously noted chemoprotective effect in the colon. The present study reveals that PEITC reduces the proliferation of human colon cancer cells in a manner dependent on concentration and time, likely through a caspase-dependent apoptotic pathway. The concentration-dependent increase in an initiator caspase (caspase 8) followed by an effector caspase (caspase 3), which is associated with DNA fragmentation in the cells, was significant, considering the crucial role of caspases in apoptosis. [17]

15. Geraniin

Geraniin, a type of dehydroellagitannin, is present in geraniums, notably in *Geranium thunbergii*, which is widely recognized as a traditional remedy and is officially used as an antidiarrheal medication in Japan.[18] Additionally, it can be found in the peel of *Nephelium lappaceum*, commonly known as rambutan.[19] Geraniin facilitates apoptosis by cleaving focal adhesion kinase through the upregulation of Fas ligand expression in human melanoma cells.[20] It also exhibits immunomodulatory effects by inhibiting tumour necrosis factor-alpha and NF-κB in ovarian cancer cells. [21] Research on geraniin's anticancer properties has demonstrated its ability to induce apoptosis by deactivating the PI3K/Akt/mTOR signalling pathway, involving NF-κB, in HT-29 human colorectal adenocarcinoma cells. [22] Structurally,

geraniin consists of one hexahydroxydiphenic acid unit, a modified hexahydroxydiphenic acid unit (dehydrohexahydroxydiphenic acid or DHHDP), and a gallic acid unit attached to a glucose molecule. It exists as an equilibrium mixture of six-membered and five-membered hemi-ketal forms. Chebulagic acid is derived from geraniin through a conversion mediated by glutathione.[23]

16. Apigenin

Apigenin, a flavone derived from *Origanum vulgare L.* (Lamiaceae), is known for inducing apoptosis, autophagy, and immune responses. It also hinders cell cycle progression, cell migration, and invasion by influencing various signalling pathways. Its positive effects are observed in colorectal, breast, lung, prostate, ovarian, pancreatic, and cervical cancers, as well as in renal cell carcinoma, adenoid cystic carcinoma, thyroid cancer, head and neck squamous cell carcinoma, and oral squamous cell carcinoma. Additionally, Apigenin suppresses the growth of melanoma, leukaemia, glioblastoma, mesothelioma, and osteosarcoma.

Apigenin, a flavonoid derived from natural sources, is gaining recognition for its potential therapeutic uses, particularly in cancer treatment. It is renowned for its wide range of biological activities, including anti-inflammatory, antioxidant, and anticancer effects. Recent research suggests that flavonoids like Apigenin can work synergistically with chemotherapy drugs. This synergy could enhance drug effectiveness while reducing the required doses, potentially minimizing associated toxicities. In the study by Seo et al., it was shown that Apigenin affects ABC transporters by reducing the mRNA and protein levels of multidrug resistance 1 (MDR1) and multidrug resistance-associated proteins (MRPs) in adriamycin-resistant MCF-7/ADR breast cancer cells. This reduction in ABC transporter expression decreases drug efflux, increasing the accumulation of chemotherapeutic agents within the cells and helping to overcome drug resistance. Despite having fewer hydroxyl groups than quercetin, Apigenin's ability to inhibit ABC transporters is due to specific structural features and molecular interactions. Many studies on flavonoids have concentrated on their ability to neutralize free radicals and interact with redox-dependent pathways. However, in Apigenin's case, its mechanism of action does not rely on antioxidant properties. Instead, Apigenin directly interacts with transport proteins through its molecular structure, allowing it to bind effectively to the transporter's active sites. This binding inhibits the transporter's ATPase activity, which is crucial for the energy-dependent efflux of chemotherapeutic drugs from cells. Additionally, Apigenin influences the expression levels of these transporters. Research shows that Apigenin downregulates the mRNA and protein expression of key ABC transporters, such as P-gp and MRP1. This modulation likely occurs through pathways independent of redox activity, possibly involving the regulation of transcription factors and signaling pathways that control transporter gene expression. This ability to modify transporter activity and expression explains how Apigenin, despite its simple structure, effectively increases the intracellular accumulation of drugs, enhancing the efficacy of treatments that are typically expelled by ABC transporters in resistant cancer cells. Unlike flavonoids with high antioxidant activity, Apigenin has a favorable structure for inhibiting ABC transporters. This advantage stems from its unique configuration of hydroxyl groups and overall molecular structure. Specifically, Apigenin lacks hydroxyl groups at positions 3, 7, and 4′, which, as studies suggest, negatively impact the inhibition of ABCG2 transporters. In contrast, the presence of a hydroxyl group at position 5 positively influences its ability to inhibit these transporters. This simpler structure, without the extensive hydroxylation commonly found in other highly antioxidant flavonoids like quercetin, allows Apigenin to interact more effectively

with ABC transporters, making it a promising candidate for overcoming drug resistance in cancer therapy. [24]

17. Carnosol

Rosmarinus officinalis L., commonly known as rosemary, is a powerful antioxidant and anti-inflammatory agent with reported anticancer properties due to diterpenes like Carnosic acid, Carnosol, and Rosmanol, which impact crucial signalling pathways. This aromatic herb, part of the Lamiaceae family, originates from the Mediterranean region. Carnosol, a polyphenol found in rosemary, exhibits anticancer effects and is proposed as a safer option compared to traditional surgery, radiotherapy, and chemotherapy. It causes cell cycle arrest by disrupting the balance between the c-myc oncogene and the p53 tumor suppressor. Additionally, carnosol enhances apoptosis, oxidative stress, and antioxidant activity, likely by regulating the STAT5, ERK1/2, p38, and NF-κB signaling pathways. It also diminishes inflammation and invasive potential by influencing the IL-6 and MMP9/TIMP-1 axes. Carnosol can partially mitigate the increase in reactive oxygen species (ROS) induced by UVB, thereby reducing DNA damage. It may also decrease the formation of cyclobutane pyrimidine dimers (CDP) in keratinocytes, possibly due to its ability to absorb UVB radiation. Furthermore, carnosol can inhibit the UVB-induced activation of NF-κB and lessen the UVB-induced transformation of keratinocytes. Carnosol targets several deregulated pathways linked to inflammation and cancer, including nuclear factor kappa B (NFκB), proteins related to apoptosis, phosphatidylinositol-3-kinase (PI3 K)/Akt, androgen and estrogen receptors, along with other molecular targets.[25]

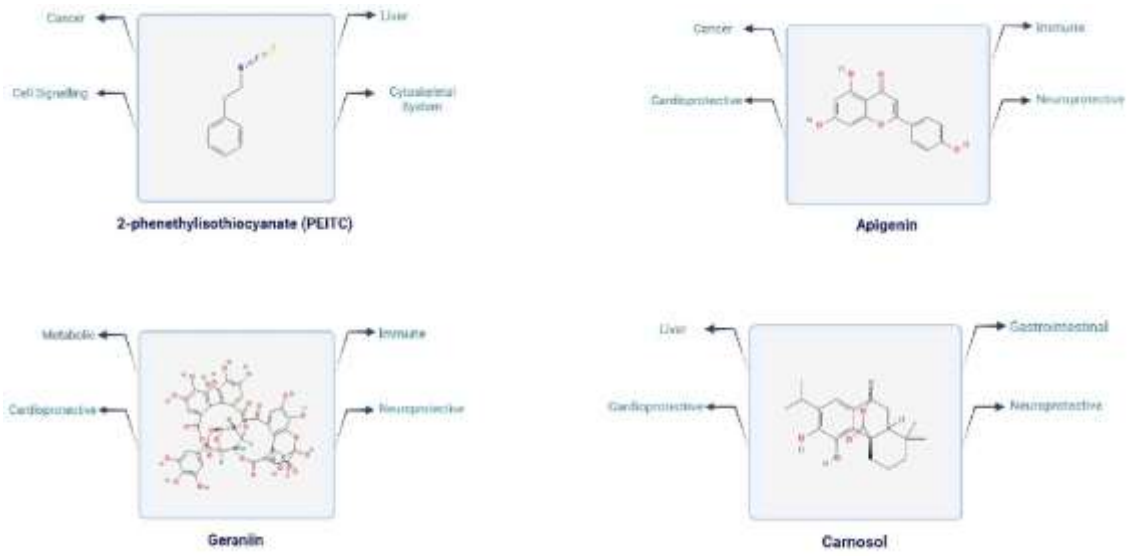

Fig 4: Phytochemicals and their major effects in the human body

18. Piperine

Piperine, recognized as the main bioactive component of black pepper, is found in the highest concentration in black pepper (*Piper nigrum L.*, 9%), with moderate amounts present in long pepper (*P. Longum* L., 4%) and Balinese pepper (*Piper retrofractum Vahl,* 4.5%). Piperine is noted for its anticancer and antimutagenic properties, as it can induce apoptosis in cancer cells and inhibit metastasis and tumor growth by influencing various proteins involved in apoptotic processes at the molecular level. These mechanisms include piperine's potential to slow cancer formation and progression by altering redox

homeostasis. Reactive forms of procarcinogens, free radicals, and reactive oxygen species (ROS) generated through metabolic activation are known to play crucial roles in cancer development. Piperine may also impact key transcriptional enzymes such as cyclins, cyclin-dependent kinases (CDKs), matrix metalloproteinase 9 (MMP-9), NF-κB, caspases, cyclic AMP-responsive element binding protein (CREB), and activated transcription factor-2 (ATF-2), potentially causing cell cycle arrest by downregulating relevant mediators. Additionally, piperine may inhibit angiogenesis. Thus, besides being involved in cell differentiation and autophagy processes, it may act as a potential inhibitor of cancer development and progression by modulating various signaling pathways. Furthermore, it has been shown that piperine can increase the sensitivity of tumor cells to antineoplastic drugs. These varied molecular interactions suggest that piperine could be a promising multi-targeted anticancer agent, offering potential benefits such as the ability to disrupt key signaling pathways and affect multiple stages of cancer progression. [26]

19. Carotenoids

Carotenoids are lipophilic pigments divided into carotenes and xanthophylls, responsible for the red, yellow, and orange hues in fruits and vegetables. Beyond their roles as antioxidants and provitamin A sources, carotenoids exhibit significant anticancer activity through mechanisms like free radical neutralization, gene regulation, and modulation of inflammatory pathways. Major dietary sources of carotenoids include algae, yeast, carrots, tomatoes, citrus fruits, and various plant by-products. Saponified lipophilic extract from sea buckthorn (*Hippophae rhamnoides L.*) has anticancer effects against breast cancer cell lines T47D and BT-549. α-Carotene inhibits metastasis by modulating MMP2, MMP2, TIMP-1, and PAI-1, thereby disrupting integrin β1/FAK/MAPK signalling without affecting primary tumour growth. β-Carotene hinders gastric cancer progression by suppressing the Notch/EMT pathway, and in neuroblastoma, it downregulates MMPs, HIF-1α, and VEGF, thereby reducing metastasis. Additionally, it modulates M2 macrophage and fibroblast activation, limiting invasiveness in colorectal cancer. Overexpression of β-carotene 15,15′-oxygenase reduces the tumorigenic potential and metastatic progression of neuroblastoma by modulating EMT and MMP activity.[27]

20. Hesperin

For many years, herbal and botanical medicines have been the focus of extensive research due to their potential positive effects in treating various diseases, including different cancers. Hesperidin and its derivative, hesperetin, are known for their beneficial biological properties. Hesperidin can inhibit the growth and trigger apoptosis in lung cancer cells without causing significant harm to normal lung epithelial cells. Additionally, it prevents the migration and invasion of lung cancer cells by modulating the SDF1/CXCR4 axis. In animal studies, pretreatment with hesperidin has been shown to protect against lung cancer induced by multiple carcinogens. Hesperetin, a glycoside ligand derivative of hesperetin, is noted for its good bioavailability. Research has demonstrated that hesperetin can prevent colorectal cancer induced by 1,2-dimethylhydrazine and induce apoptosis in colorectal cancer cells in a dose-dependent manner.[28]

21. Allicin

Allicin, a sulfur-containing natural compound derived from garlic, has gained significant clinical interest in recent years. Biochemical studies have revealed that allicin offers numerous benefits, such as enhancing immunity, and providing antioxidant, anti-inflammatory, and antibacterial effects. Furthermore, new

evidence suggests that the conformational change of GPCR (AT1R) leads to the dissociation of the heterotrimer G protein upon stimulation. GRK2, a multifunctional protein kinase from the GRK family, can phosphorylate AngII-occupied GPCR (AT1R). GRK2 is composed of three modular domains: the RH domain, a central catalytic domain, and the PH domain, where it interacts with the G protein. Since GPCR is a heterotrimer that releases Gβγ and Gα upon activation, GRK2 can be phosphorylated by various non-GPCR substrates and kinases at different residues. Rapid phosphorylation of GRK2 at its residues can accelerate its degradation and hinder its interaction with the G protein (Gβγ and Gα). Recent studies have shown that PI3K activation can promote GRK2 S670 phosphorylation, significantly impairing GRK2's interaction with Gβγ subunits. It has been previously demonstrated that the release of Gβγ ultimately activates phospholipase Cγ (PLCγ). The activation of PLCγ results in the formation of three different inositol 1, 4, 5-trisphosphate receptors (IP3Rs), which facilitate continuous Ca2+ release from the endoplasmic reticulum (ER) to the mitochondria through the mitochondrion-associated ER membrane (MAM). As previously reported, allicin plays a crucial role in activating phosphoinositide 3-kinase (PI3K). This study was conducted to explore the protective effect of allicin on MI/R injury and to investigate whether the mechanism is related to PI3K/GRK2/PLCγ-induced suppression of Ca2+ overload and mitochondrial dysfunction.[29]

Fig 5: Phytochemicals and their major effects in the human body

22. Kaempferol

Flavonoids, a type of polyphenolic compound, are prevalent in plants and form a crucial component of the human diet. These compounds have been noted for their ability to suppress VEGF expression, cancer cell growth, and angiogenesis. Kaempferol, a flavonoid of particular interest, belongs to the flavonol group and is plentiful in foods like tea, broccoli, apples, strawberries, and beans. Unlike conventional chemotherapy drugs, kaempferol exhibits significantly lower toxicity to normal cells. Numerous in vitro studies have documented kaempferol's ability to induce apoptosis, a process partly linked to its influence on the MAPK pathway. The introduction of kaempferol to cancer cells is closely associated with prolonged activation of this signaling pathway. In fact, using MAPK inhibitors can greatly reduce apoptosis, even when combined with the suppression of pro-growth proteins. Additionally, kaempferol-induced MAPK activation can avert DNA damage that leads to cell transformation. The presence of kaempferol has been shown to enhance the expression of the haeme oxygenase (HO)-1 gene, thereby boosting the antioxidant capacity of cells. Treatment with kaempferol significantly improved cell viability under oxidative stress, which involves unstable radicals that can damage DNA. Thus, kaempferol-induced MAPK activation helps protect healthy cells from becoming cancerous. Beyond extending pathway

activation, kaempferol also alters several proteins involved in the process. RSK2, a crucial inhibitor of apoptosis, has been found to down-regulate the apoptosis-promoting protein BAD and up-regulate Bcl-2 levels. Recent findings indicate that kaempferol directly binds to the RSK2 protein at the Val82 and Lys100 sites, which are vital for RSK2's function, effectively immobilizing the protein. As anticipated, treatment led to a decrease in Bcl levels and an increase in the concentrations of tumour suppressor proteins BAD and p53. Moreover, kaempferol has been shown to interfere with Src kinase activity. Src is known to activate MAPK in a pro-growth context, which in turn activates the COX-2 protein, a marker for skin tumours. UVB radiation is a major factor in Src kinase activity. However, kaempferol shows significant potential as a competitive inhibitor of Src, which requires ATP binding to function. Kaempferol readily attaches to Src at its ATP site, disrupting its role in promoting skin cancer. Kaempferol modifies the MAPK/ERK pathway at several critical points, among other cellular processes. In the highly invasive breast cancer cell line MDA-MB-231, kaempferol has shown considerable promise in hindering cancer metastasis. While the secretion of MMP-3 was largely unaffected by flavonoid treatment, kaempferol significantly inhibited MMP-3 protein activity in a dose-dependent manner. Notably, kaempferol's presence blocked the in vitro migration of MDA-MB-231 cells, suggesting its potential use in controlling tumor invasion. Additionally, the introduction of kaempferol disrupted HGF/Met signalling aling in the medulloblastoma line DAOY. [30]

23. Capsaicin

Capsaicin, the primary spicy component in red peppers, is consumed globally. Beyond its well-documented pain-relieving properties, capsaicin has demonstrated antitumor effects in various cancer models. Capsaicin significantly inhibited the proliferation of human colon cancer cells by causing cell cycle arrest at the G0/G1 phase and triggering apoptosis, which was linked to increased levels of p21, Bax, and cleaved PARP. The antitumor mechanism of capsaicin was largely due to the stabilization and activation of p53. Capsaicin notably extended the half-life of p53 and greatly enhanced its transcriptional activity. By inhibiting the interaction between p53 and MDM2, capsaicin reduced MDM2-mediated p53 ubiquitination, leading to the stabilization and accumulation of p53. Experiments using p53-shRNA further showed that knocking down p53 significantly reduced the cells' sensitivity to capsaicin, and the G0/G1 phase arrest and apoptosis induced by capsaicin were markedly diminished in p53-knockdown cells, highlighting the crucial role of p53 in capsaicin's antitumor effects. Capsaicin also inhibited the growth of human leukemic, gastric, nasopharyngeal, prostate, and hepatic carcinoma cells in vitro by inducing cell cycle arrest and apoptosis. However, the detailed molecular mechanisms behind capsaicin-induced growth inhibition and apoptosis have not been fully clarified. Several proposed mechanisms for capsaicin-induced apoptosis include the inhibition of NF-κB nuclear translocation, activation of the AMPK signalling pathway and c-Jun NH2-terminal kinases, disruption of ubiquitin-proteasome systems, as well as the upregulation of several pro-apoptotic proteins and activation of the intrinsic pathway to promote caspase activation. [31]

24. Hinokitiol

Hinokitiol, a natural monoterpenoid derived from the heartwood of *Calocedrus formosana*, has been documented to exhibit anticancer properties against a range of cancer cell lines. This natural compound, also found in *Chamaecyparis taiwanensis* and extracted from the wood of cupressaceous plants, possesses a variety of biological and pharmacological characteristics. Hinokitiol is recognized for its antiviral,

antibacterial, antifungal, antitumor, and insecticidal properties. It has demonstrated significant anti-inflammatory effects in various cell types through multiple mechanisms. Additionally, hinokitiol is noted for its ability to suppress lung tumours without affecting body weight or causing toxicity in the host. Our previous research indicated that hinokitiol reduces cell migration by decreasing MMP-1 expression, which subsequently leads to the inhibition of nuclear factor κ B (NF-κB)/mitogen-activated protein kinase (MAPKs) signalling pathways and the formation of tumour nodules in melanoma cells in vivo.[32]

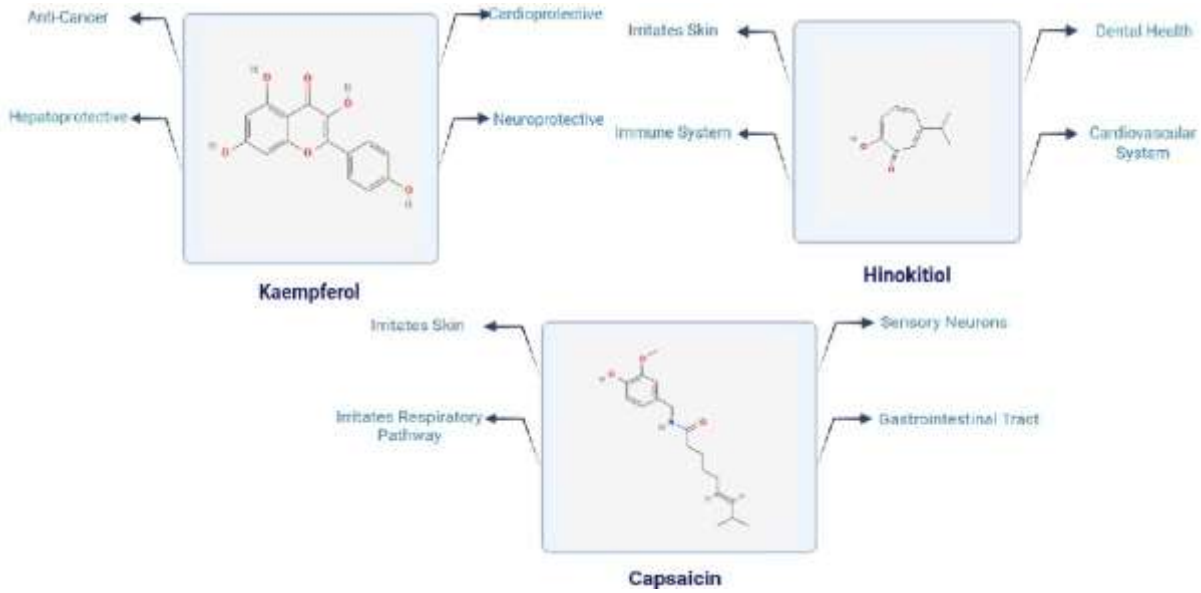

Fig 6: Phytochemicals and their major effects in the human body

Conclusion:

Phytochemicals, as naturally occurring bioactive compounds in plants, have demonstrated compelling anticancer potential through multifaceted molecular mechanisms. Across pre-clinical and early-stage clinical studies, these selected phytochemicals have been shown to modulate critical oncogenic pathways including PI3K/Akt/mTOR, MAPK/ERK, NF-κB, Wnt/β-catenin along with epigenetic regulators such as DNMTs, HDACs, and microRNAs.

Their biological activities encompass induction of apoptosis, cell cycle arrest, inhibition of angiogenesis, suppression of metastasis, antioxidant and anti-inflammatory activities, and immune modulation collectively attenuating tumour formation, progression and recurrence.

Epidemiological studies reinforce the protective efficacy of phytochemical constituents, rich diets, correlating with reduced incidence and mortality for multiple types of cancers. Furthermore, pre-clinical research underscores their capacity to enhance conventional treatments, acting synergistically with chemotherapy, radiotherapy, and targeted therapies while potentially mitigating adverse effects.

Despite, these promising attributes, the clinical translation of phytochemicals constrained limitations including poor bioavailability, rapid metabolism, and variability in pharmacokinetic and pharmacodynamic characteristics. However, advancement in formulation development such as nano-particle based delivery system, co-administration with bioenhancers, and structural analogue development, offer potential solutions to these gaps.

Additionally, standardization, dosage optimization, and rigorous clinical trials remain essential to ensure reproducibility, safety, and therapeutic efficacy.

In conclusion, phytochemicals represent a versatile and valuable class of anticancer agents that complement conventional therapies and offer avenues for preventive, adjuvant, and therapeutic applications. Future research should prioritize translational studies, integrating pharmacokinetics, mechanistic insights and clinical validation. Personalized approaches tailoring phytochemical combinatorial strategies, hold promise to maximize their therapeutic impact, advancing sustainable and accessible cancer care.

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