

Plant-Derived Bioactives in Precision Oncology: Emerging Molecular Targets, Tumor Microenvironment Modulation and Translational Opportunities

Kavita Narayan Gaisamudre (Sarwade)¹, Prakash Pralhad Sarwade², Ashwini P.³, Kalpana Sonwani⁴, Nuri Farzina Rahman⁵, Ayush Kamlakar Gaikar⁶ and Ruchita Sharma⁷

¹Assistant Professor, Department of Botany, Shriman Bhausaheb Zadbuke Mahavidyalaya, Barshi Tal. Barshi, Solapur, 413401, Maharashtra, INDIA.

^{2**}Associate Professor and Head, Department of Botany, Shikshan Maharshi Guruvarya R. G. Shinde Mahavidyalaya, Paranda Dist. Dharashiv (Osmanabad) 413502, Maharashtra, INDIA.

³Department of Pharmacology, Tamilnadu Dr. MGR Medical University, 69, Anna Salai, Little Mount, Guindy, Chennai-600032, INDIA.

⁴Head Department of Pharmacy, GSRM Memorial College of Pharmacy, Lucknow, Mohan Road, Bhadoi, INDIA.

⁵Department of Pharmaceutical Chemistry, Assistant Professor, The Assam Kaziranga University, Assam, INDIA.

⁶Department of Pharmacy, Bombay Institute of Pharmacy & Research, Next to Lodha Panacea, Near Jain Temple, Bhadra Nagar, Dombivli East 421203 Maharashtra, INDIA.

⁷GRY Institute of Pharmacy Borawan, Dist-Khargone, Madhya Pradesh, INDIA.

¹Corresponding Author: ppsarwade@gmail.com



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ABSTRACT

The advantages of the bioactives derived from plants for precision oncology include structural diversity, multipurpose pharmacology, and the modulation of tumor development and therapeutic resistance. This review discusses key classes of anticancer phytochemicals highlighting their molecular and translational implications, such as polyphenols, flavonoids, alkaloids, terpenoids, triterpenoids, quinones, organosulfur compounds, saponins and lignans. Their activity is focused on oncogenic pathways like PI3K/AKT/mTOR, MAPK/ERK, JAK/STAT, NF- κ B, and Wnt/ β -catenin pathways. Their involvement in regulating apoptosis, cell-cycle arrest, autophagy, ferroptosis, pyroptosis, redox homeostasis and DNA-damage response is also discussed. Moreover, the compounds derived from plants could alter the characteristics of the tumor microenvironment by impacting cancer-associated fibroblasts, tumor-associated macrophages, myeloid-derived suppressor cells, regulatory T cells, tumor-infiltrating lymphocytes and natural killer cells. Combination of multi-omics, AI, network pharmacology, biomarker discovery, and advanced drug-delivery systems could help to select and clinically use phytochemicals more accurately. Although there is promising pre-clinical data, issues with bioavailability, standardization, pharmacokinetics, safety, and clinical validation are still to be addressed. Moving forward, strategies based on biomarkers are needed as well as carefully designed translational studies.

Keywords- Precision oncology; Plant-derived bioactives; Tumor microenvironment; Phytochemicals; Molecular targets.

I. INTRODUCTION

1.1 Global cancer burden and limitations of conventional anticancer therapy

Cancer is one of the most important health problems in the world due to its high incidence, mortality,

biological heterogeneity and socioeconomic impact. The IARC estimated that there were nearly 10 million cancer deaths and almost 20 million new cancer cases globally in 2022 and that cases will rise to approximately 35 million per year by 2050. Much of this burden is due to lung, breast, colorectal, prostate and stomach cancer [1]. The

incidence of cancer is also projected to continue to rise due to population ageing, tobacco use, poor nutrition, overweight and obesity, environmental exposure to cancer causing agents, oncogenic infections, and inequities in access to preventative and early detection services, especially in LMICs. Traditional treatment strategies such as surgery, radiotherapy and cytotoxic chemotherapy are still at the heart of cancer care. However, the efficacy is often hindered by the lack of tumor selectivity, toxicity, dose-limiting toxicity, and acquired drug resistance. Cytotoxic drugs act selectively on rapidly dividing cells, but may also cause toxicity in normal tissues, leading to myelosuppression, gastrointestinal toxicity, alopecia, and organ-specific toxicity. Malignant tumors are also made of genetically and phenotypically diverse cellular subpopulations. Treatment may kill sensitive clones and leave resistant populations behind to grow. Therapeutic resistance, tumor recurrence and metastasis are further driven by cancer stem cells, improved DNA repair, drug transport changes, metabolic plasticity, EMT and protective signals from the tumor microenvironment. These restrictions have led to the development of a search for treatment modalities based on the molecular features of every tumor and not solely on anatomical location [2].

1.2 Evolution from conventional chemotherapy to precision oncology

The success of precision oncology has come about as a result of cancer genomics, molecular pathology, next-generation sequencing, bioinformatics, and biomarker discovery. Precision oncology tries to find molecular abnormalities that are driving an individual tumor and then choose therapies that can take advantage of that defect, as opposed to traditional methods, which may use the same treatments for patients with the same histological diagnosis. Therapeutic response can be affected by genomic changes, abnormal receptor signaling, epigenetic changes, transcriptomic signatures, alterations in protein expression and the features of the immune microenvironment. Examples of successful treatments are those for HER2 amplification, EGFR mutations, BCR::ABL1 fusion, BRAF V600 alterations and ALK rearrangements. Precision oncology is thus a change from the organ-centric approach to decision-making based on biology and patient-specific characteristics. This new molecular guided approach has revolutionized cancer classification and therapeutic decision making [3]. In addition to the role played by histopathology, the use of tumor profiling can enable the identification of clinically meaningful subgroups, whilst the use of liquid biopsy and circulating tumor DNA can offer the potential of minimally invasive monitoring of tumor evolution. Precision oncology is also getting away from targeting a single gene. Genomics, transcriptomics, proteomics, metabolomics, epigenomics, single-cell analysis and spatial profiling can uncover interactions between pathways that contribute to the maintenance of tumor growth and resistance. This information can help

with improved patient stratification and rational combination therapies. Often the cancer is conceptualized as a dynamic molecular ecosystem that needs to be characterized repeatedly as it evolves and encounters selective pressures over time. However, precision oncology has some limitations. Not all patients have a molecular change that can be targeted and targeted inhibition can kill tumor cells but trigger alternative pathways. The durability of responses may thus be limited by intratumoral heterogeneity, clonal evolution and microenvironmental adaptation. High costs, disparities in access to molecular diagnostics, poor availability of targeted therapies, and the lack of validated biomarkers for many tumors are other obstacles. These challenges provide a considerable rationale for identifying agents that are able to impact multiple interconnected pathways in cancer with tolerable toxicity [4].

1.3 Growing importance of plant-derived bioactives in precision cancer therapeutics

Plant derived bioactive compounds is a potential source of molecules for precision cancer therapeutics. The therapeutic potential of plant chemical diversity has already been established with the introduction of important anticancer drugs, such as vinca alkaloids, taxanes and camptothecin-derived drugs. Furthermore, phytochemicals like curcumin, resveratrol, quercetin, epigallocatechin gallate, berberine, sulforaphane, genistein, withaferin A and thymoquinone are shown to exhibit activity against various molecular events which are associated with tumor initiation, progression, and resistance [5]. Polypharmacology is one of the important features of many phytochemicals. They can affect multiple signaling pathways that are interconnected, including PI3K/AKT/mTOR, MAPK, NF- κ B, JAK/STAT, Wnt/ β -catenin, and p53 pathways. They can also modulate apoptosis, autophagy, ferroptosis, oxidative stress, epigenetic changes, cancer metabolism, E-M transition, cancer stemness and multidrug resistance. Importantly, there is a growing body of evidence that phytochemicals are able to actively alter the tumor microenvironment through their effects on cancer-associated fibroblasts, tumor-associated macrophages, lymphocytes, inflammatory cytokines, angiogenesis, extracellular-matrix remodeling, and immune-checkpoint signaling. They could thus be especially useful in heterogeneous tumors, where multiple, overlapping compensatory pathways exist. The intersection of natural-product pharmacology and precision-oncology technologies is of particular interest for translational opportunities. Poor solubility, low bioavailability, fast metabolism, and non-specific distribution could also be overcome by advanced nanoformulations and targeted delivery systems. Therefore, the use of plant-derived bioactives as alternative treatments for cancer should not be considered only as alternative anticancer drugs; their potential is more significant when used in a combination with chemotherapy, targeted therapy, radiotherapy, and immunotherapy based on the identification of biomarkers.

This will depend on the standardization of formulations, comprehensive pharmacokinetic assessment, a clinically relevant dose regimen, predictive biomarkers and an appropriate clinical trial design [6].

II. PLANT-DERIVED BIOACTIVES AS A RESOURCE FOR PRECISION ONCOLOGY

The natural products of plants are one of the most diverse, and abundant, sources of biologically active molecules in the search for new cancer drugs. They are structurally complex, stereochemically diverse and can interact with several cellular targets, which sets them apart from many of the traditional synthetic small molecules. Whereas, plant-based compounds have directly or indirectly played a role in several validated cancer therapeutic drugs such as vinca alkaloids, taxanes, and camptothecin-derived drugs suggesting that the plant-based structures can be successfully translated into clinically useful therapeutics [7]. Recent developments in molecular oncology have moved away from the concept of indiscriminate cytotoxicity and focused on the discovery of molecules that are bioactive to address identified vulnerabilities, tumour subtypes, resistance mechanisms and microenvironmental dependencies. In this context, compounds of plant origin are especially interesting as many of them are polypharmacological in nature and interact with several interconnected processes: linked to the malignant progression. These major families of phytochemicals with anticancer activity include polyphenols, flavonoids, alkaloids, terpenoids, triterpenoids, quinones, organosulfur compounds, saponins, lignans, and a group of structurally diverse bioactive compounds. Not all these chemical classes are mutually exclusive as individual compounds may meet more than one phytochemical classification criterion. However, classification serves as a valuable tool to relate structural attributes to molecular targets, pharmacological activity and therapeutic potential for cancer therapy based on biomarkers. Recent network-pharmacology studies also suggest that molecules found in plants often target central nodes in cancer, including members of the AKT1, EGFR, TP53, STAT3, MAPK, caspases and HSP90 families, which certainly warrants investigation of these molecules in systems-oriented precision oncology [8].

2.1 Major classes of anticancer phytochemicals

2.1.1 Polyphenols and Flavonoids

Polyphenols are a general term for a large group of plant secondary metabolites that contain one or more rings of phenols. Fruits, vegetables, tea, berries, herbs, spices and medicinal plants are rich in them. The most important polyphenols with anti-cancer properties are curcumin, resveratrol, epigallocatechin-3-gallate (EGCG), gallic acid, ellagic acid and several stilbenes and tannin-related compounds. One of the largest subclasses of polyphenols is the flavonoids and they contain

quercetin, kaempferol, apigenin, luteolin, genistein, naringenin, fisetin and catechins. These properties make them important for their possible anticancer relevance, as they can modulate a number of processes involved in the survival and progression of tumors [9]. Polyphenols have anti-proliferative signaling properties, act as antioxidant agents, modulate the activity of transcription factors, trigger apoptosis, act as angiogenesis inhibitors, and have anti-invasive/metastatic properties. Various polyphenolics have been reported to modulate PI3K/AKT/mTOR signaling, MAPK signaling, NF- κ B signaling, STAT3 signaling, Wnt/ β -catenin signaling pathways, and those associated with p53, but to a different extent depending on the compound, dose, type of cancer, and molecular background. It is important to note that flavonoids have biological activities that can be affected by the molecular abnormalities present in the tumor, which makes them pertinent to precision oncology. For instance, kinases-dependent signaling is affected by quercetin and luteolin, and genistein has been of interest due to its activity with estrogen-related signaling pathways and tyrosine-kinase signaling pathways. EGCG can modulate receptor mediated signaling, epigenetic regulation, and inflammation in tumors. The multimodal effects also suggest that phytochemicals might be targeted based on molecular fingerprint instead of being used indiscriminately for all cancers. Oral bioavailability, low aqueous solubility, rapid conjugation, metabolic instability, and inability to reach pharmacologically relevant concentrations in tumors, however, have limited the translation of polyphenols. These problems have encouraged the development of nanoformulations, prodrugs and structural analogues with the aim of achieving enhanced pharmacokinetic exposure and tumour targeting, as well as combination methods [10].

2.1.2 Alkaloids

The nitrogen containing natural compounds are known as alkaloids with a high degree of structural and pharmacological variability. They are one of the most clinically successful groups of phytochemicals in oncology. Vinca alkaloids like vincristine and vinblastine disrupt the process of microtubule assembly, while camptothecin served as the template for the development of topoisomerase I inhibitors like irinotecan and topotecan. The examples illustrate the ability of plant alkaloids to produce anticancer scaffolds that are validated in the therapeutic marketplace. In addition to the already known drugs, several alkaloids including berberine, matrine, sanguinarine, piperine, evodiamine, tetrandrine and harmine are being studied for their broader anticancer potential [11]. Berberine, for instance, has been linked to proliferation, apoptosis, mitochondrial function, metabolism and metastatic signaling modulation. Based on network-pharmacology analyses, it can be suggested that various structural subclasses of alkaloids have selective interactions to different molecular targets. The proteins that were found to interact with the protoberberine alkaloids are cyclic D1 and

HSP90; Bisbenzylisoquinoline alkaloids are known to interact with AKT and GTPase-related proteins. This diversity is very pertinent to precision oncology as the alkaloid scaffolds can be aligned with specific oncogenic dependencies. Their chemical structures are also good starting points for semi-synthetic optimization for increased potency, selectivity, solubility and pharmacokinetics. However, the therapeutic range for some alkaloids is very narrow or there is considerable systemic toxicity, which makes molecular stratification and targeted delivery crucial [12].

2.1.3 Terpenoids and Triterpenoids

Terpenoids are a very large class of natural products biosynthetically synthesized from isoprene units. They are divided into monoterpenes, sesquiterpenes, diterpenes, triterpenes and other subclasses based on the number of the C atoms and number of isoprene units. A number of terpenoids from plants have been reported to have anticancer activity, such as paclitaxel, artemisinin derivatives, limonene, ursolic acid, oleanolic acid, betulinic acid, celastrol, triptolide and various diterpenoids and triterpenoids. Paclitaxel is the most prominent example of a successful plant-based diterpenoid scaffold being translated to mainstream cancer therapy. Other terpenoids are being investigated mainly at the preclinical level, for their anti-apoptotic, anti-reactive oxygen species, anti-angiogenic, anti-metastatic and sensitizing properties in resistant tumors [13]. The broad molecular activities of triterpenoids like ursolic acid, oleanolic acid, betulinic acid and celastrol make them of particular interest. Research shows that triterpenoids have effects on inflammatory signaling, cell-cycle control, mitochondrial apoptosis, stress responses, and tumour invasion. The structural modification of naturally occurred triterpenoid structure is becoming a common approach to developing potent and pharmacologically active derivatives. Recent years have seen comprehensive analyses highlighting the structural diversity as well as the potential of templates for drug development against cancer. Precision-oncology applications could lead to discovery of tumor sub-groups specifically vulnerable to certain terpenoid derivatives through systematic structure–activity analysis and genomics and target profiling [14].

2.1.4 Quinones and phenolic compounds

Quinones are electrophilic compounds with redox active groups, containing a conjugated cyclic diketone structure. Representatives from plants are thymoquinone, plumbagin, shikonin, juglone, aloemodin, emodin and β -lapachone related structures. These compounds have been studied due to their redox activity that can selectively impair cellular oxidative balance and which is especially important in cancer cells that have a high level of oxidative stress. Quinones derived from plants have been shown to have antiproliferative and antimetastatic properties in various experimental cancer models. The class is exemplified by many mechanisms as in the case of shikonin.

Experimental data suggest it regulates apoptosis, ferroptosis, necroptosis and other cell death pathways, disrupts epithelial–mesenchymal transition and changes cancer metabolism, among others via pyruvate kinase M2. Thymoquinone has also been extensively studied for its effects on oxidative stress, inflammatory pathways, apoptosis and proliferation of tumor cells. Other simple phenols, such as gallic acid, caffeic acid derivatives, ferulic acid, and hydroxytyrosol, have a potential to modulate the cellular redox balance and signaling. It may ultimately require targeting tumors that have specific redox, metabolic and/or enzymatic weaknesses, as excessive non-specific oxidative activity may result in toxicities to normal tissues [15].

2.1.5 Organosulfur compounds

Organosulfur phytochemicals are especially large in vegetables from the cruciferous family and Alliums. There are several important examples, such as sulforaphane, phenethyl isothiocyanate, benzyl isothiocyanate, diallyl sulfide, diallyl disulfide, diallyl trisulfide, and allicin. They are interesting compounds in cancer prevention and therapy due to their interactions with detoxification systems, oxidative-stress responses, epigenetic regulators, and survival pathways. Sulforaphane is one of the most extensively researched isothiocyanate (iso) derivatives, which form naturally from glucoraphanin. Can induce NRF2-mediated cytoprotective signaling in certain contexts and inhibit cancer stem cell properties, tumor-promoting signaling in cancer cells, and cell-cycle arrest in cancer cells [16]. Organosulfur compounds can also increase sensitivity to chemotherapy or targeted therapies by altering the mechanisms of drug resistance. Predictive biomarkers that are able to detect tumors in "susceptible" redox or epigenetic or metabolic states may therefore be more useful in the future for clinical applications [17].

2.1.6 Saponins, lignans and miscellaneous bioactives

Phytochemicals that contain one or more sugar residues attached to a hydrophobic aglycone are called saponins. These can be generally classed as steroidal saponins and triterpenoid saponins. Representative are diosgenin related steroidal saponins, ginsenosides, astragalosides, and plant derived triterpene glycosides. Antitumor saponins have been known to induce apoptosis and autophagy, inhibit cell migration, induce cell cycle arrest, and modulate drug resistance. In experimental models, saponins with a steroid-like structure exhibit significant activity, but there are several important translational issues such as cytotoxicity, interaction with membranes, and weak bioavailability. Lignans are natural products derived from the phenylpropanoid family of compounds present in several medicinal plants, seeds and grains. Podophyllotoxin is significant in history as its structure was the basis for the development of the clinically established topoisomerase II inhibitors etoposide and teniposide [18]. Other lignans such as arctiin, arctigenin, sesamin, matairesinol and related compounds are being investigated for their proliferation,

apoptosis, inflammatory, metabolic and metastatic activities. For instance, arctiin and its lignans has been studied in several molecular pathways involved in the growth and progression of tumors. Other molecules found in plants include coumarins, tannins, glycosides, chalcones, carotenoids, anthraquinone-related compounds and other special metabolites which do not belong in any of the other broad categories. These compounds are chemically heterogeneous, but significantly increase the molecular space for natural product drug discovery. Together, plant derived bioactives should be considered more than just generic “natural anticancer agents”, but rather a chemically diverse library of molecular scaffolds that can engage

different vulnerabilities within cancer. To play a meaningful future part in precision oncology, it will be crucial to correlate the structure of the phytochemicals with their pharmacology, tumor genomics, transcriptomics, proteomics, metabolic state, immune phenotype, and mechanisms of drug-resistance. The selection of the suitable phytochemical or derivative in the suitable molecular tumour context could be achieved through network pharmacology, multi-omics approaches, AI, PD models and advanced drug systems. Such a strategy may revolutionize the use of phytochemicals from generally studied experimental drugs to scientifically selected agents of personalized cancer therapy [19-21].

Table 1. Major plant-derived bioactives, molecular targets and anticancer mechanisms

Phytochemical	Class	Major molecular targets/pathways	Principal anticancer effects
Curcumin	Polyphenol	PI3K/AKT/mTOR, NF- κ B, STAT3, Wnt/ β -catenin	Apoptosis induction, cell-cycle arrest, anti-inflammatory activity, inhibition of invasion and metastasis
Resveratrol	Stilbene/polyphenol	PI3K/AKT, MAPK, NF- κ B, SIRT1, STAT3	Apoptosis, autophagy modulation, inhibition of proliferation and angiogenesis
Quercetin	Flavonoid	PI3K/AKT/mTOR, MAPK, p53, NF- κ B	Cell-cycle arrest, ROS generation, apoptosis, chemosensitization
EGCG	Catechin/flavonoid	EGFR, PI3K/AKT, STAT3, NF- κ B	Antiproliferative, antiangiogenic and immunomodulatory effects
Berberine	Alkaloid	AMPK, PI3K/AKT, STAT3, Wnt/ β -catenin	Mitochondrial apoptosis, metabolic disruption, inhibition of metastasis
Genistein	Isoflavone	EGFR, PI3K/AKT, NF- κ B, estrogen receptors	Growth inhibition, apoptosis, cell-cycle arrest and antiangiogenic activity
Sulforaphane	Isothiocyanate	NRF2, HDACs, Wnt/ β -catenin, STAT3	Epigenetic modulation, cancer stem-cell inhibition, apoptosis and ferroptosis regulation
Withaferin A	Steroidal lactone	NF- κ B, STAT3, PI3K/AKT, HSP90	Apoptosis, inhibition of EMT, migration and angiogenesis
Thymoquinone	Quinone	NF- κ B, PI3K/AKT, p53, STAT3	ROS-mediated apoptosis, inhibition of proliferation and inflammatory signaling
Apigenin	Flavonoid	PI3K/AKT, MAPK, NF- κ B, STAT3	Apoptosis, cell-cycle arrest and inhibition of metastatic behavior
Luteolin	Flavonoid	AKT, MAPK, STAT3, NF- κ B	Growth suppression, apoptosis and inhibition of invasion
Ursolic acid	Triterpenoid	PI3K/AKT/mTOR, STAT3, NF- κ B	Apoptosis, autophagy modulation, inhibition of angiogenesis and metastasis
Betulinic acid	Triterpenoid	Mitochondrial pathways, ROS, NF- κ B	Mitochondrial apoptosis and selective cytotoxicity
Celastrol	Triterpenoid	HSP90, NF- κ B, STAT3, AKT	Proteotoxic stress, apoptosis and inhibition of tumor progression
Shikonin	Naphthoquinone	PKM2, ROS, GPX4-related mechanisms	Apoptosis, necroptosis, ferroptosis and metabolic disruption

III. MOLECULAR TARGETS OF PLANT-DERIVED BIOACTIVES IN CANCER

Malignant transformation and the proliferation, survival, metabolic regulation, invasion, angiogenesis, immune evasion and therapeutic resistance of cancer cells

are all controlled by aberrant intracellular signaling. The PI3K/AKT/mTOR pathway, the MAPK/ERK pathway, and the JAK/STAT, NF- κ B, and Wnt/ β -catenin pathways are among the most commonly dysregulated pathways. These signaling systems are not functionally independent, but rather one can compensate for the blockade of the other. Plant-based bioactives are consequently gaining

interest, since many possess multitarget pharmacology, that is, they modulate multiple ONCogenic signaling nodes at the same time. This property might confer special benefit in molecularly heterogeneous cancers, but would need to be specific for tumor subtypes that respond and also be validated in terms of pharmacologically attainable exposures to be clinically applicable. Evidence in recent years has continued to indicate that products from plants can serve as modulators of several of these interconnected signaling networks [22-24].

3.1 PI3K/AKT/mTOR signaling pathway

The phosphatidylinositol-3-kinase (PI3K)/AKT/mTOR pathway is a pivotal regulator of cancer-cell growth, metabolism, proliferation and survival. It typically doesn't work unless receptor tyrosine kinases like EGFR, HER2, IGF-1R, or other growth factor receptors are stimulated. Activated PI3K activates phosphatidylinositol-4,5-bisphosphate (PIP2) into phosphatidylinositol-3,4,5-trisphosphate (PIP3), which allows for membrane recruitment and activation of AKT [25]. Subsequently, AKT controls many downstream substrates such as mTOR complexes, which increases protein synthesis, utilization of nutrients, progression of cell-cycle and resistance to apoptosis. PTEN is a tumor suppressor protein that acts as an antagonist to the function of PI3K by removing the phosphate from PIP3 to convert it to PIP2. Mutations/amplification of PIK3CA, loss/abnormal inactivation of PTEN, AKT hyperactivation and aberrant mTOR signaling are found in a variety of malignancies and may play a role in therapeutic resistance. Therefore, this pathway is a key molecular target in precision oncology. Berries have been reported to inhibit various aspects of the PI3K/AKT/mTOR pathway, with curcumin, resveratrol, quercetin, EGCG, berberine, genistein, apigenin and luteolin all being shown to have inhibitory effects on various parts of this pathway. The effects may be due to decreased PI3K or phosphorylated AKT activity, inhibition of mTOR-dependent signaling, re-activation of pro-apoptotic mechanisms and suppression of proliferation of cancer cells. These compounds could also improve the sensitivity of anticancer drugs in cases where the constitutively active AKT/mTOR activity is responsible for the resistance. Their activity, however, is very context-dependent, both with respect to the type of tumor, its concentration, and the molecular context. Rationalization for the evaluation of selected phytochemicals, based on their identification of tumors dependent on PI3K/AKT/mTOR, would be therefore warranted [26].

3.2 MAPK/ERK signaling pathway

The mitogen-activated protein kinase (MAPK) pathway is a pathway that carries extracellular growth signals to intracellular responses that govern cell survival, stress adaptation, proliferation, differentiation, and cell migration. The classical oncogenic MAPK cascade is comprised of activation of RAS, RAF, MEK, and ERK. Once activated by growth factor receptors, RAS triggers

the phosphorylation of RAF kinases leading to the phosphorylation of MEK1/2. MEK then turns on ERK1/2, enabling ERK to influence the activity of cytoplasmic substrates and nuclear transcription factors that are linked to the regulation of cell-cycle progression and proliferation. The sustained activation of the MAPK pathway is especially relevant in those cancers that carry mutations in KRAS, NRAS or BRAF, and the reactivation of the pathway is a critical mechanism of resistance to targeted therapy [27]. The MAPK family also contains the pathways of JNK and p38; these proteins regulate cellular stress responses and apoptosis as well. Many natural compounds have been found to have MAPK-modulatory activity. Structurally different molecules such as flavonoids, phenolic compounds, terpenoids, alkaloids, steroidal saponins and quinones were identified in a systematic review to influence MAPK signaling. These include oridonin, diosgenin, juglone, eupatilin, carvacrol and sophoridine. Other commonly studied phytochemicals like curcumin, resveratrol, quercetin and others can also impact ERK, JNK and p38 signaling. Importantly, phytochemicals don't necessarily block all MAPKs: inhibition of oncogenic ERK signaling could occur with activation of stress-associated JNK or p38 pathways which favor apoptosis. Such context-dependent regulation should, therefore, be taken into account when using the modulation of MAPKs as a context-dependent strategy for precision therapeutics [28-30].

3.3 JAK/STAT signaling

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway is crucial in the connection between extracellular cytokine signaling and transcription regulation. Upon binding to their receptor, cytokines or growth factors trigger the activation of receptor-associated JAK proteins which causes the phosphorylation of receptor sites allowing STAT proteins to bind. JAK-mediated phosphorylation leads to STAT dimerization and nuclear translocation and that STAT complexes activate genes that regulate proliferation, differentiation, immune responses, angiogenesis and survival [31]. Continued STAT3 and STAT5 activation have been strongly linked to malignancy. STAT3 can induce the expression of genes that favor proliferation and survival, and play a role in inflammation, angiogenesis, cancer stemness, immune suppression and therapy resistance. The pathway is thus associated with the malignant cells and signals derived from the cytokine milieu in the tumour microenvironment. Several natural products have been reported to block JAK/STAT signaling on multiple levels such as inhibition of the JAK phosphorylation, blockade of STAT dimerization, inhibition of nuclear translocation, or suppression of STAT-dependent transcription. The inhibition of constitutively activated STAT3 is particularly appealing, since there is the potential to simultaneously affect cancer cells and immunosuppressive elements in the TME. However, the majority of the evidence is still preclinical, and issues of bioavailability and under validation are still

significant hurdles [32].

3.4 NF- κ B-mediated inflammatory signaling

Major transcription factor that connects chronic inflammation to tumor development in humans is nuclear factor-kappa B (NF- κ B). Within the canonical pathway, inflammatory stimuli cause activation of the I κ B kinase (IKK) complex that leads to the phosphorylation and degradation of the inhibitory protein I κ B. This liberates the NF- κ B p65/p50 complex which is able to migrate to the nucleus and transcribe genes which control cell survival, proliferation, invasion, and angiogenesis, in addition to inflammation [33]. Ongoing activation of NF- κ B can lead to the upregulation of inflammatory cytokines and anti-apoptotic proteins/molecules that are involved in metastatic progression. Non-canonical NF- κ B signaling is also linked to the regulation of immune responses and found to be important for the survival of cancer cells and chemoresistance. A number of phytochemicals have been shown to possess NF- κ B-modulating activity, including curcumin, resveratrol, EGCG, quercetin, genistein, sulforaphane and various terpenoids. Mechanisms proposed involve the inhibition of IKK activation, the stabilization of I κ B, the inhibition of NF- κ B nuclear translocation and the suppression of downstream inflammatory mediators. In such ways these plant compounds can have multiple effects that inhibit the survival of tumors and the inflammation that promotes them. NF- κ B is directly involved in both functions and therefore is important for strategies combining direct targeting of the tumor with modulation of the tumor microenvironment [34-36].

3.5 Wnt/ β -catenin signaling

The canonical Wnt/ β -catenin pathway plays a crucial role in development, tissue homeostasis, stem-cell maintenance, and cancer. Without Wnt stimulation, cytoplasmic β -catenin is sequestered into a destruction complex in which APC, AXIN, GSK3 β , and CK1 interact with it, causing β -catenin to be phosphorylated, ubiquitinated, and degraded in the proteasome. Activated Frizzled receptors and LRP5/6 co-receptors lead to the disruption of destruction complex activity and accumulation of β -catenin, which then translocates to the nucleus, and associates with TCF/LEF transcription factors to activate genes associated with proliferation, survival, stemness, and invasion. In colorectal and some other cancers, alterations leading to aberrant activation is significant, such as loss of APC or mutations in the CTNNB1 gene. Dysregulated Wnt/ β -catenin signaling is also related to epithelial-mesenchymal transition, metastasis, cancer-stem-cell maintenance, immune evasion, recurrence, and drug resistance [37]. Several natural compounds have been studied as modulators of the Wnt/ β -catenin pathway, such as curcumin, resveratrol, EGCG, quercetin, genistein, sulforaphane, berberine, and different triterpenoids. Reported mechanisms encompassed include decreased β -catenin expression, degradation of β -catenin, decreased nuclear translocation, and inhibition of downstream

transcriptional programs. Recently, dozens of phytoconstituents were identified that act on this pathway, the most striking of which are phenolic compounds and triterpenoids. These collectively demonstrate how plant-derived bioactives can affect a number of interconnected oncogenic pathways. Precision oncology is not a one-size-fits-all approach but a way to target certain bioactives to tumors with a defined activation of a certain pathway, specific mutations, molecular signatures, or resistance mechanisms. Promising pathway level observations must be translated to clinically relevant phytochemical strategies, which will require the integration of genomic profiling, functional biomarkers, network pharmacology and pharmacokinetic optimization [38].

IV. REGULATION OF CANCER CELL FATE BY PLANT BIOACTIVES

The evasion of programmed cell death, unchecked cell division, survival of genotoxic insult and adaptation to metabolic and oxidative stress are essential to the advancement of cancer and resistance to therapy. Thus, restoration or redirection of programs of regulated cell death is a valuable anticancer strategy. Bioactives derived from plants can have an impact on multiple, interconnected pathways that are involved in the fate of cancer cells, such as apoptosis, cell-cycle progression, autophagy, ferroptosis, pyroptosis, cellular redox balance, and DNA-damage responses. Importantly, such mechanisms are not independent but can be triggered in combination: Oxidative stress may trigger mitochondrial apoptosis or ferroptosis; DNA damage may lead to cell-cycle checkpoints; autophagy can either protect or eliminate malignant cells. This kind of mechanistically diverse potency offers a foundation for the use of plant molecules to target heterogeneous and drug-resistant cancer cells in a molecular-specific manner [39].

4.1 Induction of intrinsic and extrinsic apoptosis

Apoptosis is a very controlled process of cell death that removes damaged and possibly cancerous cells, but does not cause large-scale inflammatory damage. A variety of mechanisms are used to evade apoptosis by cancer cells, including increased expression of anti-apoptotic proteins, defects in tumor suppressors, and changes to death-receptor pathways. Members of the BCL-2 family regulate the intrinsic or mitochondrial pathway. Under cellular stress, activation of pro-apoptotic proteins like BAX and BAK leads to permeabilization of the mitochondrial outer-membrane and release of cytochrome-c [40]. The cytochrome c is then involved in the apoptosome complex with APAF-1 and procaspase-9, which activates caspase-9 and then executioner caspases-3 and -7. The extrinsic pathway, on the other hand, starts with the activation of death receptors like Fas/CD95, TNFR and TRAIL receptors, the activation of which triggers the formation of death inducing signaling complexes and the activation of caspase-8 or -10. The plant-derived compounds such as curcumin, resveratrol,

quercetin, EGCG, berberine, apigenin, luteolin, withaferin A and thymoquinone have been reported to cause depolarization of the mitochondrial membrane, release of cytochrome-c, activation of caspases, inhibition of anti-apoptotic proteins and shift the BAX (Apaf-1)/BCL-2 balance towards apoptosis. A number of phytochemicals can also enhance the signaling of death-receptors, which activates both arms of apoptosis. Generation of ROS is often an upstream mediator between phytochemical-induced oxidative stress and mitochondrial dysfunction and apoptosis [41].

4.2 Cell-cycle arrest

Dysregulated cell-cycle is another hallmark of Cancer. The G1, S, G2 and M phases are normally tightly regulated by cyclins, cyclin-dependent kinases (CDKs), CDK inhibitors, and checkpoint proteins. Often this regulatory system is lost, allowing cells with abnormal genes to grow. Bioactives from plants can re-establish the checkpoint control by modifying cyclins and CDKs. Among others, curcumin, quercetin, resveratrol, genistein, EGCG, berberine, and apigenin have shown to arrest tumor cells in G0/G1, S, or G2/M phase depending on the compound and tumor model. An increase in the expression of CDK inhibitors, like p21^{Cip1} and p27^{Kip1}, along with a reduction of the activity of cyclins (like cyclin D1, E, B1) or CDKs (like CDK2, CDK4 or CDK6), can block the passage through critical checkpoints. If the tumor contains a functional TP53, then activation of p53 will likely further reinforce cell-cycle arrest after the phytochemical induced stress has occurred. Continuous arrest can lead to senescence or may eventually lead to apoptosis if the injury cannot be repaired [42].

4.3 Autophagy modulation

The process of autophagy is a lysosome-dependent recycling process that degrades damaged proteins, dysfunctional organelles and intracellular macromolecules. It plays a very context-specific role in cancer. In early tumorigenesis, autophagy may function as a mechanism to counteract malignant transformation and preserve cellular homeostasis, while during later stages of tumorigenesis, cells might utilize autophagy to cope with hypoxia, nutrient deprivation, chemotherapy, and other stresses. The autophagic flux can be altered by regulators including, but not limited to, AMPK, mTOR, Beclin-1, ATG proteins, and LC3 processing, which are altered by phytochemicals such as curcumin, resveratrol, berberine, quercetin, EGCG, celastrol, and various terpenoids. In certain circumstances, the improved autophagy goes so far as to kill cancer cells. In others, the inhibition of protective autophagy makes cancer cells more vulnerable to apoptosis and/or chemotherapies. This duality is significant for therapy. The increased LC3-II or autophagosome formation was not sufficient to show that the death was autophagy-dependent, because accumulation can also occur if there is impaired clearance of autophagosomes. Thus, future precision approaches need to differentiate the cytoprotective autophagy from

the cytotoxic autophagy and decide if the process should be stimulated or inhibited in the context of phytochemical therapy [43-45].

4.4 Ferroptosis induction

Ferroptosis is a regulated cell death that involves the uncontrolled phospholipid peroxidation in an iron-dependent manner without the activation of caspases. It has a special significance with tumors that are resistant to conventional apoptosis. A primary protective pathway is related to the cystine/glutamate antiporter system Xc⁻, which is composed of SLC7A11 that allows for the uptake of cystine for glutathione synthesis. Glutathione is a cofactor of glutathione peroxidase-4 (GPX4) which is involved in detoxification of lipid hydroperoxides. Thus, disruption of the SLC7A11–GSH–GPX4 axis, accumulation of redox-active iron and increased lipid peroxidation may drive ferroptotic death. Multiple natural bioactives have been shown to promote ferroptosis by inhibiting SLC7A11, depleting glutathione, affecting iron homeostasis, affecting mitochondrial function, or causing lipid ROS accumulation. Recent experimental studies of plant-derived bioactives have directly linked inhibition of the SLC7A11 – GSH – GPX4 axis to colorectal-cancer ferroptosis. The identification of ferroptosis-specific targets may prove especially useful in therapy-resistant persister cells, characteristic iron and lipid metabolic-dependent tumors and in apoptosis-resistant tumors and could represent a new pathway to precision phytotherapy. Regulated cell death: pyroptosis and beyond.4.5 Pyroptosis and other emerging varieties of regulated cell death [46].

4.5 Pyroptosis and other emerging forms of regulated cell death

Pyroptosis is a regulated lytic and inflammatory cell death that is primarily driven by the products of the pyroptotic proteins. Canonical inflammasome signaling triggers the activation of caspase-1, which can cleave GSDMD, and caspase-3-mediated cleavage of GSDME is an important pathway that can turn apoptotic stimuli into pyroptotic death. Activated gasdermin N-terminal fragments create pores in the plasma membrane leading to cellular swelling, membrane rupture and release of inflammatory mediators and danger-associated molecules. Pyroptosis of cancer cells has been shown to be induced by plant-derivatives and the effects are being examined. Natural products can modulate inflammasomes/caspases/GSDMD/GSDME and thus make apoptosis resistant cells inflammatory. Pyroptosis, however, is a two-edged sword; on one hand, acute pyroptotic destruction has a positive effect on enhancing antitumor immunity, while on the other hand, excessive inflammation can promote tumor progression under specific conditions. Plant bioactives can also modulate new death processes like necroptosis, cuproptosis, parthanatos and immunogenic cell death, further extending their ability to overcome resistance to apoptosis. A number of classes of natural products have already been demonstrated to effect several different

forms of regulated cell death, especially the sesquiterpene lactones [47].

4.6 Oxidative stress and redox homeostasis

The high levels of basal reactive oxygen species (ROS) in cancer cells are due to high metabolic activity, mitochondrial dysfunction, oncogenic signaling and rapid proliferation. Moderate concentrations of ROS can stimulate malignant signaling, while high concentrations of oxidative stress can cause damage to proteins, lipids, mitochondria and DNA, and initiate cell death. It is therefore no surprise that cancer cells rely heavily on their antioxidant defenses to keep ROS levels low, below the lethal level. Plant bioactives exhibit context-dependent antioxidant and pro-oxidant effect. They are able to induce ROS levels by augmenting them above the threshold for causing cancer cell damage, resulting in mitochondrial dysfunction, lipid peroxidation, DNA damage, apoptosis, or ferroptosis. In contrast, antioxidants mediated by NRF2 in normal tissue may serve to protect normal tissue. This differential redox modulation provides the possibility to take advantage of the increased oxidative sensitivity of the cancer cells and to minimize damage to the cells as a result of the treatment [48].

4.7 DNA damage response and repair mechanisms

The recognition of DNA damage, activation of DNA damage checkpoints, repair of damaged DNA, and removal of irreparable cells must be coupled together to maintain genomic integrity. Such defects are commonly found in cancer cells and these cells depend on remaining mechanisms for repair to survive. Therefore, disrupting the repair of DNA may make the tumours more vulnerable. Plant-based compounds can cause DNA strand breaks, replication stress, oxidative lesions on DNA, and disrupt the function of topoisomerase enzymes, and some disrupt proteins that repair DNA. For instance, flavonoids can be catalytic inhibitors of topoisomerase I or II, can stabilize cleavage complexes, or can interact with DNA. Other phytochemicals, such as polyphenols, organosulfur compounds, indoles, and others, can also modulate or alter enzymes related to chromatin regulation and repair, making malignant cells more susceptible to chemotherapy or radiation. Therefore, plant bioactives have a much more complex role in cell fate modulation than merely causing cell death. Their ability to trigger apoptosis, cell-cycle checkpoints, autophagy, ferroptosis, pyroptosis, redox stress and DNA-damage responses offers several opportunities to overcome tumor adaptation and resistance. What is most important is when these mechanisms can be coupled with specific vulnerabilities such as inducing ferroptosis in GPX4-dependent cancer cells, exploiting DNA-repair mutants, or triggering alternative cell death programs in apoptosis-resistant tumors in precision oncology. The application of such biomarkers would enable the use of some of these broadly acting phytochemicals to become components of precision anticancer treatment, based on their mechanism of action [49-51].

V. PLANT-DERIVED BIOACTIVES AS MODULATORS OF THE TUMOR MICROENVIRONMENT

The tumor microenvironment (TME) is currently understood as an active player in the initiation, progression, metastasis, immune escape and therapeutic resistance of cancer, and not just an architectural niche that surrounds cancer cells. It features cancer-associated fibroblasts (CAFs), endothelial cells, tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), lymphocytes, regulatory T cells (Tregs), natural killer (NK) cells, extracellular-matrix components, soluble cytokines, chemokines, metabolites and growth factors. All these elements create a cross talk between the malignant cells and have a significant impact on treatment response. Bioactives derived from plants such as curcumin, resveratrol, epigallocatechin-3-gallate (EGCG), quercetin, berberine, genistein, apigenin, silibinin and several terpenoids can simultaneously modulate several components of the TME, which represents an appealing approach for interfering with tumor supporting cellular networks. Their ability to promote infiltration of immune cells, reprogramming of suppressive immune cells and modification of tumor immune microenvironmental cytokine networks has been highlighted in recent reports [52].

5.1 Tumor microenvironment as a therapeutic ecosystem

TME as a dynamic therapeutic ecosystem where tumor cells constantly interact with stromal and immune cells which in turn communicate with each other via cytokines/chemokines, extracellular vesicles, metabolites and direct cell-cell communication. This ecosystem is further molded by hypoxia, nutrient deprivation, remodeling of the extracellular matrix, chronic inflammation and metabolic competition. These conditions can act together to enable malignant cells to escape from the effects of chemotherapy, radiotherapy, targeted agents and antitumor immunity. Phytochemicals offer a significant benefit because they have the ability to modulate multiple targets in the inflammatory microenvironment (TME) of cancer cells instead of binding to one target in cancer cells. Some compounds like curcumin, EGCG, resveratrol, and silibinin may affect more than one compartment of the TME, such as stromal fibroblasts, the macrophages, MDSCs, and the endothelial components and inflammatory mediators. Plant bioactives simultaneously target inflammation (the process that promotes tumor growth), immune suppression, tumor-induced angiogenesis, and stromal support, potentially compromising the ecological factors that enable tumor persistence. This is especially true with respect to precision oncology, as the character of the TME varies considerably between the different types of cancer and even between patients diagnosed with the same cancer. Molecular and spatial characterization of immune

and stromal populations might then reveal TME phenotypes which are specifically sensitive to certain natural compounds [53-55].

5.2 Cancer-associated fibroblasts

In many solid tumors, CAFs are one of the most prevalent stromal cell types. In contrast to quiescent fibroblasts, CAFs exhibit activated phenotypes, and synthesize extracellular-matrix proteins, growth factors, cytokines and chemokines that stimulate tumor-cell proliferation, invasion, angiogenesis, and resistance to therapy. Single-cell sequencing and spatial profiling have demonstrated significant heterogeneity of CAFs, in which different subpopulations have a specific inflammatory, matrix-remodeling or immunoregulatory function. CAFs can produce a tight extracellular matrix which physically impedes drug penetration and immune-cell infiltration. They also generate mediators including TGF- β , IL-6, CXCL12, VEGF and matrix metalloproteinases that promote EMT, metastasis, stemness and immune suppression. Tumor-supportive phenotype may be disrupted by compounds found in plants. The efficacy of curcumin, resveratrol, EGCG, genistein and silibinin in inhibiting activation of fibroblasts, profibrotic signaling pathways, inflammatory mediator secretion and tumor-fibroblast communication has been studied. In the context of this CAF reprogramming via phytochemicals, extracellular-matrix deposition may be decreased and penetration of cytotoxic or immune therapies may be improved. Since CAFs may be either tumor promoting or tumor restraining in context, it is not likely that an indiscriminate depletion of CAFs is optimal. Instead of targeting specific pathogenic CAF subtypes, precision approaches should focus on other pathogenic CAF subtypes [56].

5.3 Tumor-associated macrophages

Macrophages are highly plastic cells that can assume a variety of functional phenotypes in response to environmental signals. In tumor environment, TAMs are frequently found to express many of the hallmarks of an M2 immunosuppressive phenotype, but more recent studies have shown that macrophage phenotypes exist on a continuum of function rather than a dichotomy of M1 vs M2. TAMs produce growth and immunoregulatory factors such as IL-10, TGF- β , VEGF, matrix metalloproteinases, and others, which promote tumour progression. They promote the development of angiogenesis, invasion, metastasis, and cancer-cell survival and resistance, as well as the reduction of cytotoxic T-cell activity. TAMs also cooperate with a network of immunosuppressive cells such as CAFs, MDSCs and Tregs. Bioactives found in plants can influence TAMs by blocking their recruitment, inhibiting tumor promoting macrophage polarization, and re-polarizing them towards a more anti-tumour functional state. This activity has been proven experimentally with natural products belonging to the class of flavonoids, alkaloids, saponins, lactones and polysaccharide. Macrophage reprogramming and inhibition of tumor-

promoting inflammatory signaling have been linked to curcumin, resveratrol, apigenin, vitexin, emodin, and other natural compounds. The reprogramming of TAMs rather than removal is particularly attractive as this could lead to a transformation of an abundant immunosuppressive population into a component of antitumor immunity [57-60].

5.4 Myeloid-derived suppressor cells

MDSCs are a heterogeneous population of immature myeloid cells that are a potent source of tumor-associated immune suppression in many malignancies. Generally, they can be separated into polymorphonuclear MDSCs (PMN-MDSCs) and monocytic MDSCs (M-MDSCs). MDSCs suppress the function of T-cells and NK-cells through several mechanisms, such as: arginase-1, inducible nitric oxide synthase, reactive oxygen species, immunosuppressive cytokines, amino-acid depletion, and immune-checkpoint regulation [61]. Immune dysfunction, tumour progression, metastasis and diminished responses to immunotherapy are linked with high MDSC accumulation. Thus, strategies that inhibit the development of MDSC, prevent recruitment, promote their differentiation or block their suppressive function could ultimately restore antitumor immunity. Due to their multitarget activities, plant-based natural products have come under the spotlight as possible MDSCs modulators. Other phytochemicals including polyphenols, terpenoids, alkaloids, polysaccharides, and others may disrupt pathways involved in the expansion and immunosuppressive function of MDSCs. Reducing MDSC-mediated suppression might be particularly useful when there is poor T-cell infiltration combined with strong myeloid immunosuppression in immunologically "cold" tumors in order to improve the efficacy of checkpoint blockade. The synergistic therapeutic potential of using selected phytochemicals in combination with immunotherapy is thus a promising, yet largely preclinical approach [60-62].

5.5 Tumor-infiltrating lymphocytes

Tumor-infiltrating lymphocytes (TILs) serve as an important indicator of the immune response of the host to cancer. CD8⁺ Cytotoxic T lymphocytes can detect tumor-associated antigens and directly lyse tumor cells by either activation of death receptors or by perforin/granzyme-mediated cytotoxicity [63]. In addition, CD4⁺ helper T cells may orchestrate the antitumor immune responses by providing assistance to other immune cells and also to the cytotoxic lymphocytes. Dysfunctional or exhausted T-cell states can be induced by chronic antigen exposure, immunosuppressive cytokines, metabolic deprivation, checkpoint signaling and suppressive myeloid cells. Therefore, to increase the numbers of functional CD8⁺ T cells in the tumor is a major goal of modern cancer immunotherapy. Natural products can improve the antitumor activity of T cells via various mechanisms that regulate T-cell receptor signaling, costimulatory mechanisms, inflammatory cytokines, immune checkpoints, and tumor-cell immunogenicity.

Recent reviews have shown that phytochemicals can enhance infiltration of effector cells and may help to restore antitumor immune surveillance in the TME. Berberine and EGCG, for instance, have also been studied for the ability to modulate PD-L1-associated immune suppression, which could enhance the function of the cytotoxic T-cells in preclinical studies [64-66].

5.6 Regulatory T Cells and NK Cells

CD4, CD25 and FOXP3 are typically expressed by Tregs, which are physiological regulators of immune tolerance, but can be harmful in cancer by inhibiting antitumoral immune responses. Increased activity of Tregs within the tumor can down-regulate the function of CTLs, NK cells and APCs by producing inhibitory cytokines such as IL-10 and TGF- β . There is a correlation between a low effector T-cell to Treg ratio and poor immune status in several malignancies. A number of phytochemicals have been studied for their capacity to either decrease the number of Tregs or impair their function to restore effector immunity. There are natural compounds that may affect pathways related to the differentiation of Tregs and immune tolerance, but these effects may be extremely dose- and context-dependent. On the contrary, NK cells are innate cytotoxic lymphocytes that recognize and eliminate antigen unsensitized transformed cells. Antitumor activity is through perforin/granzyme release, death-receptor signaling, production of cytokines, and antibody-

dependent cellular cytotoxicity [67]. Suppressive cytokines, checkpoint molecules and metabolic stress are commonly used to mediate tumor-mediated impairment of NK-cell trafficking and cytotoxicity. There are natural compounds that have been shown to be capable of stimulating NK-cell proliferation, activation, production of cytokines or killing in experimental models, which can be classified as polysaccharides, alkaloids, terpenoids, saponins, phenolics and quinones. Therefore, the dual effect of plant-derived bioactives to simultaneously inhibit Treg/MDSC/TAM-mediated suppression and increase the activity of CD8⁺ T-cells and NK-cells is one of the most promising immunological effects. In summary, plant-based products can modify the TME on various fronts in addition to direct cytotoxicity against malignant cells. They can be used to reprogram CAFs and TAMs, inhibit MDSCs and Tregs, and restore functions of cytotoxic T cells and NK cells, and may be able to shift an immunosuppressive and treatment-resistant microenvironment to one that is more conducive to anti-tumor immunity. But these effects are still largely supported by preclinical studies. To apply these phytochemicals to specific TMEs, and to combine them with existing anticancer therapies, rigorous pharmacokinetic studies, standardisation of formulations, immune biomarkers, spatial profiling, and patient stratification will be required [68-70].

Table 2: Modulation of the tumor microenvironment by plant-derived bioactives and precision-oncology relevance

TME component	Tumor-promoting role	Representative plant bioactives	Major modulatory effects	Precision-oncology relevance
Cancer-associated fibroblasts (CAFs)	ECM deposition, tumor growth, invasion, drug resistance	Curcumin, resveratrol, EGCG, genistein	Suppression of fibroblast activation, TGF- β signaling and ECM remodeling	Targeting CAF-rich or fibrotic tumors
Tumor-associated macrophages (TAMs)	Immunosuppression, angiogenesis, metastasis	Curcumin, resveratrol, apigenin, emodin	Reduction of M2-like phenotype and promotion of antitumor macrophage activity	Useful in macrophage-dominant tumors
Myeloid-derived suppressor cells (MDSCs)	Suppression of T-cell and NK-cell responses	Curcumin, EGCG, resveratrol, berberine	Reduction of MDSC accumulation and suppressive activity	May improve response in immunologically cold tumors
Regulatory T cells (Tregs)	Suppression of antitumor immunity	Curcumin, resveratrol, EGCG	Reduction of Treg recruitment and immunosuppressive signaling	Potential adjunct to immune-checkpoint therapy
CD8 ⁺ tumor-infiltrating lymphocytes	Direct tumor-cell killing	Berberine, EGCG, curcumin	Enhancement of T-cell infiltration and cytotoxic activity	May increase responsiveness to immunotherapy
Natural killer cells	Recognition and destruction of malignant cells	Polysaccharides, saponins, alkaloids, flavonoids	Enhancement of NK-cell activation and cytotoxicity	Useful in tumors with impaired innate immunity
Tumor vasculature	Nutrient supply and metastatic dissemination	EGCG, curcumin, resveratrol, genistein	Suppression of VEGF-mediated angiogenesis	Relevant to highly vascular tumors

Hypoxic microenvironment	Promotes resistance, metastasis and stemness	Resveratrol, curcumin, quercetin	Modulation of HIF-1α and hypoxia-responsive signaling	Potential application in hypoxic solid tumors
Extracellular matrix	Promotes invasion and prevents drug penetration	Curcumin, EGCG, ursolic acid	Reduction of MMP activity and matrix remodeling	May enhance drug delivery and immune infiltration
Pro-inflammatory cytokines	Sustain tumor-promoting inflammation	Curcumin, quercetin, resveratrol	Reduction of IL-6, TNF-α and NF-κB-associated signaling	Useful for inflammation-driven cancers
Immune checkpoints	Promote T-cell exhaustion and immune escape	Berberine, EGCG, curcumin	Potential modulation of PD-1/PD-L1-associated signaling	Potential combination with checkpoint inhibitors
Cancer stem-cell niche	Supports recurrence and resistance	Sulforaphane, curcumin, resveratrol	Suppression of stemness-associated signaling	Targeting resistant and recurrent tumor populations

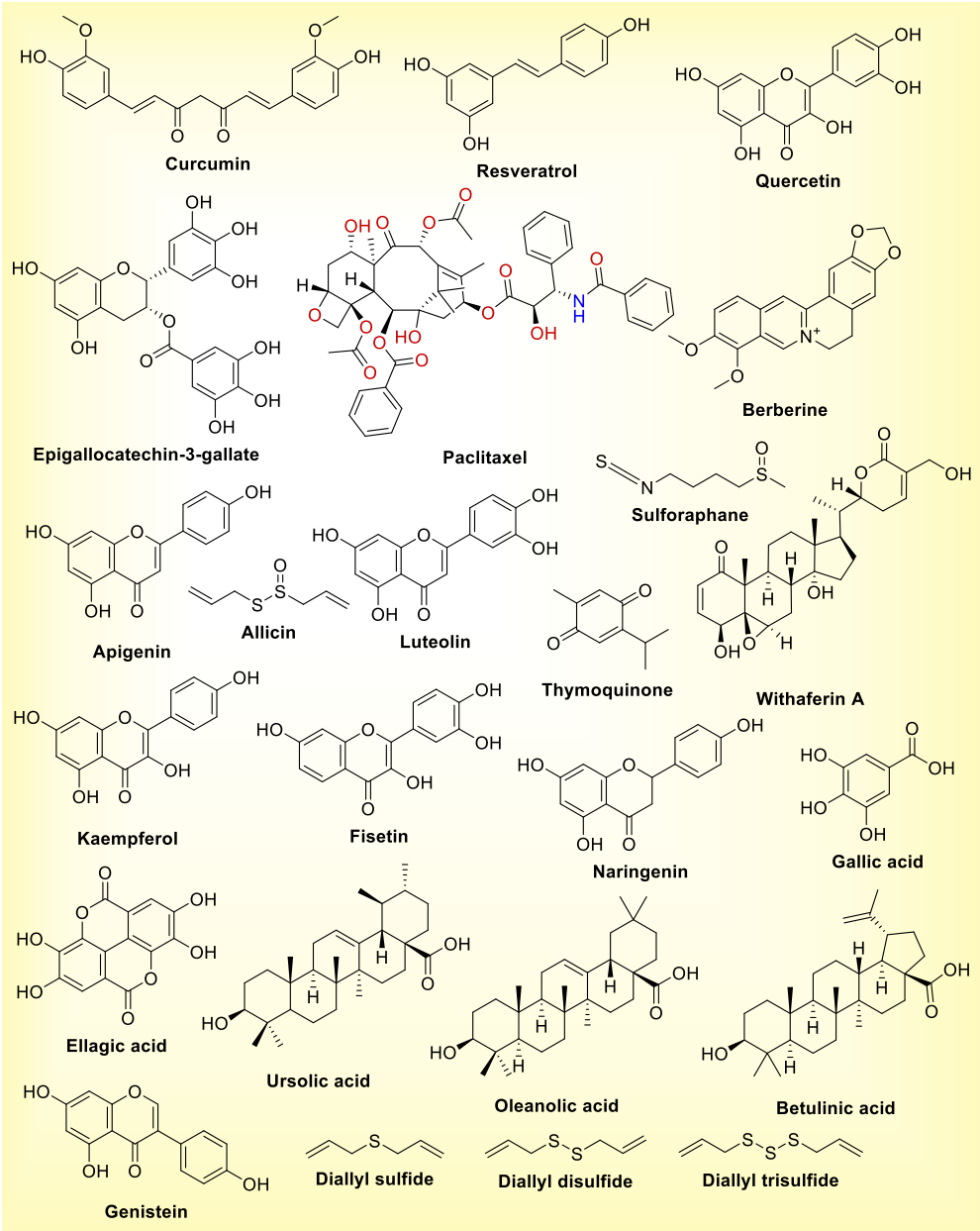


Fig.1: Plant-derived bioactives in the cancer treatment

VI. FUTURE PERSPECTIVES

Recurring elementary claims about plant anticancer properties must be translated into biomarker-based, mechanism-specific and clinically tested applications in order to be adopted in precision oncology. One of the key challenges is to identify molecular signatures that indicate response to particular phytochemicals. Genomics, transcriptomics, proteomics, metabolomics, epigenomics, and spatial profiling integration could be used to select plant-derived compounds based on the driver mutations, pathway dependency, metabolic vulnerabilities, and characteristics of the tumor microenvironment. In this context, artificial intelligence, machine learning, network pharmacology and systems biology will help speed up this shift by uncovering bioactive–target networks, forecasting synergistic combinations of drugs and prioritizing compounds with preferred pharmacological properties. These methods might be especially useful for multitarget phytochemicals that do not have a single molecular interaction to explain their biological activity. The use of patient-derived organoids, tumour-on-chip platforms and ex vivo models may also enable a pre-clinical screening of phytochemicals and rational combinations prior to clinical application. The other important is the development of more sophisticated delivery systems to address the poor solubility, rapid metabolism, limited bioavailability, and nonspecific tissue distribution. Nanoparticles, liposomes, nanostructured lipid carriers, exosomes and stimulus-responsive systems can enhance targeted delivery of nanoparticles to the tumor, while minimizing their systemic toxicity. Chemotherapy, targeted therapy, radiotherapy, and immune-checkpoint inhibitors should also be systematically evaluated in combination with rational approaches. Notwithstanding the significant preclinical evidence, the clinical translation is limited due to the source variability of botanicals, lack of standardisation, low bioavailability, inconsistent dosages, herb–drug interactions and lack of well designed clinical trials. Standardised formulations, validated biomarkers, pharmacokinetic–pharmacodynamic relationships, clinically relevant exposure levels and well-designed randomized trials should be studied in the future. Finally, plant derived bioactives will most likely make a contribution toward oncology not as alternatives, but as molecularly characterized and biomarker selected therapeutic agents or adjuvants, as part of personalized treatment strategies. A strategy like this may make precision phytotherapy as a scientifically sound part of cancer care in the future.

VII. CONCLUSION

Plant-derived bioactives are an important and chemically rich source for the development of next generation anti-cancer strategies. They are especially significant to the dynamic precision oncology as they can

modulate several oncogenic pathways, regulate the fate of cancer cells, affect oxidative and metabolic homeostasis, and shape the tumor microenvironment. Many phytochemicals show a polypharmacological activity, which allows to interact with interconnected molecular networks involved in multiple processes that promote tumor growth, metastasis, evasion and therapeutic resistance. A range of compounds such as curcumin, resveratrol, quercetin, epigallocatechin-3-gallate, berberine, sulforaphane, withaferin A, and thymoquinone have shown to have potential anti-cancer properties in a variety of preclinical cancer models. But, their clinical potential is frequently undermined due to inadequate solubility, bioavailability, metabolic instability, interindividual pharmacokinetics, lack of standardization, and lack of clinical validation. These restrictions emphasize the need for better formulation, delivery systems, patient stratification based on biomarkers, and well-designed translation studies. Combination of Multi-Omics technologies, Artificial Intelligence, Network Pharmacology, Patient-derived models, and Advanced nanocarrier system could significantly enhance the identification of responsive tumor subtypes and optimization of phytochemical-based interventions. Rational combinations of chemotherapy, radiotherapy, targeted therapy and immunotherapy have the potential to further improve efficacy and overcome treatment resistance as well. In summary, the potential of plant-derived bioactives in oncology is their evolution from naturally sourced multi-targeted compounds to novel mechanistic pharmacologic entities and clinically validated, biomarker-directed therapeutics and/or adjuvants. This kind of integration could offer a scientifically sound basis for a personalized approach to cancer treatment that includes precision phytotherapy.

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