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Phytomedicines: far Beyond Cytotoxicity in Cancer therapy. Sole Multitarget-Polypharmacology, Chemopreventive and Safety Profiles: Combinatorial Synergy, Chemosensitization and Mitigation of Chemotherapy Adverse-Reactions.

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Abstract

Phytomedicines (PMs) are bioactive phytochemicals with established health benefits. Because of their unique structure, they can bind to and modulate the activity of cellular bioactive proteins, thereby conferring numerous, mostly favorable, pharmacological effects; including anti-inflammatory, antioxidative, antidiabetic, immunostimulant, and cellular protective effects. Such multitarget-"polypharmacology", along with well-tolerability of PMs, prompted their use as sole and/or combinatorial drugs for management of "complex" and refractory "drug-resistant" diseases like cancer. Common PMs include curcumin, resveratrol, EGCG, genistein, gingerol, quercetin, lycopene, and baicalein.

Unlike chemotherapeutic drugs, PMs have been a mainstay in protection against cancer (chemoprevention) by interfering with all 3-stages of carcinogenesis; namely: initiation, promotion, or progression. They also enhance host's immune response against eruption of carcinogenesis. When concurrently used with chemotherapy, they are intended to accentuate their cytotoxic effects (synergy), reduce their doses, minimize their noxious adverse-reactions or overcome resistance to their anticancer effects (chemoresistance). Thus, chemosensitization by PMs is meant to abate, bypass, or silence the molecular machinery underlying chemoresistance, which include drug-transporters, cell cycle effectors, signaling cascades and nuclear transcription factors. In this vein, all cellular and molecular rationale and underpinnings are described and their therapeutic relevance is highlighted. The advanced recent technology (as with Omics and Nanotechnology), has helped improve PM-kinetic profiles, bioavailability, and rationalized their therapeutic utility and networking. Therefore, PMs are now gaining more ground from the bench-side to the clinic".

Keywords: *Cancer treatment; Phytomedicine; Polypharmacology; Chemotherapy; Drug Safety; Chemoprevention; Synergistic combinations; Resistance to chemotherapy; Adverse drug reactions; Chemosensitization*

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Introduction

Phytomedicines (PMs) are bioactive phytochemicals (of plant origin) with established profiles of beneficial health effects, pharmacological activity, and recognized safety spectrum [1,2]. Many such chemicals have been sold originally for nutritional and supplemental OTC use; thereby also belonging to the broader-term "nutraceuticals". PMs often have such a unique chemical structures with many key functional groups (e.g polyphenols, thiol-compounds) that mimic (and complement) those of the mammalian cell aminoacids, thereby permitting them to easily bind to cellular bioactive-proteins, such as enzymes, adaptors and receptors and modulate their activity [3,4]. Not surprisingly, PMs turned out to exhibit a broad-range of, mostly favorable, pharmacological activities including anti-inflammatory, antioxidative, antidiabetic, and cellular protective effects. Such multifaceted pharmacological effects, along with well-tolerability, spur their application as sole and/or adjunct drugs for management of diseases, especially the "complex" and "refractory" ones like cancer, heart-disease, and neurological diseases, which often mandate the use of multiple-drug regimens, rather than monotherapy, to accentuate the therapeutic efficacy and clinical outcomes [5]. With the advent of recent Omics and nanotechnology studies, existing obstacles against comprehensive clinical use of some PMs, such as limited bioavailability and absorption, have been reasonably defused [6].

Cancer, after cardiovascular disease (CVD), ranks as the second leading cause of death allover the globe. However, unlike CVD, cancer management poses more challenging, cumbersome and grieving aspects of throughout its therapy. Thus, conventional chemotherapies evoke widespread and life-threatening systemic toxicity and adverse reactions, which have mandated prohibition of their long-term use. Furthermore, resistance to chemotherapy, tumor recurrence and remote-invasion (metastasis) are coherent criteria that entail vicious and pain-stacking sequelae to cancer [7,8]. Therefore, there has been a tremendous and persisting need to identify superior anticancer therapies that can be either preventive, or rather more specific and safer than chemotherapy. In developing countries, approximately 35% of the prescribed drugs are derived from natural products, and over 60% of the anticancer drugs in clinical use originated from natural products [9-11], including plants, marine organisms, and microbes. Many investigations are being carried out worldwide to discover naturally occurring compounds that can suppress or prevent the progress of carcinogenesis, or alternatively improve their quality and efficacy against cancer, and limit their adverse reactions. Whereas some natural compounds displayed superior cytotoxic effects but limited molecular targets and safety/specificity (like vinblastine and taxel), others (PMs) showed rather multitarget molecular effects and bigger safety profiles, as demonstrated by "polypharmacology" studies.

1. Polypharmacology of PMs: Molecular-multitargeting and its significance

Cancer is a complex, devastating disease that erupts and thrives via disruption of host cellular and biological targets, thereby mandating meticulous and extensive therapeutic manipulations [12,13]. Accordingly, finding drugs that act in multiple pathways, or electing a promising drug-combination represents a major challenge, because signaling networks of human cells are often inconsistently altered in different cancers [14]. Tumors frequently develop resistance to single-target drugs, as mutations in that target protein may easily render the tumor refractory to cytotoxicity of this drug.

In treating such complex systemic diseases, as with cancer, single-target drugs (as with chemotherapy) were documented to be inferior to "the versatile multiple-target regimens" that will likely evoke maximal efficacy and minimal toxicity [15-18]. As a result, a new concept is emerging that is designated "polypharmacology", which focuses on drugs attacking multiple instead of single targets to maximally restore disease-associated pathways to a near-physiologic pace and manner [19,20]. This approach ultimately offers the potential for higher efficacy and may limit drawbacks generally arising from the chemotherapy multiple drugs, such as tumor resistance and adverse reactions.

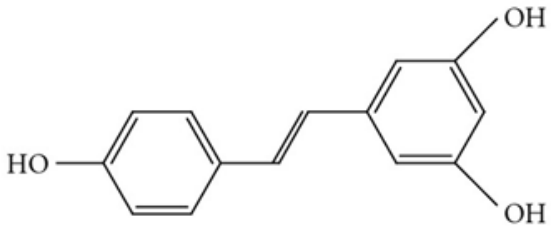
By contrast, drugs addressing multiple targets are not compromised in their activity, if mutations in one of the targets appear. Most natural products exert their bioactivity by attacking multiple rather than single targets [21]. Not surprisingly, therefore, PMs invoke a

variety of favorable responses with host cells, such as anti-inflammatory, antioxidative, antiproliferative, immunostimulant, cellular and neuroprotective effects.

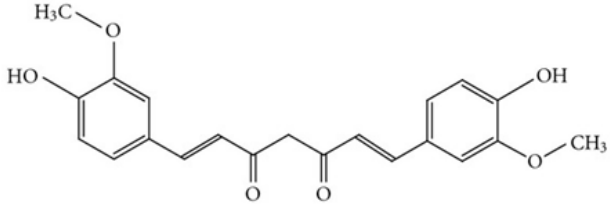
At the cellular and molecular level, PMs can trigger a plethora of scenarios and events to invoke its beneficial effects. For instance: upon entering cells, these phytochemicals can directly capture free radicals and can also generate "chemical or electrophilic-stress signals" that recruit receptors/enzymes/adaptors related to various cellular signaling pathways. One such cascade is the activation of the nuclear factor erythroid-2 (NF-E2)-related factor-2 (Nrf2)-Kelch-like ECH associated protein 1 (Keap1) complex. Recruitment of the *Nrf2-Keap1* complex induces many cellular defense mechanisms; including phase-II detoxifying enzymes, phase-III transporters, anti-oxidative stress proteins that protect normal cells from reactive oxygen and nitrogen species (RONS) and their serial-reactive metabolites of carcinogenic species [22,23].

By contrast, after cancer had developed, PMs (at tumor microenvironment) can abate oxidative stress, or additionally trigger pro-apoptotic and anti-proliferative effects, alter cell-cycle and growth-factor signaling, and perturb tumor gene transcription [24]. Among enzyme pathways that are downregulated in cancer cells by PMs are the mitotic/pro-inflammatory mitogen-activated protein kinase isoforms (MAPKs) and their downstream (dependent) signaling cascades. Likewise, Big mitogen-activated protein kinase-1 (BMK-1), also known as Erk5 has been shown to be activated various extracellular stimuli such as epidermal growth factor, IL-6, and hypoxia. As a member of MAPK family, BMK-1 has also been implicated in stress-cellular events coherent with cancer, like proliferation, migration, and apoptosis [25].

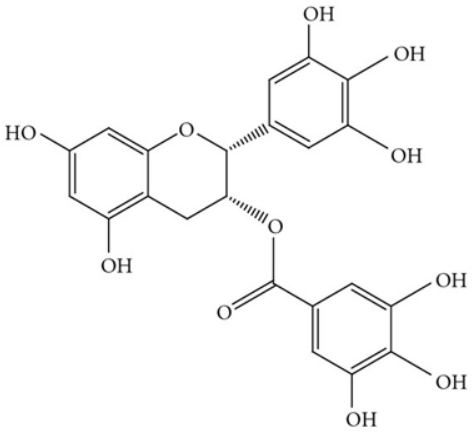
The signal transducer and activator of transcription-3 (STAT3) is a transcription factor constituent of the STAT family, known primary antecedents in carcinogenesis and cancer growth, whose activity was also proven to be regulated by numerous PMs. Thus, curcumin, resveratrol, cucurbitacin, flavopiridol, Epigallocatechin gallate (EGCG), and genistein (Figure 1) have demonstrated anticancer effects by inhibiting the growth of cancer cell through blocking of STAT3 activation [26-29].



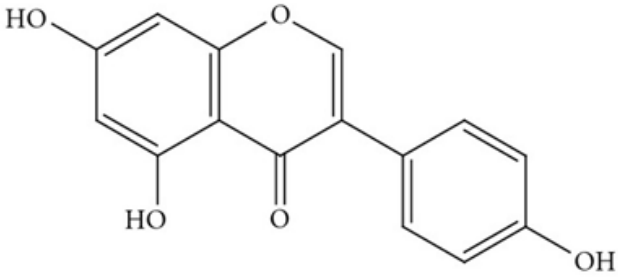
1. Resveratrol



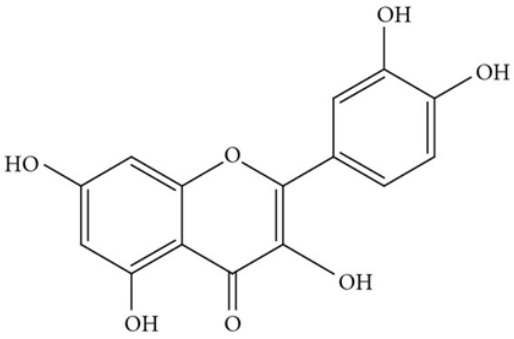
2. Curcumin



3. EGCG



4. Genistein



5. Quercetin

Figure 1: *Chemical structures of five, commonly used, phytomedicines.*

Before neoplastic transformation (cancer cell development) occurs, the PM-driven cellular protective mechanisms unequivocally help in blocking the initiation of carcinogenesis and, therefore, contribute to "chemoprevention", a concept that was originally pioneered and introduced by Wattenberg (1966) [30].

2. Chemoprevention by PMs: Significance and molecular mechanisms.

In virtue of constraints in early detection and effective treatment of cancer, preventive interventions have caught growing attention and accumulated paramount research efforts. Several such approaches and practice have shown promising outcomes in epidemiological and clinical trials allover the earth [31,32]. Chemoprevention is one of the strategies by which we can block or delay the malignant response to carcinogens or even prevent carcinogenesis via the use of natural (PMs) or synthetic chemical agents.

Exposure of normal cells to environmental carcinogens results in a series of genetic mutations. Induction of at least 1-2 mutations, in key-genes involved in cell-division such as proto-oncogenes and/or tumor suppressor genes, triggers tumor development. Activation of proto-oncogenes by qualitative or quantitative genetic changes results in promotion of proliferative/mitotic signals. An alternative scenario is when environmental carcinogen-mediated loss or attenuation of tumor suppressor genes leads to tumor development [33,34]. Genetic mutations, along with genomic instability and a series of epigenetic events, such as persistent inflammation or oxidative-stress, catalyze the transformation from normal- to malignant-cells. All transformed cells display common unusual criteria, such as prolonged proliferation, ever-lasting replication (immortality), resistance to cell death (apoptosis), and capacity to provoke new-vessel formation (angiogenesis) and translocation (invasion and metastasis) [35].

Cancer chemopreventive agents can reduce the incidence of tumorigenesis by interfering with stages of carcinogenesis; namely initiation, promotion, or progression. Many chemopreventive agents are derived from natural products, and phytochemicals (PMs) [36-38]. Natural edible products are nontoxic natural extracts or isolated individual-compounds (PMs) that, compared with synthetic chemotherapy, usually produce fewer untoward effects. Therefore, they potentially present a paramount target in achieving protection against cancer. Unlike chemotherapy, PMs also have a great deal of preference to influence rapidly-dividing cells than normal host cells [39].

Chemotherapeutic agents cannot be used for chemoprevention as they have a narrow-scoped molecular targeting and a broad-range of serious adverse reactions. Besides, they commonly lack reasonably lasting cytotoxic efficacy, specificity against tumors, and suffer resistance to its cytotoxicity in cancer patients. Conversely, PMs have remained as a precious edible and nutraceutical resource that bears fruitful prospects in the area of chemoprevention. Underpinnings are that PMs, on top of their potential safety, can exclusively enhance host's immune response against carcinogenesis, and most importantly, they possess such a molecular versatility that mimics and complements mammalian cell components, thereby achieving polypharmacologic effects, consonant with efficacious multi-targeting chemoprevention. Commonly used PMs, which are widely marketed as nutraceuticals as well, include EGCG, curcumin, resveratrol, genistein, gingerol, quercetin, lycopene, and baicalein [40-41].

The molecular mechanisms whereby PMs trigger their chemopreventive effects involve changes in redox-potential, altering of enzyme activity, modulating signaling cascades and cell cycler hythmas well as modification of transcription-factor activities and gene expression. Evidence for such profiles was mostly derived from cellular and animal model of cancer, because of the inability to reproduce the exposure/prevention conditions on human hosts, as well as lack/difficulty of learning about the mechanisms of action and toxicity in the living human beings [24].

Nevertheless, chemoprevention is mandated for individuals who are already at high risk to cancer, those with established primary tumors in order to prevent eruption of secondary tumors, or those who had been cured; for prevention of the recurrence of cancer. Thus recent efforts with clinical trials have targeted optimization of PM therapy and minimization of relevant caveats and concerns. Thus, to enhance absorption, bioavailability, or site-specific delivery and uptake of PMs, several approaches have been concertedly deployed. In this vein, nanotechnology and nano-medicine utilize minute-sized (nano) drugs via bridging the parent drug with specific carriers, polymers, proteins or lipids. Likewise, liposomes are intended for delivery of dietary PMs. Lastly, the use of PMs synthetic-analogs has been an immense realm of pharmaceutical research to improve dynamic and kinetic profiles of PMs [42-44].

3. Synergy of PMs with chemotherapy, and mitigation of its noxious adverse reactions (ADRs)

The word synergy is derived from the Greek words sunergia, which means 'cooperation', and sunergos, which means 'working together'. PMs may well elicit sole cytotoxic effects on their own in cell- and animal-based cancer models. Such envisions have been promoted and become widely accepted, in clinical trials and Chinese-herbal-medicine, especially with PM-optimization via recent omics- and nanotechnology-based studies [2]. The complexity of cancer formation and development hinders effective cancer treatment using chemotherapy alone. Thence, seeking synergistic combinations of chemotherapeutic drugs and other drugs can be a promising way to enhance prognosis, quality of therapy and overall responsiveness to chemotherapy. Synergic combinations of chemotherapy with PMs or Chinese-herbal formulae that are known for anticancer potential are designed and intended for enhancing efficacy, reducing untoward/toxic effects, optimizing anti-tumor immune response, or minimizing cancer resistance to chemotherapy [45,46].

The principles of selecting drug combinations have been based on drugs acting on the same target but via different mechanisms, drugs acting on different cellular targets via the same mechanism; or drugs working on different molecules via different avenues. Numerous such combinations have been first attempted among Chinese herbs and PMs that were reported in cancer cells, and showed multifaceted promising outcomes. For instance, curcumin has been established as a multitargeting PM that displays anti-inflammatory, antioxidant and chemotherapeutic effects; while shows no or insignificant toxicity in animals, when used even at such elevated doses [47,48]. Furthermore, curcumin modulates the cellular levels of tumor suppressor genes, apoptotic genes, expression of oncogenes, and their respective effectors such as enzymes, receptors signal adaptors [49]. Thus, many Chinese herbs (or other PMs) have been combined with curcumin to seek synergy. When curcumin was used with triptolide, they promoted apoptosis in ovarian cancer cells, effects that were ascribed to deactivation of some heat-shock proteins; HSP27 and HSP70 [50]. In addition, the joint use of curcumin and emodin has substantially reduced growth and migratory/invasive ability of breast cancer cells [51]. On the other hand, resveratrol conferred synergy with the *in vitro* and *in vivo* cytotoxic effects of Curcumin in head and neck carcinomas [52].

On the other hand, the joint use of PMs can significantly augment the clinical antitumor effects of chemotherapeutic drugs. In this vein, a meta-analysis on some two thousands of patients showed that the efficiency of platinum-based chemotherapy was enhanced by intravenous infusion of the Chinese formula *Shenqi fuzheng* [53]. Another randomized and controlled clinical trial proved that the injection also raised the therapeutic effects of "cyclophosphamide, epirubicin and 5-fluorouracil regimen" in local-advanced breast cancer patients [54]. Likewise, an *astragalus*-based Chinese herb augmented the inhibitory effects of cisplatin in advanced non-small-cell lung cancer [55].

Another aspect is that adverse events, including nausea, vomiting, and anorexia, often develop as secondary/side effects to chemotherapy. Therefore, alleviating these untoward effects is such a worthy objective to improve the quality of chemotherapy. In this context, the concomitant use of astragalus-polysaccharide markedly concealed fatigue, nausea/vomiting, gastric-pain and loss of appetite linked with the application of the chemotherapeutic-drugs, vinorelbine and cisplatin, in patients with advanced NSCLC, thereby greatly enhance the acceptance of therapy and improving patients' quality of life [56]. Quercetin, crocin and resveratrol were found to effectively lessen the cardiotoxicity evoked by doxorubicin [57]. The additive use of EGCG or resveratrol ameliorated cisplatin-induced renal toxicity, inflammation and oxidative-stress [58]. Overall, while these studies hold some promise, still more adequate, meticulous/reliable studies should be deployed, particularly to Chinese-herbal-medicine combinations, so as to precisely delineate their combinatorial actions and exact clinical utility.

4. Chemosensitization (PM-evoked abrogation of tumor resistance to chemotherapy)

Although marked progress was achieved in understanding triggers, treatments, and prognosis of cancer, its overall death rate has not declined significantly. The management options available encompass surgery, radiotherapy, and chemotherapy. However, chemotherapy is often used as a core regimen in the handling of most cancers. Nevertheless, the development of tumor resistance to

chemotherapy (chemoresistance) constitutes a major hurdle in cancer therapy, thereby aggravating the disease prognosis and patient's quality of life [24,39]. Therefore, there is a compelling demand to reach a strategy that blunts chemoresistance and get cancer cells sensitized to actions of chemotherapeutic drugs. Chemosensitization is an approach to overcome chemoresistance. It targets the use of one drug to enhance the activity of another by combating the mechanisms behind resistance. Prominent and frontier such candidate chemosensitizers have been natural phytochemicals (PMs), for their established safety and merits in chemoprevention.

PMs and herbs are intended to abate, bypass, or silence the cellular and molecular mechanisms underlying chemoresistance. Cancer cells develop resistance via a variety of pathways and targets, which include: 1) Alterations in cancer-cell "uptake or efflux" of chemotherapeutic drugs to reduce their availability at the site of action. Drug efflux from cells is mediated by the transporter proteins "multidrug transporters", of which the coherent ones with chemoresistance include multidrug resistance protein (MDR, P-gp), and breast cancer resistance protein (BRCP). Overexpression and enhanced activity of transporter proteins have further been subject to regulation by inflammation and oxidative stress, two prominent and inevitable events that accompany cancer [59-61]. 2) Metabolic inactivation of chemotherapeutic agents also sequestrates their levels available for chemotherapeutic actions. Commonly engaged enzymes in such inactivation include glutathione/glutathione S-transferase (GSH/GST) system and dihydropyrimidine dehydrogenase (DPD). The latter has been implicated in the inactivation of "5-Fluorouracil (5-FU)", thereby blunting its efficacy, as witnessed in colorectal cancer cells [62-64]. 3) Alterations in chemotherapy-target molecules (e.g. topoisomerase-II), or in signaling molecules (e.g. MAPKs, growth-factors, and apoptotic effectors) [65-68]. 4) Enhanced DNA-repair in cancer cells, which aims to circumvent the damaging effects of chemotherapeutic drugs on tumor DNA. Thus, cancer cells have the means and capacity to elicit direct repair, mismatch repair, base excision repair, and nucleotide excision repair [69,70]. 5) Constitutive or prolonged activation of nuclear transcription factors, as with (NF-κB) and (STAT-3) pathways, with consequent upregulation of their downstream genes. NF-κB regulates hundreds of genes that are involved in immunoregulation, inflammation, carcinogenesis, growth and apoptosis. Thus, constitutive activation of NF-κB delays, opposes, or blocks chemotherapy-induced apoptosis in tumor cells [71-75]. The STAT3 transcription factor is activated by tyrosine phosphorylation downstream from growth factors and cytokines. Recruitment of STAT-3 triggers multiple-gene expressional changes, which eventually mediate tumor resistance to actions of chemotherapeutic drugs [76-80]. 6) The cell cycle machinery is another likely target of resistance at the levels of its proteins and kinases (CDKs) [81]. All of the above mechanisms can be deregulated by PMs at one or more target to overcome drug resistance. Commonly reported such PMs include curcumin, EGCG, proanthocyanidins, genistein, resveratrol, silymarin, β-sitosterol, and quercetin [82]. Resveratrol, for instance, can chemosensitize tumor cells by targeting multiple avenues, including drug transporters, cell proliferative proteins, cell survival proteins, apoptosis, and members of the NF-κB and STAT-3-dependent signaling pathways [83-84].

Perspectives AND Conclusions

The complex biology of cancer development requires relatively multitarget treatment strategies. Thus, the deployment of synergy combinations of conventional chemotherapeutic drugs with PMs has promoted curative effects, reduced adverse events and improved patient immunity, eventually aiming to enhance quality of life and prolong patient lifespan. Abundance and outcomes from cell lines and animal models far exceed those from the clinic. However, thanks to advances in recent technology, as with nanomedicine, genomics, metabolomics [85], high throughput target screening and evidence-based drug and molecular networking, PMs are gaining more ground every day. Their utility in mitigating cancer cell resistance and drug-failure of chemotherapy, and records in the area of chemoprevention, remains such critical and promising enough to mandate intensive future clinical trials in such directions.

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