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Invited Review

Phytomedicine—Modulating oxidative stress and the tumor microenvironment for cancer therapy

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ABSTRACT

In spite of the current advances and achievements in systems biology and translational medicinal research, the current strategies for cancer therapy, such as radiotherapy, targeted therapy, immunotherapy and chemotherapy remain palliative or unsatisfactory due to tumor metastasis or recurrence after surgery/therapy, drug resistance, adverse side effects, and so on. Oxidative stress (OS) plays a critical role in chronic/acute inflammation, carcinogenesis, tumor progression, and tumor invasion/metastasis which is also attributed to the dynamic and complex properties and activities in the tumor microenvironment (TME). Re-educating or reprogramming tumor-associated stromal or immune cells in the TME provides an approach for restoring immune surveillance impaired by disease in cancer patients to increase overall survival and reduce drug resistance. Herbal medicines or plant-derived natural products have historically been a major source of anti-cancer drugs. Delving into the lore of herbal medicine may uncover new leads for anti-cancer drugs. Phytomedicines have been widely documented to directly or indirectly target multiple signaling pathways and networks in cancer cells. A combination of anti-cancer drugs and polypharmacological plant-derived extracts or compounds may offer a significant advantage in sensitizing the efficacy of monotherapy and overcoming drug-induced resistance in cancer patients. This review introduces several phytochemicals and phytoextracts derived from medicinal plants or dietary vegetables that have been studied for their efficacy in preclinical cancer models. We address the underlying modes of action of induction of OS and deregulation of TME-associated stromal cells, mediators and signaling pathways, and reference the related clinical investigations that look at the single or combination use of phytochemicals and phytoextracts to sensitize anti-cancer drug effects and/or overcome drug resistance.

Contents

Abbreviations: CAF, cancer-associated fibroblast; COX, cyclooxygenase; CYP, cytochrome P450; ECM, extracellular matrix; EMT, epithelial-to-mesenchymal transition; GPx, glutathione peroxidase; HIF-1, hypoxia-inducible transcription factor-1; JNK, c-Jun NH2-terminal kinase; MDSCs, myeloid-derived suppressor cells; MMP, matrix metalloproteinase; NF-κB, nuclear factor-κB; Nrf2, nuclear factor (erythroid-derived 2)-like 2; OS, oxidative stress; PCD, programmed cell death; ROS, reactive oxygen species; SOD, superoxide dismutase; TAM, tumor-associated macrophage; TAN, tumor-associated neutrophil; TF, transcription factor; TME, tumor microenvironment.

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1. Introduction

Oxidative stress (OS) is a stress signal that reflects an overwhelming production of reactive oxygen species (ROS) that exceeds the antioxidant capacity within a cell. Such OS can cause damage to cellular building blocks and disruption of cellular signaling mainly through chemical reactions with ROS. Inflammation is a mechanism generated in an organism to protect against harmful substances such as pathogens or damaged cells; however, the inappropriate or continued activation of inflammation, i.e., chronic inflammation, can be the basis of various diseases including cancer [1]. In cancer development, ROS-mediated OS and the inflammation response cannot only be found at the onset of cancer but is also found during cancer progression [2]. Compelling experimental and clinical evidence demonstrates that ROS can promote malignant and metastatic phenotypes in different tumors, and resistance to OS appears to be a pivotal mechanism of tumor resistance to chemotherapy [2].

Upon tumor formation, abnormal cell growth and metabolism can cause cancer-related inflammation and OS. Accompanied by an abnormally high cell proliferation rate, cancer cells usually have a higher tolerance to OS than normal cells. Nuclear factor (erythroid-derived 2)-like 2 (Nrf2)-mediated signaling, although acting as an antioxidant response under normal conditions, can be hijacked by cancer cells to become their weapon against or to tolerate the high OS status [2]. The constitutive stabilization and activation of Nrf2 and its downstream antioxidant genes in cancer cells has been found to be a major contributor to their radio- or chemotherapy-resistance [3]. Aberrant nuclear factor-κB (NF-κB) activation found in cancer inflammation can be due to the IL-6/STAT3/NF-κB positive feedback loop that leads to worsening cancer progression [4,5]. On the other hand, NF-κB activation can also result in cancer cell death through apoptosis or autophagy [6,7]. Excessive ROS production by chemicals with pro-oxidant activity or other signaling is able to induce intrinsic apoptosis in various cancer cells due to perturbance of mitochondrial membrane permeability and depolarization resulting in the formation of the mitochondrial apoptosis-induced channel (MAC) [8,9]. Molecules including cytochrome c and apoptotic protease activating factor-1 (Apaf-1) are then released from MAC to activate caspase-dependent cell apoptosis [10]. It was previously reported that a small molecular inhibitor (BIX) induces ROS-dependent autophagy cell death in breast cancer cells through the recruitment of RNA polymerase II and NF-κB to the gene promoter region of the autophagy-related gene Beclin-1 to activate its transcription and results in autophagic cell death [11]. Other than activating the two commonly observed types of programmed cell death (PCD), apoptosis and autophagy, ROS can also activate another type of PCD, paraptosis, which is characterized by dilation of the endoplasmic reticulum and/or mitochondria accompanied by massive cytoplasmic vacuolation and anoikis which results from the detachment of anchorage-dependent cells from their surrounding matrix [12,13]. Natural product-induced paraptosis has recently been earmarked as a possible anti-cancer approach [12].

The tumor microenvironment (TME) is known to be involved with various immune cells (lymphoid lineage and myeloid lineage) and different types of mediators, including lipid mediators, cytokines/chemokines, and inflammation-related proteins that can promote cancer progression [14]. Interactions between tumor cells and the associated stroma consist of the basement membrane, extracellular matrix (ECM), fibroblasts, immune cells, and vasculature and represent a powerful relationship that influences cancer initiation and progression and patient prognosis [14,15]. The establishment of the TME is found throughout cancer development and is capable of normalizing tumor cells, suggesting that re-education of stromal cells may be effective in cancer treatment. The cancer-related inflammatory responses can be a cause or initiator of stromal cell/immune cell interactions and ECM communications at the TME. ROS can be produced by different immune cell types, e.g., cancer-associated fibroblasts (CAF) or tumor-associated macrophages (TAM) or tumor-associated neutrophils (TAN) in the TME to elicit a pro-oxidant environment associated with cancer cell migration, invasion, angiogenesis, and immune escape [16,17]. Neutrophils release ROS during chronic inflammation which can further induce DNA damage and gene mutation frequency leading to tumorigenesis [18,19]. On the other hand, a link between myofibroblast differentiation/accumulation and oxidative stress was found in promoting HER-2(+) breast adenocarcinoma [20]. Bidirectional modulation of OS in cancer cells and/or re-education and targeting the tumor microenvironment can be considered as therapeutic strategies for cancerous diseases [14].

The role and associated signaling molecules or pathways of oxidative stress or the tumor associated microenvironment have been widely investigated in various cancers and identification of potential drug targets is anticipated. Herbal medicine has been used in treating various diseases including cancer for hundreds if not thousands of years, but the underlying molecular mechanisms of their anti-cancer activities have only started to be actively elucidated in the past decade or so. Accumulating evidence shows that the anti-cancer activities of herbal medicines or plant-derived compounds are achieved by modulation of oxidative stress and/or reprogramming TME in various cancers as evident in in vitro cancer cell line study or in mouse tumor models. We consider it important to compile and summarize the most up-to-date information about these mechanisms to expose the potential of such phytomedicines or derived compounds for further development into preventive or therapeutic agents to control cancer, especially incurable, late or metastatic tumors. In this review, we summarize selected phytomedicines or phytoagents that have been or are being studied in clinical trials as cancer therapies according to the information provided in ClinicalTrials.gov (https://clinicaltrials.gov/). The mechanisms of these compounds or extracts that result in their therapeutic effect against cancers have been reported to include