International Immunopharmacology 50 (2017) 291–304

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Review

Naturally occurring immunomodulators with antitumor activity: An insight on their mechanisms of action

Shimaa Ibrahim Abdelmonym Mohamed, Ibrahim Jantan*, Md. Areeful Haque

Drug and Herbal Research Center, Faculty of Pharmacy, Universiti Kebangsaan Malaysia, 50300 Kuala Lumpur, Malaysia

ARTICLE INFO

Keywords:
Natural immunomodulators
Antioxidant
Anti-inflammatory
Apoptosis
Cancer

ABSTRACT

Natural products with immunomodulatory activity are widely used in treatment of many diseases including autoimmune diseases, inflammatory disorders in addition to cancer. They gained a great interest in the last decades as therapeutic agents since they provide inexpensive and less toxic products than the synthetic chemotherapeutic agents. Immunomodulators are the agents that have the ability to boost or suppress the host defense response that can be used as a prophylaxis as well as in combination with other therapeutic modalities. The anticancer activity of these immunomodulators is due to their anti-inflammatory, antioxidant, and induction of apoptosis, anti-angiogenesis, and anti-metastasis effect. These natural immunomodulators such as genistein, curcumin, and resveratrol can be used as prophylaxis against the initiation of cancer besides the inhibition of tumor growth and proliferation. Whereas, immunostimulants can elicit and activate humoral and cell-mediated immune responses against the tumor that facilitate the recognition and destruction of the already existing tumor. This review represents the recent studies on various natural immunomodulators with antitumor effects. We have focused on the relationship between their anticancer activity and immunomodulatory mechanisms. The mechanisms of action of various immunomodulators such as polyphenolic compounds, flavonoids, organosulfur compounds, capsaicin, vinca alkaloids, bromelain, betulinic acid and zerumbone, the affected cancerous cell lines in addition to the targeted molecules and transcriptional pathways have been review and critically analyzed.

1. Introduction

Cancer is considered as a fatal disease that is caused by proliferation and progression of abnormal or unwanted cells [1]. Most of the therapeutic modalities including chemotherapy, radiotherapy, photodynamic therapy (PDT) and active immunotherapy have limited success due to their destructive effect not only on cancer cells but also on the surrounding normal cells in addition to the severe side effects and immunosuppression activity. The most effective cancer therapy is the one, which would combat the tumor at the initial focus and prevent the formation of any new metastases lesion. In recent years, there is a growing interest on the using of natural occurring immunomodulators mainly immunostimulants as supplements in combination with the common therapeutic modalities in treatment of cancer in order to improve the immune response against the tumors and reduce the suppression effect that is produced by the chemotherapy along with the tumor itself to escape the immune surveillance [2]. The immune system exhibits the chief function in the defense against infected pathogens and harmful antigens, which is divided into nonspecific and antigen-specific immunities. The non-specific immunity can act immediately to defense against any invading pathogens such as physical barriers as well as humoral immunity. The antigen-specific immunity or cell-mediated immunity is more complex and develops an immunological memory following the primary experience to a particular pathogen, leading to a profound immune response against the next invasion of the same antigen [3].

Immunoediting is the process that describes the relation between immune response and tumor development. It consists of three phases,

Abbreviations: AMS, allyl methyl sulfide; AIF, apoptosis inducing factor; AKT, v-akt murine thymoma viral oncogene homolog; AP-1, activator protein-1; Apaf-1, apoptotic protease-activating factor-1; ASRK1, apoptosis signal-regulation kinase 1; COX-2, cyclooxygenase-2; Cdc1, cyclin-dependent kinase 1; DAD, diallyl disulfide; DAS, diallyl sulfide; DISC, death-inducing signaling complex; Endo-g, endonuclease G; ERK, extracellular signal-regulated kinase; JNK, c-Jun NH2-terminal kinase; ECM, extracellular matrix; GA, gallic acid; iNOS, inducible nitric oxide; ICAM-1, intercellular adhesion molecule 1; INFγ, interferon gamma; IL-8, interleukin 8; LOX, lipoxygenase; MMP, matrix metalloproteinase; MHC, major histocompatibility complex; NADPH, nicotinamide adenine dinucleotide phosphate-oxidase; NO, nitric oxide; NFκB, nuclear factor kappa B; NK cells, natural killer cell; PGE2, prostaglandin E-2; RANKL, receptor activator of nuclear factor kappa-B ligand; ROS, reactive oxygen species; RONS, reactive oxygen and nitrogen species; STAT3, signal transducer and activator of transcription 3; TNFα, tumor necrotic factor alpha; TRAIL, TNF-related apoptosis-inducing ligand; TRAF1, TNF receptor associated factor 1; VEGF, vascular endothelial growth factor

* Corresponding author at: Drug and Herbal Research Centre, Faculty of Pharmacy, Universiti Kebangsaan Malaysia, Jalan Raja Muda Abdul Aziz, 50300 Kuala Lumpur, Malaysia.
E-mail address: ibj@ukm.edu.my (I. Jantan).

http://dx.doi.org/10.1016/j.intimp.2017.07.010
Received 21 April 2017; Received in revised form 13 June 2017; Accepted 12 July 2017

which are elimination, equilibrium and escape phases. In elimination phase an acute inflammatory response induced by innate and adaptive immune systems occurs, mainly to recognize and eliminate the early-generated tumor cells [4]. The major immune cells that are involved in defense against tumor cells are natural killer cells (NK), dendritic cells, macrophages, polymorph nuclear cells, mast cells, and cytotoxic T cells. Dendritic cells are the main commanding antigen presenting cells (APC) and considered as a link between innate and adaptive immune system. They have the ability to capture and present the tumor-associated antigen (TAA) to naïve T cells through MHC class I and II that leads to activation and clonal expansion of T lymphocytes mainly into $CD4^+$ helper T cell and $CD8^+$ cytotoxic T cells. This is in addition to release of pro-inflammatory cytokines such as IFNγ and IL-12 that can improve the tumor uptake by APCs and activate Th1 response that catalyzes the activation of cytotoxic T lymphocyte (CTL) [5]. Activated CTL then migrates and infiltrate the tumor microenvironment to directly attack the tumor cells by induction of apoptosis. However, some of the tumor cells start to resist the strong immune surveillance by different mechanisms and shift into the equilibrium phase between the tumor cell proliferation and apoptosis. In escape phase the tumor cells become less immunogenic and able to evade the immune control by reduction in the expression of adhesion molecules, MHC antigens on their surface as well as the release of anti-inflammatory mediators namely IL-10, PGE2, and TGF-β that inhibit the effector T lymphocytes and immune response [6]. Although the induction of an acute immune response plays the cardinal aspect in detection and combating the tumor cells but shifting into chronic inflammation such as in case of chronic gastritis, chronic inflammatory bowel diseases, prostatitis, and ulcerative colitis may increase the incidence of cancer generation due to accumulation of bioactive cytokines, chemokines, destructive oxygen species, and growth factors by the immune cells that induce mutation development and transition of the normal cells into abnormal tumor cells [7].

Plants are rich in bioactive compounds that possess anticancer and immunomodulatory activities with low risk of cytotoxicity and side effects. Many phytochemicals have been reported for their immunomodulatory activity and their uses in treatment and combating of several types of cancer [8]. This review critically discusses the immunomodulatory effects of natural products and how they contribute to their antitumor activity.

2. Mechanisms of cytotoxic and antitumor activities of natural products

Natural products with immunomodulatory activities are now widely used as protective and therapeutic agents against various types of cancer. Plants rich in flavonoids, isothiocyanates, carotenoids, organosulfur, flavonolignans, polysaccharides, and polyphenols may possess immunomodulatory and antitumor activities (Table 1). The antitumor effect of natural products can be established by inhibition of tumor initiation or suppression of growth and spread of abnormal cells. Immunomodulatory natural products that induce the host immune cell activity can exhibit cytotoxic and antitumor effects such as *Justicia spicigera* and its active constituent, kaempferitrin, that induced the phagocytic activity of murine macrophage and increased NO and ROS production and NK cells cytotoxic activity [9]. The immunomodulatory natural compounds with suppression activity can act as a protective agent and prevent the initiation of tumor development mainly due to their antioxidant activity or free radical scavenger to prevent DNA damage and interfere with the uptake of toxic materials by the cells such as resveratrol **(1)** [10], genistein **(2)** [11], quercetin **(3)** [12] and curcumin **(4)** [13,14] (Fig. 1).

Many natural products were reported to cause cell cycle arrest and anti-proliferative effect such as 6-gingerol **(5)** [15], tangeritin **(6)** [16], zerumbone **(7)** [17] and resveratrol [18]. Natural immunomodulators are able to abolish the tumor propagation through disruption of tumor cell cycle and apoptosis induction [19]. Apoptosis is a highly organized cell death process that maintains tissue homeostasis and contributes in the suppression of tumor growth. Apoptosis can act as a checkpoint since any defective or damaged cell can be eliminated by apoptosis. Cancer cells possess the ability to escape apoptosis and propagate despite their abnormalities, therefore; the anticancer agents would enforce the tumor cells to undergo apoptosis.

Immunomodulatory products can induce apoptosis through several mechanisms mainly stimulation of caspases activity that induces DNA cleavage or up-regulation of pro-apoptotic peptides Bax family such as resveratrol effect on human U251 glioma cell [20] as well as anti-apoptotic peptides Bcl2 (B-cell lymphoma-2) family suppression. The anti-proliferative effect of the methanol extract of *Phyllanthus amarus* hairy root clone 19 on human breast adenocarcinoma MCF-7 was studied by Gauri et al. [21]. They found that the extract disrupted the mitochondrial membrane potential (MMP) that leads to extrude of cytochrome *c* from mitochondria into cytoplasm and initiation of apoptosis cascade through intrinsic pathway. The cell cycle arrest was mainly induced by cyclin D1 suppression that associates with the transition of the cell from the G1 into S phase that triggers the anti-proliferative effect and accumulation of the cells at G1 phase [22].

Angiogenesis is a normal process that ensures the feeding of nutrients and oxygen into the growing tissue through formation of new blood vessel from pre-existing vasculature. In cancer, angiogenesis is an important process for tumor to develop and propagate. Angiogenesis is caused by cytokines and growth factors released by immune cells infiltration the tumor microenvironment mainly IL8, TNFα, TGFβ, and IL6 through the upregulation of vascular endothelial growth factor (VEGF) that possess angiogenic effect [23]. COX2 overexpression contributes to angiogenesis and tumor progression. COX2 angiogenesis effect can be explained by several mechanisms including the production of angiogenic factors (VEGF) [24], recruitment of MMP2/9 [25], downregulation of IL-12 release with antiangiogenic property [26] and promotion of EGFR (epidermal growth factor receptors) in endothelial cells [27]. The anti-inflammatory natural products inhibit COX-2 and VEGF expression as well as regulate the release of pro-inflammatory cytokines mainly IL-6, TNFα, and TGFβ. Curcumin from turmeric has been reported to exhibit antiangiogenic effect on implanted hepatocellular carcinoma in nude mice [28].

Metastasis is the spread of tumor cell from the site of generation into another organ or part of the body through lymphatic or blood stream. Angiogenesis can also induce the metastasis of the tumor cells through the newly formed blood vessels to depart the primary lesion to form a new tumor focal point in different site of the body [29]. Metastasis results from the disturbance of extracellular matrix (ECM) and the basement membrane adhering epithelial cells by a group of protease enzymes released by the tumor cells known as matrix metalloproteinase enzymes (MMP) such as collagenase, elastase, and proteases providing the route for tumor cell migration to form a new tumor focus [30]. Immunomodulators that downregulate the migration and invasion capabilities of the tumor cells exhibit anti-metastasis effect. The anti-metastasis activity of kaempferol **(8)** in SCC-4, a human tongue squamous cell carcinoma cell line was reported by Lin et al. [31] through the inhibitory effect on the transcriptional activity of MMP and AP-1 (the main regulator in MMP activation).

3. Natural immunomodulator with antitumor effects

3.1. Phenolic acids

Phenolic acids are aromatic acids with a phenolic ring and a carboxylic acid function group such as gallic acid **(9)**, curcumin, resveratrol, and 6-gingerol. Natural isolated phenolic acids can be used as a prophylaxis against cancer progression and initiation *via* their antioxidant, anti-inflammatory, and antimutagenic activities, in addition to their cytotoxic activity through induction of apoptosis and cell cycle arrest beside their inhibitory effect on the tumor invasion and