Innate immunity and herbs: In cancer therapeutics

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Abstract
Cancer usually initiated as a result of the stepwise accumulation of genetic and epigenetic changes in the cell. The role of the host immune system is very critical in the progression of cancer. It is an integrated system consists of different types of organs, cells and their products. Cancer cells grow and spread by avoiding detection and destruction by the immune system. A large number of evidences indicate that tumor microenvironment play crucial role in the subsequent conversion of primary tumor into more advanced malignancies. Tumor microenvironmet is occupied with the cells of immune system such as macrophages, dendritic cells, NK cells and T cells with altered functions. It is well documented that modulation of immune system helps to eliminate cancer. Plant based remedies have always been used as an integral part of traditional medicines for modulating the immune system for different types ailments including cancer throughout the world. A better understanding of the cellular constituents of tumors microenvironment and their regulation may help to develop novel therapeutic approach in cancer therapy. In this review we summaries role of innate immune system in cancer, cells in tumor microenvironments and their interaction with tumor cells and natural products in cancer therapeutics.

Keywords: Immune cells, Inflammasesomes, immunomodulation, plant peptides, tumor microenvironment

1. Introduction
Cancer is not a simple lump of malignant cells but it is complex tissue with heterogeneous cells. The immunological involvement and causes are different for different cancers. The immune system protects the body from infectious agents, damaged or transformed cells. Cells of the immune system play pivotal role in the elimination of tumor but even then rate of occurrence or the frequency of cancer is high. This indicates that the immune system not only protects the host against hyperploproliferation but also interacts with cancer cells and may leads to the formation of aggressive tumors. In immunological perspective, cancer is considered as a defect in the immune system to recognize tumor cell as a foreign body and to elicit immune response to eliminate it. The progression of tumor is the result of the cross talk between tumor cell and different types of host cells present in the tumor microenvironment [1]. Tumor microenvironment consist immune cells, fibroblast, endothelial cells, extracellular matrix signaling molecules, connective tissues, growth factors and it is found that their interaction is critical factor that determine cancer development, progression, and control [2]. Clinical and experimental data proved that modulation of immune cell function may block the initiation and progression of cancer [3, 4]. Natural compounds are of prime importance in traditional cancer therapeutics [5]. Approximately one third of the total anticancer drug sales worldwide namely, the taxanes, paclitaxel and docetaxel, and the camptothecin derivatives, irinotecan, topotecan are derived from plants [6]. They could act as immunomodulators or interfere with the cellular and molecular event involved in cell proliferation and cell death in favour of curtailing the progression and development of secondary tumors [7]. Moreover, many of them have the potential to reduce the toxicity caused by conventional therapies such as radiation and chemotherapy [8, 9]. In this review, we summarize role of innate immune system in cancer and current research advancements on herb and herbal compounds in cancer research.

2. Interactions between the immune system and cancer
During cancer initiation, cells undergo genetic alteration which may leads to changes in body’s defense mechanisms or immune system [10]. Host immune response comprised of complex and interconnected events mediated through both cell mediated and humoral immunity. It is evident that immune system have double role in tumor development. Cell of the immune system are primarily participating in immunosurveillance in which developing tumors are eliminated by immune cell mainly by NK cells, cytotoxic T cells, helper T cells, dendritic cells, macrophages and B lymphocytes which exerts antitumor effect [11]. As the tumor proceeds through, tumor and some of the immune cells secrete immune suppressive cytokines such as transforming growth factor-β, interleukin (IL)-10 and interleukin (IL)-13, and chemokines and
these factors in turn recruit cells which negatively regulate immunity such as T-regulatory cells, myeloid suppressor cells finally favouring progression of tumor [12].

3. Tumor microenvironment and the key players
The tumor microenvironment is a complex system consisting immune and nonimmune cells. Fibroblasts, carcinoma associated fibroblast (CAFs), myofibroblast, smooth muscle cells, endothelial cells and their precursor, pericytes, neutrophils, eosinophils, basophils, mast cells, T and B lymphocytes, natural killer cells and antigen presenting cells (APC) such as macrophages and dendritic cells constitute the microenvironment of tumors [12, 13, 14]. These factors interact with one another and with tumor as it grows [15]. The cross talk between cancer cells and the microenvironment determines the potential of tumor cells to invade surrounding tissues, penetrate blood vessels, and ultimately enter to distant tissues [16]. Contribution of each component is critical in determining the fate of tumor cell. The main immune cells in the tumor microenvironment includes, regulatory T cells (Tregs) [17, 18], tumor-associated macrophages (TAM) [19], N2 neutrophils [20], dendritic cells [21] and myeloid-derived suppressor cells (MDSC) [22-24]. Functional characteristics of these cells are critical determinants of cancer outcomes. Other immune components of the tumor microenvironment, include chemokines, cytokines and growth factors, may also alter immune regulatory responses [25, 26]. Non immune components within the tumor microenvironment include the tumor cell, fibroblast, epithelial and endothelial cells, pericytes, adhesion molecules and the stroma components [27]. They regulate the cancer development through collaboration with each other either directly or indirectly. Tumor associated fibroblasts are responsible for the formation and remodeling of the extracellular matrix and release growth factor which promotes the growth of cancer cells [28]. Pericytes and endothelial cells are the component of blood vessels [29]. Adipocytes, serves as component of energy supplier, are reported to promote homing, migration and invasion of tumor cells by secreting adipokines including interleukin-8 (IL-8) and also make tumors grow rapidly by providing fatty acids. [30]. The manipulation of the microenvironmental factors is a promising tool for novel cancer treatments.

4. Inflammation and oxidative stress in cancer
Inflammation is the body’s immediate response to damage to the cells and tissues by pathogens, noxious stimuli such as chemicals or physical injury and paly decisive roles at different stages of tumor development. It is a sequence of events that constitutes the inflammatory response which involves both innate and adaptive immunity. This mechanism can eliminate the agent responsible for the injury and initiate tissue repair [31]. Inflammation can be of two types acute and chronic. Acute inflammation is usually of short duration and leukocytes infiltrate in to the damaged region, to repair the tissues. Chronic inflammation, by contrast is prolonged and self-perpetuating, may last for weeks, months, or even years [32]. Such persistent inflammation is associated with many chronic pathological conditions, including allergy, atherosclerosis and cancer. Inflammation is a recognized hallmark of cancer that significantly contributes to the development and progression of malignancies [33, 34, 35]. Pathways linking inflammation and cancer are either an intrinsic which is by genetic events or extrinsic that is driven by inflammatory conditions which predispose to cancer [36]. Oxidative stress is defined as an imbalance between production of free radicals and reactive metabolites, called oxidants or reactive oxygen species (ROS), and their elimination by protective mechanisms, referred to as antioxidants [37]. ROS are products of a normal cellular metabolism and is produced from endogenous sources such as from mitochondria, peroxisomes, and inflammatory cell activation or exogenous sources, including environmental agents, pharmaceuticals, and industrial chemicals [38]. The reactive oxygen [hydroxyl radical (OH·) and superoxide (O2−)] and nitrogen species [nitric oxide (NO) and peroxynitrite (ONOO−)] generate as a part of inflammation response cause genomic damage and genetic instability, promote cell motility [39]. The free radicals generated can also cause the peroxidation of lipids in the plasma membrane of the cell which affect the cell proliferation [40]. In addition, ROS alter DNA methylation pattern in tumor cells [41]. Moreover, the up regulated redox signaling pathways exploited as a mechanism to selective killing of cancer cells.

5. Components of cancer induced inflammation
Inflammation is regarded as a “secret killer” and the inflammatory component present in the microenvironment of most neoplastic tissues significantly contribute towards further progression into aggressive tumor type [33]. The predominating cellular components in neoplastic environment include TAMs (Tumor associated macrophages), mast cells, Treg (Regulatory T cells), MDSCs (Myeloid-derived suppressor cells) and dendritic cells.

5.1 Tumor associated macrophages (TAM)
Macrophages are the major component of the inflammatory microenvironment of cancer [33, 34]. Two major categories of macrophages are identified classical M1 and alternative M2 macrophages [44-46]. Activated M1 macrophages phagocytise and eliminate tumor cells, present antigen to T cells for an adaptive immune response. M2 type promotes different aspects of tissue remodeling i.e. digestion of extracellular matrix with matrix metalloproteinases (MMPs), promotion of angiogenesis via vascular endothelial growth factor (VEGF) production to exert pro-tumorigenic activities [47, 48]. The macrophages within the tumor, referring to as tumour-associated macrophages (TAMs) and closely resemble the M2-polarized macrophages. TAMs in tumor microenvironment play master role in metastasis through promoting tumor specific angiogenesis, tumor cell migration and invasion [49, 50]. TAMs inhibit the T cell mediated anti-tumor immune response and also secrete an array of cytokines, chemokines, and that can suppress CD4+ and CD8+ functions [51].

5.2. Mast cells
Mast cells (MCs) are tissue leukocytes originating from hematopoietic stem cells in bone marrow. They accumulate in the stroma surrounding certain tumors in response to numerous chemo attractants [52]. MCs have a crucial interplay between inflammatory and tumor cells through the release of classical proangiogenic factors (e.g., vascular endothelial growth factor) and non classical proangiogenic mediators [53]. Metalloproteases they produce may contribute the majority of proteolytic components necessary for tumor invasiveness. Moreover, IL-8 secreted by MSC, is considered act as a mitogen, chemotactic and angiogenic [54]. Mounting evidences indicate that mast cells accumulate in the tumor vicinity and either promote or inhibit tumor growth depending on the local stromal conditions.
5.3. Regulatory T cells (Tregs)
It is well documented that T cells not only augment but also suppress the immune system. The immunosuppression is mediated by a subpopulation of T cells, called suppressor T cells, now termed “regulatory” T cells (Treg cells). They are CD4+ and CD25+ T cells are critical to the maintenance of immune cell homeostasis [55]. Regulatory T cells (Tregs) play an indispensable role in maintaining immunological unresponsiveness to self-antigens and in suppressing excessive immune responses deleterious to the host. It also proved to have tumor promote the tumor development [56, 57]. There is increasing evidence that Treg cells can migrate into tumors and suppress effective anti-tumor responses in the tumor microenvironment, thus contributing to immune evasion and the progression of human tumors [58, 59]. Therefore, manipulation of Treg cells, including depletion, blocking trafficking into tumors, or reducing their differentiation and suppressive mechanisms, represent new strategies for cancer treatment.

5.4. Myeloid-derived suppressor cells (MDSCs)
MDSCs represent an intrinsic part of the myeloid-cell lineage and are a heterogeneous population that is comprised of myeloid-cell progenitors and precursors of myeloid cells [60]. Immature myeloid cells (IMCs) generated in bone marrow quickly differentiate into mature granulocytes, macrophages or dendritic cells (DCs). In various diseases including cancer, a partial block in the differentiation of IMCs into mature myeloid cells occurs, which results in the expansion of the MDSC population. MDSCs, lack the expression of cell-surface markers that are specific for monocytes, macrophages or DCs and are comprised of a mixture of myeloid cells with granulocytic and monocytic morphology [61]. They suppress the immune response by enhancing the production of arginine, nitric oxide (NO) and Reactive Oxygen Species (ROS) [62]. MDSCs are induced by tumor-secreted and host-secreted factors, many of which are proinflammatory molecules. MDSC inhibit both innate and adaptive immunity, they are likely to subvert immune surveillance and prevent an individual’s immune system from eliminating newly transformed cells. In addition to this, MDSCs also promote the growth of blood vessels in the tumor vicinity to promote metastasis [63]. To sum up, accumulation of MDSC that down-regulate immune surveillance and antitumor immunity, thereby facilitating tumor growth. Thus MDSC act as a powerful target molecule to inhibit the development of cancer.

5.5. Dendritic cells
Dendritic cells (DCs) are known as professional antigen presenting cells (APCs), which can uptake, process and present different types of antigen, including tumor antigens to antigen specific naïve T cells [64]. DCs also play an important role in maintaining innate and adaptive immune responses in normal and various pathophysiological conditions. These cells exhibit the antitumor immune responses in cancer immunosurveillance [65]. In the tumor microenvironment the maturation and function of dendritic cell is inhibited. Moreover, tumor-derived factors such as gangliosides, neuropeptides, NO and other molecules decrease longevity of DCs in the tumor microenvironment [66]. Tumor associated Dendritic cells (TA-DCs) are immunosuppressive, incapable of inducing specific immune responses, or can induce regulatory T cell expansion. They usually express low level of costimulatory molecules and produce angiogenic factors to promote tumor cell metastasis [67, 68]. Thus the elimination of DCs from the tumor environment is one of the factors responsible for inefficient induction of anti-tumor immunity and tumor escape from immune recognition [69].

5.6. Inflammasomes
The inflammasome is a part of the innate immune system that induces maturation of inflammatory cytokines such as Interleukin 1 (IL-1β) and IL-18 in response to infection or endogenous danger signals. It is a multimolecular cytosolic protein complex, composed of a NOD-like protein (NLR), the adaptor apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), and caspase-1. Inflammasomes activation also leads to pyroptosis, inflammatory cell death, through a pore-forming protein gasdermin D [70]. Inflammasome play significant role in tumor progression. They function as a double-edged sword in tumorigenesis; either tumor promoting or tumor suppressive depending on types of tumors, specific inflammasomes and effector molecules. Thus inflammasomes offer a new therapeutic target in the treatment of cancer.

6. Immune system as cancer therapeutic target
Immune system is capable of killing tumor cells either directly or indirectly by producing soluble chemicals as a part of immunosurveillance. The major cells involved in the process are NK cells, cytotoxic T lymphocytes, macrophages, dendritic cells etc. But, as tumor develops, they themselves recruit functionally modified immune cells like TAMs into the tumor microenvironment and secrete chemicals that suppress the immune system which inturn support the proliferation and metastasis of cancer cells. Meanwhile cancer cell develops some mechanism to escape from hosts’s immune detection self-recognition that favour the tumor growth, proliferation and spread to distant organ. Thus immune cells have been implicated in both protective and suppressive roles during cancer progression [71]. Since the immune system play dual role against the developing tumors the modulation of the immune system is integral part of current cancer-fighting therapies. Moreover, commonly practiced cancer treatment methods such as chemo and radiotherapy produced toxicity or side effects which may induce the development of tumor in secondary sites, metastasis. In this context, it is possible to target different immune cells and their functional activities to reduce/block the formation of aggressive tumors or metastasis and is considered as nontoxic anticancer therapeutic strategies.

7. Plant as modulators of immune system
Plants are the indispensable source of natural products for medicine and their therapeutic potentials have been exploited from time immemorial. They produce various types of molecules including terpenoids, alkaloids, polyphenols, saponins, flavonoids, tannins, enzymes, minerals, etc. These phytochemicals have antioxidant, antiinflammatory, antidiabetic, antimicrobial and anticancer activities [72]. The herbal extract or isolated compounds have showed the immunomodulatory activity which could be of high impact as far as the cancer therapeutic is concerned [73, 74]. Recent research has revealed that plants produce small bioactive peptides also. They are part of the defense system of plants [75, 76]. The plant peptides could trigger the antioxidative, antimicrobial, and immunomodulatory activities in the living system [77]. Medicinal herbs are major source of synthetic and herbal drugs and almost 60% of the drug isolated from natural
products [78]. A large number of chemo preventive agents are available as anticancer agents but they produce side effects that prevent their extensive usage. Moreover, there is a continuing demand for development of new anticancer drugs, combinations and chemotherapy strategies with less toxicity. The identification of plant or plant derived molecule with immunomodulatory or anticancer potential could lead to the development of an alternative and complementary method for cancer prevention and/or treatment.

8. Plants with anticancer activity

8.1. Andrographis paniculata

Andrographis paniculata [Burm. F] Nees (family: Acanthaceae) is a potent drug used in Ayurveda, Siddha and Homeoepathy systems of medicine. Whole plant extracts have been used for the treatment of various disorders and shown to have antitumoral, anti-inflammatory, and antiviral properties. Active principle phytochemical present in the plant is andrographolide which is a diterpenoid lactone [79]. The plant extract and andrographolide augmented the NK cell activity, Antibody dependent cell mediated cytotoxicity (ADCC) and Antibody dependent complement mediated cytotoxicity (ACC) in normal as well as in tumor bearing animal models [80]. It could down regulate the proinflammatory cytokine (TNF-α, IL1β) and up regulate antiinflammatory cytokine such as IL-2 [81]. Similarly, the administration of extract elevated cytokt T Lymphocytes activity through enhanced secretion of IL-2 and IFN-gamma by T cells and thereby inhibit the tumor growth [82]. Molecular analysis revealed that andrographolide interferes with cancer signaling pathways in various types of tumor and prevent the progression [83, 84]. Altogether, this plant exerts the antitumor activity by modulating of cell mediated and humoral immune response and interfering different cancer signaling pathways. The published data proved that Andrographis paniculata could be a good natural anticancer drug candidate and can be used as adjuvants during chemotherapy and hyperthermia.

8.2. Centella asiatica L.

Centella asiatica (Linn.) is commonly known as Indian Pennywort, a genus of Apiaceae. It has been used traditional medicine to treat skin problems ulcer, improving memory, as, kidney troubles, and urethritis, in maternal health care, in treatment of stomach disorders for revitalizing the nerves, hence known as “Brain tonic” in India. It is used as vegetables also. Aerial part of the plant inhibit the proliferation of different human cancer cells in in vitro condition [85]. C. asiatica induces apoptosis in MCF-7 cells and Human colon cancer cells by inducing nuclear condensation, flip-flop movement of the membrane and loss of mitochondrial membrane potential and by inducing DNA strand breaks [86]. C. asiatica is well known to have a high antioxidant activity [86]. Administration of the plant extracts could stimulate the immune system and effectively preventing radiation-induced behavioral changes during clinical radiotherapy [87, 88].

8.3. Withania somnifera (Ashwagandha)

Withania somnifera belongs to the family Solanaceae. Withania somnifera is one of the major herbal components of geriatric tonics and a known immunomodulator in indigenous medicine. In India it is used commonly in the management of various ailments [89]. The main therapeutic properties of this plant include anti-inflammatory, sedative, diuretic anticancer and immunomodulatory activities [90, 91]. Administration of Withania somnifera extract could stimulate the immune system by enhancing the activity of cytotoxic T lymphocytes [92, 93]. In addition, administration of extract inhibited delayed-type hypersensitivity reactions and enhanced phagocytic activity of macrophages [94]. This plant exhibited chemo preventive properties by scavenging the free radical generated during conventional cancer treatment modalities [95]. Phytochemical analysis revealed that the plant contains withanafoloids and Withaferin A which is responsible for the immunostimulatory and anticancer activity [96].

8.4. Vernonia cinerea L.

Vernonia cinerea Lees. (Fam. Asteraceae) commonly known as purple fleabane is traditionally used to treat inflammation, diarrhoea, cough, smoking cessation, asthma, Parkinson's disease [97, 98]. It also possess antitumor and immunomodulatory activity [99, 100]. Vernoldes are major sesquiterpenoids in this plant [101, 102]. In 2011, Pratheesh kumar and Kuttan reported that Vernolide-A could prevent the cancer cell metastasis by blocking the tumor specific angiogenesis in mice model by inhibiting the proinflammatory cytokine production such as IL-1β, IL-6, TNF-α, and GM-CSF and increasing the level of antiangiogenic cytokine IL-2 [103]. In LPS induced macrophages Vernonia cinerea was found to down regulate the iNOS, COX2 and proinflammatory cytokine expression (TNF-α, IL-1β) which mediate the antitumor immune response in mice [104].

8.5. Tinospora cordifolia

Ayurveda refers to Tinospora cordifolia as ‘Amrita’ or the ‘Nectar of Immortality. It is used as “rasayana” which has powerful immunostimulant activity. This plant belongs to the family Menispermaceae to the family Menispermaceae. T. cordifolia has been extensively investigated for its immunomodulatory and antioxidant potential in vitro and in vivo and found to possess immunomodulatory and antitumor activities [105, 106]. It has also been observed that T. cordifolia could stimulate the macrophages, leucocytosis and enhances neutrophil activity in various cell lines and animal models [107]. In mice, T. cordifolia extracts has been shown to result in up-regulation of IL-6 cytokine, activation of cytotoxic T cells, and B cell differentiation [108]. The active compound present in the plant include alkaloids, di-terpenoid lactones, glycosides, steroids, sesquiterpenoid, phenolics, aliphatic compounds or polysaccharides and it is reported that the immunostimulatory activity is due to the synergistic effect of these compounds [109].

8.6. Emblica officinalis

Emblica officinalis (Amla), normally known as Indian gooseberry, has been used extensively in the Indian Ayurveda as a potent rasayana i.e. a herbal formulation that helps attain longevity and rejuvenation [110]. It is a rich source of vitamin C and is the main constituent in of chyavanprash, a traditional Ayurvedic herbal jam and Triphala, an Ayurvedic herbal formulation which is considered an important rasayana in Ayurveda [111, 112]. E. officinalis due to their strong antioxidant and biological properties prevent various health disorders related to oxidative stress, cardiovascular diseases, neurodegenerative diseases and cancer. It has been reported to possess antioxidant and antiinflammatory activity and could reduce the side effect of chemo and radiotherapy [113].

9. Bio active plant Peptides as immunomodulators

Natural peptides of great number and diversity occur in all
organisms from plants to microbes to man. Peptides are molecules containing fewer than 50 amino acids, and this discriminate them from proteins and other ‘biologics’. Plants produced peptides to defend themselves against pathogen attack. The first functional plant peptide to be identified was tomato systemin, an 18 amino acid polypeptide which produce as a part of defense mechanism [114]. The peptides exhibit potential health-enhancing property and comprise a vast area within the pharmaceutical industry. The beneficial health effects of bioactive peptides include antioxidant, antiobesity, anti diabetic and immunomodulatory and anticancer activity [115]. These peptides have advantages over chemical or synthetic product/s. They have simple structure and relatively low molecular weight. Moreover, they show low antigenicity, fewer adverse actions and easy absorption [116, 117].

9.1. Plant Defensins

Plant defensins are small antimicrobial peptides (AMP) playing a key role as part of the in defense mechanism of plant system and acting against a broad spectrum of plant pathogens [118]. Apart from its antimicrobial and antifungal activity, plant defensins possess anticancer effect. Sesquin from Vigna sesquipedalis is the first defensin reported to have anticancer activity [119]. They inhibited the proliferation of breast cancer cells and leukemia cells. Phaseolus species produce different peptides like, Limenin, Lunatins, Phaseococcin, Mitogenic defensin, Vulgarinin and Nepalese. These peptides were shown to have anticancer effect in different cancer cell lines [120]. Defensin peptides are also present in some other plants also. The details of the molecular mechanism of anticancer activity of these peptides are not elucidated completely.

9.2. Cyclotides

Cyclotides are macrocyclic peptide with a unique head-to-tail cyclized backbone, which is stabilized by three disulfide bonds. It was first discovered in Oldenlandia affinis DC. (Rubiaceae) leaves have been used as herbal remedy used in traditional African medicine. Members of Violaceae, Cucurbitaceae, Poaceae and Fabaceae may also contain bioactive peptides [121-124]. CycloviolacinO2 from Viola odoratissima found to be cytotoxic towards cancer cells by disrupting the cell membrane [125, 126]. Similarly, HB7 cyclotide from Hedysorhiza biflora inhibited the tumor development in in vivo xenograft model significantly [127].

9.3. Thionins

Thionins are small Cys-rich peptides, generally 45-47 amino acids long that occur in a vast number of dicotyledonous and monocotyledonous plant species [128]. This plant peptide has been classified into 5 subclasses, type I to type V. The anticancer activity of plant thionins has been reported. Pyrularia pubera, the mistletoe contains pyrulariathionin which showed anticancer activity against cervical cancer cells (HeLa) and mouse melanoma cells [129]. Phorotoxins A-F identified in Phoradendron tomentosum, exhibit cytotoxic effect to different cell lines [130]. Viscum album produces a peptide known as viscotoxin B2, showed anticancer activity against rat osteoblast-like sarcoma [131].

10. Conclusion

Immune system is on constant surveillance for foreign substances in the body including transformed cells. But tumor cells are extremely clever, to develop mechanism to avoid detection by their host’s immune system. One of the most important alterations that is being observed during the progression of tumor is that the tumor themselves suppress the immune system by blocking or decreasing the activities of various immune cells with which involved in antitumor defense mechanism of the host. In short, the immune system may act as pro or antitumorogenic system. This dual role of the immune system can be exploited to develop new and effective therapeutic strategies. Natural products derive from medicinal plants including secondary metabolite and small bioactive peptides have provided considerable value to the pharmaceutical industry in the field of anticancer drug production. They act as drug designer molecule since and they could modulate the activities of the immune cells such as NK cells, macrophages, lymphocytes to fight against and to eliminate the defective cells as well as to reduce the side effect of tumor treatment such as chemotherapy and radiation.

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12. References


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