International Journal of Herbal Medicine
Available online at www.florajournal.com

E-ISSN: 2321-2187
P-ISSN: 2394-0514
IJHM 2018; 6(4): 26-34
Received: 07-05-2018
Accepted: 12-06-2018

Sheeja K
DBT Scientist Laboratory of Molecular Medicine, Division of Cancer Research, Regional Cancer Centre, Medical College, Thiruvananthapuram, Kerala, India

Correspondence
Sheeja K
DBT Scientist Laboratory of Molecular Medicine, Division of Cancer Research, Regional Cancer Centre, Medical College, Thiruvananthapuram, Kerala, India

Innate immunity and herbs: In cancer therapeutics

Sheeja K

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 microenvironment 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 aliments 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, Inflammasomes, immunomodulation, plant peptides, tumor microenvironment

1. Introduction
Cancer is a 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 hyperproliferation 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 has 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, 13,1 4]. 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 arginase, 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' simmune 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 naive T cells [64]. DCs also play an important role in maintaining innate and adoptive 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 metastasisand 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, antiinflammtory, 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 Homoeopathy 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 cytotoxic 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 *Andrograpahis 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 revitializing the nerves, hence known as "Brain tonic" in India. It is used as vegetables also. Arial pat of the plant inhibit the proliferation of different human cancer cells in *in vitro* condition [85]. *C. asiatic* a 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 plantextracts 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 withanaloids and Withaferin A which is responsible for the immunostimulatoy 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]. Vernolides 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 cineria* was found to down regulate the iNOs, COX2 and proinflammatoy 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 synergestic 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 antiinflammtory 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, antidiabetic 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 leukemic cells. Phaseolus species produce different peptides like, Limenin, Lunatusin, 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 odoratais* found to be cytotoxic towards cancer cells by distrupting the cell membrane [125, 126]. Similarly, HB7 *cyclotide* from *Hedyotis biflora* inhibited the tumor development in *in vivo* xenograft model significantly [127].

9.3. Thionins

Thioninsare 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. Pyrulariapubera, the mistletoe contains pyrulariathionin which showed anticancer activity against cervical cancer cells (HeLa) and mouse melanoma cells [129]. Phoratoxins 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 ac 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.

11. Acknowledgement

I sincerely thank to Dr. Lakshmi.S, Additional Professor, Regional Cancer Centre, Thiruvananthapuram, for her support and encouragement for writing this review.

12. References

1. Joyce JA, Pollard JW. Microenvironmental regulation of metastasis. Nat Rev Cancer. 2009; 9(4):239-252.
2. Liotta LA, Kohn EC. The microenvironment of the tumour–host interface. Nature. 2001; 411(6835):375
3. Yang AK, He SM, Liu L, Liu JP, Qian Wei M, Zhou SF. Herbal interactions with anticancer drugs: mechanistic and clinical considerations. Curr Med Chem. 2010; 17(16):1635-1678.
4. Naidoo J, Page DB, Wolchok JD. Immune modulation for cancer therapy. Br J Cancer. 2014; 111(12):2214-2219.
5. Mantle DD, Wilkins RM. Medicinal Plants in the prevention and therapy of cancer. Yaniv Z and Bachrach U. eds. 2005, 281-318. The Haworth Press. N.Y. In: Handbook of medicinal Plants Wolchok.
6. Rao GV, Kumar S, Islam M, Mansour SE. Folk medicines for anticancer therapy-a current status. J Cancer Ther. 2008; 6(2):913-922.
7. Amirghofran Z, Bahmani M, Azadmehr A, Javidnia K, Miri R. Immunomodulatory activities of various medicinal plant extracts: effects on human lymphocytes apoptosis. Immunol Invest. 2009; 38(2):181-192.
8. Yamini K, Gopal V. Natural radioprotective agents against ionizing radiation–an overview. Int J Pharm Tech Res. 2010; 2(2):1421-1426.
9. Baliga MS. Anticancer, chemopreventive and radioprotective potential of black plum (*Eugenia jambolana* Lam.). Asian Pac J Cancer Prev. 2011; 12(1):3-15.
10. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell. 2010; 140(6):883-899.
11. Smyth MJ, Dunn GP, Schreiber RD. Cancer immunosurveillance and immunoediting: the roles of immunity in suppressing tumor development and shaping tumor immunogenicity**.** Adv Immunol**.** 2006; 90:1-50.
12. Chimal-Ramírez GK, Espinoza-Sánchez NA, Fuentes-Pananá EM. Protumor activities of the immune response: insights in the mechanisms of immunological shift, oncotraining, and oncopromotion. J Oncol. 2013.
13. Coussens LM, Werb, Inflammation and cancer, Nature. 2002; 420:860-700

14. Albini A, Sporn MB. The tumour microenvironment as a target for chemoprevention. Nat Rev Cancer. 2007; 7(2):139.
15. Kharaishvili G, Simkova D, Bouchalova K, Gachechiladze M, Narsia N, Bouchal J. The role of cancer-associated fibroblasts, solid stress and other microenvironmental factors in tumor progression and therapy resistance. Cancer Cell Int. 2014; 14(1):41.
16. Quail DF, Bowman RL, Akkari L, Quick ML, Schuhmacher AJ, Huse JT *et al*. The tumor microenvironment underlies acquired resistance to CSF-1R inhibition in gliomas. Science. 2016; 352(6288):aad3018.
17. Gajewski TF. Failure at the effector phase: immune barriers at the level of the melanoma tumor microenvironment. Clin Cancer Res. 2007; 13(18):5256-5261.
18. Janikashvili N, Bonnotte B, Katsanis E, Larmonier N. The dendritic cell-regulatory T lymphocyte crosstalk contributes to tumor-induced tolerance. Clin Dev Immunol. 2011; 3:2011.
19. Sica A, Larghi P, Mancino A, Rubino L, Porta C, Totaro MG *et al*. Macrophage polarization in tumour progression Semin Cancer Biol. 2008; 18(5):349-355.
20. Fridlender ZG, Sun J, Kim S, Kapoor V, Cheng G, Ling L *et al*. Polarization of tumor-associated neutrophil phenotype by TGF-β:"N1" versus "N2" TAN. Cancer cell. 2009; 16(3):183-194.
21. Shurin MR, Naiditch H, Zhong H, Shurin GV. Regulatory dendritic cells: new targets for cancer immunotherapy. Cancer Biol Ther. 2011; 11(11):988-92.
22. Gabrilovich DI, Ostrand-Rosenberg S, Bronte V. Coordinated regulation of myeloid cells by tumours. Nat Rev Immunol. 2012; 12(4):253.
23. Ostrand-Rosenberg S. Myeloid-derived suppressor cells: more mechanisms for inhibiting antitumor immunity. Cancer Immunol Immunother. 2010; 59(10):1593-600.
24. Young PP, Ardestani S, Li B. Myeloid cells in cancer progression: unique subtypes and their roles in tumor growth, vascularity, and host immune suppression. Cancer Microenviron. 2011; 4(1):1-11.
25. Wilson, Julia, Fran Balkwill. The role of cytokines in the epithelial cancer microenvironment. Semin Cancer Biol. 2002; 12(2):113-120.
26. Balkwill F. Cancer and the chemokine network. Nat Rev Cancer. 2004; 4(7):540-550
27. Chew V, Toh HC, Abastado JP. Immune microenvironment in tumor progression: characteristics and challenges for therapy. J Oncol. 2012,
28. Bhowmick NA, Neilson EG, Moses HL. Stromal fibroblasts in cancer initiation and progression. Nature. 2004; 432(7015):332-337.
29. Gabriele B, Steven S. The role of pericytes in blood-vessel formation and maintenance. Neuro Oncol. 2005; 7(4):452-464.
30. Nieman KM, Kenny HA, Penicka CV, Ladanyi A, Buell-Gutbrod R, Zillhardt MR *et al*. Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth. Nat Med. 2011; 17(11):1498-1503.
31. Eiró N, Vizoso FJ. Inflammation and cancer. World J Gastrointest Surg. 2012; 4(3):62-72
32. Morrison WB. Inflammation and cancer: A comparative view. J Vet Intern Med. 2012; 26(1):18-31.
33. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature. 2008; 454(7203):436-444.
34. Coussens LM, Werb Z. Inflammation and cancer, Nature. 454(6917):860-867.
35. Lu H, Ouyang W, Huang C. Inflammation, a key event in cancer development. Mol Cancer Res. 2006; 4(4):221-233.
36. Dep Prete A, Allavena P, Santoro G, Fumarulo R, Corsi MM, Mantovani A. Molecular pathways in cancer-related inflammation. Biochem Med (Zagreb). 2011; 21(3):264-275.
37. Durackova Z. Some current insights into oxidative stress. Physiol Res. 2010; 59(4):459-469.
38. Klaunig JE, Kamendulis LM. The role of oxidative stress in carcinogenesis. Annu. Rev. Pharmacol. Toxicol. 2004; 44:239-267.
39. Klaunig JE, Wang Z, Pu X, Zhou S. Oxidative stress and oxidative damage in chemical carcinogenesis. Toxicol Appl Pharmacol. 2011; 254(2):86-99.
40. Barrera G. Oxidative stress and lipid peroxidation products in cancer progression and therapy. ISRN Oncol. 2012; 17:2012.
41. Das PM, Singal R. DNA methylation and cancer. J Clin Oncol. 2004; 22(22):4632-4642.
42. Chanmee T, Ontong P, Konno K, Itano N. Tumor-associated macrophages as major players in the tumor microenvironment. Cancers. 2014; 6(3):1670-1690.
43. Hayashi N, Kataoka H, Yano S, Tanaka M, Moriwaki K, Akashi H *et al*. A novel photodynamic therapy targeting cancer cells and tumor-associated macrophages. Molecular cancer therapeutics. Mol Cancer Ther. 2015; 14(2):452-460.
44. Gordon S, Taylor PR. Monocyte and macrophage heterogeneity. Nat Rev Immunol. 2005; 5(12):953-964.
45. Martinez FO, Helming L, Gordon S. Alternative activation of macrophages: an immunologic functional perspective. Annu Rev Immunol. 2009; 47(27):451-483.
46. Pollard JW. Trophic macrophages in development and disease. Nat Rev Immunol. 2009; 9(4):259-270.
47. Van Ginderachter JA, Movahedi K, Ghassabeh GH, Meerschaut S, Beschin A, Raes G *et al*. Classical and alternative activation of mononuclear phagocytes: picking the best of both worlds for tumor promotion. Immunobiology. 2006; 211(6-8):487-501.
48. Mantovani A, Locati M. Tumor-associated macrophages as a paradigm of macrophage plasticity, diversity, and polarization: lessons and open questions. Arterioscler Thromb Vasc Biol. 2013; 33(7):1478-1483.
49. Shih JY, Yuan A, Chen JJ, Yang PC. Tumor-associated macrophage: its role in cancer invasion and metastasis. J Cancer Mol. 2006; 2(3):101-106.
50. Sangaletti S, Di Carlo E, Gariboldi S, Miotti S, Cappetti B, Parenza M *et al*. Macrophage-derived SPARC bridges tumor cell-extracellular matrix interactions toward metastasis. Cancer Res. 2008; 68(21):9050-9059.
51. Noy R, Pollard JW. Tumor-associated macrophages: from mechanisms to therapy. Immunity. 2014; 41(1):49-61.
52. Theoharides TC, Conti P. Mast cells: the Jekyll and Hyde of tumor growth. Trends Immunol. 2004; 25(5):235-241.
53. Norrby K. Mast cells and angiogenesis, APMIS. 2002; 110(5):355-371.
54. Möller A, Lippert U, Lessmann D, Kolde G, Hamann K, Welker P *et al*. Human mast cells produce IL-8. J Immunol. 1993; 151(6):3261-3266.
55. Sakaguchi S, Wing K, Miyara M. Regulatory T cells–a brief history and perspective. Eur J Immunol. 2007;

37(S1):116-123.
56. Whiteside TL. Regulatory T cell subsets in human cancer: are they regulating for or against tumor progression?. Cancer Immunol Immunother. 2014; 63(1):67-72.
57. Oleinika K, Nibbs RJ, Graham GJ, Fraser AR. Suppression, subversion and escape: the role of regulatory T cells in cancer progression. Clin Exp Immunol. 2013; 171(1):36-45.
58. Ke X, Wang J, Li L, Chen IH, Wang H, Yang XF. Roles of CD4+ CD25 (high) FOXP3+ Tregs in lymphomas and tumors are complex. Front Biosci. 2008; 13:3986-4001
59. Schabowsky RH, Madireddi S, Sharma R, Yolcu ES, Shirwan H. Targeting CD4+ CD25+ FoxP3+ regulatory T-cells for the augmentation of cancer immunotherapy. Curr Opin Investig Drugs (London, England: 2000). 2007; 8(12):1002-1008.
60. Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. Nat Rev Immunol. 2009; 9(3):162-174.
61. Youn JI, Nagaraj S, Collazo M, Gabrilovich DI. Subsets of myeloid-derived suppressor cells in tumor-bearing mice. J Immunol. 2008; 181(8):5791-5802.
62. Peranzoni E, Zilio S, Marigo I, Dolcetti L, Zanovello P, Mandruzzato S *et al*. Myeloid-derived suppressor cell heterogeneity and subset definition. Curr Opin Immunol. 2010; 22(2):238-244.
63. Schmid MC, Varner JA. Myeloid cells in the tumor microenvironment: modulation of tumor angiogenesis and tumor inflammation. J Oncol. 2010.
64. Shurin MR. Dendritic cells presenting tumor antigen. Cancer Immunol Immunother. 1996; 43(3):158-164.
65. Shurin MR, Smolkin YS. Immune-mediated diseases: where do we stand?. InImmune-Mediated Diseases 1-12. Springer, New York, NY, 2007.
66. Ma Y, Shurin GV, Peiyuan Z, Shurin MR. Dendritic cells in the cancer microenvir-onment. J Cancer. 2013; 4(1):36-44.
67. Curiel TJ, Cheng P, Mottram P, Alvarez X, Moons L, Evdemon-Hogan M *et al*. Dendritic cell subsets differentially regulate angiogenesis in human ovarian cancer. Cancer Res. 2004; 64(16):5535-5538.
68. Fainaru O, Almog N, Yung CW, Nakai K, Montoya-Zavala M, Abdollahi A *et al*. Tumor growth and angiogenesis are dependent on the presence of immature dendritic cells. FASEB J. 2010; 24(5):1411-1418.
69. Chen M, Wang J. Regulation of immune responses by spontaneous and T cell-mediated dendritic cell death. J Clin Cell Immunol, 2011.
70. Kantono M, Guo B. inflammasomes and Cancer: The Dynamic Role of the inflammasome in Tumor Development. Front Immunol. 2017; 8:1132.
71. Gardner AB, Lee SK, Woods EC, Acharya AP. Biomaterials-based modulation of the immune system. Biomed Res Int, 2013.
72. Kaur R, Singh J, Singh G, Kaur H. Anticancer plants: a review. J Nat Prod Plant Resour. 2011; 1(4):131-136.
73. Ji HF, Li XJ, Zhang HY. Natural products and drug discovery: can thousands of years of ancient medical knowledge lead us to new and powerful drug combinations in the fight against cancer and dementia?. EMBO reports. 2009; 10(3):194-200.
74. Nawrot R, Barylski J, Nowicki G, Broniarczyk J, Buchwald W, Goździcka-Józefiak A. Plant antimicrobial peptides. Folia Microbiol. 2014; 59(3):181-196.
75. Fukuda H, Higashiyama T. Diverse functions of plant peptides: entering a new phase. Plant Cell Physiol. 2011; 52(1):1-4
76. Danquah MK, Agyei D. Pharmaceutical applications of bioactive peptides. OA biotechnol. 2012; 1(2):1-7.
77. Pan SY, Zhou SF, Gao SH, Yu ZL, Zhang SF, Tang MK, *et al*. New perspectives on how to discover drugs from herbal medicines: CAM's outstanding contribution to modern therapeutics. eCAM. 2013.
78. Niranjan A, Tewari SK, Lehri A. Biological activities of kalmegh (Andrographis paniculata Nees). and its active principle: A Review, IJNPR. 2010; 1(2):125-135.
79. Sheeja K, Kuttan G. Modulation of natural killer cell activity, antibody-dependent cellular cytotoxicity, and antibody-dependent complement-mediated cytotoxicity by andrographolide in normal and Ehrlich ascites carcinoma-bearing mice. Integr Cancer Ther. 2007; 6(1):66-73.
80. Sheeja K, Kuttan G. Andrographis paniculata downregulates proinflammatory cytokine production and augments cell mediated immune response in metastatic tumor-bearing mice. Asian Pac J Cancer Prev. 2010; 11(3):723-729.
81. Sheeja K, Kuttan G. Activation of cytotoxic T lymphocyte responses and attenuation of tumor growth *in vivo* by Andrographis paniculata extract and andrographolide. Immunopharmacol Immunotoxicol. Immunopharmacology and immunotoxicology. 2007; 29(1):81-93.
82. Zhang QQ, Ding Y, Lei Y, Qi CL, He XD, Lan T *et al*. Andrographolide suppress tumor growth by inhibiting TLR4/NF-κB signaling activation in insulinoma. Int J Biol Sci. 2014; 10(4):404-414.
83. Zhai Z, Qu X, Yan W, Li H, Liu G, Liu X *et al*. Andrographolide prevents human breast cancer-induced osteoclastic bone loss via attenuated RANKL signaling. Breast Cancer Res Treat. 2014; 144(1):33-45.
84. Mutua PM, Gicheru MM, Makanya AN, Kiama SG. Actividades Antiproliferativas del Extracto de Centella Asiatica sobre Células Epiteliales Respiratorias Humanas *in vitro*. Int J Morphol. 2013; 31(4):1322-1327.
85. Pittella F, Dutra RC, Junior DD, Lopes MT, Barbosa NR. Antioxidant and cytotoxic activities of Centella asiatica (L) Urb. Int J Mol Sci. 2009; 10(9):3713-3721.
86. Punturee K, Wild CP, Kasinrerk W, Vinitketkumnuen U. Immunomodulatory activities of Centella asiatica and Rhinacanthus nasutus extracts. Asian Pac J Cancer Prev. 2005; 6(3):396-400.
87. Criscitiello C, Esposito A, Gelao L, Fumagalli L, Locatelli M, Minchella I *et al*. Immune approaches to the treatment of breast cancer, around the corner?. Breast Cancer Res. 2014; 16(1):204.
88. Verma SK, Kumar A. Therapeutic uses of Withania somnifera (Ashwagndha) with a note on withanolides and its pharmacological actions. Asian J Pharm Clin Res. 2011; 4(1):1-4.
89. Uddin Q, Samiulla L, Singh VK, Jamil SS. Phytochemical and Pharmacological Profile of Withania somnifera Dunal: A Review. J Chem Pharm Res. 2012; 4(1):559-561.
90. Verma SK, Kumar A. Immunomodulatory activity of *Withania somnifera* (L.), J Chem Pharm Res. 2012; 4(1):559-561.
91. Davis L, Kuttan G. Immunomodulatory activity of Withania somnifera. J Ethnopharmacol. 2000; 71(1-

2):193-200.
92. Iuvone T, Esposito G, Capasso F, Izzo AA. Induction of nitric oxide synthase expression by *Withania somnifera* in macrophages. Life Sci. 2003; 72(14):1617-1625.
93. Ziauddin M, Phansalkar N, Patki P, Diwanay S, Patwardhan B. Studies on the immunomodulatory effects of Ashwagandha. J Ethnopharmacol. 1996; 50(2):69-76.
94. Patel DS, Shah PB, Managoli NB. Evaluation of In-vitro Anti-oxidant and Free Radical Scavenging activities of *Withania somnifera* and *Aloe vera*. Asian J Pharm Clin Res. 2012; 2(4):144-148.
95. Davis L, Kuttan G. Effect of *Withania somnifera* on CTL activity. J Exp Clin Cancer Res. CR. 2002; 21(1):115-118.
96. Mazumder UK, Gupta M, Manikandan L, Bhattacharya S, Haldar PK, Roy S. Evaluation of anti-inflammatory activity of *Vernonia cinerea* Less. extract in rats. Phytomedicine. 2003; 10(23):185-188.
97. Singh A, Saharan VA, Kumawat IC, Khatri A, Bhandari A. A pharmacognostical study of *Vernonia cinerea* Less (Asteraceae) and evaluation of anti-inflammatory and antibacterial activities of stem. Egypt J Pharm Sci. 2014; 13(2):104-112.
98. Sangeetha T, Venkatarathinakumar T. Antitumor activity of aerial parts of *Vernonia cinerea* (L.) Less. against Dalton's Ascitic Lymphoma. Int J Pharmtech Res. 2011; 3(4):2075-2079.
99. Laosim T, Chuchawankul S, Tencomnao T. Immunomodulatory effect of hexane extract of *Vernonia cinerea* Less. trunk on human peripheral blood mononuclear cells. J Chem Pharm Res. 2011; 3:188-195.
100. Kuo YH, Kuo YJ, Yu AS, Wu MD, Ong CW, Kuo LM *et al*. Two novel sesquiterpene lactones, cytotoxic vernolide-A and-B, from Vernonia cinerea. Chem Pharm Bull. 2003; 51(4):425- 426
101. Misra TN, Singh RS, Upadhyay J, Srivastava R. Chemical constituents of Vernonia cinerea, Part I. Isolation and spectral studies of triterpenes. J Nat Prod. 1984; 47(2):368-372.
102. Pratheeshkumar P, Kuttan G. Vernolide-A inhibits tumour specific angiogenesis by regulating proinflammatory cytokines, VEGF, MMPs and TIMP. Eur J Pharmacol. 2011; 656(1-3):10-18.
103. Pratheeshkumar P, Kuttan G. Modulation of immune response by *Vernonia cinerea* L. inhibits the proinflammatory cytokine profile, iNOS, and COX-2 expression in LPS-stimulated macrophages. Immunopharm Immunot. 2011; 33(1):73-83.
104. Singh N, Singh SM, Shrivastava P. Effect of Tinospora cordifolia on the antitumor activity of tumor-associated macrophages-derived dendritic cells. Immunopharm Immunot. 2005; 27(1):1-4.
105. Desai VR, Kamat JP, Sainis KB. An immunomodulator from Tinospora cordifolia with antioxidant activity in cell-free systems. J Chem sci. 2002; 114(6):713-719.
106. More P, Pai K. Immunomodulatory effects of *Tinospora cordifolia* (Guduchi) on macrophage activation. Biology and Medicine. 2011; 3(2):134-140.
107. Sudhakaran DS, Srirekha P, Devasree LD, Premsingh S, Michael RD. Immunostimulatory effect of *Tinospora cordifolia* Miers leaf extract in Oreochromis mossambicus. Indian J Exp Biol. 2006; 44:726-732.
108. Sharma U, Bala M, Kumar N, Singh B, Munshi RK, Bhalerao S. Immunomodulatory active compounds from *Tinospora cordifolia*. J Ethnopharmacol. 2012; 141(3):918-926.
109. Satyavati GV, Raina K, Sharma M. Medicinal Plants of India, New Delhi: Indian Council of Medical Research, 1976, 337.
110. Scartezzini P, Antognoni F, Raggi MA, Poli F, Sabbioni C. Vitamin C content and antioxidant activity of the fruit and of the Ayurvedic preparation of Emblica officinalis Gaertn. J Ethnopharmacol. 2006; 104(1, 2):113-118.
111. Vani T, Rajani M, Sarkar S, Shishoo CJ. Antioxidant properties of the ayurvedic formulation triphala and its constituents. Int J Pharmacogn. 1997; 35(5):313-317.
112. Khosla S, Sharma S. A short description on pharmacogenetic properties of *Emblica officinalis*. Spatula DD. 2012; 2(3):187-193.
113. Pearce G, Strydom D, Johnson S, Ryan CA. A polypeptide from tomato leaves induces wound-inducible proteinase inhibitor proteins. Science. 1991; 253(5022):895-897.
114. Guzmán-Rodríguez JJ, Ochoa-Zarzosa A, López-Gómez R, López-Meza JE. Plant antimicrobial peptides as potential anticancer agents. Biomed Res Int. 2015.
115. Bellmann-Sickert K, Beck-Sickinger AG. Peptide drugs to target G protein-coupled receptors. Trends Pharmacol Sci. 2010; 31(9):434-441.
116. Ma X, Wu C, Wang W, Li X. Peptides from plants: a new source for antitumor drug research. Asian J Tradit Med. 2006; 1(2):85-90.
117. Guaní-Guerra E, Santos-Mendoza T, Lugo-Reyes SO, Terán LM. Antimicrobial peptides: General overview and clinical implications in human health and disease. Clin Immunol. 2010; 135(1):1-1.
118. Wong JH, Ng TB. Sesquin, a potent defensin-like antimicrobial peptide from ground beans with nhibitory activities toward tumor cells and HIV-1 reverse transcriptase. Peptides. 2005; 26(7):1120-1126.
119. Wong JH, Ng TB. Lunatusin, a trypsin-stable antimicrobial peptide from lima beans (*Phaseolus lunatus* L.). Peptides. 2005; 26(11):2086-2092.
120. Craik DJ. Discovery and applications of the plant cyclotides. Toxicon. 2010; 56(7):1092-1102.
121. Poth AG, Colgrave ML, Philip R, Kerenga B, Daly NL, Anderson MA *et al*. Discovery of cyclotides in the fabaceae plant family provides new insights into the cyclization, evolution, and distribution of circular proteins. ACS chemical biology. 2011; 6(4):345-355.
122. Nguyen GK, Lian Y, Pang EW, Nguyen PQ, Tran TD, Tam JP. Discovery of linear cyclotides in monocot plant *Panicum laxum* of Poaceae family provides new insights into evolution and distribution of cyclotides in plants. J Biol Chem. 2013; 288(5):3370-3380.
123. Poth AG, Mylne JS, Grassl J, Lyons RE, Millar AH, Colgrave ML *et al*. Cyclotides associate with leaf vasculature and are the products of a novel precursor in petunia (Solanaceae). J Biol Chem. 2012; 287(32):27033-27046.
124. Gerlach SL, Rathinakumar R, Chakravarty G, Göransson U, Wimley WC, Darwin SP *et al*. Anticancer and chemosensitizing abilities of cycloviolacin O2 from *Viola odorata* and psyle cyclotides from *Psychotria leptothyrsa*. Peptide Science. 2010; 94(5):617-625.
125. Henriques ST, Huang YH, Castanho MA, Bagatolli LA, Sonza S, Tachedjian G *et al*. Phosphatidylethanolamine binding is a conserved feature of cyclotide-membrane interactions. J Biol Chem. 2012; 287(40):33629-33643.
126. Ding X, Bai D, Qian J. Novel cyclotides from Hedyotis

biflora inhibit proliferation and migration of pancreatic cancer cell *in vitro* and *in vivo*. Med Chem Res. 2014; 23(3):1406-1413.
127. Stec B. Plant Thionins-the structural prespective. Cell Mol Life Sci. 2006; 63(12):1370-1385.
128. Evans J, Wang YD, Shaw KP, Vernon LP. Cellular responses to *Pyrularia thionin* are mediated by Ca2+ influx and phospholipase A2 activation and are inhibited by thionin tyrosine iodination. Proc Natl Acad Sci. USA. 1989; 86(15):5849-5853
129. Sauviat MP, Berton J, Pater C. Effect of phoratoxin B on electrical and mechanical activities of the rat papillary muscle. Acta Pharmacologica Sinica. 1985; 6(2):91-93
130. Kong JL, Du XB, Fan CX, Cao Y. Purification and primary structure determination of a novel polypeptide isolated from mistletoe *Viscum coloratum*. Chinese Chem Lett. 2004; 15(11):1311-1314.