Editorial

iMedPub Journals
http://www.imedpub.com/

Journal of Allergy and Inflammation

2017
Vol.1 No. 2:e101

Immunomodulatory and Natural Immunomodulators

Walaa Najm Abood

College of Medicine, University of Diyala, 32001 Baquba, Iraq

Corresponding author: Walaa Najm Abood, College of Medicine, University of Diyala, 32001 Baquba, Iraq,Tel: +964 772 698 1148; E-mail: walaaabood@gmail.com

Receiving date: March 15, 2017; **Acceptance date:** March 20, 2017; **Published date:** March 25, 2017

Citation: Abood WN (2017) Immunomodulatory and Natural Immunomodulators. J Allergy Inflamm 1: e101.

Immunomodulatory

The immune system is a remarkably developed defense system inside vertebrates which guards against attacking factors. It is capable of producing diverse molecules and cells able to distinguish and reduce unlimited changes from external and unwanted agents. Modulation of the immune system refers to some alteration in the immune response which includes stimulation, amplification, expression or inactivation of some stage of the immune response. Therefore, an immunomodulator is a material used to have an effect on the immune system. There are commonly two kinds of immunomodulatory depending on their influence: immunostimulators and immunosuppresses [1]. Materials, which show a modifying immune system response to a threat, are immunomodulators. They modulate and arm the immune system by keeping them in a highly prepared state against any threat [2]. In different parts of the world, plant extracts have been widely investigated for their possible use for immunomodulation.

Many studies have demonstrated isolation of the potential bioactive molecule [3]. For example, *Acorus calamus* a rhizome extract exhibited growth of many cell lines for humans and mice. It could also inhibit the formation of interleukin-2 (IL-2), nitric oxide (NO) and tumor necrosis factor-α (TNF-α). In addition, it causes down-regulation expression of the CD25 marker and many other plant derived compounds like sterols, sterolins, polysaccharides, alkaloids, flavonoids, lectin and glycoprotein are used for immunomodulation [4].

Immunomodulatory Dietary Agents

There are many ways immunomodulation resists a huge range of human and animal diseases such as cancers, viral diseases, inflammatory conditions and autoimmune diseases. Living and non-living factors surrounding us interact with the immune system. A diet should be balanced with its components coming from vitamins, trace minerals and energy. All these have a critical effect on the immune system, starting from their active role in developing immunity, therefore any deficiency predominantly ends in disease. Both living and non-living factors are able to work as immunomodulators.

The living factors include many infectious agents such as different plants, parasites, protozoa, fungi, bacteria and viruses, whereas non-living factors include microparticles and food additives such as titanium dioxide and aluminium silicate. Other non-living factors which co-contribute to the immune system response are environmental factors like air, temperature, radiation, water, pressure, food and toxins [5].

Microparticles are small, non-biological particles that are used in numerous areas of daily life as food additives. The most common food-derived ingested compounds are titanium dioxide and aluminium silicate. Titanium dioxide is a white pigment used in sugar toppings or toothpaste. Becker et al. proved that macrophage-like cells easily take up titanium dioxide after a 6 h incubation period with titanium dioxide resulting in the assembly of caspase-1 and increased secretion of IL-1β. In intestinal epithelial cells, titanium dioxide microparticles may be swallowed by macrophages and intestinal epithelial cells and induce IL-1β and IL-18 secretion. This may trigger inflammation in susceptible individuals [6] Wischke et al, showed the effect of special carriers from poly rac-lactide-co-glucolide to particulate which is to prompt a dose dependent maturing of human monocyte derived dendritic cells to a proinflammatory phenotype with a high level of released cytokines [7]. Pre- pro- and synbiotics enhance innate immunity.

Several plant fibers (prebiotics) have recognized significant effects, which are to increase the function of the innate immune system and the physical barrier in order to increase resistance to disease [8]. The food that we eat is fundamentally composed of proteins, carbohydrates, fats, minerals and vitamins. A suitable integration of these materials is essential to preserve the health of humans. Fats have a potential role in manipulating the immune response.

Fatty acids in the metabolism process are changed to powerful biological mediators, which play a crucial role as immunomodulators. For example, linoleic acid converts in the individual body to arachidonic acid in the plasma membrane of the immune cell and produces leukotrines and prostaglandins, which have an important role during inflammation [9]. Proteins are an essential source of amino acids, important in building cells, and have a critical role in the immune system. Antibodies are proteins in origin; arginine is important in the activation of myeloid cells and includes many different cellular types, from polymorph nuclear to monocytes/macrophages [10].

In one study, arginine and glutamine were given as supplementation to a macrophage culture media and, the results showed that this enhanced macrophage phagocytosis and killing ability and proliferation of T- and B-lymphocytes significantly. These results suggest that *in vitro*, arginine and glutamine are essential substrates and immunomodulators of both innate and adaptive immunity responses in fish leukocytes [11]. Vitamins are crucial for the normal body's defense system through their various roles in the immune system. Vitamin A, B, C, D and E have been proven in previous studies to be important in improving both the innate and adaptive immune response [5].

Minerals like vitamins have a main function in the modulation of the immune response. A deficiency of copper cause decreases in interleukin-2 and T cell proliferation. Selenium deficiency in the diet results in the reduction of macrophage stimulation [12]. In conclusion, immunity is the defence system of the body. Its optimum function depends on essential factors, which can be supplemented by diet and the balance between these factors are important to maintain an optimal function of the immune system.

Recent Improvements on the Ethno-Medicinal Plants as Immunomodulatory Agents

Modulation of the immune response to reduce diseases has long then been of interest and there have been many studies on ethnomedicinal plants as immunomodulatory agents. Immunopharmacology is a relatively innovative and developed branch of pharmacology which aims to search for immunomodulator. The possible uses of immunomodulator in the treatment of AIDS and suppression of normal or exaggerated immune roles as in the treatment of autoimmune diseases. An important source of immunomodulator is medicinal plants and their active components. Therefore, the improvement of drugs for immunomodulation and anti-tumor potential from natural compounds is an interesting project [13].

Immunomodulatory Activity of Natural Source

Previous studies have demonstrated that many of the plant crude extracts have immunomodulatory activity. Ethanol extract of the *Acorus calamus* rhizome has immunosuppressive potential *in vitro*. It inhibits proliferation and encourages human peripheral blood mononuclear cells (PBMCs) to produce interleukin-2, TNF-α, IFN-γ, nitric oxide and expression of cell surface markers CD16 [14]. Crude extract of *Tinospora cordifolia* produces a polyclonal B cell mitogen that improves immune response in mice. Arabinogalactan polysaccharide isolated from the stem of *T. cordifolia* was tested to modulate induction of immunosuppression. Mice pre-treated with arabinogalactan polysaccharide showed protection against lipopolysaccharide (LPS) prompted mortality and increased serum inteleukin-1β, interleukin-6, IFN-γ levels and decreased serum in inteleukin-10 compared to the controls [15]. Other studies investigated the effect of polysaccharide isolated from *T. cordifolia* on phenotypic and functional maturation of murine bone marrow derived dendritic cells. Results showed enhancement of surface expression of CD80, CD40, CD86 and MHCII on derived dendritic cells and stimulated T cells for the secretion of TNF-α and interleukin-12 [16]. Also, Immunomodulatory effect of an isolated fraction from Tinospora crispa on intracellular expression of INF-γ, IL-6 and IL-8 [13].

Ethanol extract of *Boerhaavia diffusa*, a plant used in Indian traditional medicine, significantly suppressed human NK cell cytotoxicity *in vitro* and inhibited production of nitric oxide in mouse macrophage cells, interleukin-2 and TNF-α in human PBMCs. The results demonstrated the immunosuppressive potential of ethanol extract of *B. diffusa* [14]. The β-sitosterol, phytosterols, and its glucoside, were investigated *in vitro*. There was an enhanced proliferative response of T-cells activated by sub-optimal concentrations of phytohaemagglutinin, which significantly improved the expression of CD25 and increased the secretion of interleukin-2 and TNF-γ [17]. Although most studies have focused on the effect of phytosterols on cholesterol-lowering activity, one study on phytosterols showed a modulatory effect on the T-helper immune response *in vivo* using a mouse model, which caused increased interleukine-2 and IFN-γ secretion [18].

Polysaccharides from plants have prompted researchers to study their physical properties and industrial uses depending on their properties. Over the past 20 years, there has been an increase of interest in the biological activity of biomolecules that has led to new sources of bioactive plant polysaccharides [19]. Botanical polysaccharides exhibit a number of advantageous therapeutic properties, and it is assumed that the mechanisms implicated in these effects are through the modulation of innate immunity and more specifically macrophage function. Moreover, botanical and microbial polysaccharides react with common surface receptors and stimulate similar immunomodulatory responses in macrophages; this suggests that evolutionarily covered polysaccharide structural properties are collaborating with these organisms. Thus, the development of botanical polysaccharides provides a unique chance for the discovery of new therapeutic agents and adjuvants that exhibit advantageous immunomodulatory properties [20].

Lee et al investigated the immunostimulatory activity of polysaccharides from Cheonggukjang in RAW264.7 macrophage cells and in an animal model. The results showed that Cheonggukjang polysaccharides stimulate mRNA expressions of inducible nitric oxide synthase and TNF-α. These results suggested that the Cheonggukjang polysaccharide has a potential function in promoting immunity through its regulatory effects on immunological parameters, nitric oxide, TNF-α productions and alterations in indicators related to stress [21].

The polysaccharides from peduncles of *Hovenia dulcis* and their bioactivity potential were studied *in vitro* for immunostimulatory activity. Analysis revealed that they could significantly induce the proliferation of splenocytes and encourage phagocytosis and the nitric oxide production activity of peritoneal macrophages. These results suggest that polysaccharides have effective immunostimulatory activity and could be explored as potential natural immunomodulatory

agents [22]. Other studies have proved that the *in vivo* immunostimulatory activity of polysaccharide from *Cipangopaludina chinensis* could significantly increase the spleen and thymus signals and enhance the macrophage function. These findings suggest that polysaccharides have a potential immunostimulatory activity and could prove to be potential natural immunomodulatory agents.

A polysaccharide-enriched fraction isolated from Curcuma longa exhibited stimulatory effects on PBMC proliferation and cytokine production [23]. Alkaloids and flavonoids are the main components in plants. Various studies around the world have mentioned the bioactivity of these components and their immunomodulatory activity. Berberine, a chief alkaloid constituent of *Coptidis rhizoma* has an anti-inflammatory, anti-bacterial action, and an antitumor and anti- motility effect. A previous study investigated the effect Berberine had on the simulation of macrophage. RAW264.7 cells in LPS stimulation. This alkaloid caused suppression of nitric oxide gene expression that resulted in the reduction of nitric oxide protein production. Besides the production of PGE2 in LPS stimulated RAW264.7 cells was significantly reduced. While there was increased creation of IL-12 in LPS stimulated RAW264.7 cells macrophages [24].

Conclusion

Immunomodulation using medicinal plants could supply alternate predictable chemotherapy for different diseases, particularly once there is a weakened immune response and when discriminatory immunosuppression happens, as in the case of autoimmune syndromes. There is intense activity to detect additional particular immunomodulators that imitate or antagonize the biological properties of interleukins and cytokines. Improvement of evaluation of these mediators will create sensitive and specific screenss. We should reconsider natural medications that could be important sources of innovative ligands capable of directing specific cellular receptors.

References

1. Saroj P, Verma M, Jha KK, Pal M (2012) An overview on immunomodulation. J Adv Sci Res 3: 7-12.
2. Mishra K, Ganju L, Sairam M, Banerjee PK, Sawhney RC (2008) A review of high throughput technology for the screening of natural products. Biomed Pharmacother 62: 94-98.
3. Alamgir M, Uddin SJ (2010) Recent advances on the ethnomedicinal plants as immunomodulatory agents. Ethnomedicine: a source of complementary therapeutics pp: 227-244.
4. Kolm G, Knapp E, Wagner R, Klein D (2007) Lactoferrin a glycoprotein with immunomodulatory and mast cell stabilising properties in skin of horses suffering from culicoides hypersensitivity. Res Vet Sci 83:165-70.
5. Mahima, Ingle AM, Verma AK, Tiwari R, Karthik, et al. (2013) Immunomodulators in day to day life: A review. Pak J Biol Sci 16: 826-843.
6. Becker HM, Bertschinger MM, Rogler G (2013) Microparticles and their impact on intestinal immunity. Dig Dis 30: 47-54.
7. Wischke C, Mathew S, Roch T, Frentsch M, Lendlein A (2012) Potential of NOD receptor ligands as immunomodulators in particulate vaccine carriers. J Control Release 164: 299-306.
8. Bengmark S (2012) Integrative medicine and human health-the role of pre- pro-and synbiotics. Clin Transl Med 1: 6.
9. Calder P, Grimble R (2002) Polyunsaturated fatty acids inflammation and immunity. Eur J Clin Nutr 56: 14-9.
10. Peranzoni E, Marigo I, Dolcetti L, Ugel S, Sonda N, et al. (2008) Role of arginine metabolism in immunity and immunopathology. Immunobiology 212: 795-812.
11. Pohlenz C, Buentello A, Mwangi W, Gatlin DM (2012) Arginine and glutamine supplementation to culture media improves the performance of various channel catfish immune cells. Fish Shellfish Immunol 32: 762-768.
12. Ren F, Chen X, Hesketh J, Gan F, Huang K (2012) Selenium promotes T-cell response to TCR-stimulation and ConA but not PHA in primary porcine splenocytes. PLoS One 7: e35375.
13. Abood WN, Fahmi I, Abdulla MA, Ismail S (2014) Immunomodulatory effect of an isolated fraction from Tinospora crispa on intracellular expression of INF-γ IL-6 and IL-8. BMC Complement Altern Med 14: 205.
14. Mehrotra S, Mishra KP, Maurya R, Srimal RC, Yadav VS, et al. (2003) Anticellular and immunosuppressive properties of ethanolic extract of Acorus calamus rhizome. Int Immunopharmacol 3: 53-61.
15. Desai VR, Ramkrishnan R, Chintalwar GJ, Sainis KB (2007) G1-4A an immunomodulatory polysaccharide from Tinospora cordifolia modulates macrophage responses and protects mice against lipopolysaccharide induced endotoxic shock. Int Immunopharmacol 7: 1375-1386.
16. Pandey VK, Shankar BS, Sainis KB (2012) G1-4 A an arabinogalactan polysaccharide from Tinospora cordifolia increases dendritic cell immunogenicity in a murine lymphoma model. Int Immunopharmacol 14: 641-649.
17. Bouic PJ, Etsebeth S, Liebenberg RW, Albrecht CF, Pegel K, et al. (1996) Beta-sitosterol and beta-sitosterol glucoside stimulate human peripheral blood lymphocyte proliferation: Implications for their use as an immunomodulatory vitamin combination. Int J Immunopharmacol 18: 693-700.
18. Calpe-Berdiel L, Escolà-Gil JC, Benítez S, Bancells C, González-Sastre F, et al. (2007) Dietary phytosterols modulate T-helper immune response but do not induce apparent anti-inflammatory effects in a mouse model of acute aseptic inflammation. Life Sci 80: 1951-1956.
19. Suárez ER, Syvitski R, Kralovec JA, Noseda MD, Barrow CJ, et al. (2006) Immunostimulatory Polysaccharides from Chlorella p yrenoidosa. A New Galactofuranan. Measurement of Molecular Weight and Molecular Weight Dispersion by DOSY NMR. Biomacromolecules 7: 2368-2376.
20. Schepetkin IA, Quinn MT (2006) Botanical polysaccharides: macrophage immunomodulation and therapeutic potential. Int Immunopharmacol 6: 317-333.
21. Lee SJ, Rim HK, Jung JY, An HJ, Shin JS, et al. (2013) Immunostimulatory activity of polysaccharides from Cheonggukjang. Food Chem Toxicol 59: 476-484.

22. Wang M, Jiang C, Ma L, Zhang Z, Cao L, et al. Preparation preliminary characterization and immunostimulatory activity of polysaccharide fractions from the peduncles of Hovenia dulcis. Food Chem 138: 41-47.

23. Yue GG, Chan BC, Hon PM, Kennelly EJ, Yeung SK, et al. Immunostimulatory activities of polysaccharide extract isolated from Curcuma longa. Int J Biol Macromol 47: 342-347.

24. Lee DU, Kang YJ, Park MK, Lee YS, Seo HG, et al. (2003) Effects of 13-alkyl-substituted berberine alkaloids on the expression of COX-II TNF-α iNOS and IL-12 production in LPS-stimulated macrophages. Life Sci 73: 1401-1412.