



Inventing the Immunomodulatory Action of Food Plants with Utilization of Metabolomics: A Narrative Review

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Abstract

The eatable plants illustrate immunomodulatory actions which are advantageous on human health. These actions are inclusive of capacity to activate, multiply or repress immune reactions. Certain of these plants facilitate health by escalating host defenses against variable diseases. Here subsequent to reviewing advantageous action of different plant constituents inclusive of flavonoids polyphenols, terpenes and epigenetic drugs in diabetes we have attempted to extensively review the components of different eatable plants, their immunomodulatory actions along with modes behind Caricapapaya, Coffea spp., Asparagus cochinchinens Dioscoreaalata, beans, herbs, spices, mushrooms, vegetables, and herbal medicinal plants. The studies revealed have been preclinical (in vitro, and in vivo) along with clinical studies (restricted). The bioactive substances implicated in immunomodulatory actions in these plants still have to be isolated. This is In view of the complicated nature of immune system (where multiple cells, cytokines and chemokines) are involved along with that of chemistry of plant extracts is further very complicated. Metabolomics portrays a crucial gadget for performing global profiling of metabolites existing in a complicated system. Thereby it provides a great opportunity for isolating the components present in plant extracts correlated with immunomodulatory actions. In the same manner utilization of metabolomics is feasible for determination of alterations in metabolites in the cells as reactions to treatment. Thereby impacted metabolic pathways which result in activation of some immune reactions might be estimated by just a single experimental study. Nevertheless, the observations here are that metabolomics strategy is not totally generated regarding immunomodulator study of food plants. This is significant for guiding a path for future research on this topic as apart from medicinal plants, food plants get ingested on daily basis in small quantities with greater clear actions on the immune system. Knowledge with regards to probable bioactive substances, their crosstalk (synergism, antagonism) and the way body reacts needs to be assessed in a holistic manner.

Keywords: Eatable Plants; Immunomodulatory Actions; Immune System; Metabolomics

Introduction

Immune system impairment has been implicated in numerous diseases like autoimmune diseases, allergies as well as malignancies [1]. Invention of agents which can work in the form of immune reaction modulators, thereby utilized for procuring cure of different diseases or avoidance of different diseases is a topic that has gained significance recently. Numerous immunomodulators have been generated which are both synthetic in addition to natural products, Nevertheless, the isolation of newer natural immunomodulators persists to be significant in view of some of the present medicines might possess lesser effectiveness or inimical actions [2].

Despite numerous studies have been performed regarding the probable utilization of plant obtained immunomodulators, occasional have propagated to the clinical stage. Of these 6 inclusive

of resveratrol, curcumin, colchicine, capsaicins epigallocatechin gallate (EGCG), quercetin have been reviewed previously by us [3,4]. Nevertheless, dependent on the accessibility of outcomes prolonged research are needed even now for reaching a drug status with approval obtained. First as well as Zudorf [2] revealed absence of studies of quality with treatments which possessed any meaning in the form of a crucial hurdle. Specifically randomized double blind placebo controlled studies, that are believed to be the gold standard for estimating an agent's probability of procuring cure or avoidance are needed for validation. Other germane problems implicate. the natural presence of plant extracts in the form of complicated mixtures of separate phytochemicals. This property might be advantageous or be of disadvantage plant obtained bioactive chemical invention attempts. The enrichment of molecular variation of plants is associated with their particular biological working which cannot be contrasted to that from synthetic agents.

Furthermore their requirement is for an expansive step regarding purification step for identification of newer pure agents. Antagonism or synergism amongst constituents in this complicated provides a considerable difficulty which might be involving plenty of time as well as expenditure. Metabolomics, recently, has got acquisition of remarkable significance recently for evaluating these hurdles. Metabolomics dependent studies regarding isolation of agents from *Orthosiphon stamineus* Benth. whose binding takes place at the adenosine A1 receptors. Identifying cytotoxic agents from *Plectranthus amboinicus* (Lour.) Spreng, along with cytotoxic agents from rice brans are certain instances. Other successful metabolome applications have further been revealed with regards to herb quality control for estimation of purity of commercial oregano samples in addition to discrimination of ginger samples that were grown in 2 different places.

Paucity of studies are present with regards to plant obtained immunomodulatory substances however maximum are medicinal plants. In the recent publications a list of medicinal plants possessing immunomodulatory actions has been displayed. For example, oleanane kind saponins from *Cephalaria tchihatchewi* Boiss, tchihatchewoside A as well as tchihatchewoside B significantly modulated liberation of cytokines (interleukin-1 β (IL-1 β) *in vitro* pointing to their probable activation of innate immune reactions. Terpenoid taraxerone which was identified from Indian medicinal plant taraxerone *Leukas levadulifolia* Sm revealed an *in vitro* immune repression action by reduction of peripheral blood mononuclear cells (PBMC) proliferation along with IL-4 as well as IL-6 in Phytohaemagglutinin (PHA) stimulated Polymorphonuclear leukocytes (PMN) cells. This substance further illustrated a significant *in vivo* phagocytosis repression in experimental mice.

Numerous isolated plants which have immunomodulatory actions are eatable in addition to have assumed a part of our routine diet in life. This is particularly significant in view of routine consumption of these substances in minute quantities might possess a noticeable influence on the body. This takes place by induction of the immune reaction for avoidance or attenuate of the actions of the disease or to hamper once there is escalated immune reaction. Thereby the objective of this review is i) evaluation of recent studies with regards to Immunomodulatory activities of different food plants (*in vivo*, as well as *in vitro*, clinical trial) to estimate in case they were inclusive of isolation of active components along with probable modes of effects) assessment of utilization of metabolomic strategies to find immunomodulators in food plant as well as ii) to crucially assess the present plant obtained immunomodulators in addition to detail scientific work in the manner in which application of metabolomics is feasible in enhancement of the isolation of bioactive substances of significance.

Methods

We conducted a narrative review utilizing the Pubmed search engine on metabolomics, along with transcription factors regulating it using the MeSH terms T2D; food; herbs ; spices ; immunomod-

ulatory role; immunostimulatory activities ; innate immune system ; immune response ;adaptive immune system; 1H-NMR ; nuclear magnetic resonance spectroscopy; LC-MS; PPAR's; from 2000 till date in aug 2023.

Results

We found a total of 1751 articles out of which we selected 90 articles for this review but due to restrictions of journal decreased to 57. No Meta analysis was done.

Immune reaction along with inflammation

Immune system portrays the effects of number of cells a, tissue as well as a organs for picking up, fight along with depletion of foreign agents that manage entry in human body along with might be implicated in disease formation [5]. 2 kinds of immune reaction are present for example innate immune system along with acquired response. Innate immune system works in the form of initial defense system which possess genetic programming with regards to conf prot against pathogenic substances. Pathogen recognition takes place by recognition of pathogenic Molecular pattern liberated from damaged cells with the utilization of foraging receptors in addition to pattern recognition receptors (PRR).

Maximum PRR's are observed on macrophages, as well as IgA dendritic cells along with further might get stimulated to work in the form of the antigen presenting cells (APC's). PRR's further might be observed on the natural killer (NK) cells, endothelial cells as well as the cells of the adaptive immune system [6]. On cell surface or intracellular PRR's at fast pace or effectiveness pass the information to the host with regards to presence of infection which results in activation of the proinflammatory as well as antimicrobial reaction by modulating a variety of intracellular signaling pathways inclusive of adaptor molecular kinases in addition to transcription factors. Thereby liberation of proinflammatory cytokines as well as interferon take place [7]. Nevertheless, the innate immune system is not particular to any pathogen. It possesses dependence on the capacity of a group of proteins along with phagocytic cells for recognition of properties of pathogen followed by fast activation for degradation of the invading pathogens [8]. Nevertheless, the adaptive immune system is substantially particular which implicate antigenic receptors which are formed in every subject [6]. With regards to humoral immunity, a part of the adaptive immune system, T helper (Th) cells aid in generation of B cells into plasma B cells that possess the capacity of generating antibodies against any antigen target. This immune reaction is fashioned to abrogate extracellular infection. Binding of antigen gets neutralized by antibodies which results in breakdown or phagocytosis. As compared to cell mediated immunity the other role of adaptive immune system is its fashioning for working against intracellular infections that get modulated by T cells. Recognition of pathogen by T cells takes place just subsequent to antigen digestion along with presentation over antigen presenting cells (APC), with a major histocompatibility complex (MHC) molecule. The liberated cytokines which aid in adhesion to the infected cells with the MHC- antigen

complex as well as differentiating into cytotoxic T cells. This results in degradation of infected cells [5]. Both T cells along with B cells possess considerable significance in conferring protection against infectious disease in addition to possess the capacity of depletion of malignant cells [9]. Maximum PRR's which belong to the innate immune system; specifically the family of toll like receptors (TLRs) possess the capacity of invoking an adaptive immune reaction of different effectors for instance immunoglobulin (IgM), immuno-

globulin (IgG), immunoglobulin (IgA), T helper (Th1), Th 17 CD4⁺T cells along with CD8⁺T cell reactions [9].

The total immune system is a substantially complicated inter-communicating network which is inclusive of proinflammatory substances in addition to anti-inflammatory substances. Crosstalk amongst cells stimulated by antigen presentation or soluble factor (cytokines, chemokines) promotes connection amongst, adaptive along with innate immune system along with humoral in addition to cell mediated immunity. (see Figure 1).

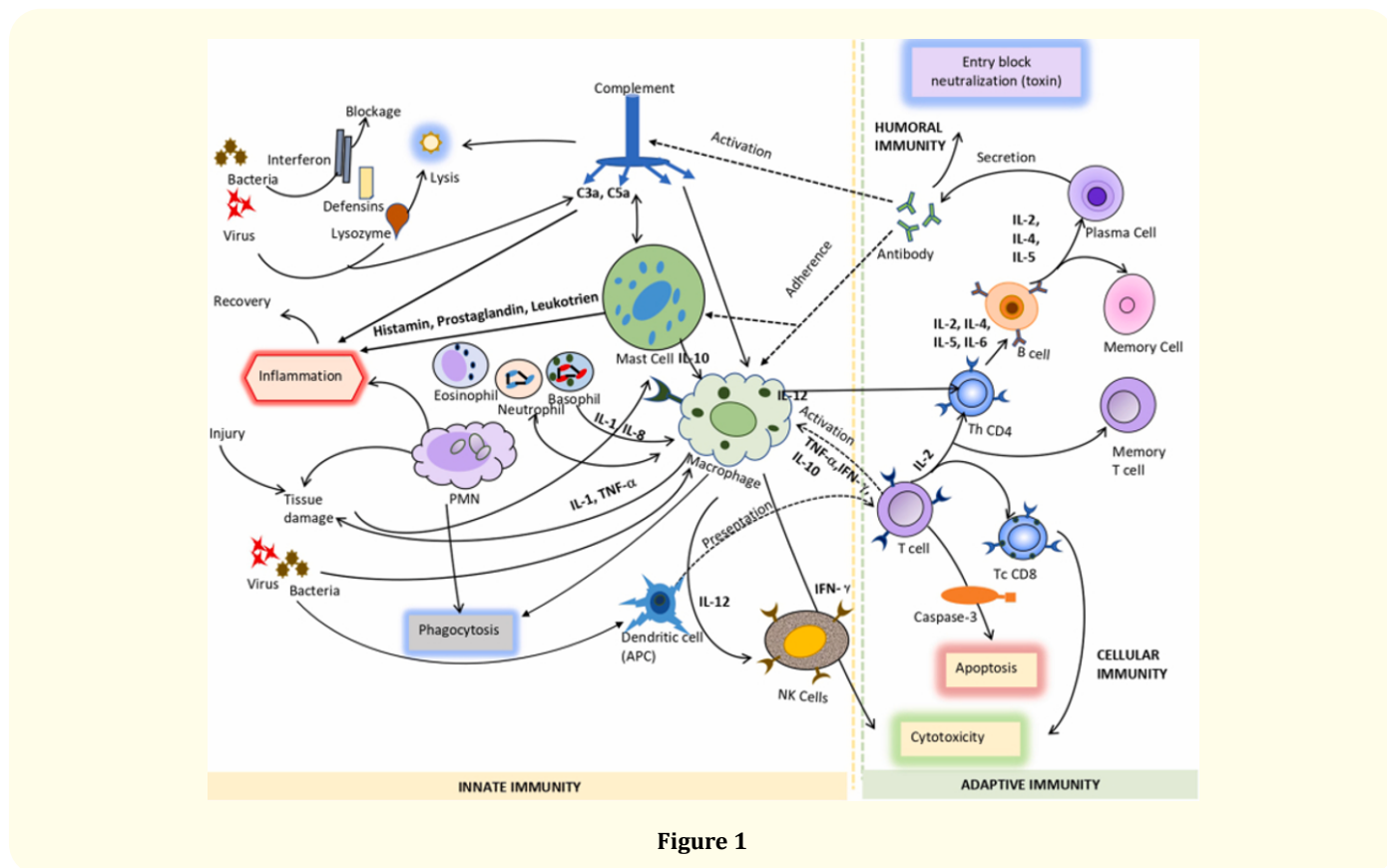


Figure 1

Courtesy ref no-10-A simplified representation of the immune system, displaying the complex interaction network that involves both pro- and anti-inflammatory chemicals.

Black arrows depict immune-cell interactions induced by antigen presentation or soluble molecules (cytokines, chemokines) that facilitate communication between the adaptive and innate immune systems, as well as the cellular and humoral immune systems.

Such crosstalk's are not needed to be limited mutually. The responses to antigens is more commonly the primary source with regards to adaptive immune cells activation for cytokines production. These responses might be implicated in activation/suppression of target cells. These connection networks take place on the in the form of a sequel of crosstalk amongst adaptive along with innate immune system or of their mediators [6]. Inflammation takes place once isolation of infection occurs by innate immune cells or subse-

quent to tissue injury [9]. The body's defense modes implicate alteration in circulation, for instance escalated blood flow in addition to escalated permeability with regards to bigger molecules/cells crossing blood cap from the circulating blood in to the adjacent tissues. The maximum acknowledged symptoms of this event are redness, swelling, fever as well as pain [5]. Escalated inflammatory mediators are liberated by macrophages, monocyte in addition to other inflammatory cells at the time of inflammation. Despite the significant part of inflammatory reaction in protecting at the time of physiological situations, this event is present simply till its requirement regarding avoidance of enhancement of any inimical situations. Unregulated along with escalated inflammation might result in different health situations [9]. Over generation of proinflammatory cytokines (for instance Tumor necrosis factor alpha (TNFα), interleukin-1 (IL-1), IL-6, IL-8, prostaglandinE2 (PGE2) as well as nitric oxide (NO), in addition to Reactive oxygen species (ROS) generation are the properties of inflammatory reaction [5].

Recent Illustrations on Eatable Plant Possessing Immunomodulatory Activity

Caricapapaya Linn

The commercially available fruit of *Carica papaya* Linn., more frequently known as papaya is usually ingested in the form of food. Its leaves along with flowers intake further takes place in the form of vegetables. Regarding the immunomodulatory actions of papaya greater scientific work has been further conducted with regards to probability of the non eatable constituents of papaya (for instance seeds) in contrast to papaya flesh by itself to find any activity [11]. Here just the illustrations on eatable part are described. In Indonesia papaya leaves are ingested in certain parts in the form of vegetables. The immunomodulatory activity of a water extract of papaya leaves (CP) on human PBMC has been illustrated [12]. The PBMC cytokine generation with as well as without presence of CP fraction was determined. The observation was that the generation of IL-2, as well as IL-4 diminished in a dosage based fashion. In comparison Th1 liberated cytokines IFN- γ , TNF α , IL-12p40, IL-12p70 enhanced at lesser quantities (0.124%) which was followed by reduction in escalated quantities (0.25% as well as 0.50%) whereas no impact was found on IL-5 IL-6, IL-10 as well as IL-15. CP did not influence PBMC proliferation. Thereby the conclusions drawn was that CP impacted both innate along with adaptive immune system by their modifications. For finding the active constituents, CP was further fractionated into parts having variable molecular weights with the utilization of cellulose membrane. Nevertheless, no evaluation was performed for finding the active components. CP was further observed to induce apoptosis in jurkat cells by activation of caspase -3/7.

A study regarding the immunomodulatory actions of the maximum consumed eatable part of papaya; its fruit, in healthy humans was performed approximately 10yrs back. 6 healthy male as well as 6 healthy female subjects taking part (23-26yrs) had 2 pre exposure days. 100gm of papaya fruit were administered for every 3 main meals for 2 days concurrently [13]. Peripheral blood samples were collected in the morning prior to meals on day 3 and 5. Significant suppression of IFN- γ ⁺ CD24⁺ along with upregulation of IL-4⁺ CD4⁺ T-cells in addition to upregulation of CD3⁺ CD24⁺ CD27⁺ were observed in subjects ingesting controlled diets in contrast to controls, whereas CD8⁺ T-cells were not influenced. Furthermore, Abdullah, *et al.* [13], further performed an *in vitro* study with the utilization of PBMC of 6 male as well as 6 female subject (21-32yrs age). The cells received treatment with 125,1000, 4000, 16000 μ g/ml papaya extract. This resulted in significant escalation of CD3⁺ CD24⁺ CD127⁺ at the dosage of 4000 μ g/ml in case of male subjects subsequent to 48hr incubation. In comparison, TNF α , IL-6, IL-8 as well as IL-10 cytokines were significantly repressed in total subjects. Just IL-1 β of male subjects was upregulated as well as possessed positive association with Tregs, however no significant association was found in female subjects. It got documented that IL-1 β along with Tregs expression are significant regarding the Th2 part [14]. Dependent on these observations Abdullah, *et al.* [13], assumed that the immunomodulatory actions of the papaya fruit was through esca-

tion of Th2 part with regards to modulating humoral immunity. Th2 possessed greater susceptibility to reduction in CD25⁺ Tregs in contrast to Th1 [15].

In Japan usually fresh papaya (FP) gets fermented with the utilization of yeast as well as lactic acid bacteria which gets commercially marketed in the form of a health food supplementation. In case of a study oral FP extract administration in mice led to sensitization by FITC (fluorescein isothiocyanate) or oxazolone (4 ethoxymethylene -2phenyloxazol) repressed allergic reactions. FITC/oxazolone challenge was performed on both dorsal/ventral right ears. It was illustrated that mice treated with FP possessed minimal lower ear swelling (in mm) in contrast to that observed in control mice. Colon Immunohistochemical finding illustrated that mice who were FP treated possessed significantly lesser IgA along with dendritic cells expression in colon. Treatment with FP considerably diminished quantities of the IFN- γ , TNF α , along with IL-10 in plasma. Hiramoto K., *et al.* [16], thereby concluded that enrichment of antioxidants observed in papaya (for instance Vitamin C as well as carotenoids) might aid in the immunomodulatory activities of FP despite no experiments were performed to confirm this [16]. Fujita Y., *et al.* [17], in a more recently conducted study administered fermented papaya preparation (9gdaily) in tube fed old patients. 30 days continuous administration replenished the PBMC cytolytic activity as well as caused remarkable escalation of natural cell cytotoxicity. Other cytokines estimated in this study (IL-2, IL-6, IL-10 as well as IFN- γ , TNF α) were not impacted. The phenolic profile of fermented papaya was evaluated with the utilization of capillary electrophoresis (CE) in addition to liquid chromatography (LC), time of flight (TOF) mass spectrometry (LC -TOF-MS). Numerous substances were determined (2-hydroxy-4 methyl valeric acid-m-hydroxybenzoic acid, 2,5 di hydroxybenzoic acid, shikimic acid, hippuric acid, homovanillic acid, quinic acid, as well as m-aminophenol). Nevertheless, the mode by which these substances escalated cytolytic activity was not assessed.

Coffee sp

From the instant coffee powder of *Coffea Arabica* beans, a low mass arabinogalactan protein (AGP) was identified which comprised of galactose as well as arabinose. Its immunomodulatory activities have been assessed in mice splenocytes *ex vivo* [18]. There was upregulation of liberation of various Th1 cytokines (IFN- γ , TNF α along with IL-2). Thereby the conclusions drawn were AGP functioned in the form of a proT1 polarization in addition to bio-immunogenic factor with concentration on cellular immunity. In a later study *in vivo* assessment was performed with the utilization of T-cell receptor (TCR) transgenic DO11.10 male as well as female mice allergic model [19]. Daily administration of commercially available sugar free liquid coffee (50% v/v) ad libitum in drinking water for 2wks. Determination of liberation of IFN- γ , IL-2 along with IL-12p40 in mice splenocytes was conducted, however just IL-12p40 upregulation was found in coffee treated mice. The quantities of the IgE in coffee treated mice was lesser in contrast to control mice whereas IgG1 as well as IgE were not impacted.

Both of these studies did not reason out the active ingredients implicated in the probability of the displayed immunomodulatory action. Caffeine portrays the maximum acknowledged constituent in coffee, however whether it is implicated in the revealed actions has to be further evaluated. In a review earlier regarding active constituents implicated in the immunomodulatory action displayed in multiple assessments, caffeinated as well as non caffeinated coffee had akin actions on some cytokines in addition to immunomodulator pointers however variable actions have been revealed in other studies. Other constituents observed in coffee (for instance cafestol, kahweol, chlorogenic acid along with trigonellin acid were associated with antioxidant as well as anti-inflammatory characteristics of coffee [20].

Herbs spices along with vegetables

Detailed publications regarding scientific work on immunomodulatory activities of vegetables are available. Of the commonest recently performed studies is the one where screening of *in vitro* proliferation of methanolic extracts of vegetables along with spices on human lymphocytes was done. Adjustment was done for the per day quantities of every sample for the normal ingestion of the evaluated quantities. The maximum robust samples were observed to be flowers of torch ginger (*Elingera elatior* (Jack) R.M. Sm, lemon basil (*Ocimum Albostellatum* (Verdc.) A. J. Paton, aromatic ginger (*Kaempferia galanga* L.) as well as celery (*Apium graveolens* L.). Despite Safriani N., *et al.* [21] did not isolate the active constituents they posited that the implicated active compounds were not essentially phenolic compounds in view of ¹H-NMR spectra of the 4 maximum active samples differed. Just aromatic ginger illustrated clarity of signals in the aromatic area of ¹H-NMR spectra [32]. Over 10yrs back numerous spices along with vegetables ingested in Japan were screened regarding hampering action against IgE modulated β hexominidase were liberated from RBH-2H3 cells. Methanolic extracts of estragon and thyme were observed to be maximum robust. The active constituent in estragon (IC₅₀ 5 x 10⁻⁵ M) was isolated in the form of 7 methoxy coumarin, whereas luteolin 5,4' dihydroxy-6,7,3'-tri methoxy flavone, 5,4' dihydroxy-6,7,8 3'tetra methoxy flavone as well as 5 hydroxy-6,7,8 3' 4'penta methoxy flavone were isolated in the form of maximum active constituents of thyme having IC₅₀ values of 6.4x10⁻⁶ M, 1.1 x 10⁻⁵ as well as 3.4 x 10⁻⁶ M respectively. No cytotoxicity was apparent at coumarin quantities < 1.1 x 10⁻⁴ M along with flavone quantities < 5 x 10⁻⁴ M). Subsequently Watanabe J., *et al.* [22], assessed the hampering activity of every substance against phorbol 12 myristate 3 acetate (PMA) in addition to A23187 β stimulated hexominidase activity liberated from RBH-2H3 cells [22]. Earlier Zakaria-Rungat F., *et al.* [23], in 2003 scientifically supported the association of ginger (*Zingiber officinale* Roscoe) with its canonical utilization in common cold. They displayed NK cell lysis activity was significantly escalated Subsequent to treatment with ginger water extract in both *in vitro* in humans (no dose provided) as well as mouse (10.4mg/kg BW experiments with the utilization of lymphocytes culture. Moreover, the improvement of proliferative action of T cells along with B cells, as well as CD3⁺ and CD4⁺ T cell subsets was subsequent to treatment

with oleoresin or gingerol as well as shingol fraction in practically akin way [23].

The immunomodulatory activity of water extract of different common vegetables from Umbelliferae activity of vegetables along with spices; for instance celery (*Apium graveolens* L. leaves as well as stem), coriander (*Corianderum satium* L., whole plant), carrot (*Daucus carota* L., root) fennel (*Foeniculum vulgare* Mil., root as well as aerial plant) along with parsley (*Petroselinum crispum* Nyman Ex AW Hill. whole plant), were evaluated. *In vitro* assessment of human PBMC which were obtained from healthy volunteers with utilization of vegetables along with spices extract dosages of 50,100, as well as 200 μ g/ml. At all quantities evaluated the extract possessed the capacity of significantly stimulating PBMC proliferation (other than fennel root) in contrast to blank control. Celery (leaves as well as stem), significantly stimulated IFN- γ liberation in addition to aerial part of fennel. Cherng JM., *et al.* [24], further evaluated different compounds usually observed in the evaluated vegetables along with spices; for instance bergapten, isopimpinellin, xanthotoxin, quercetin, along with rutin. 20 μ g/ml dosage of quercetin, along with isopimpinellin significantly stimulated PBMC proliferation. Acquisition of robust escalation of IFN- γ liberation took place by bergapten, quercetin, along with rutin at dosage of 2 as well as 20 μ g/ml quantities. Lesser stimulation was revealed by isopimpinellin just at 20 μ g/ml dosage, whereas, xanthotoxin action at 2 μ g/ml dosage was more robust in contrast to 20 μ g/ml. Significant escalation of total T cells, total B cells, CD4⁺, CD8⁺ T cells, as well as NK cells was stimulated by quercetin at 20 μ g/ml dosage for 3 days incubation in contrast to control (just buffer). Subsequent to 6 days just active T cells along with CD4⁺ T cells were significantly escalated [35]. Earlier, Menchiriani T., *et al.* [25], in 2007 displayed that aqueous ethanol (1:1) celery extract in addition to its maximum component apelin (*Apium graveolens*) significantly hampered NO₂ liberation by LPS stimulated J774.A1 macrophages having an IC₅₀ of 0.073 mg/ml as well as 0.08 mg/ml respectively. The expression of inducible nitric oxide synthase (iNOS) was significantly hampered by celery extract in addition to apelin having an IC₅₀ of 0.095 mg/ml as well as 0.045 mg/ml respectively. No influence on cell viability was observed on adding extract or apelin. *In vivo* addition of celery extract decreased inflammation on application to mice ears at dosage of 900 μ g/cm² [25].

The immunomodulatory actions of Okra pods (*Abelmoschus Esculentus*) polysaccharides was evaluated. The conclusions of Puji S., *et al.* [26], was that crude polysaccharides might possess the capacity of improvement of immune responses (for instance phagocytic action, spleen index, splenocytic proliferation as well as modulating immunological reactions through cytokines liberation. This was dependent on the outcomes obtained following 2wks of treatment with Okra raw polysaccharides extract in mice having bacterial infections. It escalated phagocytic action, spleen index as well as, splenocytic proliferation at dosage of 75 as well as 100mg/kg dosages; whereas the TNF α quantities escalated in groups receiving crude polysaccharides at dosages of 25,50 as well as 100mg/

kg. Reduction of IL-17 quantities occurred in all treatment groups. Furthermore, crude okra polysaccharides escalated NK cells actions as well as IFN- γ quantities minimally [26]. Further work by Hayaza S., *et al.* [27], of same group as Puji S concentrated on action of Okra raw polysaccharides extract (ORPE) on immune cells along with cytokines in mice with diethyl nitrosamine stimulated hepatocarcinogenesis situation. This study illustrated that ORPE worked in the form of an immune system repressive agent or stimulator. Treatment with ORPE at 50, 100 as well as 200mg/kg body weight directly hampered regulatory T cells accrual, repressed activation of macrophages along with balanced the quantities of effector T cells. Nevertheless, at lesser dosage it stimulated activation of CD8⁺ T-cells as well as increased the quantities of IL-2 at all dosages. No currently available revelation with regards to non polysaccharides substances which illustrate immunomodulatory characteristics is there.

Red seawoods (*Nematodian helminthoides* [Velley] Batters) sulphated xylomannans possess the capacity of stimulating macrophage cells as well as significantly escalating quantities of cytokines (IL-6 along with TNF α) in addition to forms nitric oxide (NO) in murine RAW264.7. Akin actions were seen *in vivo* in BALB/c mice inoculated intravenous with xylomannans. sulphated as well as pyruvated polysaccharides (SP) from green seawood *Caulerpa cupresoides var flabellate* illustrated equal immunostimulatory actions in cultured murine macrophages. Escalation of NO, ROS pro-inflammatory cytokines ((IL-6 along with TNF α) production were seen in all. Earlier, xylogalactans from *Caulerpa lentilifera* possessing carboxyl as well as sulphated polysaccharides were observed to stimulate macrophage proliferation *in vitro* by escalating phagocytosis, NO production as well as acid phosphatase actions.

A food product known as *Gelidium spp* and *Ulvalactuca* Linn seawoods were displayed to escalate human lymphocytes proliferation along with IL-2 generation *in vitro*. Akin actions were displayed with treatment of unprocessed dried *Ulvalactuca or Gelidiumalone* [28]. Geluring was revealed to possess greater quantities of dietary fibers (29.19-29.83%w/w). It possessed a full phenolic as well as flavonoid quantities of 1.38mgGAE/g as well as 1.11mgQE/g respectively by same group of Erniati FZ., *et al.* [28]. Nevertheless, no clarification was there regarding stimulatory action of this food product was secondary to fibers/phenolic as well as flavonoid quantities.

Beans

Subsequent to cereals, legumes (Fabaceae/Luminosae) possess a necessary part in the human diet in the form of a source of proteins, Vitamins, minerals as well as phytochemicals significant for human health [29]. The work regarding Immunomodulatory activity of beans detailed here are correlated with activation of macrophages that is the key step in modulation of innate along with adaptive immune reactions.

The Immunomodulatory activity of 5 frequently ingested eatable beans inclusive of Mung bean (*Phaseolusradiatus* L var typi-

cus) rice bean (*Phaseolus calcaratus* Roxb), soyabean (*Glycinemax* L Merr) small beans (*Phaseolusradiatus* L var. aureua) as well as wild soyabean (*Glycinesoja* Siebold and Zucc) as well as their correlated substances were evaluated in human PBMC [30]. Aqueous extract of soyabean remarkably escalated human PBMC proliferation as well as IFN- γ liberation along with aqueous extract of mung bean, rice bean, small beans as well as wild soyabean just considerably escalated human PBMC proliferation. 5 acknowledged bioactive substances identified in soyabean (genistein, quercetrin, phytic acid, syringic acid, indoles-3 acetic acid) were assessed in this study. Genistein at 2 μ g/ml dosage significantly escalated CD4⁺ T cells along with, diminished active T cells. Syringic acid resulted in immune cell changes akin to genistein as well as diminished active T cells. Phytic acid significantly escalated both full B along with T cells; however did not result in significant escalation of CD4⁺ T cells. Moreover, at 20g/ml genistein, phytic acid as well as syringic acid facilitated a major Th1 immune reaction by escalation of IFN- γ (Th1cytokine) along with substantially decreasing immunorepressive IL-10 liberation.

A study regarding *in vivo* immunomodulatory actions of soyabean were displayed in an earlier study [31]. The immunomodulatory actions of methanol as well as ethanol soyabean extracts (SBM,SBE)at variable dosages (800g/ml to 6.25g/ml) were evaluated regarding their actions on murine macrophage phagocytosis, NO, lysosomal enzyme action, myeloperoxidase actions. Their observations were that SBM, as well as SBE both had an impact on immunomodulatory actions on the phagocytic reaction of peritoneal mouse macrophages in addition to proliferation action of mouse bone marrow cells as well as splenocytes. Nevertheless, no dose response association was found. Liberation of cellular lysosomal enzyme was observed at 200 μ g/ml as well as 100 μ g/ml of both SBM as well as SBE. The extracts significantly stimulated enhancement of quantities of nitrite generation significantly stimulated myeloperoxidase actions at 50,100 as well as 200 μ g/ml. Both SBM along with SBE illustrated stimulation of proliferation actions of bone marrow cells as well as splenocytes, whereas greater quantities illustrated repression of proliferation. SBE illustrated the maximum enhancement of proliferation with as well as without mitogen. Dependent on these outcomes obtained Anitha T., *et al.* [31], observed that SBM as well as SBE activated the non particular immune system through phagocytosis as well as B cells proliferation via T cells independent pathways. The precise substances correlated with these actions were not isolated.

In a separate study immunomodulatory actions of intake of 240 ml of soya milk prepared from black soybeans (enriched with Crude palm oil possessing 295.24 μ g carotenoids) on Type 2Diabetes mellitus (T2DM) patients each day x 1mth [32]. Fasting blood glucose along with glycated haemoglobin A1c (HbA1c) quantities were significantly lesser in the assessed group whereas significant enhancement of IL-6 along with insulin quantities were seen. Moreover, this treatment elevated CD4⁺ T cells along with CD8⁺ T

cells. Thereby they drew conclusions that black soy milk ingestion resulted in probable antidiabetic as well as immunomodulatory actions in T2DM patients.

In contrast to soybeans there exist greater studies on the immunomodulatory actions of mung bean. The anti-inflammatory actions of mung bean ethanol extracts on lipopolysaccharides (LPS) stimulated mouse macrophage cells (J774) was assessed. All pro-inflammatory cytokines inclusive of, IL-1 β , IL-6, TNF α , as well as iNOS were significantly diminished in the cells that got treatment with 3.7mg/ml of mung bean fraction derived from stepwise gradient of methanol in methylene chloride. Gallic acid, vitexin, along with isovitexin were observed to be the major constituents in the active fraction [33].

In a separate study anti-inflammatory actions of mung bean (MB), germinated mung bean (GMB), fermented mung bean (FMB), were assessed *in vivo*, as well as *in vitro*. The murine macrophages cells RAW264.7 viability subsequent to treatment with extracts at 1.25, 2.5, 5 along with 10mg/ml were assessed with utilization of MTT assay. All the extracts at greater dosage (10mg/ml) had a cytotoxic impact on cells following 72 hrs of incubation. Just GMB along with FMB aqueous extract hampered NO liberation in a dose based manner in RAW264.7 cells at 2.5, along with 5 mg/ml quantities. GMB along with FMB aqueous extracts at 1000 mg/kg were illustrated *in vivo* experiments to drastically decrease oedema in mice. These actions possessed greater efficiency in contrast to those of MB along with FMB. AliNM., *et al.* [34], indicated that flavonoids as well as phenolic substances present as chemicals possessed greater enrichment at the time of germination along with fermentation might reason out why GMB along with FMB possessed greater anti-inflammatory actions [34]. Nevertheless, no experiments were conducted to validate this.

Furthermore, MB has enrichment of fibers along with main constituents are of non starch polysaccharides. Numerous studies have revealed the advantages of non starch polysaccharides on immunomodulatory actions. For instance polysaccharides identified from water-alkaline extract was observed to activate RAW264.7 macrophages by escalating the liberation of NO, TNF α along with IL-6 from macrophages [44]. Veribascose, a pentasaccharide from MB possessed the capacity of stimulating RAW264.7 cells proliferation *in vitro*. Maximum immunomodulatory actions of veribascose were obtained following treatment with 200g/ml that illustrated an escalation of IL-1 β , IL-6, IFN- α as well as IFN- γ liberation. More *in vivo* studies displayed that veribascose treatment with 90mg/kg body weight x8days significantly resulted in improvement of spleen index, lysosomal enzyme action in spleen and serum, serum haemolysin quantities, along with ear swelling rate in mice [35].

Mushrooms

Eatable mushrooms have been acknowledged to be a very significant source of proteins, vitamins, minerals as well as dietary fibers. It has further been revealed to possess numerous health

advantages inclusive of immunomodulatory actions. Of the numerous studies just occasional ones are described here. Methanolic extracts from eatable mushrooms *Agaricus bisporus* (JELange) Imbach, *Cantharellus cibarius* E Shield, *Cratellus cornucopoides* Lag as well as *Lactarius deliciosus* (0.5 mg/ml) repressed LPS stimulated NO production in LPS activated RAW264.7 macrophages by hampering the expression of iNOS mRNA. Intriguingly, mushroom extracts diminished LPS stimulated IL-1 as well as IL-6 expression, however did not have the capacity of blockade of TNF α generation of TNF α mRNA expression in activated macrophages. MoroC., *et al.* [36], pointed that the anti-inflammatory actions found, might have been modulated by selective hampering of various upstream factors in activation of macrophages by LPS. Other species assessed in this study which had good anti-inflammatory actions were, *A. bisporus*, *C. cibarius*, as well as *L. deliciosus*. They had the capacity to repress the formation of NO in addition to the expression of iNOS, IL-1 β as well as IL-6 in the macrophages [36]. Akin outcomes were obtained in a separate study with utilization of wild Irish mushrooms extracts. Ethanol extracts of different wild Irish mushrooms inclusive of *Russula mairei*, *Lactarius blennius*, *Cratellus tubaeformis*, *Russula fellea*, as well as *Cratellus cornucopoides* illustrated anti-inflammatory actions of mushroom extracts by decreasing the formation of NO as well as IL-6 in LPS activated RAW264.7 cells. Nevertheless, there was no influence on TNF α [37].

The actions of five commercially available mushroom species, white button as well as honey brown (*Agaricus bisporus*) shiitake (*Lentinus edodes*), enoki (*Flamulina velutipes*) along with oyster (*Pleurotus ostreatus*), on NO as well as TNF α liberation in LPS along with IFN- γ activated murine RAW264.7 macrophages were revealed. All the five mushrooms stimulated the hampering of NO formation (IC₅₀ values of <0.1mg/ml). Nevertheless, just oyster, shiitake as well as enoki mushrooms (IC₅₀ values of 0.35mg/ml, 0.047 mg/ml along with 0.099 mg/ml respectively) illustrated robust hampering of TNF α liberation. Furthermore, Gunawardan D., *et al.* [38], revealed the anti-inflammatory actions of mushrooms which had been processed twice inclusive of ultrasonication along with heating. In contrast to fresh samples processed mushrooms revealed remarkable decreased anti-inflammatory bioactions, pointing that the implicated bioactive chemicals broke down at the time of processing in view of proneness to heating along with other processing treatments [38].

7 Eatable mushroom spp like *A. subrufescens*, *G. Frondosa*, *L. edodes*, *H. tessellatus*, *P. eryngii*, *P. nameko*, *P. ostreatus* were assessed regarding their capacity of stimulating dendritic cells (DC) in addition to their following actions on T cells. Evaluation of stimulating DC was done via determination of IL-6, IL-10, IL-12, IL-17, TNF α along with IFN- γ quantities along with expression of DC. It was observed that every mushroom extract facilitated DC's in unique manner as validated by liberation design of different cytokines of DC's. Mushrooms spp having bad cytokine reactions appeared to decrease different maturation markers inclusive of

MHCII, CD40, CD86, CD11c. Just *A. subrufescens* illustrated full DC maturation markers of the 7 eatable mushroom spp assessed. Other species (spp) assessed escalated MHCII along with CD 36 expression however had no actions on CD40, or CD11c expression. DC 'S endocytosed all of the mushroom spp assessed via activation of C-type lectin receptor (CLR). Moreover, stimulated DC 's were observed to escalate T cells; however without requirement of physical intricacy amongst DC 's as well as T cells. This suggested the significance of CLR in mushroom immune system stimulation action [39].

Dioscorea.alata L.

The eatable part of *Dioscorea.alata* (DA) or water yam is the tuber. In South east Asia along with Africa DA ingestion takes place in the form of a dietary supplement [40]. The fresh tuber slices are broadly utilized in the form of functional foods in Taiwan in addition to dried slices utilization takes place in China in the form of canonical medicine (Liu., et al. 1995). The *in vitro* immunomodulatory activity of aqueous methanolic extract was assessed in Swiss albino mice splenocytes at dosage of 5,10,20,40, as well as 80 µg/ml [58]. Dey P., et al. [41], estimated proliferation as well as liberation of cytokines (IL-2, IFN-γ, IL-4 as well as IL-10). Methanolic extract of DA was illustrated to significantly escalate proliferation of splenocytes in contrast to untreated cells. Th1 correlated liberation of cytokines (IL-2, IFN-γ) were significantly upregulated at DA quantities of 20µg/ml as well as greater in contrast to untreated cells. Nevertheless, the Th2 correlated cytokines liberation (IL-4 in addition to IL-10) were significantly downregulated at DA quantities of 10µg/ml as well as greater. This observation pointed that *D.alata* activity switched the Th0 lymphocytes differentiation into the activation of Th1 immune reactions.

Asparagus cochinchinens Merrill

Asparagus cochinchinens Merrill tuber portrays a canonical herbal treatment which possesses calming characteristics whose utilization is done for treatment of different immune correlated diseases. The assessment of anti-inflammatory actions of 70% ethanolic extract from *Asparagus cochinchinens* Merrill (ACE) was performed by Lee D., et al. [42], in diminishing ear oedema stimulated by 12-Otetradecanoyl-phorbol-13acetate (TPA). The outcomes obtained revealed 10 days treatment of ACE at 200mg/kg body weight dose significantly diminished ear oedema thickness as well as weight. In view of the generation of proinflammatory cytokines IL-1β in addition to TNFα was repressed; thereby Lee D., et al. [42], posited that anti-inflammatory actions of ACE were correlated with hampering of IL-1β, TNFα in addition to proliferation of leukocytes [42].

Akin outcomes were found in a more recent study. The actions of ethyl acetate extract of *A. cochinchinens* (EaEAC) in repressing phthalic anhydride (PA) induced skin inflammation in case of IL-4/Luc/CNS-1 transgenic (Tg) mice were assessed [43]. The part of IL-4 cytokines at the time of anti-inflammatory activity of EaEAC was assessed subsequent to a 2wks therapy. The observations were that EaEAC treatment significantly diminished general phenotypic markers inclusive of ear thickness, lymph node weight, quantities of IgE as well as mast cells infiltration. EaEAC treatment further diminished liberation of IL-1β along with TNFα. Nevertheless, they did not detail the correlated active substances.

Figure 2 shows the structure of *Asparagus cochinchinens*. Courtesy ref no-57

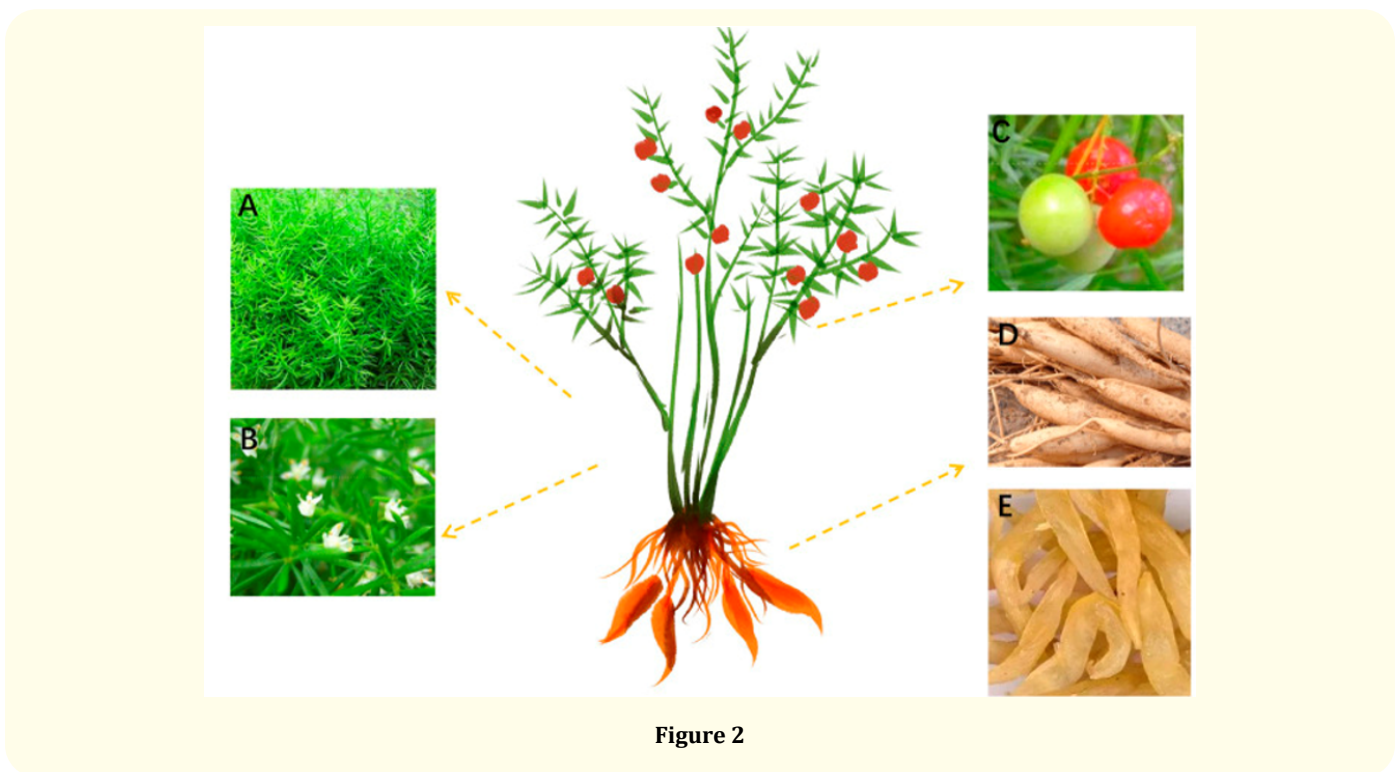


Figure 2

Figure3 is the mapping of every plant reviewed hereto show the influence on the total immune system network. Every plant has the placement at the probable place where it might have an action.

Courtesy ref no-10 Overall immune system regulation in which the plants discussed in this review are placed in positions where they may have an impact there 27-32 is 16-21, 21-26 is 9-14.

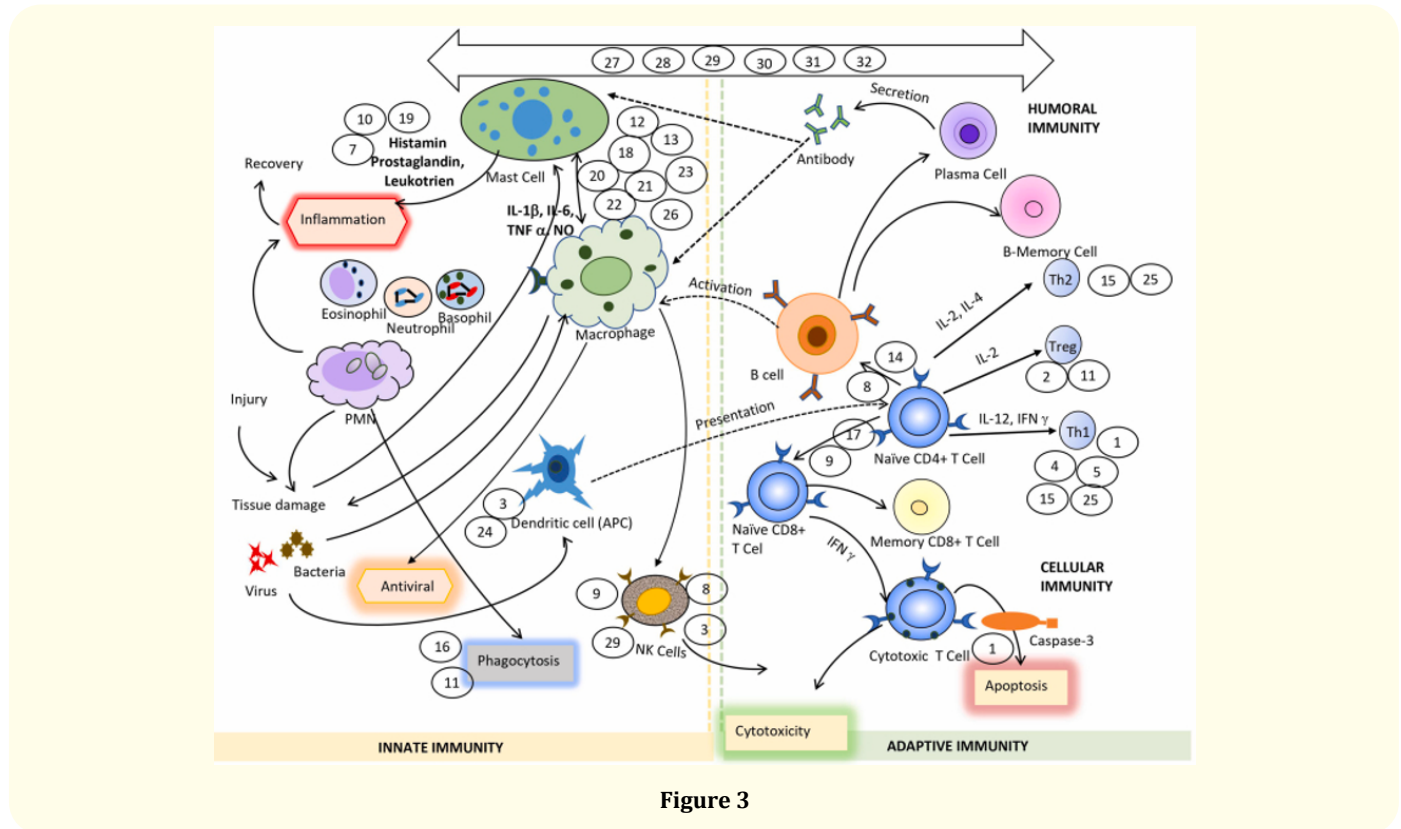


Figure 3

Metabolomics application in investigations of immunomodulatory substances obtained from eatable plant

On search of different engines illustrated paucity of studies regarding metabolomics strategies in displaying the immunomodulatory actions of eatable plants. Just studies were observed that were applicable- are described below.

Seeds of date palm (Phoenix dactyliferaL)

The date palm is a homegrown crop possessing significant nutritional, medicinal, as well as commercial value. Furthermore, the pulp along with seeds are also utilized in canonical medicine for the treatment of different diseases. 1H-NMR dependent metabolomics utilization was made for evaluating the Algerian Deglet date palm seed extract on the extracellular along with intracellular metabolome of LPS along with IFN-γ stimulation on RAW264.7 cells. This study was further fashioned to evaluate the changed metabolic pathways as well as isolate crucial metabolites which are correlated with inflammation. LPS along with IFN-γ stimulated RAW264.7 cells had treatment with 100µg/ml date seed ethanolic extracts. The culture medium along with cell suspensions went through 1H-NMR evaluation. Multivariate analysis principal component analysis (PCA) as well as orthogonal partial squares least discriminant analysis (OPLS-DA) utilization was done for finding the differentia-

tion of normal (NML), induced (IND) as well as treated (DGS) cells along with to isolate probable differentiating metabolites in extracellular along with intracellular metabolomes. Of the outcomes obtained intracellular metabolites of NML revealed a separate design in contrast to IND cells. Nevertheless, no clearcut grouping of intracellular constituents isolated amongst the NML along with DGS groups was seen. 11 of the DGS metabolites were substantially separate from the IND groups, which were inclusive of various amino acids (glycine, serine, leucine along with phosphocholine) as well as succinate. These observations pointed that the anti-inflammatory actions of DGS was correlated with an enhancement of energy along with amino acids metabolism [44]. Various amino acids for instance glycine as well as leucine were posited to possess a part in the immune system by impacting effector cells, liberation of cytokines, presentation of antigen along with immune cells proliferation [45]. The oxidation quantities of succinate were further revealed to be significant in shifting proinflammatory macrophages into anti-inflammatory macrophages.

Camellia nitidissima C.W. Chi

Camellia nitidissima C.W.Chi represents a canonical medicinal, as well as eatable herb observed in Southern China along with Northern Vietnam. 3-cinnamoylribuloside (3CT) which is a cinnamoyl

glycol flavonoid extract from the flowers of *C. nitidissima* Chi was evaluated with regards to its anti-inflammatory actions in LPS activated RAW264.7 cells. The outcomes obtained displayed that in LPS activated RAW264.7 cells, 3CT repressed formation of NO as well as expression of iNOS mRNA. Moreover, expression of mRNA along with ELIS Assay outcomes revealed that 3CT possessed the capacity of decreasing liberation inflammatory cytokines, like TNF α , IL-1 as well as IL-6 in LPS activated RAW264.7 cells. The anti-inflammatory metabolic pathways was assessed with the utilization of 1H-NMR dependent metabolomics. Metabolites of LPS activated RAW264.7 cells (LPS, control, greater dose, medium dose as well as lesser dose treated groups) were extracted as well as went through 1H-NMR evaluation. Multivariate data analysis, PCA as well as orthogonal signal correction partial squares least discriminant analysis (OSC-PLS-DA) for evaluating viability amongst cell groups. greater dose treated cells were further segregated from other groups, however the medium dose as well as lesser dose treated cells were in overlapping positions with the LPS group. Choline, taurine, glucose, lactic acid, alanine along with various other amino acids were observed in the form of unique markers amongst cell groups. This associated with alterations in estimated cytokine quantities resulting in a conclusion that in LPS activated RAW264.7 cells, 3CT influenced the cholinergic anti-inflammatory system, Oxidative stress (OS), energy along with amino acids metabolism [46].

Ganoderma lucidum (Leyss, ex Fr) Karst

Ganoderma lucidum (Leyss, ex Fr) Karst Lingzhi is an advantageous eatable fungus utilized world over in the form of supplement in diet for health sustenance. It further represents a medicinal fungus for treating fatigue, immunological diseases along with cancer. A recent study that attempted to identify the immunoenhancing features of oil of *Ganoderma lucidum* spores (GLSO) that is one of the maximum acknowledged *G.lucidum* products was displayed. Initially, they assessed the immunostimulant activity in mice treated with 400 as well as 800mg/kg of GLSO by estimating macrophages phagocytosis activity in their splenocytes which was followed by utilization of LC-MS dependent metabolomics for assessing the properties of GLSO stimulated mice faecal metabolome modifications. Their observations pointed that greater dose of GLSO (800mg/kg) possessed immunostimulating activity in mice by escalating macrophages phagocytosis as well as NK cells cytotoxicity. The metabolomics study displayed 143 considerable alteration in metabolites subsequent to GLSO treatment (29 downregulated as well as 114 up regulated). PLS-DA illustrated there were considerable alteration in metabolites amongst control along with GLSO treatment groups dependent on the germane enrichment of these metabolites which are differentially expressed. Subsequent to GLSO treatment, EGG metabolic pathways i.e. arginine, proline metabolism tyrosine metabolism, porphyrin as well as chlorophyll metabolism in addition to serine/threonine metabolism were substantially escalated. This study further validated the conclusions that amino acids metabolism possessed key part in immune system controlling [47].

Clinacanthus Nutans (Burm. f) Lindau

Clinacanthus Nutans is a shrub indigenous to Southeast Asia having utilization in the form of canonical herbal medicine, apart from ingesting as vegetables. A study by Khoo LW, *et al.* [48], regarding utilization of 1H-NMR metabolomics for associating the chemical constituents of *C. Nutans* with its anti-inflammatory actions in LPS along with IFN- γ activated RAW264.7 macrophages were revealed. The extracts of *C.Nutans* were formed with various solvents (deionized water along with ethanol, 60 extracts in toto) and constituents of cells of the extracts were evaluated utilizing *in vitro* NO hampering assay in LPS-IFN- γ activated RAW264.7 macrophages, with the water extract being the maximum robust kind. subsequently, all of the extracts went through 1H-NMR evaluation along with outcomes obtained were associated with partial least squares analysis (PLS). PLS displayed that clinacoside B, lactic acid, alanine, clinacoside A along with valine were observed in water extract might have possessed a greater hampering impact on the found NO hampering action in contrast to others. Other substances (Clinamide A, B, C, phytosterols, glutamine, crientin, along with isocrientin) were further observed to possess positive however weaker association with the action [66]. One more study by Khoo LW, *et al.* [49], on utilization of 1H-NMR metabolomics displayed the necessary biomarkers apart from modes behind antianaphylaxis characteristics of *C.Nutans* leaf extract in an ovalbumin-induced anaphylaxis rat model. The rats received 125,500 as well as 2000mg/kg body weight *C. Nutans* water extract. Their plasma as well as urine went through 1H-NMR evaluation which was followed by analysis utilizing Multivariate analysis. OPLS assessment of NMR outcomes illustrated that *C. Nutans* extract conferred protection against ovalbumin-induced anaphylaxis by downregulating carbohydrate as well as lipids metabolism apart from upregulating citrate cycle intermediates, propanoate, amino acids in addition to nucleotide metabolism [49]. Despite not determined in this study, *C. Nutans* leaf extract might have disturbed adaptive immunity. Earlier studies have illustrated that alterations in cellular nutrient quantities possessed a complicated action on the signalling pathway as well as working of the immune cells.

Courtesy ref no-10 The proposed work flow for the use of metabolomics approach in the immunomodulator study of food plants.

Metabolomics application in investigations of immunomodulatory substances obtained from medicinal plant

Akin to food plants search of different engines illustrated paucity of studies regarding metabolomics strategies in displaying the immunomodulatory actions of medicinal plants which are not part of daily food.

Echinocacea species

Echinocacea species portray the maximum utilized herbs regarding the treatment of flu along with upper respiratory diseases world over. A metabolomics strategy dependent on ultra high

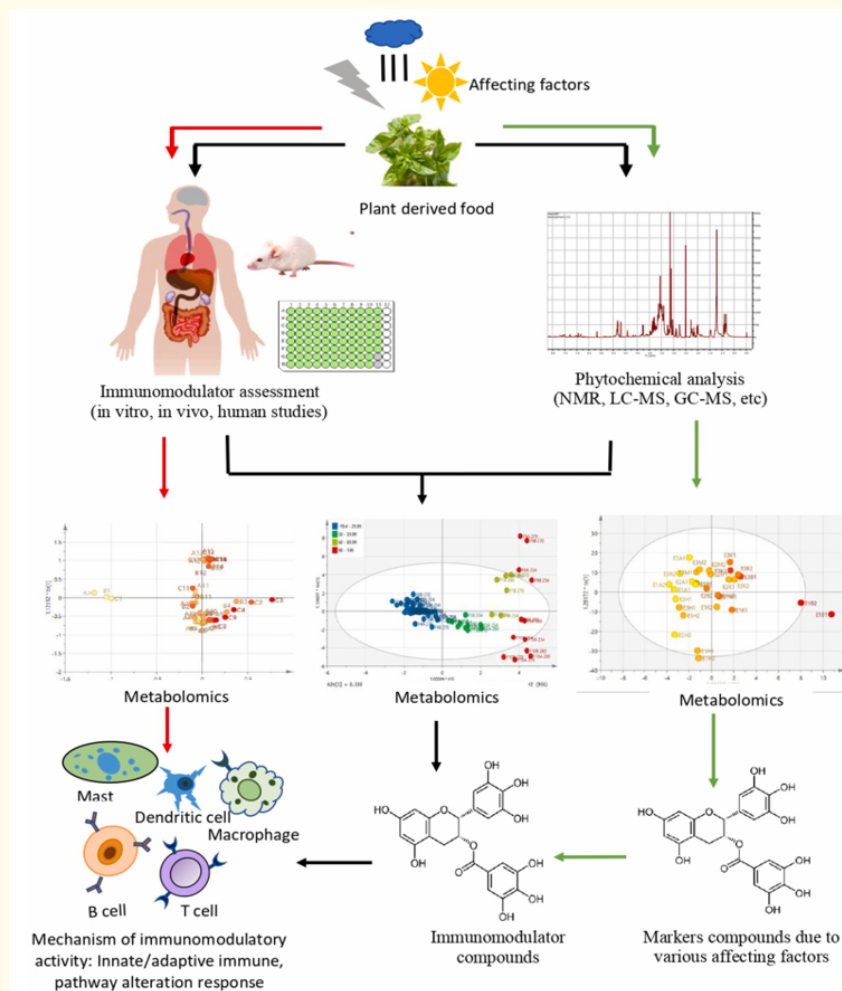


Figure 4

performance liquid chromatography (LC), coupled with triple quadrupole mass spectrometry (UPLC-Qq Q-MS) utilization was done for performing an extensive evaluation of immunomodulatory biomarkers of different substances observed in roots in addition to plants of 3 Echinocaceae species *Echinocaceae. purpurea* (L.) Moench, *E. angustifolia* DC and *E. pallida* (Nutt). OPLS analysis which associated UPLC-Qq Q-MS along with activity outcomes illustrated that 8,11di hydroxy -2,4,9dodecatricenoic acid isobutylamide, dicaffeoylquinic acid, Echinacoside as well as 8 hydroxy pentadeca (9E,13Z)dien-11 yn-2-one, were substances positively associated to RELA (nuclear factor κ B (NF κ B) downstream transcription factor p65) intermediate pathway activation in the humans colorectal adenocarcinoma cell line Caco2. Over expression of NF κ B was further positively associated with 2-undecene -8,10 diynoic as well as isobutylamide along with dicaffeoylquinic acid. The observations further indicated that polyenes immunomodulatory actions were associated with IL-6 generation along with diminished RELA as well as NF κ B pathways. Furthermore, alkylamides further aided in escalation of IL-6, NF κ B along with NO generation generation [50].

Yupingfeng granules

Yupingfeng granules (YPPG) portray part of canonical/traditional Chinese medicine (TCM) which constituted of 3 herbal medicines; *Astrali Radix* (Huangqi); *Astracytoides macrocephalae* Rhizoma (Baizu) as well as *Saposhnikoviae Radix* (Fangfeng). An integrated metabolomics and network pharmacology approach was utilized for estimating physiologically active components, probable biomarkers as well as modes behind immuno controlling actions of YPPG in Sprague Dawley rats. The rats had intraperitoneal treatment at dosage of 1.6g/kg bw that was akin to adult dose/day of the TCM prescription. The metabolomics approach displayed that YPPG modulated the quantities of different bile acids as well as glycerophospholipids for restoration of immunodeficient rats back to their normal conditions. The compounds target network was generated with 9 acknowledged constituents in YPPG in the form of target substances. Maximum modes behind YPPG actions were estrogen receptor, Peroxisome Proliferator Activated Receptor (PPAR), mitogen activated protein kinase (MAPK), phosphatidylinositol 3 - kinase (PI3K) protein kinase B (mTORC2- AKT)/c-Jun-N-terminal kinase (JNK) signaling pathways along with ubiquitin

modulated protein breakdown. This implied that immunomodulatory modes were intricately associated with lipids metabolism along with inflammatory reactions. Dependent on the observations of metabolomics as well as pharmacology network, YPGF impacts

lipid metabolism along with inflammation [51]. Bile Acids work in the form of anti-inflammatory of DC, along with regulatory T cells in the large intestine, whereas varied kinds of glycerophospholipids were significant nutrients for macrophages polarization.

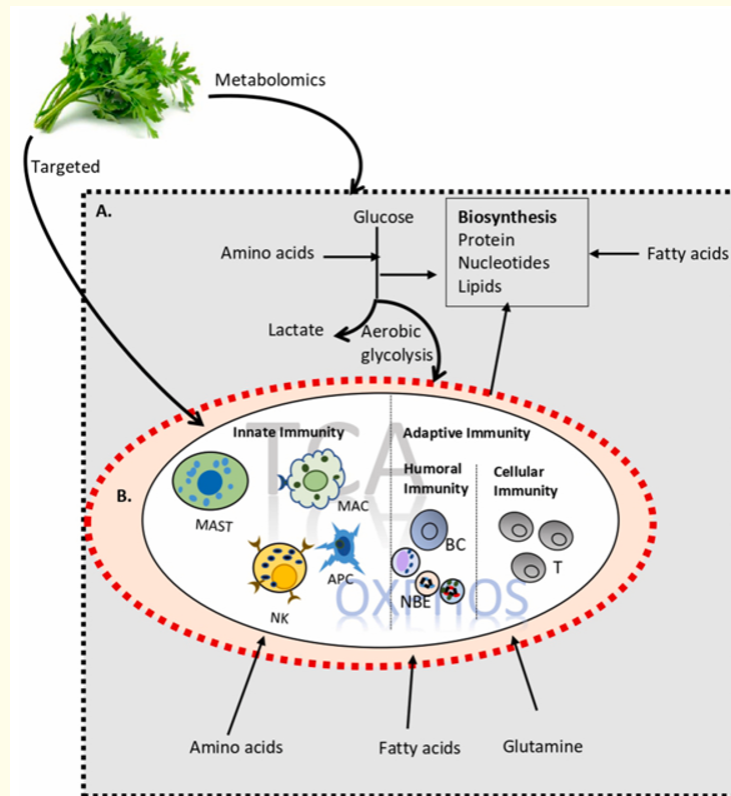


Figure 5

Courtesy ref no-10 -Comprehensive information is retrieved when a conventional targeted approach is used together with the metabolomics method for immunomodulator potential assessment of food plants. When metabolomics is used alone, or in combination with targeted research, a more comprehensive picture is obtained of how the intervention of bioactive components contained in plant-based foods affects the dynamics of the immune system. A. Comprehensive information obtained from metabolomics based-research to elucidate the effect of plant-based food to the immune-system. B. Information obtained from targeted research. MAST ¼ mastocyte, MAC ¼ macrophage, APC ¼ antigen presenting cell, NK ¼ Natural Killer, NBE ¼ Neutrophil-Basophil-Eosinophil, BC ¼ B cell, T ¼ T cell, TCA ¼ tri carboxylic acid cycle, and OXPPOS ¼ oxidation phosphorylation that occurs in each immune cell.

Discussion

Maximum of studies have been utilized in the form of a targeted strategy. It appears that the metabolomics strategy has not been broadly used for evaluating the health actions of food although the greater as well as deeper insight over advantages metabolomics give in contrast to targeted strategy. In case of metabolomics, the metabolome of cells that is the aim of *in vitro* experiment, or clinical studies gets determined by some gadgets meant for evaluation.

Different chromatographic along with spectroscopic techniques as well as combination can be selected. The techniques which get utilized maximally in metabolomics are gas chromatography- mass spectrometry (GC -MS), liquid chromatography-mass spectrometry ((LC- MS) as well as 1H-NMR.Each of these approaches possess their benefits as well as restrictions that have to be taken into account. NMR is a very good gadget regarding isolation as well as quantification of substances in particular in a complicated mixture. 1H-NMR determinations are dependent on enrichment of isotopes that exists in practically all metabolites. This aids in determination of broad spectrum of metabolites. There is no requirement of any calibration curves for the estimation of germane quantities of substances existing in samples in view of the absolute quantities of hydrogen atoms implicated in the signal gets portrayed by the inherent part of every signal. NMR further possesses good replication characteristics as well as requires simple preparation. The restrictions of NMR are correlated with complicated spectra as well as lesser sensitivity in contrast to MS [52].Furthermore, MS gets usually combined with a chromatography approach (LC or GC).It yields greater sensitivity however portrays problems in quantification of substances in view of separate substances require particular calibration curves [52].The results from this estimation requires preprocessing (for instance-baseline correction as well

as noise quantities) prior to subjecting to multivariate analysis. Variable multivariate analysis can be utilized; the commonest are unsupervised as well as supervised PLS-DA or OPLS-DA [53]. Orthogonal partial least square (OPLS) or partial least square (PLS) evaluation - might be further utilized for associating a plant's metabolome results with their immunomodulatory actions. The ultimate results are the invention of differentiating plant's metabolites for every group studied in addition to understanding the actions of metabolome of cells or organism treated. In contrast to the actions of acknowledged drugs metabolomics along with probability of other omics can aid in isolating probable mode behind effects or probably isolation of innovative effects. Thereby the ultimate mode behind immunomodulatory actions of the extract as well as distinct substance which present can get mapped in the human pharmacology network. Estimation of metabolome of plant's extract by itself is significant taking into account variable geographical originators, various cultivators, various processing approaches or time of harvesting. These factors impact plant's metabolome profile hence its health associated bioactions [54,55]. Taketa AT, *et al.* [56], utilized metabolomics for isolating sedative substances in the plant *Galphinia glauca* for evaluating plant material from various sources as well as checking *in vivo* sedative actions of all Eco kinds with subsequent supervised Multivariate results analysis where there was combined chemistry as well as pharmacology. This illustrated greater variation; however by segregating the active along with lesser active extracts PLS-DA illustrated that modified triterpenes as well as flavonoids were actually associated with activity [56]. Thereby the metabolomics represents a multifunctional gadget which possesses the capacity of generating knowledge with regards to active components as well as their pharmacological actions. Further it is the approach of choice regarding quality regulation. Khoo LW, *et al.* [48,49], works over *Clinacanthus Nutans* are great works with regards to metabolomics. The posited workflow for utilization of metabolomics strategies are depicted in figure 4 and 5 reveals how extensive knowledge might be gathered on use of canonical targeted strategy is utilized with metabolomics strategies for immunomodulator probable evaluation of food plants.

Conclusions

The objective of this review was evaluating earlier performed in past 10 yrs regarding food plant immunomodulation. Actually, occasional publications are accessible on this area where the outcomes obtained were too early for giving a definition on evidence dependent utilization of food plant in the form of medicine. Here we conducted the assessment of different food plants which were inclusive of *Caricapapaya*, *Coffea* spp., *Asparagus cochinchinens* *Discoreaalata*, beans, herbs, spices, mushrooms, vegetables, in addition to herbal medicinal plants. Where it was germane, the phytochemical constituents were further detailed. Nevertheless, this knowledge was restricted. Extensive scientific work is the need of hour in the context of immunomodulatory actions for generating evidence dependent functional foods as well as innovative drugs

invention. The final goal is enhancement of human immune system with lesser inimical actions. Furthermore, downregulation of the immune system is an intriguing target for the drugs generation (in case of patients having transplant) or is advantageous in disease where immune system is overactive (like in COVID19). As earlier described maximum studies have utilized canonical targeted strategies by assessing the plant extracts or fractions in cell lines, mainly for targets of the immune system. Experimental animals utilization further concentrated on determination of target proteins or genes. The similar was applicable in human subjects. Studies performed in human subjects were scarce as well as utilized targeted strategy. In view of the complicated nature of immune system along with that of chemistry of plant extracts, a systems biology strategy needs to be used where unknown constituents crosstalk with variable parts of the immune system. Till date metabolomics strategy has hardly been utilized in immunomodulatory invention studies. In contrast to canonical targeted strategies metabolomic studies were more Comprehensive in finding the properties of immunomodulatory actions of the targeted plants which traditional studies do not capture. This needs highlighting in fashioning future research. Here are certain examples of metabolomics dependent studies which might be performed regarding enhancement of outcomes obtained.

- Associating the metabolome profiling of the food plant with *in vitro*, *in vivo* study as well as immunomodulator outcomes. The ultimate results would be the active implicated in immunomodulator actions.
- Performing metabolome profiling for the food plants with immunomodulator actions for finding the actions of variable factors on the isolated bioactive constituents
- Performing metabolome profiling for evaluating the reactions of cells from the research individuals (cell lines, animals, humans) subsequent to treatment with the food plant for estimating metabolic pathway changes in addition to, immunomodulator actions of plant.

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