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A REVIEW ON THE IMMUNOMODULATORY POTENTIAL OF PLANT BASED EXTRACTS IN PRECLINICAL MODELS

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ABSTRACT

In addition to physical and chemical barriers to infections, the immune system includes two primary defence mechanisms: innate immunity and adaptive immunity. Innate immunity is the body's first line of defence against an invading infection. It's a non-memorable immunological reaction that starts minutes or hours after aggressiveness. Adaptive immunity, on the other hand, is antigen-dependent and antigen-specific, with the ability to remember the antigen, allowing the host to build a more quick and efficient immune response when exposed to it again. When the immune system targets self-molecules as a result of a breakdown in immunological tolerance to autoreactive immune cells, autoimmune illness develops. The objective of this review is to give information on the use of phytochemicals to treat autoimmune illnesses that impact the immune system.

KEYWORDS: Immunosupressants, autoimmune disease, immunostimulants, cytokines.

INTRODUCTION

Immunity: Immunity refers to the body's ability to fight infection and disease by activating certain defences. The immune system encompasses all cells and tissues involved in the creation of immunity.[1]

Immune system: The immune system is a complex system that defends the body from infections. Infections are caused by microbes, which are microscopic creatures such as bacteria, parasites, viruses, and fungus. The human immune system is always on the lookout for foreign matter in the initial phases of its arrival.[2] It recognizes a wide range of natural and artificial chemicals, as well as the organism's immune competence, which is directly proportional to its ability to tackle pathogenic organisms or cells. As a result, it is a highly sophisticated system capable of producing a wide range of responses, adapting from experience, and expressing memory. Multiple cell types, hundreds of signaling molecules, and various receptor-ligand interactions all are engaged in immune system regulation.[3] A well-defined communications network is the key to its success. In response to an infection, tens of millions of cells organized into sets and subsets exchange information. Immune cells become activated when they access the information and start producing potent substances. These chemicals allow cells to regulate their growth and vigor, communicate with other immune cells, and direct recruits to dangerous locations.[4] Self/non-self-recognition has been the most essential of the immune system's dual natures. The immune system has evolved to be able to distinguish between self and non-self. Every cell displays a signal based on the Histocompatibility Complex (MHC), which permits for self/non-self-recognition (MHC). Any cell that does not have this signal is considered a non-self-cell and is attacked. A transplanted organ or endogenous tissue can both be considered non-self. Undigested proteins are treated as antigens due to the efficacy of the process.[5]

Epidemiology

A. Autoimmune Disease

These are a group of over 80 chronic, frequently severe diseases that arise when the immune system malfunctions and the body attacks its cells, tissues, and organs. The incidence of Alzheimer's disease is on the rise for unknown causes. These illnesses are, on the whole, fatal. About 5% of persons in developed countries are affected.[6] It is one of the leading causes of death among women under 65, as well as the second-leading source of chronic disease and the leading cause of morbidity in most developed countries.[7] Additionally, Alzheimer's disease has been reported to be on the rise around the world, making this poorly understood disease a public health problem on par with heart disease and cancer. Based on NIH epidemiology research as well as individual patient group statistics from members of the National Coalition of Autoimmune Patients, the American Autoimmune Related Diseases Association (AARDA) estimates that 50 million Americans have an autoimmune disease (NCAP).[8] Women were 75 percent

more likely than men to be affected by Alzheimer's disease. Estragon has also been shown to enhance autoimmune reactions. There have also been some links discovered between Alzheimer's disease and pregnancy.[6]

Rheumatoid arthritis (RA)

It's a systemic, chronic autoimmune illness that can affect a variety of tissues and organs but primarily targets synovial joints. It has a global distribution and a prevalence of 1-2 percent. The prevalence rises with age, attaining 5% in women over 5. The average point and period prevalence of RA were 51 and 56 in 10,000 people respectively. Due to poor case discoveries in areas with less healthcare or changes in the risk environment, higher urban vs rural incidence could be affected. Population database studies were more consistent than sample research, and linked databases across the globe appeared to provide a consistent estimate of RA period prevalence, validating the high usefulness of rheumatologist diagnosis as a categorization criterion.[9]

Psoriasis

It's an autoimmune illness that shows up on the skin when the immune system misidentifies skin cells as a pathogen and sends out inaccurate signals, speeding up the skin's growth cycle. In 2019, there were 4,622,594 (95 percent uncertainty interval or UI 4,458,904–4,780,771) incident cases of psoriasis worldwide, according to the Global Burden of Disease 2019 methodology. In 2019, the age-standardized incidence rate was 57.8 per 100,000 individuals (95 percent UI 55.8–59.7). Psoriasis affects the majority of people between the ages of 60 and 69, with men and women experiencing similar levels of psoriasis. The burden is disproportionately heavier in North American and European countries with high incomes and high SDI indexes. Objective assessment of psoriasis disease risk is now possible because of advancements in psoriasis therapies.[10]

Type 1 diabetes mellitus

In type 1 diabetes, the body produces antibodies against its tissues, which target the pancreas insulin-producing islet cells. In 2017, the global numbers of type 1 diabetes incidents and prevalent cases were 234,710 and 9,004,610, respectively. Rising countries accounted for 49 percent of worldwide incident cases and 52 percent of prevalent cases, with 17 percent of the global population. Asia, which accounts for 60% of the world's population, has the highest number of type 1 diabetes events (32%), as well as the most prevalent instances (31%). The age categories 0–14, 15–39, 40–64, and 65+ years had 6 percent, 35 percent, 43 percent, and 16 percent of prevalent cases, respectively.[11]

Multiple sclerosis (MS)

Multiple sclerosis (MS) is a neurodegenerative, inflammatory illness of the central nervous system (CNS) that is one of the most common nontraumatic neurologically degenerative disorders that patients must deal with throughout their major working hours. MS is a severe condition that affects not just sufferers and their families, but also society. MS was projected to impact approximately 2.3 million people worldwide in 2013, with a global median prevalence of 33 per 100,000 people. The prevalence and incidence of MS differed significantly across the globe, with the prevalence ranging from 2.2 per 100,000 people in East Asia to 2.2 per 100,000 people in Europe.[12]

B. Immunodeficiency diseases (IDD)

IDD is caused by a genetic or functional abnormality in the immune system, as well as acquired conditions. Primary and secondary causes of immunodeficiency exist. Primary immunodeficiency affects about one person out of every 10,000. Immunoglobulin (Ig) A deficiency, which affects one out of every 400 people, is not included in this figure. Because the majority of cases are hereditary, about 80% of patients are younger than 20 years old when they are diagnosed.[13] 70% occur in males due to X-linked inheritance in many syndromes. During the 31-year study period, the overall primary immunodeficiency (PID) incidence rate was 4.6 per 100,000 people.[14] T cell abnormalities are linked to secondary immunodeficiency (SID).[13] Secondary immunodeficiency (SID)13 has been associated with defective T cells. The most generally reported prevalence figure for severe combined immunodeficiency (SCID) is 1 in 100,000 births around the world. According to recent studies, one in every 2,500 Navajo children receives severe combined immunodeficiency, the leading cause of sickness and death among Navajo children.[15]

C. Allergic disorders

Many diseases associated with allergic disorders, such as hay fever and asthma, are on the rise. In developed countries, allergic asthma and other autoimmune illnesses are on the rise.[16] According to studies conducted in developed countries, over 10 million people suffer from asthma and allergies. Between 1980 and 1994, the prevalence of asthma grew by 75%. African Americans have a greater rate of asthma than Europeans. Atopic eczema affects approximately 9% of the population. Anaphylaxis to penicillin caused over 400 deaths. Latex allergy causes about 220 cases of anaphylaxis and 3 deaths per year. An estimated 150 people perish each year as a result of food allergy anaphylaxis.[17]

Ideal immunomodulator characteristics

- It should be non-teratogenic, non-carcinogenic, and free of long-term negative effects.
- It must be antigenic and pyrogenic, and it must not pass-through milk or eggs.
- It should be active when taken orally and stable in its natural state as well as when incorporated into food and water.

- It should elicit both targeted and nontargeted immune responses.
- It should be affordable and non-toxic to people and animals at high doses.
- When used in combination with the vaccination, it should have an adjuvant effect.
- It must have a rapid withdrawal period as well as little tissue metabolites.
- Its biological activity and chemical composition should be well-define
- It should work with a wide range of medications.

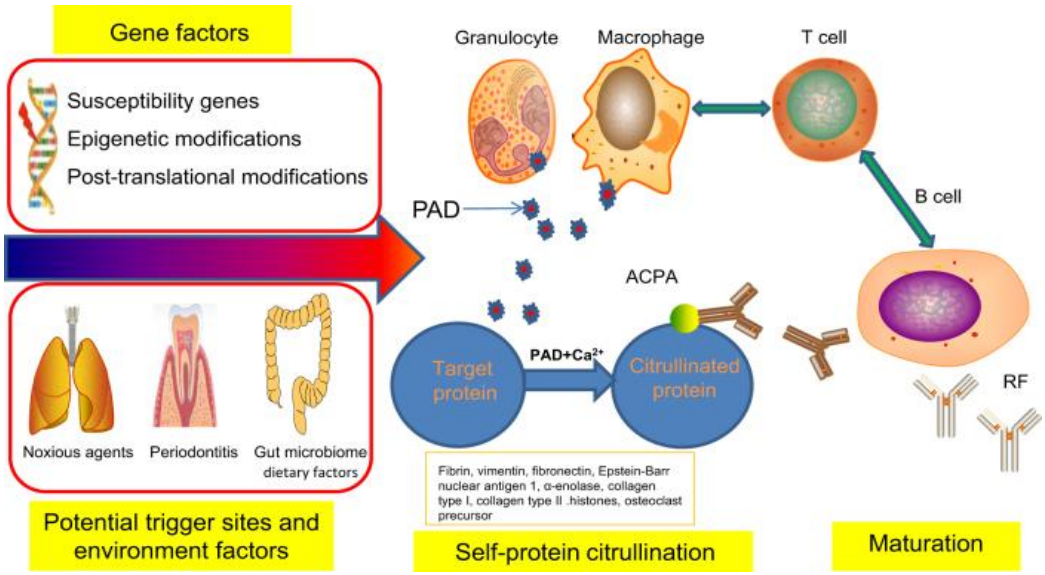
Pathophysiology

When a molecule is injected into the body, it stimulates the immune system to produce an antibody, which kills or neutralizes the antigen, which is identified as a foreign and potentially hazardous invader. Invaders can be substances such as pollen or bacterium and viral foreign proteins.[18] Antibodies can be generated in the human body in response to an antigen. Each antibody binds to come into contact with a specific target, much like a key does in a lock. When an antigen and an antibody, the antigen is labeled for destruction by the antibody. Each antibody consists of two identical heavy chains and two identical light chains arranged in a 'Y' shape. The variable region is made up of parts that make up the tips of Y's arms and vary widely from one antibody to the next. The antigen-binding site's specificity permits the antibody to recognize a specific antigen.[19]

Rheumatoid arthritis (RA)

Active RA induces synovitis, swelling, and joint damage as a result of a complex autoimmune and inflammatory process involving both the innate and adaptive immune systems. Anti-citrullinated protein antibodies identify two primary subgroups of RA based on their presence or absence (ACPAs). Citrullination is a post-translational alteration mediated by peptidyl arginine-deiminase (PAD), a calcium-dependent enzyme that transforms a positively charged arginine to polar but neutral citrulline. The interaction of genes and environmental factors might cause RA at potential trigger sites (lung, mouth, gut, and so on), which is defined by the start of citrullination of self-proteins and the emergence of autoantibodies against citrullinated peptides.

Noxious and infectious pathogens can cause self-protein citrullination and maturation of ACPA (Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, and Epstein-Barr virus), Dietary factors, as well as the intestinal microbiota Citrullination, occur when the calcium-dependent enzyme PAD transforms a positively charged arginine into polar but neutral citrulline. In RA, granulocytes and macrophages can secrete PAD. Abnormal unusual antibody response to citrullinated proteins such as fibrin, vimentin, and fibronectin causes ACPA.[20]

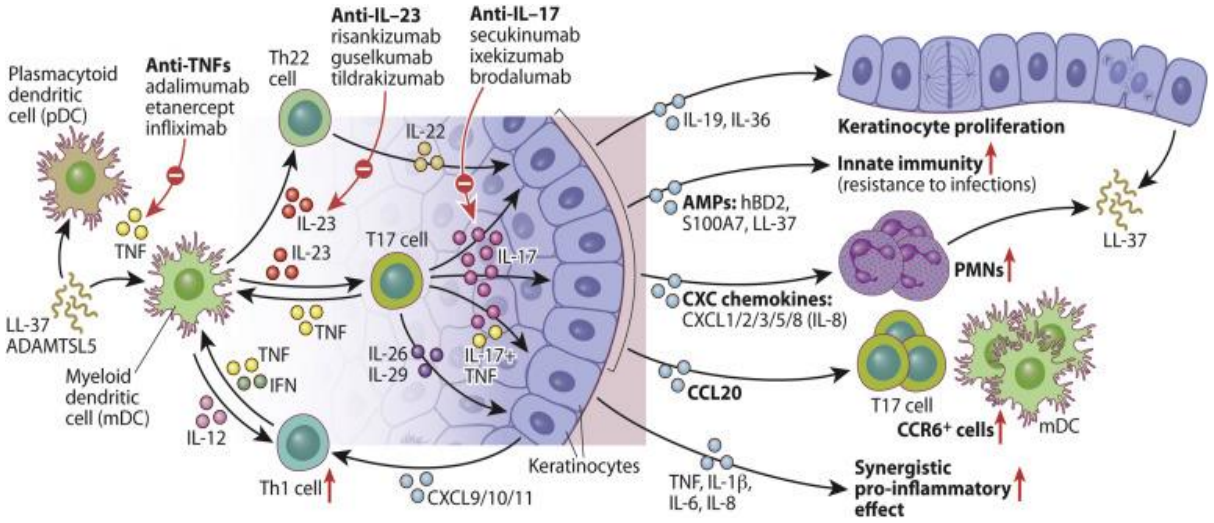


Psoriasis

Psoriasis is a skin condition that can also damage the joints and has been connected to a variety of disorders. Inflammation has been demonstrated to impact different organ systems in addition to the psoriatic skin. As a result, it's been suggested that psoriasis is more of a systemic disease than a dermatological one. Keratinocyte proliferation and differentiation become uncontrolled as a result of inflammation. Acanthosis (epidermal hyperplasia) overlies inflammatory infiltrates comprised of dermal dendritic cells, macrophages, T lymphocytes, and neutrophils in psoriatic plaques. Another notable aspect is neovascularization. Plaque psoriasis and other clinical disorders involve inflammatory pathways.

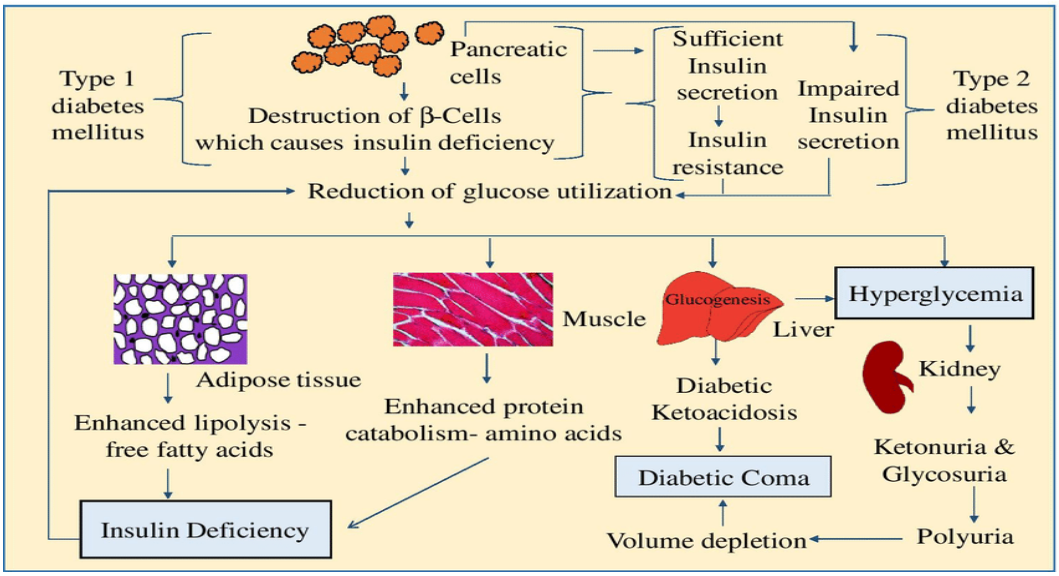
Psoriasis has its own set of autoimmune processes. Researchers will be able to better understand how autoantigen-specific T cells related to the disease's development, chronification, and overall course as a result of this important field of research. LL37 is one of two well-studied T cell autoantigens in psoriasis. In one study, two-thirds of those with moderate to severe plaque

psoriasis showed LL37-specific CD4+ and CD8+ T cells. LL37-specific T cells produce IFN-, while CD4+ T cells produce IL-17, IL-21, and IL-22. In lesional skin or blood, T cells specific for LL37 can be found, and their presence corresponds with disease activity.[21] LL37-activated CD8+ T cells interact in epidermotropism, autoantigen detection, and production of Th17 cytokines. An autoreactive CD8+ T cell TCR was identified to detect the HLA-C*06:02-restricted autoantigen ADAMTSL5. This finding provides evidence that melanocytes are autoimmune target cells, but it does not rule out the possibility of other biological targets. Lipid antigens produced by phospholipase A2 (PLA2) group IVD (PLA2G4D) and keratin 17 derived from hair follicles are two further autoantigen options. Surprisingly, only patients with the HLA-Cw*0602 genotype saw CD8+ T cell growth after being exposed to keratin 17.[22]



Type 1 diabetes mellitus

A complicated interaction between the pancreatic -cell and the innate and adaptive immune systems causes type 1 diabetes. Type 1 diabetes is caused by the autoimmune destruction of endocrine pancreas cells (T1DM). Insulin resistance and decreased insulin synthesis by cells have a synergistic role in the pathogenesis of T1DM, whereas insulin resistance and decreased insulin production by cells play a synergistic function in the pathogenesis of type 2 diabetes. To identify foreign from self, the human immune system is exposed to a wide spectrum of antigens. Apoptosis, a type of programmed cell death involving a cascade of cysteine-asparaginase activations called caspases, is more likely to kill the endocrine pancreas cells in T1DM. Necrosis and necroptosis are critical in humans. According to one concept, autoreactive T lymphocytes in the islet microenvironment trigger an inflammatory response characterized by increased levels of the proinflammatory cytokines IL-1, TNF-, and INF- (interferon-). Apoptosis is thought to be caused directly by autoreactive T lymphocytes engaging with cells via the perforating mechanism or Fas/Fas ligand interaction, according to certain theories. Even in this setting, cytokine secretion dysregulation is critical.[23]



Immunomodulatory Agents: Mode of Action and Associated Adverse Effects[24-26]

Immunomodulators	Class and examples	Mechanism of action	Side effects
Immunosuppressants	Glucocorticoids e.g.: Dexamethasone, prednisolone	It inhibits cell-mediated immunity by suppressing both B and T cells.	osteoporosis, Adrenal suppression, mood changes, diabetes, peptic ulceration
	Alkylating agent e.g.: Cyclophosphamide	It strongly affects B cells and humoral immunity, as it hinders cell proliferation and protein synthesis by intertwining DNA strands.	Thrombocytopenia, electrolyte disturbances, alopecia, Neutropenia, GI disturbances
	Cytotoxic agents (Antimetabolites) Eg: Mycophenolate mofetil	Inhibit de novo synthesis of guanine by inhibiting inosine monophosphate dehydrogenase.	vomiting, leukopenia, and Diarrhoea.
	Azathioprine	The proliferation of lymphocytes is inhibited by inhibiting de novo purine production.	Myelosuppression, Hepatotoxicity, and hypersensitivity increased susceptibility to infections in patients with cyclosporine toxicity.
	Drugs that bind to immunophilins e.g.: Cyclosporine	It reduces T lymphocyte proliferation, the generation of IL-2 and other cytokines, and the response of inducer T cells to IL-1 without affecting suppressor T cells.	
	Tacrolimus	Calcineurin inhibition inhibits T-cell activation.	hyperkalemia, nephrotoxicity, Neurotoxicity, hyperglycemia
	Sirolimus	T-lymphocyte activation and proliferation are inhibited, while T-cell growth factor receptor and IL-2 are downregulated.	Prolong delayed graft function, Increased level of serum cholesterol and triglycerides, Impaired renal functions
Immunostimulants	Synthetic drugs e.g.: Levamisole	Repair the suppressed immune function of B and T lymphocytes, macrophages, and monocytes	Dizziness, Insomnia, allergic infestation, muscle pain and nausea, Thrombocytopenia.
	Hormonal analogs e.g.: Isoprinosine e	It promotes lymphocyte proliferation and increases the production of cytokines like IL-1, IL-2, and IFN-gamma.	It raises uric acid levels in the blood and urine, depresses the central nervous system, and causes nausea.
	Recombinant cytokines Interferon α interferon-gamma, and IL-2	Increased phagocytosis when cell growth was inhibited and immunological activities were improved.	Myocardial infarction, cardiomyopathy, hypotension, depression, flu-like symptoms

The current state of autoimmune disease treatment

Conventional autoimmune disease medications have depended on immunosuppressive drugs that inhibit immune responses all across the body. These drugs are quite effective for many individuals, and they remain the current "gold standard" of treatment. Long-term, high-dose interventions are typically required to maintain disease control, leaving the patient sensitive to life-threatening serious diseases and long-term risk of cancer.[27]

Type 1 Diabetes: Management Strategies

Type 1 diabetes (T1D) is an autoimmune illness that attacks the pancreatic insulin-secreting cells, resulting in a loss of the ability to regulate blood glucose and other metabolites. The present age of T1D immunomodulatory therapy began with studies of the immunosuppressant cyclosporine for the treatment of patients with newly diagnosed T1D. Since then, numerous immune-targeted medicines that either target individual antigens or broad-based immune modulation have been created. Insulin and proinsulin are important antigens in T1D; insulin

autoantibodies are generally the first that appear in high-risk patients, and preclinical studies have shown that the autoimmune disease is prevented in the absence of native insulin.

Type 1 Diabetes – reported a decline in the level of the stimulated inflammatory mediator IL-1β in response to treatment with vitamin D and docosahexaenoic acid, an omega-3 fatty acid, but it was not clear whether there were long-term effects on autoimmunity. Rituximab is a humanized monoclonal antibody that depletes B cells by binding to human CD20. It was first created to treat B cell lymphomas, but its immunomodulatory properties have led to its usage in a range of autoimmune situations. A recent randomized controlled trial found that treating individuals with new-onset illness reduced the loss in cell function, glycosylated hemoglobin levels, and insulin use over a year.[28]

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Psoriasis: Management Strategies

Psoriasis is a chronic T lymphocyte-mediated systemic inflammatory disease characterized by recurring chronic conditions and remissions of thicker, inflamed, and scaling plaque, as well as many complications. The goal of psoriasis treatment is to minimize skin inflammation and cleanse the skin. Topical, light and systemic medications are commonly used in conventional therapy. Several recent therapeutic developments have attempted to modulate T cell expression by suppressing it.

Alefacept

Immunosuppressive medication that has been genetically modified. It inhibits lymphocyte activation and proliferation, both of which are utilized to decrease inflammation and plaque development. Because it is a fusion protein, it binds to an antibody protein, preventing T cell proliferation and activation even though these compounds are utilized, they have been linked to side effects such as increased sensitivity to sunlight, skin irritation, itching, and skin stains.

Apremilast

It is a phosphodiesterase 4 inhibitor (PDE4) that is taken orally and is used to treat plaque psoriasis and psoriatic arthritis. PDE4 has a role in immunological modulation by degrading cAMP. It causes cAMP buildup, which alters the downstream signaling of innate and adaptive immune system pathways a result, TNF and IL-23 levels fall, while anti-inflammatory mediators such as IL-10 rise.[29]

Rheumatoid arthritis (RA): - Management strategies

The Food and Drug Administration recently approved leflunomide (Arava) for the treatment of rheumatoid arthritis (RA). The medicine has been designated as a disease-modifying anti-rheumatic drug because of its preventive effects against structural joint degradation (DMARD). leflunomide is structurally distinct from other RA medicines already on the market, and it works differently different-different ways. In vivo, leflunomide is rapidly metabolized to A77 1726, a pharmacologically active metabolite. This metabolite inhibits the enzyme dihydroorotate dehydrogenase (DHODH), a critical enzyme in the de novo synthesis of uridine monophosphate, in a non-cytotoxic manner (UMP). Activated lymphocytes rely on pyrimidine de novo syntheses to meet their metabolic needs for clonal proliferation and effector t cells terminal differentiation. Pyrimidine synthesis from scratch is required not only for new RNA and DNA synthesis but also for phospholipid synthesis and the pyrimidine sugars required for protein phosphorylation, all of which enable the tremendous growth in membrane biosynthesis required to generate daughter cells.

Leflunomide's activity as a Disease modifying antirheumatic drug in RA and other autoimmune disorders are likely influenced by this mechanism.[30]

Role of phytochemicals in improving immune disease

The host body's immune system serves a critical role in maintaining normal physiological and immunological activities, as well as the internal environment. Due to exposure to chemicals, medicines, and environmental contaminants, the immune system has become a more important target of toxicity. Several synthetic and traditional medications are available on the market, all of which quickly cause a slew of unpleasant side effects and pathogenic resistance.

Phytoconstituents are naturally occurring molecules that play a key role in immune response modulation. Low-molecular-weight immunomodulatory substances include terpenoids, phenolic compounds, and alkaloids, whereas high-molecular-weight molecules include polysaccharides. Phytochemicals have beneficial effects against different diseases including autoimmune disorders.

Tetrandrine (Tet), a bis-benzyl isoquinoline alkaloid that has been used in autoimmune disorders in China for decades, is isolated from the root of the plant Stephania tetrandra. Tet has been proven to have a synergistic effect when used with cyclosporin and FK506 (an immunosuppressive drug that is more effective than cyclosporin). Tet's apoptotic mechanisms may have a role in the regulation of autoimmune diseases. Curcumin improved inflammatory bowel disease, rheumatoid arthritis, psoriasis, multiple sclerosis, and rheumatoid arthritis in humans. Green tea Polyphenols- Green tea extracts, such as epigallocatechin-3-gallate (EGCG), cause transformed cells to undergo apoptosis and cell cycle arrest. In an in vivo experimental animal model, EGCG was shown to suppress autoimmune encephalomyelitis (EAE). Traditional herbal therapy has employed Andrographis paniculata for a long time. Andrographis paniculata's active ingredient Patients with rheumatoid arthritis were administered the extract, which contained 30% total andrographolides, three times a day for 14 weeks.[31]

Ginseng with its steroidal saponin has immune-stimulating properties including cytokine production (IL-2, IL-6, TNF-α, and IFN-γ), macrophage activation, and lymphocyte activity. Saponins can stimulate the cell-mediated immune system and enhance antibody production. Saponins reportedly induce the production of cytokines such as interleukins and interferons.[32] Anthocyanin and anthracene are two biologically active glycosides. These molecules are primarily used to stimulate the immune system. Alkaloids are a major source of performance enhancers and immune system improvement. Berberine is considered to be a powerful immunomodulator with a wide range of health benefits.[33]

CONCLUSION

Immune function is the result of a complicated chain of events involving cognitive-communication among all of the body's tissues. Diseases are caused or progressed by changes in immune function balance. Natural substances will assist in the delivery of optimal immune function and the regulation of undesired inflammatory responses in the body. Nature's Immune Stimulator is a combination of well-researched herbal remedies that support and stimulate the immune system, fight infections, aid in the healing of infections-related injuries, and regulate other issues that could lead to disease. As an outcome, nature's Immune Stimulator will assist to strengthen the entire body, allowing individuals to live a higher quality of life.

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