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IMMUNOMODULATOR AND NEPHROPROTECTIVE EFFECT OF AYURVEDIC HERBS IN CHILDREN WITH NEPHROTIC SYNDROME

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ABSTRACT

Idiopathic nephrotic syndrome is the most common form of nephrotic syndrome in children, with more than 90% of cases occurring before the age of 10 years. Several studies have shown that non-familial NS is associated with the presence of circulating permeability factors and with complex disturbance in immune system. Steroid therapy is the backbone of treatment of children with INS irrespective of histopathological type. The drug of choice is prednisolone which has been used by ISKDC for more than 60 years. Alternative therapy in case of children having severe side effect of steroid are Levamisole, Alkylating agents like cyclophosphamide and Chlorambucil, others like Cyclosporine, Tacrolimus, Mycophenolatemofetil, mizoribin and azathiopurine, Rituximib. These agents have side effects like Growth retardation, osteoporosis, cataracts, behavior disturbance, bone marrow depression, nephrotoxicity, hypertension, diabetes mellitus etc. There is a basic need for search of a safe treatment for INS, *Ayurveda* serves the purpose of these needs by providing various herbs having immunosuppressive action and in the same time are nephroprotective and some are immunomodulators. This review focuses on effect of various herbs having immunosuppressive, nephroprotective and have immunomodulatory actions and can be used as an adjuvant treatment for children with INS.

Keywords: Idiopathic nephrotic syndrome, MCNS, FSGS, Immunosuppression, Immunology, *Ayurveda.*

INTRODUCTION

Nephrotic syndrome is common chronic disorder, characterized by alteration of permeability at the glomerular capillary wall, resulting in its inability to restrict the urinary loss of protein. Nephrotic range proteinuria is defined as proteinuria exceeding 1000mg/m² per day or spot (random) urinary protein to creatinine ratio exceeding 2mg/mg. The proteinuria in childhood nephrotic syndrome is relatively selective, constituted primarily by albumin. Urine is practically devoid of high molecular mass proteins, which is achieved by sieving characteristics of the glomerular filtration barrier and reabsorption of proteins in the proximal tubules of kidney. Many glomerular disease results in a pa-

thological increase in glomerular permeability to proteins. If proteinuria exceeds 40m/m², hypoalbuminemia accompanied by oedema will ensue. The clinical picture of proteinuria, hypoalbuminemia and oedema is referred as Nephrotic syndrome.(1,2)

More than 80% patients with nephrotic syndrome show minimal change disease (MCD) characterized by normal renal histology on light microscopy. The remaining is contributed by focal segmental glomerulosclerosis (FSGS) and mesangioproliferative glomerulonephritis and membranous nephropathy are uncommon condition in childhood. The age at initial presentation is useful in assessing the underlying aetiology. The usual age at the onset of symptoms in patients with MCD is between 2-6 yrs; FSGS may occur throughout childhood, though the median age is usually below 8 yr. Membranoproliferative glomerulonephritis is typically seen in older children and adolescents.(1,2,3)

Ayurveda, the Indian traditional system of medicine, lays emphasis on promotion of health concept of

Strengthening host defenses against different diseases. These plants, labelled as *'Rasayana'*, have been endowed with multiple properties like delaying the onset of senescence and improving mental functions by strengthening the psycho-neuro-immune axis. Several plants from these texts have been studied for their immunomodulatory properties and found to have the potential of providing new scaffolds for safer, synergistic, cocktail immunodrugs. Thirty four plants have been identified as *Rasayanas* in the *Ayurvedic* system of medicine. Besides these, several other medicinal plants which are not included as *Rasayana* in Ayurveda have also been found to possess immunomodulatory properties.(4,5)

Methods to enhance Immunity-*Vyadhiksamatva*

In *Ayurvedic* texts, various codes of conducts are described for each person (from conception to old age) to be followed in different seasons, during healthy and diseased conditions in terms of dietetic (*ahara*) and mode of life *(vihar*).(5,6)

Concept of immunomodulation in *Ayurveda*

"Rasayana" is made up of two words: *'rasa'* and *'ayana'*.*'Rasa'* primarily means essential seven vital tissues *(saptadhatu*e.g. *rasa, rakta, mansa, meda, asthi, majja and shukra). 'Ayana'* means the path or channel. So, *rasayanas* are those that bring about proper uptake, growth and improvement of essential *dhatus*. According to acharya Charaka, use of*rasayanas* results in diseasefree long life (*dirghamaayu), smiriti* (recapitulating power), *medha, aarogyam* (healthy well being), *tarunvaya* (youthfulness), *prabha, varna (*complexion), voice and strength (Cha. Sam. Chikitisasthana 1/1/7-8, p.5).

According to Acharya Sarangdhara, various drugs, diet and regimens which promote longevity by delaying aging and preventing diseases are called *Rasayana* such as *amrita*, *guggul*, and *haritaki* (Sar. Poorvakhanda 4/13, p.48). *Rasayana* is a treatment in which the body constituents are prepared to adapt to a selective tissue endowment program. This concept in modern scientific understanding would mean the enhancement of immune responsiveness of an organism against pathogens by activating the immune system with immunomodulatory plant agents. *Rasayana Chikitsa* or rejuvenation therapy helps in promoting and maintenance of health and longevity in the healthy, and to cure disease in sick.(4,5,6)

PATHOGENESIS

Glomerular basement membrane (GBM) acts as size and charge selective barrier that prevents excessive loss of proteins in normal conditions. In nephrotic syndrome there is increased permeability of GBM to proteins leading to massive proteinuria which is most important event in pathophysiology. Negatively charged GBM restricts passage of macromolecules like albumin (which is negatively charged) much more than neutral or positively charged molecules with same molecular weight. Substances with high molecular weight are re-

stricted by slit diaphragms which cover the micropores situated between foot processes of glomerular basement membrane. Thus both size or molecular weight and charge of molecule are important factors which determine the passage across glomerular capillary in to urine. Negatively charged anionic sites on GBM are due to heparan sulfate and other glucosaminoglycans. A loss or reduction in anionic sites leads to loss of negative charge which then allows albumin to pass the glomerular barrier.

There are two main mechanisms which are responsible for massive proteinuria in nephrotic syndrome that are currently under study.

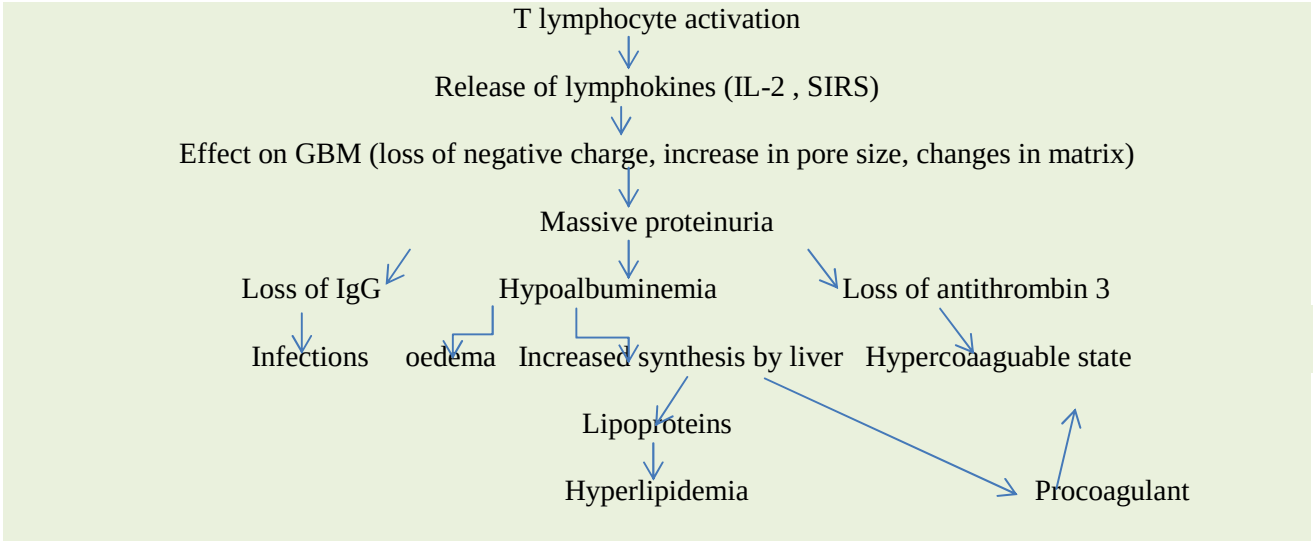
1. Mutation in 2 genes NPHS1 and NPHS2 which influence synthesis of proteins nephrin, podocin and actinin by podocytes. These proteins keep the integrity of slit diaphragms which cover the micropores tightly and prevent proteinuria. Deficiency of these proteins is known to occur in congenital nephrotic syndrome of Finnish type and familial focal glomerulosclerosis –both are inherited types of nephrotic syndrome with massive proteinuria.

2. Reduction in anionicor negative charge of GBM which allows passage of negatively charged plasma proteins esp albumin in urine. This mechanism is postulated to be responsible for massive proteinuria of minimal change nephrotic syndrome. What causes loss of anionic site is not known but is believed to be due to effect of circulating factors probably lymphokines. In 1974 shalhoub postulated that minimal change nephrotic syndrome was caused by abnormal lymphocytes based on the observation of increased susceptibility of nephrotic children to infections, remission induced by measles and association with lymphoma or hodgkin's disease. He proposed that T cells released a factor that changed glomerular basement membrane. A vascular permeability factor was described which when injected into rats caused prolonged nephroticsyndrome . Another lymphokine, soluble immune response suppressor (SIRS) is belived to be responsible for some of the immune hyporesponsiveness noted in nephrotic syndrome. Several other lymphokines like interleukin2, interleukin 2 receptor have been found to be elevated in nephrotic plasma during relapse.

An inherent genetic factor linked to the major histocompatibility complex (HLA) seems to play an important role in increasing susceptibility to nephrotic syndrome.

Increased permeability of glomerular basement membrane to protein esp. albumin is responsible for massive proteinuria of NS and all clinical, biochemical, immunological and coagulation abnormalities are a result of excessive losses of protein in urine.(1,3)

Mechanisms and consequences of proteinuria in idiopathic nephrotic syndrome



ROLE OF IMMUNE SYSTEM

The immunological basis of nephrotic syndrome is suggested by these observations:

a. Induction of remission following diseases known to depress cell mediated immunity like measles.
b. Association of MCNS with leukemia and lymphoma.
c. Responsiveness of most form of NS to medications that inhibit T cell function such as corticosteroids and alkylating agents.

Antigen presentation to T lymphocytes causes polarized immune response which could be type 1 or type 2. Type 1 cytokines are associated with cell-mediated immunity and Type 2 with humoral immunity.

An expansion of CD4+ and CD8+ T-cell population has been identified by immunophenotyping of peripheral lymphocytes in NS with an increase in CD4+ T-cells expressing CD25 (IL2 receptors) during relapse.

An increase in serum levels of soluble interleukin 2 receptor, interleukin 8 (IL8) and Tumor necrosis factorα (TNF-α) have been demonstrated.

Thus it is presently hypothesized that T-cell activation may lead to the production of cytokines which may affect the filtration of proteins by glomerular capillaries by interfering with the polyanionic charge.

The beneficial effect of rituximab, a monoclonal antibody directed against CD20 cells in steroid resistant nephrotic syndrome also suggest a role of B-cell in causation of INS. Bcells may be involved via an unidentified antibody, independent pathway that may be controlling T-cells.(1,2,3)

Drug therapy

Steroid therapy is the backbone of treatment of all children with INS irrespective of histopathological type (even FSGS). Because most of the children presenting with NS are responsive to steroids a therapeutic trial of steroids without prior biopsy is justified. The drug of choice is prednisolone which has been used by ISKDC for more than 60 years.

Patients with primary NS mostly need immunosuppression (Corticosteroids) to achieve remission but many of them either relapse after immunosuppression therapy or resistant to it. On the other hand, immunosuppressive therapy is associated with adverse effect. The most important factor that determines prognosis in children with NS is steroid responsiveness. More than 70% of children with steroid sensitive NS relapse and almost 50% have frequent relapses or steroid dependence. Long term alternate day corticosteroids, alkylating agents (Cyclophosphamide), calcineurin inhibitors (cyclosporine, tacrolimus) immunomodulator drugs (Levamisole) are primary medications used to treat frequent relapses, steroid dependence (SD) or steroid resistant (SR) NS. While many of these are effective regimens in treating SR/SD NS but most of them are associated with side effects like infection, osteoporosis, and suppression of bone marrow, corticosteroid toxicity and Hepato-renal toxicity etc. Significant number of patients are at risk for complications, progressive kidney disease and end stage renal disease , lack of efficacy and safety of existing treatment protocols make the treatment of NS a difficult challenge; Clearly warranting need of alternative treatment.(1,2,3)

Studies have shown during a relapse the T- suppressor lymphocyte cell activity increases and interleukin-2 levels as well as those of tumor necrosis factor –alpha and other permeability factors levels are high. Decrease antioxidant defense and an increase in apoptosis rate contribute to the functional abnormalities of T cell in NS. Investigation on herbs is revealing the therapeutic benefits of medical herbs in treating immunological disorders. Keeping in view of above aforementioned immunological theory in pathogenesis of NS, Ayurvedic herbs having immunosuppressant, immunomodultor, nephroprotective and antioxidant properties

can be used to preserve renal function in conjugation with modern therapeutic drugs for synergistic effect, lowering potential side effects and to achieve maximum efficacy and safety profile in treating SD/SR NS.

Role of immunosuppressive drugs

The favorable response of NS to immunosuppressive drugs in most patients has been regarded as additional proof of the involvement of the immune system in the pathogenesis of NS. Interestingly, levamisole is a potent down-regulator, specifically of Th2 immune responses, whereas it augments Th1 responses. The beneficial effect of levamisole would again advocate the role for Th2-mediated immune responses in the pathogenesis of NS. However, the efficacy of immunomodulatory drugs may be explained by another mechanism, i.e. by direct effects on the glomerular capillary filter. For example, both podocytes and endothelial cells express glucocorticoid receptors through which corticosteroids may exert direct actions on the glomerular capillary wall.(7,8)

Ayurvedic herbs having immunosuppressant, immunomodulatory and nephroprotective action

Immunomodulators exert their effect by modulating the defense mechanism and have capability to either augment or suppress an immune response. In addition to an altered immune response, modulation of hematopoiesis, including increased RBC and WBC counts, increased PCV and enhanced macrophage activation have also been reported.

Currently, it is estimated that almost 50% of the synthetic medicines are derived from, or patterned after phytochemicals. Various physiological products, microbial products, synthetic chemicals, cow therapy (*Panchagavya*) and herbal products have immunomodulatory effect. Traditionally used natural medicines may well provide the basis for the development of a modern and highly successful phyto-pharmaceutical that meets the international criteria required for quality, safety and efficacy for an evidence based therapy.

The capacity of herbal medicines to inhibit cellular and humoral immune responses can have useful applications in some immune mediated disorders including autoimmune diseases. Both activation of T and B lymphocytes and macrophages and defective apoptosis of immune effector cells play critical role in pathogenesis of these disorders. There is an ever increasing interest in research of different plant species to document their therapeutic application.There are various Ayurvedic herbs having immunomodulatory and nephroprotective action which can be used along with the therapeutic modern medicine to have synergistic effect on patient with Nephrotic syndrome (9,10). Some of these herbs are mentioned below:

Haridra (curcuma longa)

Curcuma longa (Zingiberaciae), a perennial plant native to tropical south Asia, has been extensively utilized in folk medicine for treatment of infections and inflammatory diseases. InTurmeric , the bright yellow pigment extracted from tuberous rhizome of this plant has been shown to inhibit the activation of human DC's in response to inflammatory cytokines. The main biological actions of turmeric have been attributed to curcumin, a major curcumanoid found in turmeric. This naturally occurring polyphenolic phytochemical is a strong anti-inflammatory and antioxidant agent which can change expression of various transcription factors, cell cycle proteins, and signal transducing kinases. Curcumin has been shown to be active on lymphocytes and affect on series of immunological functions including antigen presentation, humoral and cell mediated immunity, and cytokine production. This compound can inactivate the transcription factor NF-KappaB and by this function down regulates the secretion of a variety of proinflammatory cytokines and chemokines. Several clinical trials indicate curcumin may have potential as a therapeutic agent in diseases such as inflammatory bowel disease, pancreatitis, arthritis, Nephritis, Chronic anterior uveitis. The effect of this compound on B cell activation has also been studied.

Curcumin at high doses reduced the proliferation of B cells stimulated with the Toll like receptor(TLR) ligands LPS and CpGoligodeoxynucleotides and at low doses enhanced antibody responses indicating that curcumin could be strong modulator of B cell activation (11,12,13,14).

Guduchi (Tinosporacordifolia)

*Guduchi*is one of the most important and widely used herb in ayurvedicmedicine.In*Ayurveda* it is considered as "*Rasayana*" because it improves immune system and the body resistance against infections.

Immunomodulatory Activity: The compounds which are responsible for immunomodulatory and cytotoxic effects are 11-hydroxymuskatone,N-methyle-2pyrrolidone, N formylannonain, cordifolioside A, magnoflorine, tinocordioside and syringin. These compounds have been reported to improve the phagocytic activity of macrophages, enhancement in nitric acid production by stimulation of splenocyte. *Tinosporacordifolia*gives stimulation to macrophage activity leads to increase in secretion of granulocyte-monocyte colony stimulating factor [GM-CSF]. As a result, increases in IL2 and IFN-gamma result in increases natural killer cell activity

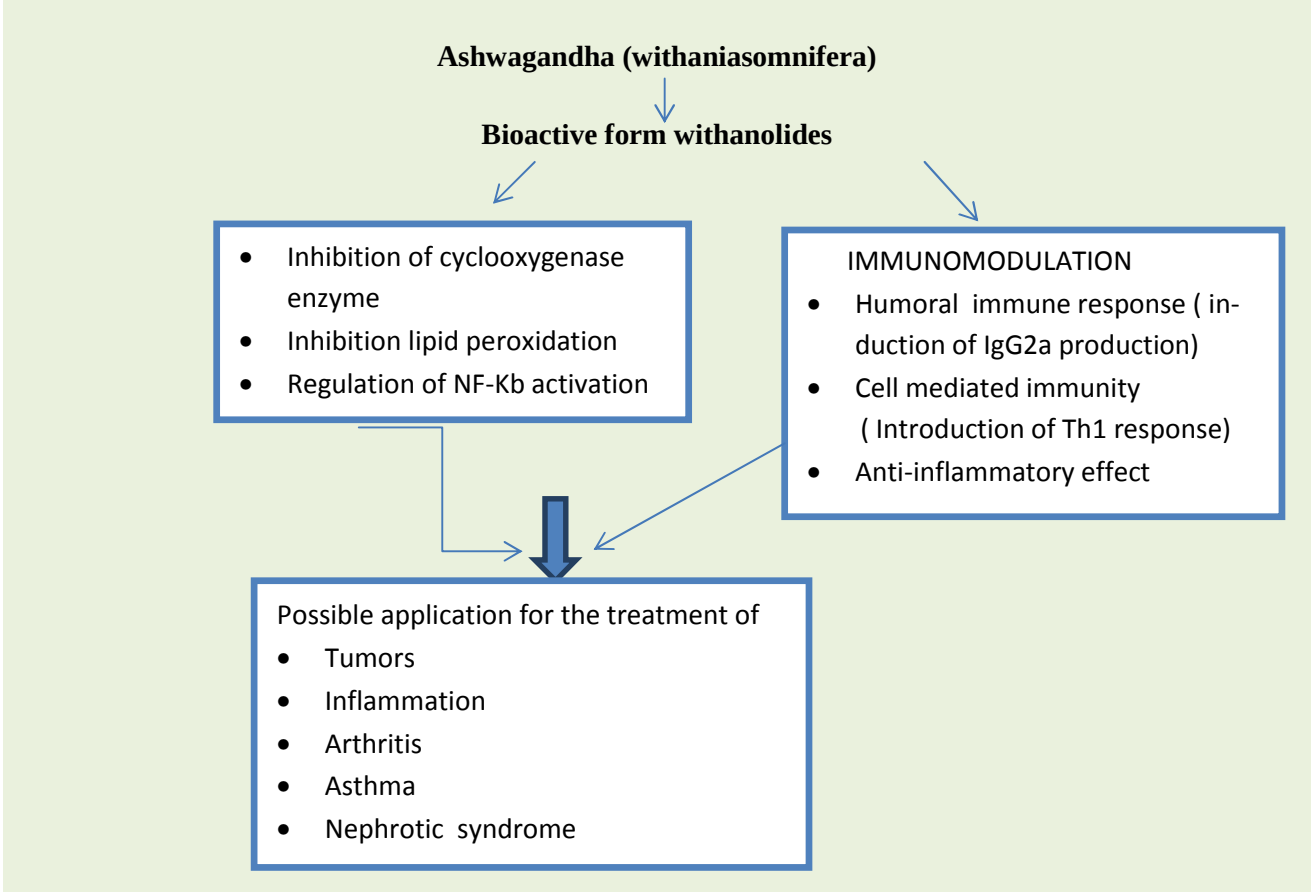
Nephroprotective Activity: The effect of *Tinosporacordifolia*was studied on Swiss albino mice model related to urotoxicity when acute dose of cyclophosphamide was induced. After administration of an extract of *Tinosporacordifolia* (200 mg/kg)for 5 days with reduced cyclophosphamide. It was evident from the morphological analysis of bladder and also decreased level of Urea, Nitrogen in blood as well as protein in urine.Lowered level of Cytokines IFN-IL-2 because of Cyclophosphamide were found to be increased.The study clearly shows Nephroprotective property of *Tinosporacordifolia*as it reduces cyclophosphamide induced toxicity

Anti-Oxidant Activity: Methanolic extract of stem of Tinosporacordifolia shows anti-oxidant activity, by increasing the erythrocytes membrane lipid peroxide and catalase activity (15,16,17,18,19,20).

***Ashwagandha* (Withaniasomnifera)**

Withaniasomnifera is a member of the plant family Solanaceae and is known by many names as "*Ashwagandha*", "Queen of Ayurveda", "Indian ginseng" and winter cherry, has been an important herb in Ayurvedic and indigenous medical systems for more than 3000 years. Its root has been used as herb remedy to treat a variety of ailments and to promote general wellness. It has received much attention in recent years due to presence of alkaloids and steroidal lactones. Research has shown that *Ashwagandha* possess anti-inflammatory, antioxidant, anti tumor and immunomodulatory properties. It is also considered as adaptogen, facilitating the ability to withstand stressors. *Ashwagandha* showed a significant modulation of immune reactivity in animal models. Understanding the immune-modulatory mechanism of *Ashwagandha* can provide insight into immune function and regulation that could further help in immune-regulatory procedures. Chemical investigations with the extact of roots and leaves of withaniasomnifera have yielded bioactive withanolides, which inhibit cyclooxygenase enzymes, lipid peroxidation, and the proliferation of tumor cells. It has been reported that WS extract preferentially reduces inflammatory processes by inactivating nuclear factor-kappaB (NF-KB) activation, by inducing cellular death by apoptosis, inhibiting inflammation and abolishing osteoclast genesis through suppression of NF-Kb activation and NF-KB regulated gene expression. Similar studies show that the leaf extract of WS, as well major constituent withaferin A, potentially inhibits NF-KB activation by preventing tumor necrosis factor induced activation of l-kappaB kinase beta. It has been proposed that the anti-proliferative, pro-

apoptotic, anti-invasive, anti-osteoclastogenic, antiangiogenic, antimetastatic, radiosenstizing, anti-arthritic, and cardioprotective effects assigned to withanolide may be mediated in part through suppression of NF-KB and NF-KB regulated gene products (21).



Punarnava (Boerrhaviadiffusa)

The word punarnava literally means, one which renews the body, that is, which brings back the youth. Punarnava enjoys an important place among medicinal herbs in India since ancient times. Various parts of Boerhaaviadiffusa are used for the treatment of numerous disorders. It possesses immunomodultory effects due to the immunosuppressive action. Ethanolic extract of *Boerhaaviadiffusa* was shown to inhibit the cell proliferation significantly . Extracts of *B. diffusa* roots inhibited human NK cell cytotoxicity **in vitro**, production of **nitric oxide** in mouse macrophage cells, interleukin-2 and tumor necrosis factor-α (TNF-α), in human PBMCs, demonstrating its immunosuppressive potential effect . It also exhibits antidiabetic, anti-metastatic, antioxidant, antiproliferative and antiestrogenic, analgesic, anti-inflammatory, antibacterial activity. Maximum diuretic and anti-inflammatory activities of Punarnava have been observed in samples collected during the rainy season. Due to the combination of these two activities, Punarnava is regarded therapeutically highly efficacious for the treatment of renal inflammatory diseases and common clinical problems such as nephritic syndrome, oedema, and ascites developing at the early onset of the liver cirrhosis and chronic peritonitis. The root is used

to treat other renal ailments (calculations and cystitis), seminal weakness and blood pressure. The extract of Boerhaaviadiffusa) is found to be diuretic with special effect to nephrotic syndrome. The extract of Boerhaaviadiffusa) is found to diuretic (22).

Gokshura (Tribulusterristris)

Tribulusterrestris (family Zygophyllaceae), commonly known as *Gokshur* or *Gokharu* or puncture vine, has been used for a long time in both the Indian and Chinese systems of medicine for treatment of various kinds of diseases. Its various parts contain a variety of chemical constituents which are medicinally important, such as flavonoids, flavonol glycosides, steroidal saponins, and alkaloids. It has diuretic, aphrodisiac, antiurolithic, immunomodulatory, antidiabetic, absorption enhancing, hypolipidemic, cardiotonic, central nervous system, hepatoprotective, anti-inflammatory, analgesic, antispasmodic, anticancer, antibacterial, anthelmintic, larvicidal, and anticariogenic activities.

Immunomodulatory activity

Saponins isolated from the fruits of TT demonstrated dose-dependent increase in phagocytosis, indicating stimulation of nonspecific immune response. An alcoholic extract of the whole plant of TT exhibited a significant dose-dependent increase in humoral antibody titre and delayed type hypersensitivity response, indicating increased specific immune response (23).

Yashtimadhu (Glycyrrhizaglabra)

This plant is used for its antimicrobial, hepatoprotective, cardio-protective and immune-modulatory properties in folk medicine. The inhibitory effects of flavonoids extracted from plant on LPS-induced acute pulmonary infiltration in mice have been shown. Liquorice root contains glycyrrhizin and the major metabolite of glycyrrhizin is Glycyhrritinic acid, which has shown anti-inflammatory effects in different animal models. The inhibition of calcineurin activity and T cell proliferation by glycyrol from glycyrhhizauralensis has been reported.

Many more Ayurvedic herbs mentioned in classics as Rasayan have been studied to have immune-modulator effect, but the herbs mentioned above acts especially on renal sysyem (24)**.**

CONCLUSION

In summary, Idiopathic NS is associated with complex disturbance in immune system, such as atopy, allergy, and a cytokine bias towards Th2 cytokines .Although these cytokines can act directly on podocytes and the glomerular filtration barrier. Number of synthetic immunomodulators and immunosuppressants have been used for treatment of NS, but these drugs have potential harmful side effects, hence an alternative mode in form of herbal immunomodulators can be opted for treatment of NS. Various herbal medicines have been used for centuries in treatment of different diseases including those related to immune system. The studies of herbal drugs listed in this review paper are although of preliminary nature and most of them are experimental studies on animal model. However it shows great potential of Ayurvedic immunomodulator and nephroprotective herbal drugs that can be used to treat Steroid dependent/ Steroid resistant NS or atleast preserve its renal function and slow its progression to end stage renal disease. It may be used as add on therapy with modern therapeutic drugs for more efficacious and safety profile in such patients. Therefore the comprehensive clinical trials of polyherbal preparation can gain importance as one of the better alternative management after proper validation. Further researches are indicated to support the hypothesis presented in this article.

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