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A REVIEW ON HERBAL PLANTS AS IMMUNOMODULATORS

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ABSTRACT: Herbal immunomodulator is substance which stimulates or suppresses the components of immune system including both innate and adaptive immune responses. The modulation of immune system by various medicinal plant products has become subject for scientific investigations currently worldwide. A number of Indian medicinal plants and various 'Rasayana' have been claimed to possess immunomodulatory activity. Some of these plants are, *Allium sativum*, *Morus alba*, *Acacia catechu*, *Tinospora cordifolia*, and *Mangifera indica*. A lot more are still to be explored and offer scope for further investigation.

INTRODUCTION: Modulation of immune functions using medicinal plants and their products as a possible therapeutic measure has become an accepted therapeutic approach. Plants and minerals have been used since ancient times for the treatment of many ailments and diseases. It is now being recognized that immunomodulation of immune response could provide an alternative to conventional chemotherapy for a variety of disease conditions, especially when the host's defense mechanism has to be activated under conditions of impaired immune responsiveness or when a selective immunosuppressant has to be induced in situation like autoimmune disorders and organ transplantation. Immunity is a homeostatic process, a series of delicately balanced complex, multicellular and physiologic mechanisms that allow an individual to distinguish foreign material from "self" and neutralize and/or eliminate the foreign matter.[1]

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Immunomodulation:

Development in clinical and experimental immunology strongly suggests that many infectious diseases and disorders arise because of stressful environmental conditions associated with suppression of immune system. It is evident that certain types of stress evoke physiological changes that influence susceptibility to infection and malignance. The ability to modify the immune response in animals and humans evolved from a desire to confer greater protection against infectious agents through a more complete understanding of the functioning of the immune system, and of the ways in which nonspecific and specific immune mechanisms developed. Naturally occurring or synthetic compounds capable of altering those mechanisms offered further possibilities for modulating immune responses. [2]

History of Immunology:

Immunology is a science that examines the structure and function of the immune system. It originates from medicine and early studies on the causes of immunity to disease. The earliest known mention of immunity was during the plague of Athens in 430 BC. Thucydides noted that people

who had recovered from a previous bout of the disease could nurse the sick without contracting the illness a second time. [3] In the 18th century, Pierre-Louis Moreau de Maupertuis made experiments with scorpion venom and observed that certain dogs and mice were immune to this venom. [4] This and other observations of acquired immunity were later exploited by Louis Pasteur in his development of vaccination and his proposed germ theory of disease.[5] Pasteur's theory was in direct opposition to contemporary theories of disease, such as the miasma theory. It was not until Robert Koch's 1891 proofs, for which he was awarded a Nobel Prize in 1905, that microorganisms were confirmed as the cause of infectious disease. Viruses were confirmed as human pathogens in 1901, with the discovery of the yellow fever virus by Walter Reed.

Methods for Testing Immunological Factors:

The routine process for screening is to extract single ingredient or single distilled fraction from herbal drugs, determine its bioactivity by the classic pharmacological means. The whole animal model is the most classic pharmacological screening model, which is very important at the aspect of medicine evaluation because it can apparently respond to the efficacy, side effect and toxicity of medicines in whole. Several *in vitro*, *in vivo* methods of pharmacological screening of medicinal plants having immunomodulatory activity have been listed. [6].

***In vitro* methods:**

- ✓ Inhibition of histamine release from mast cells
- ✓ Mitogen induced lymphocyte proliferation
- ✓ Inhibition of T cell proliferation
- ✓ Chemiluminescence in macrophages
- ✓ PFC (plaque forming colony) test *in vitro*
- ✓ Inhibition of dihydro-orotate dehydrogenase

***In vivo* methods:**

- ✓ Spontaneous autoimmune diseases in animals
- ✓ Acute systemic anaphylaxis in rats
- ✓ Anti-anaphylactic activity (Schultz-Dale reaction)
- ✓ Passive cutaneous anaphylaxis
- ✓ Arthus type immediate hypersensitivity
- ✓ Delayed type hypersensitivity
- ✓ Reversed passive arthus reaction
- ✓ Adjuvant arthritis in rats
- ✓ Collagen type II induced arthritis in rats
- ✓ Proteoglycans - induced progressive Polyarthritic in mice
- ✓ Experimental autoimmune thyroiditis
- ✓ Coxsackievirus B3-induced myocarditis
- ✓ Porcine cardiac myosin-induced autoimmune myocarditis in rats
- ✓ Experimental allergic encephalomyelitis
- ✓ Acute graft versus host disease (GVHD) in rats
- ✓ Influence on SLE-like disorder in MRL/lpr mice
- ✓ Prevention of experimentally induced myasthenia gravis in rats
- ✓ Glomerulonephritis induced by antibasement membrane antibody in rats
- ✓ Auto-immune uveitis in rats
- ✓ Inhibition of allogenic transplant rejection.

Mechanism of Immuno-stimulation:

Immunological defense is a complicated interplay between nonspecific and specific, cellular and humoral immune responses, stimulation and suppression of immunocompetent cells, and the

influence of endocrine and other mechanisms upon the immune system. Primary targets of the Immunostimulant are T or B lymphocytes or the complement system, an increase in phagocytosis by macrophages and granulocytes plays a central role in immunostimulation. [7] Activation of macrophages is probably important for the stimulating agents to remain in contact with the reactive cell. The second most important role is the stimulation of T lymphocytes, which can be achieved either directly or indirectly, via macrophages. [8]

Immunosuppression:

These agents could be used for control of pathological immune response in autoimmune diseases, graft rejection, graft versus host disease, hypersensitivity immune reaction (immediate or delayed type), and immune pathology associated with infections. Out of the list the maximum use of these agents has been for prevention of graft rejection and treatment of autoimmune diseases.

Immunomodulation by Allopathic Drugs:

Immunosuppressant: Immunosuppression implies mainly the decrease in resistance against infections, stress and may occur on account of environmental or chemotherapeutic factors. [9]

Clinical applications of immunosuppressant are as follows.

- To suppress rejection of transplanted organs and tissues (kidney, bone marrow, heart, liver, etc.)
- To suppress graft-versus-host disease (i.e. response of lymphocytes in the graft to host antigens) in bone marrow transplants.
- To treat a variety of conditions, which, while not completely understood, are believed to have an important autoimmune component in their pathogenesis i.e. myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis, psoriasis and ulcerative colitis.
- Selective immunosuppression for prevention of Rh hemolytic disease of the newborn.

Immunostimulant:

The term immunostimulation comprise a prophylactic or therapeutic concept which aims at the stimulation of our nonspecific immune system. This implies primarily the non antigen dependent stimulation of the function and efficiency of granulocytes, macrophages, complement and natural killer (NK) cells. [9]

Side Effects of Immunomodulator Drugs:

There are various side effects are associated with the use of these drugs i.e. Pulmonary toxicity, Myelosuppression, Alopecia, Increased risk of infection, Hepatic fibrosis, Lymphoma (Epstein–Barr virus associated), Nephrotoxicity, neurotoxicity (tremor, headache, motor disturbances and seizures), GI complaints, hypertension, hyperkalemia, hyperglycemia, and diabetes, Renal dysfunction, tremor, hirsutism, hypertension, hyperlipidemia, gum hyperplasia, hyperuricemia, hyper cholesterolemia, nephrotoxicity, hypertension, diabetogenic, Elevated LDL cholesterol etc. [10]

Immunomodulation by Medicinal Plants:

Plant extracts used in traditional therapy are being reviewed for their chemo protective and Immunomodulatory activities. Immunomodulators are biological response modifiers; exert their antitumor effects by improving host defense mechanisms against the tumor. They have a direct anti-proliferative effect on tumour cells and also enhance the ability of the host to tolerate damage by toxic chemicals that may be used to destroy cancer.

Immunomodulatory therapy could provide an alternative to conventional chemotherapy for a variety of diseased conditions, especially when host's defense mechanisms have to be activated under the conditions of impaired immune responsiveness or when a selective immunosuppression has to be induced in a situation, like inflammatory diseases, auto-immune disorders ad organ/bone marrow transplantation.[11] A number of Indian medicinal plants and various 'Rasayana' have been claimed to possess immunomodulatory activity. Some of these planta are *Withania somnifera*, *Tinospora cordifolia*, and

Mangifera indica. [12-13, 9] A lot more are still to be explored and offer scope for further investigation.

Herbal Plants as Immunomodulator:

Withania somnifera:

Administration of an extract from the powdered root of the plant *Withania somnifera* was found to stimulate immunological activity in Babl/c mice. Treatment with five doses of Withania root extract (20 mg/dose/animal; i.p.) was found to enhance the total WBC count (17125 cells/mm(3)) on 10th day. Bone marrow cellularity (27x10(6) cells/femur) as well as alpha-esterase positive cell number (1800/4000 cells) also increased significantly ($P<0.001$) after the administration of Withania extract. Treatment with Withania extract along with the antigen (SRBC) produced an enhancement in the circulating antibody titre and the number of plaque forming cells (PFC) in the spleen. Maximum number of PFC (985 PFC/10(6) spleen cells) was obtained on the fourth day. Withania extract inhibited delayed type hypersentivity reaction in mice (Mantoux test). Administration of Withania extract also showed an enhancement in phagocytic activity of peritoneal macrophages (76.5 pigmented cells/200) when compared to control (31.5/200 cells) in mice. These results confirm the immunomodulatory activity of W. somnifera extract, which is a known immunomodulator in indigenous medicine. [12]

***Morus alba* Linn. (Mulberry):**

Methanolic extract of *Morus alba* was administered orally at low dose and high dose of 100 mg/kg and 1 g/kg respectively and Ocimum sanctum (100 mg/kg, po) was used as standard drug. It showed significant increase in the phagocytic index in carbon clearance assay, a significant protection against cyclophosphamide induced neutropenia and increased the adhesion of neutrophils in the neutrophil adhesion test. Hence, it was concluded that Morus alba increases both humoral immunity and cell mediated immunity. [14]

Sophora subprosrate:

The results showed that SSP1 stimulated proliferation and IFN-gamma secretion of murine splenic lymphocytes at concentrations of 50, 100, 200 or 400 mg/L in vitro. SSP1 increased the levels of interleukin-6 and tumor necrosis factor-alpha in immunosuppressed mice induced by subcutaneous injection of dexamethasone at 1.25 mg/kg. Administration of SSP1 by intraperitoneal injection significantly raised spleen index, glutathione level, glutathione peroxidase activity and lysozyme activity in the immunosuppressed mice. [15]

Acacia catechu:

Acacia catechu extract showed an increase in the neutrophil adhesion to the nylon fibres, produced a significant increase in the phagocytic index and a significant protection against cyclophosphamide induced neutropenia indicating its effect on cell mediated immunity. On the other hand, Acacia catechu extract produced a significant increase in the serum immunoglobulin levels, increase in the haemagglutination titre values and decreased the mortality ratio in mice, suggesting its effect on the humoral arm of the immune system. From the above results, it was concluded that the aqueous extract of Acacia catechu has a significant effect on both cell mediated and humoral immunity.[16]

***Jatropha curcas* L.:**

The immunomodulatory effect of an 80% aqueous methanol extract (AME) and compounds 1-5 (0.25 mg/kg body wt) to one-day-old specific pathogen-free (SPF) chicks was determined. Stimulation of both humoral and cell-mediated seroresponse was observed. Remarkable effective increases of the antibody titers, lymphocyte and macrophage cells, in blood were recorded.[17]

Achillea wilhelmsii:

Immunomodulatory activity of aqueous extract of Achillea wilhelmsii (25, 50 and 100 mg/kg body weight for 5 days) was evaluated on body weight, relative organ weight, delayed type of hypersensitivity (DTH) response and haemagglutination titre (HT) in female Swiss albino mice. No significant body weight gain differences were recorded in various groups of animals. Significant increase in relative organ weight of spleen at 100 mg/kg was observed. No elevation in the levels of liver function test (LFT) enzymes and kidney relative weight was observed in tested doses of the plant. The extract of A. wilhelmsii elicited a significant increase in the DTH response at the dose of 100 mg/kg. In the HT test, plant extract showed stimulatory effect in all

doses; however this hanges were significant at 50 mg/kg. No mortality was occurred in tested doses. Overall, A. wilhelmsii showed a stimulatory effect on both humoral and cellular immune functions in mice. [18]

Picrorhiza Scrophulariiflora:

One glycoside (scrocaffeside A,) from the methanol extract of *Picrorhiza scrophulariiflora*, shows immunomodulatory properties by structure. The scrocaffeside A enhanced proliferation of splenocytes and their response to polyclonal T cell mitogen concanavalin A (Con A) and lipopolysaccharide (LPS). There was also a significant increase in the activity of peritoneal macrophages and natural killer cell when treated with doses of scrocaffeside A between 5 microg/ml and 125 microg/ml. A dose-dependent increase was also observed in the populations of mature T cell subsets. The production of cytokines and the CD4/CD8 population of splenocytes were also elevated. The levels of interleukin (IL)-2, IL-4, IL-12, and (IFN)-gamma expressed by cultured splenocytes were significantly increased when the cells were exposed to scrocaffeside A. These results indicate that scrocaffeside A may exert immunoenhancement effects on immune system. In addition to its traditional use in some diseases, it may become a new immunostimulating agent in the future. [19]

***Plantago asiatica* L.:**

The seeds of *Plantago asiatica* L. were often used as a traditional Chinese medicine for some immunologically weak patients suffering from chronic illness. These uses could be related to immunomodulatory properties of the plant. AIM OF THE STUDY: In this study, effects of extract of the seeds of Plantago asiatica L. (ES-PL) were investigated on the maturation of dendritic cells (DCs), which play significant role in primary immune system. [20]

Panax ginseng:

Ginseng is believed to have beneficial effects against human diseases, and its active components, ginsenosides, may play critical roles in its diverse physiological actions. However, the mechanisms underlying ginseng's effects remain to be investigated. We hypothesize some biological effects of ginseng are due to its anti-inflammatory effects. Seventy percent ethanol-water extracts of ginseng significantly inhibited the transcription and secretion of CXCL-10 following TNF-alpha stimulation. Nine ginsenosides including Rb1, Rb2, Rc, Rd, Re, Rf, Rg1, Rg3 and Rh1 were identified in our extract by HPLC. Seven out of nine ginsenosides could significantly inhibit TNF-alpha-induced CXCL-10 expression in U937 cells and give comparable inhibition of CXCL-10 transcription to those with the extract. However, the CXCL-10 suppressive effect of individual ginsenosides was less than that of the crude extract or the mixture of ginsenosides. The CXCL-10 suppression can be correlated with the inactivation of ERK1/2 pathways by ginseng. [21]

Caesalpinia bonducella:

The evaluation of immunomodulatory potential by oral administration of ethanolic seed extract of *Caesalpinia bonducella* (200-500 mg/kg) evoked a significant increase in percent neutrophil adhesion to nylon fibers as well as a dose-dependent increase in antibody titre values, and potentiated the delayed-type hypersensitivity reaction induced by sheep red blood cells. Also it prevented myelosuppression in cyclophosphamide drug treated rats and good response towards phagocytosis in carbon clearance assay. [22]

Garlic (*Allium sativum*):

Garlic (Allium sativum), an important medicinal spice, displays a plethora of biological effects including immunomodulation. Although some immunomodulatory proteins from garlic have been described, their identities are still unknown. The present study was envisaged to isolate immunomodulatory proteins from raw garlic, and examine their effects on certain cells of the immune system (lymphocytes, mast cells, and basophils) in relation to mitogenicity and hypersensitivity. Three protein components of approximately 13 kD (QR-1, QR-2, and QR-3 in the ratio 7:28:1) were separated by Q-Sepharose chromatography of 30 kD ultrafiltrate of raw garlic extract. All the 3 proteins exhibited mitogenic activity towards human peripheral blood lymphocytes, murine splenocytes and thymocytes. [23]

Cynodon dactylon:

Fresh juice of the grass was prepared as indicated for use in traditional medicine and standardized for solid content. Its total phenol content was estimated by Folin-Ciocalteau method. Freshly prepared juice was investigated for its effect on doxorubicin-induced DNA damage in vitro. Its immunomodulatory activity was tested on balb/c mice by the humoral antibody response which was determined by haemagglutination antibody titer and spleen cell assay. [24]

Terminalia arjuna:

Terminalia arjuna back powder (400 mg/kg, po) significantly reduced formalin-indued paw oedema at 24 h but not carrageenan-induced paw oedema. It significantly increased the anti-SRBC antibody titre in the secondary phase of immune response. The same dose significantly reduced the duration of licks and bites in both phases of formalin-induced pain response and showed significant increase in tail flick latency at higher dose (800 mg/kg, po). These effects of T. arjuna were antagonised by pretreatment with naloxone (1 mg/kg, ip). These findings support the hypothesis that T. arjuna has anti-inflammatory potential against some phlogistic agents along with some immunomodulatory activity and also has antinococeptive action probably mediated via central opioid receptors. [25]

Schisandra arisanensis

An acetone extract of the fruits of the Taiwanese medicinal plant Schisandra arisanensis has yielded 11 new oxygenated lignans. Four of these, named arisantetralones A-D (1-4), possess the aryltetralone skeleton, while the other seven, named arisanschinins F-L (5-11), are polyoxygenated C(18)-dibenzocyclooctadiene lignans. Structures were determined on the basis of spectroscopic analyses, especially 2D-NMR techniques. The structure of compound 1 was confirmed by X-ray crystallographic analysis. Immunomodulatory activity of the isolated lignans was tested and evaluated. [26]

***Rhus toxicodendron* (Rhus tox):**

Toxicodendron pubescens is a botanical name of *Rhus toxicodendron* (Rhus tox). This plant is widely used in its homeopathically diluted form in the treatment of inflammatory and edematous conditions. In this study, various dilutions of Rhus tox including its crude form have been evaluated for their effects on immune response in the in vivo and in vitro experimental models. Rhus tox in the form of mother tincture, 6cH, 30cH, 200cH and 1000cH dilutions was tested through in vivo models including sheep red blood cells (SRBCs) induced cellular and humoral immune response in C57/BL6 mice. The effects of Rhus tox dilutions were also evaluated in vitro on the functions of human polymorphonuclear (PMN) cells such as phagocytosis and intracellular killing of Candida albicans, chemotaxis, and reduction of nitroblue tetrazolium (NBT) dye. [27]

***Pteridium aquilinum* (bracken fern):**

Pteridium aquilinum (bracken fern) is one of the most common plants. The overall objective of this study was to evaluate the immunomodulatory effects of bracken fern following daily ingestion of its extract by a murine host over a period of 14 (or up to 30) days. In C57BL/6 mice administered (by gavage) the extract, histological analyses revealed a significant reduction in splenic white pulp area. Among a variety of immune response parameters/functions assessed in these hosts and isolated cells, both delayed-type hypersensitivity (DTH) analysis and evaluation of IFNgamma production by NK cells during T(H)1 priming were also reduced. Lastly, the innate response in these hosts-assessed by analysis of NK cell cytotoxic functionality-was also diminished. The results here clearly showed the immunosuppressive effects of P. aquilinum and that many of the functions that were modulated could contribute to the increased risk of cancer formation in exposed hosts. [28]

***Actinidia eriantha* Benth:**

The roots of *Actinidia eriantha* Benth (Actinidiaceae) have been used for cancers in the Chinese folk medicine. The present study aimed at evaluating the antitumor potentials of the polysaccharides from the roots of Actinidia eriantha and elucidating their immunological mechanisms by determining the effects on the growth of tumor transplanted in mice and the immune response in tumor-bearing mice. The antitumor activity of AEP and four purified polysaccharides might be achieved by improving immune response, and the composition of the

monosaccharides, uronic acid contents and molecular weight could affect their antitumor and immunomodulatory activity. [29]

Boerhaavia diffusa:

The effect of Punarnavine on the immune system was studied using Balb/c mice. Intraperitoneal administration of Punarnavine (40 mg/kg body weight) was found to enhance the total WBC count on 6(th) day. Bone marrow cellularity and number of alpha-esterase positive cells were also increased by the administration of Punarnavine. Treatment of Punarnavine along with the antigen, sheep red blood cells (SRBC), produced an enhancement in the circulating antibody titer and the number of plaque forming cells (PFC) in the spleen. Maximum number of PFC was obtained on the 6(th) day. Punarnavine also showed enhanced proliferation of splenocytes, thymocytes and bone marrow cells both in the presence and absence of specific mitogens in vitro and in vivo. More over administration of Punarnavine significantly reduced the LPS induced elevated levels of proinflammatory cytokines such as TNF-alpha, IL-1beta, and IL-6 in mice. These results indicate the immunomodulatory activity of Punarnavine. [30]

Dioscorea japonica:

The aim of this study was to elucidate the effect of the major storage protein dioscorin isolated from two different yam species, Tainong No. 1 (TN1-dioscorins) and Japanese yam (Dj-dioscorins), on the immune activities of mice. Dj-dioscorins, like TN1-dioscorins, could induce expression of the pro-inflammatory cytokines and stimulate phagocytosis of RAW 264.7. Intraperitoneal injection of the TN1-dioscorins into mice stimulated phagocytosis of bone marrow, spleen, and thymic cells. In contrast, the T and B cells in bone marrow, spleen, and thymus isolated from mice injected with Dj-dioscorins had higher proliferative responses to mitogens. Furthermore, Dj-dioscorins enhanced proliferation of CD4(+), CD8(+), and Tim3(+) (Th1) cells in spleen and CD19(+) cells in both spleen and thymus. Supplement of Dj-dioscorins in the lymphoid cells isolated from Dj-dioscorins primed mice induced cell proliferation of both spleen and thymic cells. [31]

Andographis paniculata:

The immunomodulatory activity of HN-02, an extract containing a mixture of andrographolides (i.e., andrographolide [88 +/- 5 %] plus 14-deoxyandrographolide and 14-deoxy-11,12-didehydroandrographolide together [12 +/- 3 %]) in a pure powder form was evaluated at 1.0, 1.5, and 2.5 mg/kg on different in vivo and in vitro experimental models. In a delayed-type hypersensitivity (DTH) mouse model, potentiation of the DTH reaction was observed after treatment with cyclophosphamide (CYP) and HN-02 individually. However, CYP potentiation of the DTH reaction was reversed by HN-02 pretreatment. Furthermore, HN-02 treatment elevated the depressed hemagglutination antibody (HA) titer and increased the number of plaque-forming cells (PFCs) in the spleen cells of mice that had been treated with CYP and challenged with sheep red blood cells (SRBC). Further, it was also found that HN-02 treatment stimulated phagocytosis in mice. A significant increase in total WBC count and relative weight of spleen and thymus was observed in mice during 30 days of treatment with HN-02. [32]

Curcuma longa:

Curcumin is a polyphenol derived from the dietary spice turmeric. It has been shown to regulate numerous transcription factors, cytokines, adhesion molecules, and enzymes that have been linked to inflammation. In addition to inhibiting the growth of a variety of pathogens, curcumin has been shown to have nematocidal activity. The present study was designed to evaluate the schistosomicidal activity of curcumin in vivo as well as immunomodulation of granulomatous inflammation and liver pathology in acute schistosomiasis mansoni. In conclusion, curcumin treatment modulates cellular and humoral immune responses of infected mice and lead to a significant reduction of parasite burden and liver pathology in acute murine schistosomiasis mansoni. [33]

Tinospora cordifolia:

An immunomodulatory protein (ImP) in guduchi was purified from dry stem powder extract by anion-exchange chromatography on Q-Sepharose. Characterization of guduchi ImP was performed by SDS-PAGE, periodic acid-Schiff staining, HPLC,

and immunochemical analyses. Immunostimulatory activity was assessed by lymphocyte proliferation and macrophage activation assays. Fresh guduchi stem/leaf, guduchi satwa and guduchi capsules were also analyzed for the presence of guduchi ImP. The confirmation of an immunomodulatory protein in guduchi stem showing lymphoproliferative and macrophage-activating properties reinforces the rationale of the use of guduchi preparations in several Ayurvedic medicines for immunomodulation. To our knowledge, this is the first report of an immunomodulatory protein isolated from guduchi. [13]

CONCLUSION: The use of various plant extracts and herbal fed additives in specific dose during the scheduled vaccination regimen may be helpful in obtaining higher protective antibody against different infections including production and development of more effective cell mediate immune response for protection against various bacterial, viral and other diseases. Herbal formulation may be therefore recommended for use as positive immunomodulator. There are several botanical products with potential therapeutic applications because of their high efficacy, low cost and low toxicity.

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