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Role of *Panchamruta Rasa* (*Panchadasha*) as a immunomodulator w.s.r. *Rasayana* : A Review

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ABSTRACT

In Ayurveda, text immunity had been described by Chakrapani in terms of *Vyadhikshamatva* and it is termed as a state of equilibrium of *Oja, Bala, Prakrit Kapha*. The modulation of immune response by using Ayurvedic herbal medication as a possible therapeutic measure has now become a subject of scientific investigation. Immunomodulators can be defining as substance which can affect any function of the immune system including both innate and adaptive immunity. In Ayurveda, this concept of immunomodulation correlated with *Rasayana*. *Rasayana* acts in the body at three levels i.e. *Rasa, Agni, Strotas*. The present review is undertaken for screening minerals & herbs (ingredients) of *Panchamruta Rasa* (*Panchadasha*) to evaluate their immunomodulatory properties and establish the correlation between *Rasayana* and immunomodulatory effect. Critical review of minerals & herbs to show immunomodulatory property is compiled from various Ayurvedic texts as well as from multiple articles on the internet to justify their immunomodulatory property on the basis of data collected. This also shows their potential to act as antioxidant, anti-stress, anti-inflammatory, anti-bacterial, vaccine adjuvant, or immunity against diseases property.

Key words: *Immunity, Immunomodulators, Rasayana, Vyadhikshamatva.*

INTRODUCTION

Immunity is a biological term that describes a state of having sufficient biological defenses to avoid infection, disease or other unwanted biological invasion. More recently it became clear that immune system not only protects against infections, but also limits excessive responses that might lead to auto immune diseases.[1] Dysfunction or deficiency of immune response leads to a wide variety of diseases, involving every organ system in the body. The rapidly changing lifestyle, uncertain climate and unhealthy habits of health-conscious generations results in poor immunity. This leads to production of free radicals which causes oxidative stress. These cytotoxic free radicals not only raise the oxidative stress but also play an important role in immune system dysfunction, due to which mankind is prone to various major ailments. Infectious diseases are now primarily considered immunological disorders while neoplastic and several autoimmune diseases may be involved in immunosuppressive state.[2]

Modulation of the immune system denotes to any change in the immune response that can involve induction, expression, amplification or inhibition of any part or phase of the immune response.[3] Immunomodulators are considered now as one of the most potent tools in the management of health and disease by modern medicine. They are biological or synthetic substances that can stimulate suppress or modulate several aspect of immune system including both adaptive and innate arms of immune system.

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Immunomodulator usually act as stimulant or suppressant.[4]

The modulation of immune response by using Ayurvedic herbal formulation as a possible therapeutic measure has now become a subject of scientific research. The basic concept of immunomodulation existed in Ayurveda and practiced by ethnic therapists for centuries. One of the therapeutic strategies in Ayurvedic medicines is to enhance the body's overall natural resistance towards disease causing agent rather than directly neutralizing it. Ayurveda has always given preference to maintain the wellbeing of healthy person rather than to cure the disease.

Vyadhikshamatva has direct role with respect to disease incidence and progress. When etiological factors come in contact with the body results into diseases progression; at the same time body try to resist the disease either by avoiding its manifestation or to suppress its intensity. This power of the body resistivity which prevents the development of disease or resists the influence of disease collectively called as body's defensive mechanism or '*Vyadhikshamatva*'.[5]

Ayurvedic concepts like *Vyadhiksamatva, Oja* and *Bala* resembles with immunity. *Vyadhikshamatva* depends upon *Bala* and *Oja* of the body. The above mentioned objective for immune enhancement is achieved through the use of the *Rasayana* therapy and *Ojovardhaka* remedies. *Rasayana* enhances physical and mental strength, intelligence. The drug formulation which increases the strength of all *Rasadi Dhatu* is called as *Rasayana.*[6]

Rasayana Tantra is one of the eight clinical specialties of Ayurveda which deals with the nutrition, natural resistance and geriatrics. *Rasayana* can be a drug, diet or even a life style i.e., *Achara Rasayana*, which may be helpful in achieving *Vyadhikshamatwa*. Concept of *Rasayana* is designed for both conditions i.e. health as well as diseased. *Rasayana* works at various levels in the body and overall result is absolute state of *Vyadhikshamatava.* Also, previous studies reported that *Rasayana* works as immunomodulator.[7]

Panchamruta Rasa (*Panchadasha*) is mentioned in '*Rasa Yogsagar*' in *Rasyana Adhikara* which contains *Bhasma* of *Parada, Abhraka, Lauha, Naga, Vanga,* and *Gandhaka*. *Bhavana Dravya* of *Panchamruta Rasa* (*Panchadasha*) are *Kanji, Talmooli, Shatavari, Varahi, Aajagandha, Vidari Ashwagandha*. It is indicated as *Sarvroghara, Vali, Palit, Prameha, Grahani, Arsha, Kshya, Kushta, Aamvata, Asthishoola, Halimaka*, *Balya, Rasayana, Sarvdhatupushtikar*. Most of the ingredients of *Panchamruta Rasa* (*Panchadasha*) are proven for immunomodulatory effect.[8]

Aims and Objectives

To review on *Panchamruta Rasa* (*Panchadasha*) as a immunomodulator w.s.r. to its *Rasayana Karma.*

Materials and Methods

The main objective of this review article is to discuss immunomodulatory activities of *Panchamruta Rasa* (*Panchadasha*). This review was mainly focused to find out the pharmaceutical properties of individual drugs of *Panchamruta Rasa* (*Panchadasha*) and their immunomodulatory activities. All the classical texts of Ayurveda (*Samhita* along with their commentaries), online journals, and research articles were thoroughly reviewed for compiling the relevant data about *Panchamruta Rasa* (*Panchadasha*).

Review of Immunity[9]

Definition

Immunity is defined as the capacity of the body to resist pathogenic agents. It is the ability of body to resist the entry of different types of foreign bodies like bacteria, virus, toxic substances, etc.

Types of Immunity

Immunity is of two types:

1) Innate immunity. 2) Acquired immunity.

Innate Immunity or Non-Specific Immunity

Innate immunity is the inborn capacity of the body to resist pathogens. By chance, if the organisms enter the body, innate immunity eliminates them before the development of any disease. This type of immunity

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represents the first line of defense against any type of pathogens. Therefore, it is also called non-specific immunity.

Acquired Immunity or Specific Immunity

Acquired immunity is the resistance developed in the body against any specific foreign body like bacteria, viruses, toxins, vaccines or transplanted tissues. So, this type of immunity is also known as specific immunity. It is the most powerful immune mechanism that protects the body from the invading organisms or toxic substances. Lymphocytes are responsible for acquired immunity.

Types of Acquired Immunity

Two types of acquired immunity develop in the body:

1) Cellular immunity 2) Humoral immunity.

Lymphocytes are responsible for the development of these two types of immunity.

The two categories are:

1. T lymphocytes or T cells, which are responsible for the development of cellular immunity

2. B lymphocytes or B cells, which are responsible for humoral immunity.

ANTIGENS

Definition and Types

Antigens are the substances which induce specific immune reactions in the body. Antigens are of two types:

1. Auto antigens or self-antigens present on the body's own cells such as 'A' antigen and 'B' antigen in RBCs.

2. Foreign antigen s or non-self-antigens that enter the body from outside.

Development of Cell-Mediated Immunity

Introduction

Cell-mediated immunity is defined as the immunity developed by cell-mediated response. It is also called cellular immunity or T cell immunity. It involves several types of cells such as T lymphocytes, macrophages and natural killer cells and hence the name cell mediated immunity. Cell-mediated immunity does not involve antibodies. Cellular immunity is the major defense mechanism against infections by viruses, fungi and few bacteria like tubercle bacillus.

Antigen-Presenting Cells: Antigen-presenting cells are the special type of cells in the body, which induce the release of antigenic materials from invading organisms and later present these materials to the helper T cells.

Types of Antigen-Presenting Cells

Antigen-presenting cells are of three types:

1. Macrophages

2. Dendritic cells

3. B lymphocytes.

Development of Humoral Immunity

Introduction

Humoral immunity is defined as the immunity mediated by antibodies, which are secreted by B lymphocytes. The humoral immunity is the major defense mechanism against the bacterial infection. As in the case of cell-mediated immunity, the macrophages and other antigen-presenting cells play an important role in the development of humoral immunity also.

Transformation B Cells

Proliferated B cells are transformed into two types of cells:

1. Plasma cells: Plasma cells destroy the foreign organisms by producing the antibodies.

2. Memory cells: The memory cells are in inactive condition until the body is exposed to the same organism for the second time.

Antibodies or immunoglobulin

An antibody is defined as a protein that is produced by B lymphocytes in response to the presence of an antigen. Antibody is gamma globulin in nature and it is also called immunoglobulin (Ig). Immunoglobulin form

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20% of the total plasma proteins. Antibodies enter almost all the tissues of the body.

Types and functions of Antibodies

Five types of antibodies are identified

1. IgA (Ig alpha): plays a role in localized defense mechanism in external secretions like tear.
2. IgD (Ig delta): is involved in recognition of the antigen by B lymphocytes.
3. IgE (Ig epsilon): is involved in allergic reactions.
4. IgG (Ig gamma): is responsible for complement fixation
5. IgM (Ig mu): is also responsible for complement fixation.

Among these antibodies, IgG forms 75% of the antibodies in the body.

Mechanism of actions of Antibodies

Antibodies protect the body from invading organisms in two ways

1. By direct actions

2. Through complement system.

Cytokines

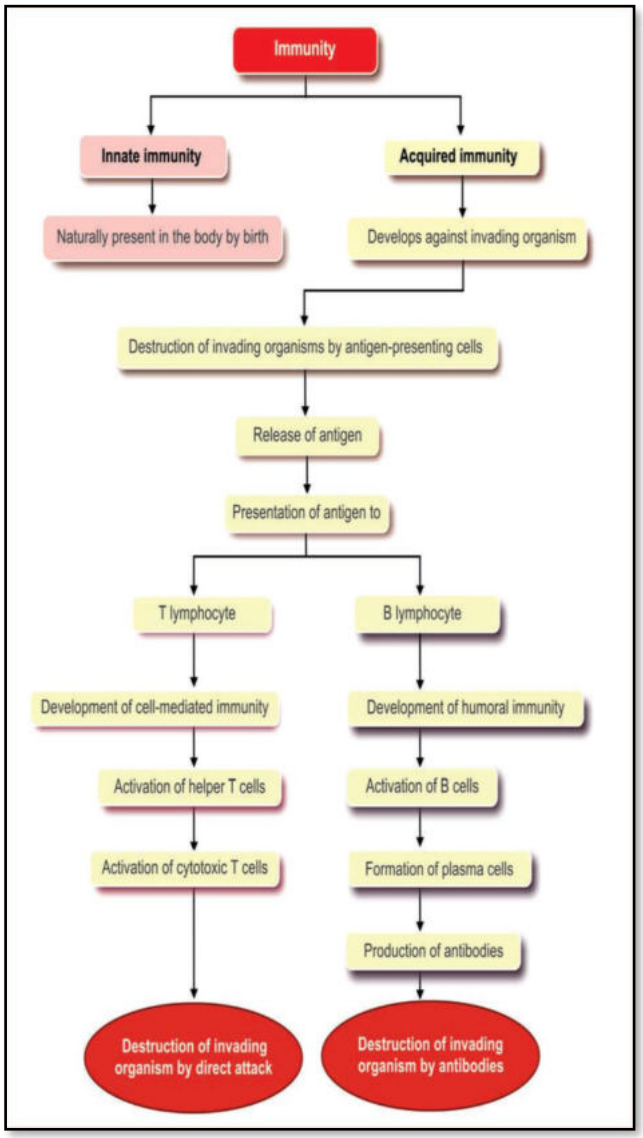
Cytokines are the hormone-like small proteins acting as intercellular messengers (cell signaling molecules) by binding to specific receptors of target cells. These non-antibody proteins are secreted by WBCs and some other types of cells. Their major function is the activation and regulation of general immune system of the body. Cytokines are distinct from the other cell-signaling molecules such as growth factors and hormones.

Types of Cytokines

Depending upon the source of secretion and effects, cytokines are classified into several types:

1. Interleukins
2. Interferon
3. Tumor necrosis factors
4. Chemokines
5. Defensins
6. Cathelicidins
7. Platelet-activating factor.

Schematic diagram showing development of immunity (courtesy: Sembulingum).



VYADHIKSHAMATVA

Introduction

When an extensive epidemic of an infectious disease comes into being, many people turn out to be infected at the same time, but several of them remain healthy because of a resistance power against the causes of illnesses within them, or the state of not being susceptible or ill. This is known as immunity in modern medicine and *Vyadhikshamatva* in Ayurveda.

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Definition[10]

The word *Vyadhikshamatva* is composed of two words;

1. ***Vyadhi*** - means disease, non-equilibrium state of physiological entities and
2. ***Kshamatwa*** - means tolerance or to resist.

The term *Vyadhikshamatva* is found in *Charak Samhita Sutrasthana* 28th *Adhyaya* viz. *Vividhashitpitiya Adhyaya* but not explained in detail. *Vyadhikshamatva* is well defined and explained with its types by commentators specially Chakrapani.

Types of *Vyadhikshamatva*[11]

Chakakrapani quoted two types of *Vyadhikshamatva*. *Vyadhikshmatvam Nam Vyadhi Bala Virodhitwam Vyadhyutpada Prathibhadakatwam* | Chakrapani Tika (Cha. Su.28)

1. ***Vyadhibala Virodhitvam*** - action taken against disease or strength to stop the progress of disease i.e. improving the strength against a specific disease, which can be achieved by *Naimittika Rasayana*. May be correlated with *Yuktikrut Bala* or artificial immunity or acquired immunity.
2. ***Vyadhyutpada Pratibandhakatvam*** - as capability of preventing diseases or as strength of the body is strong enough to stop the occurrence and re-occurrence of disease. May be correlated with *Sahaja Bala* or innate immunity.

Concept of *Vyadhikshamatva*[11]

Vyadhikshamatva can be well understood with the help of synonyms used in one or other aspect like 1.*Vikaravighatakar Bhava*, 2. *Bala* 3. *Ojas* 4. *Shleshma* 5. *Satmya* 6. *Rasayana* etc. Some *Vaidyas* consider, *Bala* alone as a synonym for *Vyadhikshamatva*.

1. ***Vikara Vighatakar Bhava*** - means when the resistance power of the body is sufficiently strong enough to destroy the cause, there will be no manifestation of diseases. The *Bhavas* that create the defensive mechanisms against diseases are called as *Vikara Vighataka Bhava*. Hence, *Vikarvighatkar Bhava* are the main reason for *Vyadhikshamatva*.
2. ***Bala*** - is only power that controls *Doshas* or *Rogas* (disease). *Bala* usually referred as strength. Also used as a synonym for *Vyadhikshamatva*. *Bala* is the output state of equilibrium of *Dosha, Dhatu* and *Mala* in our body, thus it is an important functional identity of body. There are three types of *Bala* mentioned in Ayurveda.
   a) *Sahaja*: congenital (by birth) or natural
   b) *Kalaja:* with respect to time, season,age
   c) *Yuktikruta*: acquired.
3. ***Ojas*** - *Ojas*, the quintessence of all the tissues of the body is known as *Ojas* because, it is the final and excellent essence of all seven *Dhatus*. *Ojas* is the main determinant of our immune status and hence our resistance to disease.
4. ***Shleshma / Kapha*** - Equilibrium state of *Kapha* promotes strength, that's why normal *Kapha* is used as synonym for *Bala/ Vyadhikshamatva*. Presence of *Ojas* in our body can be compared to functions of normal *Kapha*.
5. ***Satmya*** - Use of all six *Rasas* in diet creates maximum strength in the body whereas consumption of one or two *Rasas* gives rise to minimum *Bala*. This directly affects the *Vyadhikshamatva* of a person. Similarly use of *Aahar, Vihar* and *Aushadha* opposite in qualities to *Desha , Kala, Roga* and *Prakruti* is termed as *Satmya*.
6. ***Rasayana*** - It is the therapy given / taken to obtain best qualitative and quantitative *Rasadi Dhatu* thereby giving rise to excellent *Vyadhikshamatva* because of excellence of *Ojas*. It strengthens the individual's capabilities at both physical and psychological levels. So *Rasayana* will surely help in improving *Vyadhikshamatva* of an individual.

Variability of *Vyadhikshamatva* in different individuals.[12]

It is observed that many people with appropriate daily and seasonal habits also develop disease and some people, though indulging in improper diet and

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behaviour hardly develop any disease. Charak has further described two types of *Sharira* (individuals) - *Vyadhisaha* and *Avyadhisaha* which are similar and can be easily correlated to *Vyadhi Kshamatva* and *Akshamatva.*

REVIEW OF OJAS

Introduction

Beyond *Dosha*, *Dhatu* and *Mala* concept, there is one separate entity due to which every tissue of the body remains integrity in functions and structure for strength and vitality of human body is called as *Ojas*. The physical, mental and spiritual strength totally depends on *Ojas*. *Ojas* gets formed first in the body of living beings.

Formation of *Ojas*[13]

The best way to describe formation of *Ojas* is to understand how honey is made. Nearly ten to twenty thousand bees collect the nectar or essence of thousands of fruits and flowers and stored them into their hives for the formation of honey. Similarly *Ojas* is also the nectar or essence and is the end product of various physiological process.

Dwelling place of *Ojas*[14][15]

Primary location of *Ojas* is the heart, from where it circulates to and circulated in the entire body. There are two places where *Ojas* prevails.

1. ***Para Ojas*** - *Hridya Sthana* (in the heart). The amount of *Para Ojas* is eight drops. It is situated in the heart and it is *Pradhana*, and its decrease produces death.
2. ***Apara Ojas*** - *Sarva Sharira Vyapi* (all over the body) like ghee in milk or honey in flowers. The amount of *Apara Ojas* in the body is half *Anjali*. *Apara Ojas* circulates in the *Dhamanis* and it is *Apradhana*. Its decrease produces different *Ojaskshaya* symptoms in the body.

Functions of *Ojas*[16]

Ojas is very useful to maintain the condition of the good health. It not only nourishes all the body constituents but also nourishes the mind. It controls or regulates all the physiological activities and immunity power of the body. In Ayurveda it is believed that life cannot exist without *Ojas* in the body. Some of the functions are as follows:

Balen (strength bestows), *Sthira Upachita Mamsata* (stability and growth of muscles), *Sarva Cheshta Swapratighatah* (ability to perform all activities without any hindrance), *Swara Varna Prasado* (clarity of voice and brightness of color or complexion), *Karana Nama Aatma Karya Pratipatti* (ability of external and internal sense organs to perform their own functions.)

REVIEW OF IMMUNOMODULATION

Introduction

Immunomodulation is a very broad term which denotes to any changes in the immune response and may involve induction, expression, amplification or inhibition of any part or phase in the immune response. Immunomodulation may be specific or nonspecific. The immunomodulation drugs are needed for the treatment of various disease statuses such as infections, organ transplantation, cancer, rheumatoid arthritis, systemic lupus erythematous, Down syndrome, Crohn's and autoimmune diseases and the acquired immune deficiency syndrome (AIDS).

Definition[17]

Immunomodulators

These are biological or synthetic substances that can stimulate, suppress or modulate any aspect of the immune system including both adaptive and innate arms of the immune system.

Immunoadjuvant: These agents are used for enhancing vaccines efficacy and therefore, could be considered specific immune stimulants.

Immunostimulant: These agents are inherently nonspecific in nature as they envisaged enhancing body's resistance against infection. They can act through innate immune response and through adaptive immune response.

Immunosuppressants: These are a structurally and functionally heterogeneous group of drugs, which are often concomitantly administered in combination

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regimens to treat various types of organ transplant rejection and autoimmune diseases.

Objective of Immunomodulation

1. To induce effective and sustained immune response against infections
2. Speed up the maturation of nonspecific & specific immunity during neonatal period and in young animals.
3. To enhance local immunity.
4. Overcome the immunosuppressive effects of stress and environmental pollution.
5. To maintain immune surveillance.

Mechanisms of action of Immunomodulators[18]

- Immunomodulators act at different levels of the immune system. Therefore different kinds of drugs have been developed that selectively either inhibit or intensify the specific populations and subpopulations of immune responsive cells, i.e. lymphocytes, macrophages, neutrophils, natural killer (NK) cells, and cytotoxic T lymphocytes (CTL).
- Immunomodulators affect the cells producing soluble mediators such as cytokines. Thus, in immunotherapy the immune system is targeted in order to help the healing of a given disease.
- Immunosuppressants inhibit the immune response in organ transplantation and autoimmune diseases, whereas immunostimulants increase the immune response in infections, immunodeficiency (for example AIDS) and cancers.
- The term immunomodulation is used rather than immunostimulator for a substance that causes measurable alterations in immune function. Their action can be specific or non-specific. System of the cells according to the presence of a particular antigen or immunogen, with selective specificity for immune response. Immunomodulation is selective when the stimulation translates into an immunoreaction to one or several antigens, as in the case of adjuvants or therapeutic vaccines.
- Immunological adjuvants enhance the effect of vaccines with synthetic antigens, including new-generation antigens. These agents are also used in experimental immunization to obtain polyclonal antiserums and monoclonal antibodies for utilization in vaccines.
- Non-specific-action immunomodulators are used to stimulate or suppress the immune response, without directing the activity of stimulated cells to a specific antigen. They are divided into three types: type I, acting on normal immune system; type II, acting on immunosuppressed immune system; and type III, acting on functionally normal and immunosuppressed immune system.

Adverse effects

By acting on the immune system, all these drugs may increase the risk of infection. Although usually mild and risk-free, the infections can also be severe, including those caused by opportunistic agents. Reactivation of latent tuberculosis is also a known untoward effect particularly reported in connection with the new generation immunomodulatory drugs. In general, adverse effects impair the quality of life of the immunosuppressed patient, and pharmacological effects represent the leading cause of death in transplant patients.

Need of Herbal Immunomodulators[19]

The modulation of immune response by using Ayurvedic herbal medications as a possible therapeutic measure has now become a subject of scientific investigation. The concept in modern scientific understanding would mean enhancement of immune responsiveness of an organism against a pathogen by non-specifically activating the immune system using immunomodulatory agents of plant origin. Immunomodulators are considered now as one of the most potent tools in the management of health and disease by modern medicine. In fact the role of immunomodulators in modern medicine is yet to be fully appreciated or perceived as our understanding of immune system is changing at a rapid pace. The basic concept of immunomodulation not only existed in Ayurveda but is being really practiced by the

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Ayurvedists for centuries. In fact, one of the therapeutic strategies in Ayurvedic medicines is to enhance the body's overall natural resistance to the disease causing agent rather than directly neutralizing the agent itself. Here lies the difference between the fundamental therapeutic approach of Ayurveda and modern medicine, which emphasize on direct attack on the disease causing agents using chemotherapeutic drugs. In Ayurvedic practice, the objective of immune enhancement is achieved through the use of the *Rasayana* therapy and also by use of *Ojovardhaka* remedies.

REVIEW OF RASAYANA

Introduction

Rasayana or *Jara Chikitsa* is one amongst the eight branches of Ayurveda; practiced extensively and effectively since ages. *Acharya Charaka* has quoted as *Jara-Chikitsa* where as *Acharya Sushruta* has mentioned it as *Rasayana-Tantra*. Though chiefly concerned with improving the health status, *Rasayana* is used as curative. Thus, it serves the dual purpose of eradicating the ailments and keeping them away thereby promoting and prolonging the life span.

Etymology

The word *Rasayana* is formed from two words viz. *Rasa* and *Ayana*.

The word *'Rasa'* is formed from *'Ras Gatau' Dhatu* and *'Ac' Pratyaya. Acharyas* have given various meanings for *Rasa* at different contexts. The word *Ayana* has various meanings as given in *Shabda Kalpa Druma* and *Vacaspatyam*. They are pathway, movement, road, place, site, abode, a way of entrance, an entrance etc. In total, *Rasayana* is meant as *Rasayana* means the pathway for essence of foodstuffs towards all body tissue elements so as to nourish and replenish them.

Definitions

1. ***Shabdakalpadruma*** - *Rasayana* is that by which *Rasa, Rakta* etc. *Dhatus* are obtained.
2. ***Acharya Charaka***[20] - It means the measures by which one can get excellence of *Rasa* etc. *Dhaatus* are called *Rasayana*.
3. ***Acharya Sushruta***[21] - In addition to this later described that the one which nourishes, *Rasa, Rakta* etc. *Dhatus* or the one which stabilizes youthfulness and prolongs life with activities through its *Rasa, Virya* etc. is called *Rasayana*.
4. ***Acharya Vagbhata***[22] - *Arunadatta* has described that *Rasayana* is one by which *Rasa, Raktadi Dhatus* get benefited through proper nourishment.
5. ***Acharya Sharangdhara***[23] - *Rasayana* is one which wards off *Jara* as well as *Vyadhi*. The one which cures *Jara* and *Vyadhi*, stabilises youthfulness; increases acuity of *Chakshu* etc. *Indriyas*; nourishes the whole body and aphrodisiac is known as *Rasayana*.

Classifications

1. *Charaka Samhita*[24]

Two types of *Rasayana* based on the mode of administration.

a) Kutipravesika b) *Vatatapika*

One more *Rasayana* variety has been mentioned by *Acharya Charaka* i.e., *Achara Rasayana*[25] or *Nitya Rasayana.*

2. *Sushruta Samhita*[26]

Three types of *Rasayana* by *Dalhana*. It is probably based on the utility of *Rasayana*.

a) *Kamya Rasayana* - it is subdivided into *Pranakamiya, Srikamiya* and *Medhakamiya*

b) *Naimittika Rasayana*

c) *Ajasrika Rasayana*

Another two types of *Rasayana* mentioned by *Dalhana* based on their mode of action.

Samshodhana and *Samshamana*

Utility of *Rasayana*

Enhances the intelligence, memory power, will power, body strength, skin luster, sweetness of voice and physical strength.

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It nourishes the *Sapta Dhatu* and thus prevents chronic degenerative changes and illness.

Rasayana is thought to improve metabolic processes, which results in the best possible biotransformation and produce best quality body tissues, eradicate senility and thus help prevent diseases of the old age.

It helps attain optimal physical strength and sharpness of sense organs.

Rasayana Dravyas have significant action on reproductive system and nourish *Shukra Dhatu, Rasayana* nourishes the whole body, helps maintain physiological functions at optimum level, thus also improve body's natural resistance against infections by increasing Immunity.

Rasayana invigorates the body in general by sustaining the required balance between anabolism and catabolism.

Pharmacodynamics of *Rasayana*[27]

Rasayana drugs have varied pharmacodynamic properties. Probably there is no much relation with their properties of *Rasa, Guna, Veerya, Vipaka.*

1. *Rasayana* may act at the level of *Rasa*

By improving the nutritional status of *Rasa* and in turn by improving tissue nourishment. Probably *Rasayana* drugs having *Madhura, Guru, Snigdha*, and *Sheeta Guna* may act at this level by promoting the nutritional value of *Poshaka Rasa*, which in turn helps in obtaining the best qualities of *Dhatus*.

2. *Rasayana* may act at the level of *Agni*

The *Rasayana* drugs possessing the *Ushna, Laghu, Ruksha, Guna* and *Katu, Tikta, Kashaya Rasa* may be acting at the level of *Agni* (digestion and metabolism) by improving the digestive capacity and by vitalizing the metabolic activities (improving *Jatharagni* and *Dhatwagnis*) of the body.

3. *Rasayana* may act at the level of *Srotas*

Similarly the drugs with *Katu, Tikta, Kashaya Rasa Ushna Veerya, Katu Vipaka, Vishada, Ruksha* and *Laghu Gunas* may produce the *Rasayana* effect at the level of *Srotas* by improving *Sukshma Samvahn* and the quality of *Deepana* and *Pachana.* These drugs cause *Srotoshodhana* (cleansing of channels) and thus allow efficient blood circulation and improve tissue nourishment and there by maintains its structural integrity and functional capacity.

Review of mode of action of *Rasayana* in modern aspect[28]

Rasayana contains immuno modulators of varying chemical structures and molecular sizes. These exert their effects by modulating several steps of immune system such as activation of macrophages for enhanced generation, stimulation of phagocytosis, proliferation of lymphocytes leading to production of t helper cells and activation of complement pathways. Immunostimulants offer promise in enhancing antigen specific and nonspecific immune response against infection.

- It has been reported that the '*Rasayanas'* are rejuvenators, nutritional supplements and possess strong antioxidant activity. They also have antagonistic actions on the oxidative stressors, which give rise to the formation of different free radicals.
- They are used mainly in ageing, atherosclerosis, cancer, diabetes, rheumatoid arthritis, autoimmune and Parkinson's disease. Their antistress actions have made them therapeutically more important.
- Some *Rasayana* activate mononuclear cells to produce cytokines like GM-CSF and IL-1 in a dose dependent manner. These results indicate it is possible that the *Rasayana* (particularly those with *Madhur Vipaka* that are advocated as adaptogens in Ayurveda) primarily activate immune cells, leading to secretion of cytokines, which in turn act on multiple target organs to produce the myriad effects ascribed to these treatments .
- Administration of herbal preparation, *Rasayana* has been found to be enhance the natural killer cell activity in normal as well as in tumor bearing animals.
- *Rasayana* are also found to stimulate antibody dependent complement mediate tumour cell lysis.

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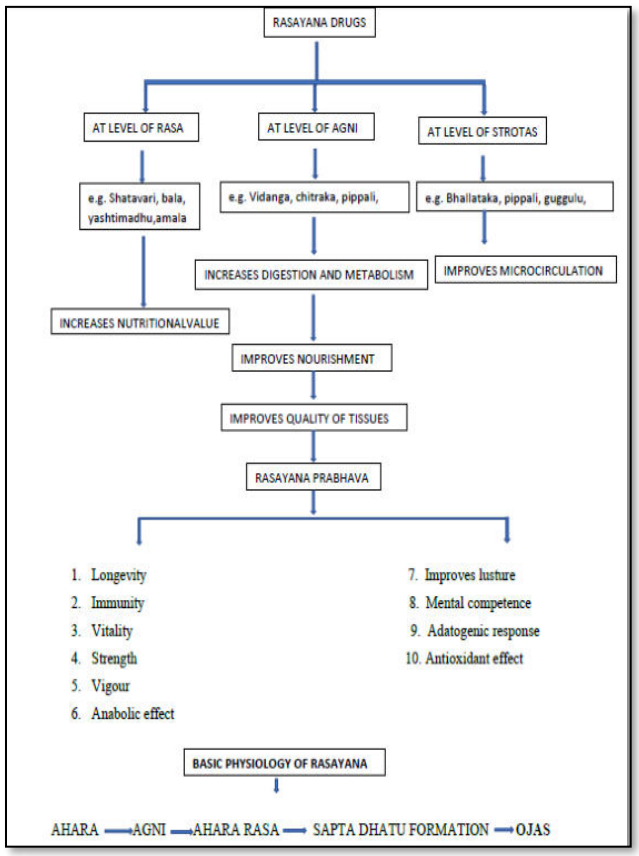
The *Rasayana* herbs seem to exert their effect through immunosuppressant, immunostimulant and immunoadjuvant activities or by affecting the effector arm of the immune response. It has been found that the nervous, endocrine and immune systems are all interrelated. Immune products like various cytokines have been found to stimulate the hypothalamus-pituitary-adrenal axis and corticotrophin release factor (CRF), which ultimately enhances the production of adrenal corticotrophic hormone (ACTH) resulting into increased secretion of glucocorticoids which have an overall suppressive effect on the immune system.

- Stress also acts on the same axis and brings about changes in the immune status of the body. These Rasayana drugs probably reduce stress levels by affecting antioxidant levels. So these *Rasayana* drugs act as potent antioxidants and neuroendocrine immunomodulators.

Schematic diagram showing mode of action Rasayana Drugs

(courtesy: Bhagwan et al.WJPR Vol 9, Issue 4, 2020.)



REVIEW OF PANCHAMRUTA RASA (PANCHADASHA)

Panchamruta Rasa (Panchadasha) was prepared according to ref Ra.Yo.Sa.Part-2, *Rasayana Adhikara, Sholka*(69)297-301.

Table 1: Ingredients of *Panchamrita Rasa (Panchadasha).*

SN	Ingredients	Quantity
1.	*Abharka Bhasma*	1 Part
2.	*Lauha Bhasma*	1 Part
3.	*Parad Bhasma*	1 Part
4.	*Vanga Bhasma*	1 Part
5.	*Naga Bhasma*	1 Part
6.	*Shuddha Gandhaka*	5 Part
Bhavana Dravya		
1.	*Kanji*	Q.S.
2.	*Godugdha*	Q.S.
3.	*Shatavari Kwatha*	Q.S.
4.	*Vidari Kwatha*	Q.S.
5.	*Varahi Kwatha*	Q.S.
6.	*Talmooli Kwatha*	Q.S.
7.	*Ashwagandha Kwatha*	Q.S.
8.	*Ajagandha Kwatha*	Q.S.

Indication - It is indicated as *Sarvroghara, Vali, Palit, Prameha, Grahani, Arsha, Kshya, Kushta, Aamvata, Asthishoola, Halimaka, Balya, Rasayana, Sarvdhatupushtikar*.

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Table 2: *Rasapanchaka* and chemical constituents of *Panchamruta Rasa (Panchadasha)*

SN	Drug	Latin Name	*Rasa Panchaka*	Chemical Constituents	*Karma*
1.	*Parad*[29]	Hydrargyrum	*Rasa - Shadarasa* *Virya - Ushna* *Vipaka - Madhura* *Guna - Sara, Guru* *Dosghanuta - Tridosaghana* *Prabhava - Vrsya, Balya, Rasayana*	Hg	*Sarvarogajita, Shodhana, Ropana, Krmighna*
2.	*Gandhak*[30]		*Rasa - Madhura, Katu, Tikta, Kashya* *Vipaka - Katu* *Virya - Ushna* *Guna - Snigdha and Sara* *Doshaghnata - Kapha vatahara, Pittavardhaka*	S	*Vrishya, Deepana, Pachana, Rasayana, Shoshan, Vishaghna, Krimighna, Pleehagna, Balya, Aamdoshanasha, Divya Drishti Karaka.*
3.	*Abhrak*[31]	Mica	*Rasa - Kashaya, Madhura* *Virya - Sheeta* *Vipaka - Madhura* *Guna - Snigdha, Laghu* *Prabhava - Rasayana* *Doshaghnata - Vata Pittaghna, Kaphakara, Tridosaghna*	Fe,Ca, K, Si, Mg, Al and Ti	*Buddhismritikshaya , Apasmara, Unmada, Bhrama, Shirovikara, Kasa, Shwasa, Garbhashaya Shodhaka, Netra Roga, Kshaya,*
4.	*Lauha*[32]	Ferrum	*Rasa - Kashaya, Tikta* *Virya - Sheeta* *Vipaka - Madhura* *Guna - Ruksha, Guru.* *Prabhava - Rasayana* *Doshaghnata - Vata Pittaghna, Kaphakara, Tridosaghna*	Fe, Ca, K, Si, Mg, Al, Cl, S.	*Lekhan, Raktapittahara, Shwasahara, Kasahara, Arshahara, Shothahara, kshayanashaka, Balya, Raktavardhaka.*
5.	*Vanga*[33]	Stannum	*Rasa - Tikta, Amla, Katu, Kashaya.* *Virya - Ushna,* *Vipaka - Madhura* *Guna -*	O, Sn, C, Ca, Zn, Mg, Si, Fe, Al, S, Cu	*Balya, Deepana, Pachana, Medohara, Vrishya*

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			Ruksha,Laghu,Sara,Ushna,Teekshna; *Doshaghnata -Kaphapittahar, Ishat Vataprakopaka.*		
6.	*Naga*[34]	Plumbum	*Rasa - Tikta, Madhura.* *Virya - Atyushna.* *Vipaka - Madhura* *Guna - Snigdha, Dipana, Rasayana, Guru, Sara, Vangavat.* *Doshaghnata - Tridoshanashaka*	Pb, O Ca, K, Si, Mg , As.	*Tridoshaghna, Chakshushya, Medoghna, Rajataranjanakrit, Viryadardhyakara, Ruchivardhaka, Kamavardhaka, Lekhana.*
7.	*Kanji*[35]	-	*Rasa - Amla* *Virya - Ushna* *Vipaka - Amla* *Guna - Tikshna, Laghu* *Prabhav - Bhedana*	---	*Bhedana*
8.	*Godugdha*[36]	-	*Rasa - Madhura* *Guna - Guru, Snigdha* *Virya - Sheeta* *Vipaka - Madhura* *Prabhava* - Not specified *Doshghnata - Vata* and *Pitta Doshashamaka.*	lipase, aryl esterase, choline esterase, alkaline phosphatase, acid phosphatase, xanthine oxidase, lactoperoxidase, protease, and amylase, catalase, aldolase.	*Rasayana, Tarpaka, Jivaniya, Hrdya, Ahladakara* and *Buddhi Prabodhaka.*
9.	*Ajagandha*[37]	*Cleome gynandra*	*Rasa - Katu* *Virya - Sheeta* *Vipaka - Katu* *Guna - Laghu, Ruksha* *Doshghnata - Vatahara & Pittala*	Fixed oil, essential oil and oleoresin.	*Shulaghna, Dipana, Hridya, Pittala, Vatahara*
10.	*Ashvagandha*[38]	*Withania somnifera*	*Rasa - Tikta, Kashya* *Virya - Ushna* *Vipaka - Madhura* *Guna - Laghu* *Doshghnata - Vatakaphapaha*	Alkaloids and with anolides.	*Rasayana, Vatakaphapaha, Balya, Vajikarana*
11.	*Shatavari*[39]	*Asparagus recemosus*	*Rasa - Madhura, Tikta* *Virya - Sheeta*	Sugar, Glycosides, Saponin and Sitosterol.	*Shukrala, Balya, Hridya, Medhya,Pittahara, Rasayana,Vrishya, Shukraja,*

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			Vipaka - Madhura *Guna - Guru, Snigdha* *Doshghnata - Pittahara, Kaphaghna, Vatahara*		*Kaphavataghna, Vataharaa, Stanyakara, Netrya, Agnipushtikara.*
12.	*Talamuli*[40]	*Curculigo orchioides*	*Rasa - Madhura, Tikta* *Virya - Ushna* *Vipaka - Madhura* *Guna - Guru, Picchila* *Doshghnata - Pittahara*	Tannin, Resin, Sapogenin and Alkaloid	*Shramahara, Dahahara, Pittahara, Vrishya, Brihana, Rasayana, Pushtiprada, Balaprada*
13.	*Varahi*[41]	*Dioscorea bulbifera*	*Rasa - Madhura, Katu, Tikta* *Virya - Ushna* *Vipaka - Katu* *Guna - Laghu* *Doshghnata - Pittakara, Sleshmaghna.*	Saponins-Steroidal, Saponins.	*Balya, Pittakara, Rasayana, Svarya, Vrishya, Varnya, Sleshmaghna, Ayurvardhana, Agnivriddhikara*
14.	*Vidarikanda*[42]	*Pueraria tuberosa*	*Rasa - Madhura* *Guna - Guru, Snigdha* *Virya - Sheeta* *Vipaka - Madhura* *Doshghnata- Pittahara*	Pterocarpan-tuberosin, pterocarpanone hydroxytuberosone,two pterocarpenes-anhydrotuberosin and 3-O-methylanhydrotuberosin.	*Balya, Hridya, Jivaniya, Mutral, Pittahara, Svarya, Vajikarana,Vatahara, Vrishya, Varnya, Brihana, Stanyadu, Rasayana*

Research studies about ingredients of *Panchamruta Rasa (Panchadasha)*

As per literature survey the same research study has not been documented or published across India but ingredients of *Panchamruta Rasa (Panchadasha)* are proven for various immunomodulatory activity. Observed literature ingredients of *Panchamruta Rasa (Panchadasha)* was mentioned as follows;

1. ***Abhrak Bhasma***[43] **-** *Shataputi Abhraka Bhasma* was subjected to Invitro screening to assess its Immunomodulatory effect using the Nitroblue Tetrazolium (NBT) assay. The results were self-conclusive and indicated that *Shataputi Abhrak Bhasma* brings about stimulation of Leucocytes in concentration dependent manner. 5% and 10 % solutions of *Shataputi Abhrak Bhasma* stimulated 93% and 93.5% leucocytes respectively, which is an indicator of highly significant phagocytic activity. Thus, the study revalidates the reference of *Shataputi Abhrak Bhasma* as a *Rasayana* and hence also establishing it as an Immunomodulator.
2. ***Lauha Bhasma***[44] **-** The results of the study confirm that the traditionally used *Lauha Bhasma* have significant antioxidant activity. Moreover the activity is comparable with that of ascorbic acid as *Lauha Bhasma* shows more than 80% of antioxidant activity as that of ascorbic acid.
3. ***Vanga Bhasma***[45] **-** *Vanga Bhasma* have shown highly significant stimulation of neutrophils for phagocytic activity, potentiates neutrophils to kill foreign organisms and also facilitates neutrophils locomotion towards the stimulus. From above results it is stated that *Vanga Bhasma* having significant Immunomodulatory activity.

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4. ***Ajagandha***[46] - The overall pharmacological investigations conclusively demonstrate immunosuppression activity in the ethanolic extracts of *Cleome gynandra* Linn. was done. The aerial parts of *Cleome gynandra* Linn. was studied for immunomodulatory activity in phagocytic activity, cell mediated and humoral immune system on albino rats. Results of present studies suggest that ethanolic extract significantly (P>0.05) diminish immune system in dose dependent manner whereas aqueous extract exhibit feeble immunosuppressive effect.

5. ***Ashwagandha***[47] - *Ashwagandha* (*Withania somnifera*) was studied in mice with myelosuppression induced by one or more of the following three compounds: cyclophosphamide, azathioprin, or prednisolone. A significant modulation of immune reactivity was observed in all the three animal models used. *Ashwagandha* prevented myelosuppression in mice treated with all three immunosuppressive drugs tested and also report an immunostimulatory activity: treatment with *Ashwagandha* was accompanied by significant increases in hemolytic antibody responses towards human erythrocytes.

6. ***Shatavari***[48] - In vivo effects of *Shatavari* on effector T cell immunity and suggest its use in conditions where broader stimulation of Th1 and Th2 immunity is required (Whelan et al., 2003;Patwardhan and Gautam, 2005). Standardized extracts *Shatavari* such as may provide newer adjuvant moieties for safer modulation of host immunity .

7. ***Talmuli***[49] - In the present study ethyl acetate extract and nanoparticle synthesized from *Curculigo orchioides* possess significant antioxidant and anticancer activities. The antioxidant ability could be attributed to the phenolic compounds. From the analysis reported from above it can be concluded that ethyl acetate extract and nanoparticle synthesized from *Curculigo orchioides* possess anticancer properties against breast cancer cell line (MCF-7). Nanoparticle synthesized from *Curculigo orchioides* showed higher anticancer activities than ethyl acetate extract.

8. ***Vidarikanda***[50] - *Pueraria tuberosa* has immunomodulatory potential. The ethanolic extract of P. tuberose was found to increase phagocytic capability of macrophages. The extract protected myelo suppressive effect of cyclophosphamide. The extract has inhibited both Cell mediated immunity and Humoral immunity. Hence, it can be concluded that, the plant extract has suppressive effect on adaptive immunity without affecting innate immune system and bone marrow cells proliferation. Further fractionation and purification of extract may yield potent immunomodulatory compounds.

DISCUSSION

Immunity may be correlated to *Vyadhikshamatva*. Resistance to diseases or immunity against diseases is of two kinds i.e. the one which attenuate the manifested disease (*Vikara Vighata Bhava*) and other variety prevents the manifestation of diseases (*Vikara Vighata Abhava*) are depending on three factors like *Nidana*, *Doshas* and *Dushyas*. Among these three factors *Doshas* is important because it controls the internal environment of the body. Derangement of internal environment of the body occurs, when *Doshas* get aggravated by taking the suitable *Nidanas* (*Ahita Ahara Viharas*). If the internal environment of the body is maintained properly, it will not be suitable to produce the diseases. This depends on the *Vikara Vighata Bhava* otherwise known as *Vyadhikshamatva* of the body. This *Vyadhikshamatva* depends on the presence of *Bala* or *Ojas* in the body. *Ojas* is the *Sara* or essence of *Dhatus.*

Immunomodulators are considered now as one of the most potent tools in the management of health and disease by modern medicine. In fact the role of immunomodulators in modern medicine is yet to be fully appreciated or perceived as our understanding of immune system is changing at a rapid pace.

Rasayana is a dedicated type of treatment influencing the basic aspect of the body i.e. *Dhatu, Agni, Strotasa.*

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Rasayanas are those that bring about proper uptake, growth, and improvement of fundamental seven *Dhatu*, which is ultimately increases *Ojas*. Thus there is *Vyadhikshamatava* is depends on the presence of *Bala* in the body. *Rasayana* drugs also influence *Ojas* which increases *Sharira Bala*. This provides the capacity to resist the external disease-causing agents. Thus, *Rasayana* can act as immunomodulator by improving the immunity.

As previously stated that *Rasayana* acts in the body at three levels i.e. *Rasa, Agni, Strotas*.

At the level of *Rasa*

Most of drugs in *Panchamruta Rasa (Panchadasha)* having *Madhura, Guru, Snigdha*, and *Sheeta Guna* may act at this level by promoting the nutritional value of *Poshaka Rasa*, which in turn helps in obtaining the best qualities of *Dhatus*.

At the level of *Agni*

Most of drugs in *Panchamruta Rasa (Panchadasha)* possessing the *Ushna, Laghu, Ruksha, Guna and Katu, Tikta, Kashaya Rasa* may be acting at the level of *Agni* (digestion and metabolism) by improving the digestive capacity and by vitalizing the metabolic activities (improving *Jatharagni* and *Dhatwagnis*) of the body.

At the level of *Srotas*

Most of drugs in *Panchamruta Rasa (Panchadasha)* with *Katu, Tikta, Kashaya Rasa, Ushna Veerya, Katu Vipaka, Vishada, Ruksha* and *Laghu Gunas* may produce the *Rasayana* effect at the level of *Srotas* by improving *Sukshma Samvahn* and the quality of *Deepana* and *Pachana.* These drugs cause *Srotoshodhana* (cleansing of channels) and thus allow efficient blood circulation and improve tissue nourishment and there by maintains its structural integrity and functional capacity.

Also according to modern research, It has been reported that the "*Rasayanas*" are rejuvenators, nutritional supplements and possess strong antioxidant activities. They also exert antagonistic action on oxidative stressors, giving rise to the formation of different free radicals. The *Rasayana* herbs seem to operate through immunostimulant, immunoadjuvant, and immunosuppressant activities or by affecting the effector arm of the immune response. Mechanisms of immunomodulation activity occur mainly via phagocytosis stimulation, macrophages activation, immunostimulatory effect on peritoneal macrophages, lymphoid cells stimulation, cellular immune function enhancement and nonspecific cellular immune system effect, antigen-specific immunoglobulin production increase, increased nonspecific immunity mediators and natural killer cell numbers, reducing chemotherapy induced leukopenia, and increasing circulating total white cell counts and interleukin.[51]

Many studies have described the identification of immunomodulatory compounds with pharmacological activity and a limited toxicity. The phytochemical analysis of *Panchamruta Rasa (Panchadasha)* plants has revealed a large number of compounds contains Fixed oil, essential oil and oleoresin, lipase, Alkaloids and with anolides, Sugar, Glycosides, Saponin, Sitosterol Tannin, Resin, Sapogenin, Alkaloid, Steroidal Saponins. etc., which have been shown to have potent immunomodulatory properties. The herbomineral mixture preparations may stimulate immunomodulation due to their content of plants with immunomodulatory properties that probably act synergistically. From the above review it should be evident that there are many medicinal mineral and plants which exert immunomodulatory activity in experimental models at a particular dose. Different types of screening methods both In vivo and In vitro have been employed to determine their pharmacological activity.

CONCLUSION

Panchamruta Rasa (Panchadasha) is a polyherbal polymineral formulation. Immunomodulatory activity of *Panchamruta Rasa (Panchadasha)* is discussed in current research paper with the study of different texts, articles, and research studies. From these studies we conclude that contents of *Panchamruta Rasa (Panchadasha)* possess Immunomodulatory activity, antioxidant activity, anti-inflammatory

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activity. Hence, *Panchamruta Rasa (Panchadasha)* is useful as *Rasayana* i.e. Immunomodulator.

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