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Review Article

COMPREHENSIVE REVIEW ON THE PROSPECTS AND CONUNDRUMS OF ANCIENT TO CONTEMPORARY MODERN IMMUNO-MODULATION TECHNIQUES PRACTICED IN HUMAN AND ANIMAL HEALTHCARE

Shibabrata Pattanayak[1]

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ABSTRACT: Prevention of diseases by modifying the body's immune system is considered the most important aspect of healthcare from a very early stage of human civilization. Before the development of modern healthcare, nature-derived and easily available materials were used for that purpose. Along with old techniques like the use of parts of specific medicinal plants and also of some animals, the use of self or animal urine, auto-haemotherapy, autologous vaccination, etc., many modern techniques are developed to modulate the immunity of the individuals. These include techniques like vaccination by the use of weak or attenuated microorganisms of infectious diseases, their nucleic acids, artificially synthesized immunogenic proteins, etc. Research is underway for the development of vaccines to control non-infectious diseases like Alzheimer's disease, early aging (Senolytic), Type 2 diabetes, etc. Use of stem cells for different serious health problems, including cancers, is considered a highly valued area in contemporary research for modulation of immunity of the body. Along with proper validation of the commonly used techniques targeting mainly modulation of the acquired immunity, a detailed study is required on the old procedures as well as the techniques targeting modulation of the innate immunity of the body - like following of a designed lifestyle, food-drink-nature exposure-body clock maintaining style, minimizing psychological stress, etc., that influence the biological age of the individuals; effect of use of specific succulent fruits, vegetables, nuts and spice mixtures in the diet schedule as well as use of succulent biomedicines as preventive and curative medicines, etc.

Keywords: Disease susceptibility, Innate immunity, Urine therapy, Auto-vaccine, DNA vaccine, mRNA vaccine, Succulent biomedicines.

INTRODUCTION

Efforts to prevent different diseases by using available tools were perhaps started from a very early stage of human civilization. Dietary and local use of the parts of some medicinal plants, animals in their different forms, and extracts were used for that pupose. Many of such efforts were not continued afterwards, may be due to lack of availably of the items, or considering their suitability for use. From the twelfth century, modern medicine has been considered the main area of healthcare. But still today, doctors practicing modern medicine remain in a dilemma considering many aspects of that branch of science [1, 2, 3]. On the other hand, many ancient procedures of healthcare are still in practice in some parts of the world. Now, the time has come to perform a thorough investigation and analysis of such time-tested practices and procedures scientifically, without any pre-decision or prejudice to get the best possible benefits from them [2, 3]. A brief analysis of some such procedures developed and under study is performed in the light of modern medicine to find out the new avenues of research for better healthcare in the coming days.

IMMUNITY SYSTEM OF THE BODY: SOLDIERS AND WEAPONS FOR DEFENSE AND FIGHT

As per the concepts of modern medicine, the soldiers protecting the health are of different types with a variety of weapons in their stock. Broadly, the functioning immunity system of the body can be categorized into two sections: the innate and the acquired immunity. The innate immunity starts functioning from birth and has the systems and soldiers performing the first line

[1]*Assistant Director, ARD (Vet. Research & Investigation), Govt. of West Bengal, India.*
**Corresponding author e-mail: pattanayak1966@gmail.com*

of defense of the body. It is subdivided mainly into four parts: physical, physiological, cell derived, and cytokine-related immunity. This type of immunity is not generally disease-specific and can act to protect health in various aspects and from various types of diseases. The acquired immunity of the body develops as a response of encountering the disease causing agents or their parts. It is subdivided into two parts: active and passive immunity.

The active immunity is controlled by the immune system of the body after encountering the disease agents. Individuals can get such immunity after the recovery from any disease or after vaccination against any disease. It is mainly a disease-specific immunity (Fig. 1).

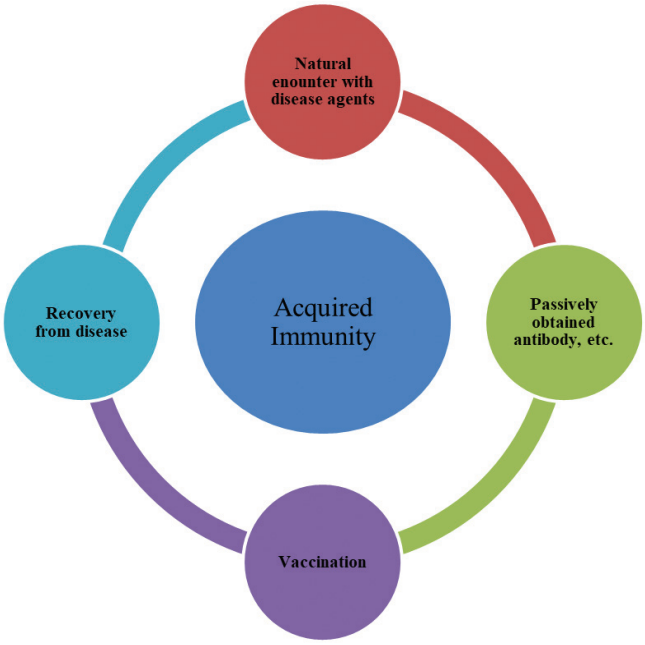

Fig. 1. Acquired Immunity factors for immunomodulation.

The passive immunity is achieved after getting antibodies, etc., from other sources, not prepared inside the body. The antibodies supplied to the babies through maternal colostrum, and the external antibodies introduced inside the body to counter some diseases are of this type [4, 5, 6].

Both innate and acquired immunity can involve immunity related cells as well as antibody, complements, etc. (cellular and humoral types of immunity) [4, 7].

USE OF URINE FOR THERAPEUTIC PURPOSES

Use of urine as a therapeutic and preventive measure against diseases in ancient times

Urine was considered "the elixir of long life" in different ancient traditions, and it was used as a therapeutic means in different ancient civilizations. Its use is noted in '*Shiwambukalpa*' (an ancient Sanskrit book) as well as documented by the philosophers of Assyrian-Babylonian, Egyptians, Sumerian, Essenians, Jewish-Christians, as well as Greek and Roman civilizations and dynasties [8, 9].

Composition of urine

As per the chemical analysis related to modern medicine, urine contains water, urea, uric acid, creatinine, various electrolytes, phosphates, organic acids, trace amounts of proteins (albumin, antibodies, enzymes), traces of hormones, glucose, and water-soluble vitamins [10].

Use of human urine

It was/is used as a drink, applied on the whole body, open skin, scalp; as a drop inside the ear or nose; on the infected wound and other affected areas, etc. Urine is used as/in asthma, allergies, arthritis, liver and other tumors, acne, indigestion, antacid, gastric ulcer, wrinkles, migraines, treating burns, sores, other early wound therapies, anal afflictions, baby rash, scorpion stings, itchy eyelids, and many other diseases [11, 12, 13].

Use of animal urine for therapeutic purposes

Like human urine, urine collected from the cow is also used for different therapeutic purposes. Oral intake and local applications are the main ways of such uses. Apart from the use of cow urine, urine collected from different animals is also used for different therapeutic purposes. These include worm infestation, abdominal enlargement, dropsy, colic, flatulence, abdominal tumor, anemia, anorexia, tuberculosis, leukoderma, leprosy, poisons, amenorrhea, hemorrhoids, etc. [11].

Research reports on urine

Urine is found to be bactericidal and effective in blocking the growth of Koch's bacilli in the laboratory [9, 14]. It possibly contains anti-cancer substances [14, 15].

The stem cells collected from the urine are a promising source for stem cell therapy, drug testing by renal toxicity study, identification of renal disease biomarker, and a potential source for tissue engineering and regenerative medicine [12, 16].

All five classes of antibodies are found in the urine samples. Disease-specific antibodies are detected from the urine of patients suffering from Dengue [17],

Covid-19, Hepatitis A [18], Strongyloidiasis [19], Human Immunodeficiency Virus type 1 [20], etc. The antibodies available in the urine may have further therapeutic as well as diagnostic value [21, 22].

Possible mechanism of action of urine therapy

Many hypotheses have been postulated to explain the therapeutic efficacy of urine. It is assumed that the components available from the urine work together to show the actual effects. The effects include re-absorption and reuse of different nutrients, hormones, and enzymes, immunological effects of some components, effect of reabsorbed urea, detoxification of the body system, bactericidal and veridical effects, transmutation effect, diuretic and psychological effects, etc. [13, 16, 21].

AUTOHEMOTHERAPY

In autohemotherapy, blood or some specific cells of the blood of the patients are collected and then reintroduced into the patients (with or without any treatment of it outside the body) as a therapeutic mean. It is either used alone or along with autologous vaccines, other pharmaceutical drugs, or surgical procedures to get the maximum beneficial effects [23, 24, 25].

In human

Use of autologous blood

Injection of autologous whole blood is performed directly to control chronic urticaria and some other diseases. In urticaria, activity of this procedure is proposed to be the modulation and control of the patients' immune response to autologous antigens involved in activation of mast cells and basophils, and also influence on other components leading to the secretion of histamine, etc. [24]. It is further suggested that such treatments can incur the activation of the T regulatory cells by Immunoglobulin G [24, 25].

Ozonated autohemotherapy

In that technique, the ozonated self-blood is reintroduced into the patients. Along with or without pharmacological therapy, that can effectively improve conditions like pain intensity, insomnia, and negative mood, as well as alleviate fatigue [25, 26]. It can induce health benefits among the patients suffering from hepatitis B, hepatitis C, and coronavirus infection [27].

In animals

In Bovine papillomatosis

Bovine papillomatosis, caused by different types of the Bovine Papilloma virus, are extensively studied to evaluate the effect of autohemotherapy. It is found effective alone [23], with an autologous vaccine prepared from the incised wart mass treated with formalin, etc. [28], or added with surgical intervention [29].

Autohemotherapy by the ozonized blood can give good result in the treatment of foot rot in animals [30].

On the health status of animals

Autohemotherapy can be used to improve the health status of the ailing animals. It can act by subsiding the biodegradation of the soft tissues to form pus, improving metabolism of the cells, influencing the immune system of the body in a positive direction, incurring homeostasis in blood and lymph circulation, etc. [30].

Requirement of a thorough investigation of the procedures practiced

Along with the development and spread of modern medicine, the applications of immunomodulation techniques involving gross materials have declined. That may be due to problems such as psychological rejection, non-acceptance of the procedures in social life (such as using urine on the scalp or skin), lack of trust due to not getting instant results like modern medicine, lack of positive reports of scientific validation of the techniques, etc.

The procedures developed for modulation of the body's immunity to reject or control different diseases requires thorough scientific investigation. These procedures are mostly cheap and easy to apply, even without taking any assistance from the costly tools and techniques used in modern medicine.

But the concept of scientific validation of all such techniques requires conceptual adjustment. Most of the time, such procedures involve gross materials and techniques, so direct study on them is to be performed for proper validation. But the combinational effect of the ingredients present in the gross materials used as some medicines is neglected in the contemporary validation techniques. Following the procedures developed to study a single molecule may not be suitable for that purpose, and so may lead to some wrong results about their actual activities. Modifications to such available analytical procedures are required for proper scientific validation of old techniques. By use of the efficient techniques and materials, the modern healthcare system may be benefitted by addition of these procedures as a principal or adjunct therapeutic system [31, 32].

VACCINATION: THE PRINCIPAL TECHNIQUE OF PREVENTIVE HEALTHCARE IN MODERN MEDICINE

In a general sense, vaccination is the introduction of foreign immunogenic materials inside the body to stimulate the body's immune system to develop protective power against those immunogenic materials. The term antigen is used to name such immunogenic materials (mainly protein). As a response against the antigen introduced in the body, some protein molecules are formed by some specific cells, called antibodies. There are involvement of different cells and their secretions in the entire procedure. Generally, the antigens of the infective microorganisms are introduced inside the body with the purpose to develop antibody against them so that the body can fight against the original microorganisms in the future. This is the main target of vaccination.

Through vaccination, the acquired immunity arm of the body is influenced for the prevention of some diseases. Vaccination has the limitation that it cannot be used to prevent all diseases, as useable vaccines are developed against some diseases only, and a very large number or quantity of vaccines cannot be introduced inside the body system of any individual [4, 33].

Sometimes, due to some reasons, the body system wrongly considers some proteins of its own as a foreign antigen and develops antibodies against its own body protein. These are antibodies called autoantibodies, and the diseases developed by them are termed as autoimmune diseases. Diseases that evolve due to the development of the autoantibody are very difficult to cure. On the other hand, due to improper development of antibodies, different hypersensitivity-related health problems can develop. When antibodies develop automatically against some antigens of the environment (available in food items, animal or insect-related materials, flowers, and other parts of some plants, etc.) in some individuals, then such antigens are termed allergens, and the hypersensitivity reactions that develop in the body due to the allergens are called allergy [4, 34].

Common vaccines used to prevent diseases

Antigen vaccines

Generally, the protein portions of any infective microorganism are considered as non-self (antigen) by the individuals if introduced in them, and so the recipient's immunity system try to remove such materials by developing antibodies along with other cellular involvement against them. Uses of a replica of antigen/s or addition of some materials with any weak antigen to stimulate the immunity system etc. techniques are also followed in some cases. These are broadly termed as antigen vaccines.

Experience of encountering such foreign antigens by the body's immunity system is utilized when facing the original infective organisms and that leads to initiating an effective fight against such agents. This general principle is followed to prepare almost all commonly used vaccines developed to prevent different diseases of infectious origin [4, 35]. Presently used bacterial and viral antigen-based vaccines are developed following that basic principle.

Anti-allergy vaccines

The allergic response of the body towards any allergen is dependent on factors like genetic predisposition, quantity of exposure to allergen/s, activity threshold of the immunity system of the body against the allergens, lifestyle, health condition of the individuals, etc. [4, 34, 36].

The anti-allergy vaccines aim to reduce the severity of the allergic response, shown by the patients due to the release of different chemicals, including some vaso-active amines, for hypersensitivity reactions. In anti-allergy vaccines, the suspected allergens, actually acting as some antigen to the body, are introduced in the body with gradually increased dose to develop tolerance of the immune system of the patients to the allergen/s. So, it may be termed as allergen-specific immunotherapy rather than vaccination, and it is not suitable for all allergens [36, 37, 38].

IMMUNO - PREVENTION AND IMMUNO-THERAPY TRIALS AGAINST CANCERS AND OTHER DISEASES

Apart from the common techniques of using the protein part of the cells of the causative organisms as an antigen to produce antibodies to protect the individuals from future attack of the same or closely related infective organisms, some other techniques of vaccine preparation are presently followed or under trials. The highest number of such research is performed on cancers, and fewer researches are performed on some other diseases. Almost similar basic principles are applied in all such efforts.

Preparation principle of recently developed anti-cancer vaccines

Protein/ peptide cancer vaccines

These are not whole cell vaccines, only some specific antigenic protein parts or even the smaller peptides of the cancer cells are used alone or in

combination with some carrier (generally some virus or some other molecules) as some anti-cancer vaccines. Vaccines of this category against some types of cancers (as for some breast cancers) are under different levels of clinical trials [39].

DNA cancer vaccines

The specific DNA associated with the targeted tumor antigens is made as DNA rings like the plasmids of bacterial cells. After entering the body cells, these rings can stimulate and use the mechanisms of the body cells to produce specific tumor antigens that ultimately trigger the body's immune system. After such stimulation, the body's own immune system is forced to recognize such antigens present in the tumor and attack them to kill. Clinical trials of DNA vaccines against prostate cancer, breast cancer, human papilloma virus cancers, melanoma, etc., are underway [40, 41].

Messenger RNA (mRNA) vaccines

Messenger RNA (mRNA) is one type of Ribonucleic acid that takes a very important part in the production of amino acid (protein) in the body. Just after production of the amino acid, the mRNA is broken down. For vaccination, a specific mRNA is prepared and introduced in the body to develop a specific antigenic protein so that the body can develop antibody against such proteins [4, 42].

Messenger RNA (mRNA) cancer vaccines

This type of vaccine may be autogenic or allogenic in nature, though both of them mainly target to stimulate cytotoxic T lymphocytes to attack and kill the tumor cells [43, 44, 45].

In autogenic mRNA cancer vaccines, the tumor sample of the suffering individuals is studied to identify cancer-causing mutations (the tumor neo-antigens). Then, specific mRNA molecules are developed artificially in the laboratory. Then these are generally introduced inside lipid nanoparticles to make an injectable vaccine [44, 46, 47].

During preparation of the allogenic mRNA vaccines, the tumor-associated antigens (TAA) common in patients suffering from the same type of cancer are identified, and the specific mRNA is synthesized artificially. Then they are generally placed under a lipid nanoparticle envelope to prepare the vaccine [48, 49, 50].

Messenger RNA antiviral vaccines

For the prevention of some viral infections, some specific mRNAs have been developed. Generally, the mRNAs coding for specific viral protein/s, mainly the viral outer membrane proteins, are developed and introduced inside the body system. The intended proteins are developed in the body, and then the immune system of the body develops antibodies against the antigen (viral outer membrane protein), making the individual ready to face the infection of the original virus.

The mRNA vaccines developed against the viral spike protein of Covid 19 virus was efficiently used to combat the Covid 19 pandemic (Comirnaty and Spikevax vaccines) [42].

Viral vector vaccines for cancer and other diseases

The engineered viruses carrying the specific genetic materials are used to instruct the recipient's cells to produce desired antigenic proteins to initiate an immune response against such antigens. Such vaccines can modulate both cellular and humoral immunity of the individuals against the specific antigens. Generally, Vaccinia virus, Adenovirus, and some oncogenic viruses are used as vectors [51, 52].

Classification of other cancer vaccines developed or under trial

The cancer vaccines developed or under different levels of trials can be categorized in different ways. Depending upon the source and the type of work they performed, the following classifications are made.

Preventive cancer vaccines

Some vaccines are developed to prevent and control the virus-induced tumors and cancers. The Hepatitis B vaccine (use of Hepatitis B virus surface antigen produced by yeast and some other cells) [53], Human papilloma vaccine (as - particles are prepared from the L1 capsid protein of different types of human papilloma viruses and placed in some specific cells to prepare the non-infectious and immunogenic vaccine) [54], prostate cancer vaccine (autologous vaccine prepared by activating the patients' white blood cells outside the body) [41, 55], BCG bladder cancer vaccine (attenuated *Mycobacterium bovis* bacteria solution is introduced inside the bladder to stimulate immunity soldiers of the body), etc. [41, 56].

Curative cancer vaccines

The main target of such vaccines is to reduce the spread and severity of the cancers by destroying existing cancer cells in the body [57, 58]. Stimulated immune cells of the patients, designed mRNA, oncolytic viruses,

etc., are used along with some sophisticated technologies like the use of virus-like particles, replication-defective viruses, the use of dendritic cells or other viruses as vectors, etc. [59, 60, 61].

Autogenic/ autologous tumor/cancer vaccines

The old, crude method of preparation of autogenic vaccine by triturating the tumor tissues (as papilloma virus-induced tumor of bovines) in normal saline, filtration of the mass, and then inactivation of the material by formalin to prepare the vaccine [62] is substituted or modified by some modern techniques. Many such vaccines are under different levels of trials and waiting for a license for marketing.

Due to the inherent genetic instability of tumor cells, expression of novel tumor antigens is common among cancer patients [46]. So, the concept of using an autologous cancer vaccine appears to be relevant in humans and even in animals [63].

In most of the autogenous vaccines, the specific type/s of immune cells are separated from the blood of the patient, stimulated artificially by specific cancer antigens and other stimulators, and then injected into the patient's body to target cancer cells. Sensitized intact lymphocytes, dendritic cells, etc., are employed for this purpose [56, 64, 65], with good safety and efficacy reports in many cases [66]. This category of vaccines is developed for treatment-resistant metastatic prostate cancer, early breast cancers, etc. [67, 68, 69].

Among the other vaccines covered in this category, Melanoma vaccine (use of oncolytic virus based vaccine to counter advanced stage Melanoma cancer), Pancreatic cancer vaccine (a mRNA vaccine), Head and neck cancer vaccine (Human papilloma virus proteins used), Intra-tumoral therapies (by injection of immune activating drugs, oncolytic viruses, some bacteria, etc. inside the tumor to activate the immunity soldiers of the body) [70, 71, 72], the lung cancer vaccines (protein based, mRNA based and mutated protein based), etc. are important [73, 74, 75].

Allogeneic cancer vaccines

These vaccines are targeted to make from the non-self cancer cells, mainly grown in the laboratory. Trials are at different stages for the development of effective vaccines against melanoma, pancreatic cancer, non-small cell lung cancer, leukemia, prostate cancer, etc. [41, 43, 76].

NEW HORIZON OF VACCINE RESEARCH

Anti-Alzheimer's vaccine

The recent efforts of preparation of an anti-Alzheimer's disease vaccine have the main target to prevent or slow down the disease. Two important abnormally configured or accumulated protein deposits of the brain of Alzheimer's disease patients, causing disruption of nerve cell functions, the Amyloid plaques and Tau tangle, are targeted by generating antibodies against them and clearing them outside the body [77, 78, 79]. The trials are performed mainly in three directions. The peptide-based vaccines, by using these two protein molecules as antigens; the DNA and mRNA vaccines generate these two proteins inside the body to act as antigens; and the genetically engineered monoclonal antibodies are directed towards these antigens [79, 80].

Malaria vaccine

The malaria vaccines aim to prevent the growth and multiplication of the malaria parasite *Plasmodium falciparum* after its introduction into the blood by the *Anopheles* mosquitoes. The circum-sporozoite proteins (CSP), the surface protein of the sporozoite stage of the malaria parasite, are neutralized by the vaccine-derived antibodies before their entry into the liver cells for further development. On the other hand, the activated T lymphocyte cells destroy the infected liver cells before their further multiplication in the cells, if some sporozoites can reach there [81, 82].

Presently, two types of malaria vaccines are used, and both follow more or less similar technology of addition of CSP fragment with a cell surface protein of hepatitis B virus, generally developed in yeast, and also have a similar type of mechanism of action. Production and use of that type of malaria vaccine has already started. Some other techniques, like attenuated malaria parasite, DNA vaccine, etc., are under different levels of trials [82, 83].

Senolytic (anti-ageing) vaccine

The senescent cells are the living, aged cells that fail to divide. Research documented that the selective elimination of the senescent cells can positively modulate the immune system of the body and can also reduce inflammation. These cells express some different types of surface antigens that are either not present or present at a very low level among the normal healthy cells. These antigens are targeted by such proposed vaccines for removal of such antigens or destruction of the cells bearing such antigens by developing antibodies against them or by stimulating the cytotoxic T lymphocytes of the body against them [84, 85, 86].

Other important diseases covered under vaccine research at present

Ongoing research is underway against some other diseases also. Chronic obstructive pulmonary disease

(COPD), Type 2 diabetes, etc., so-called lifestyle-related or age-related diseases are also targeted for prevention by vaccination. For type 2 diabetes, the targeted molecules are mainly interleukin-1 beta (IL-1β) and dipeptidyl-peptidase 4 (DPP4). Antibodies against them can be produced inside the body to prevent or reduce their activities and reduce the severity of the disease. For age-related vascular diseases like aortic aneurysm, hypertension, atherosclerosis, etc., molecules like angiopoietin 1 (Ang I) are targeted. But many problems are encountered during testing of such vaccines for use at the present stage [85].

QUESTIONS ROSE AGAINST THE CONTEMPORARY VACCINES

Many questions are raised against the modern technologies used to prepare vaccines, mainly the viral vaccines. Along with the question of possible effects of the chemical ingredients introduced inside the body with vaccine antigens, there are also questions of modification of previously considered non-pathogenic or mildly pathogenic viruses to some highly pathogenic viruses after getting new gene segments inside their genome through the genetically modified vaccines used [35, 86].

OTHER IMMUNOTHERAPY TRIALS TO CONTROL CANCERS AND OTHER IMPORTANT DISEASES

Use of Stem cells for the prevention/cure of diseases

Stem cells can be grossly categorized as embryonic or adult stem cells depending on their source. As per the ability to differentiate into various types of cells (according to the diminishing spectrum of activity), these can be categorized as totipotent, pluripotent, multipotent, oligopotent, and unipotent stem cells. Stem cells can be derived from day-old embryos, adult tissues of bone marrow, adipose tissue, blood, umbilical cord, aborted fetus, amniotic fluid, pulp of the teeth, and also by reprogramming the cells of adult persons. Stem cells can be used for different purposes related to tissue repair or tissue regeneration, drug discovery, modeling of diseases, and for other therapeutic purposes [87, 88].

So, stem cells are used to replace or repair different types of damaged tissues in the body and can assist in their proper healing. They can be used with some specific direction to modify their cellular character to fit with the specific cells of different organs and systems. They are commonly used as hematopoietic stem cells, obtained from blood or bone marrow, to treat blood cancers and some other diseases. Trials are underway to use stem cells in some heart diseases, diabetes, Parkinson's disease, spinal cord injuries, and some other neurodegenerative diseases, etc. [88, 89, 90].

Use of cytokines

Artificially prepared cytokines such as interferon, interleukins, granulocyte-macrophage colony-stimulating factor, etc., can be used to stimulate the body's immunity to attack cancer cells. These are generally applied as some adjunct therapy procedures in cancer treatment [91]. Some cytokines, like some interferones, can assist in immunomodulation for the prevention of some viral diseases also [92].

Use of monoclonal antibody

The monoclonal antibodies prepared against the specific antigen/s present in a tumor are used to attack the target so that the body's immune cells can identify them easily and can attack these cells to destroy the tumor [41, 93].

Monoclonal antibodies are also used to counter health problems like asthma, osteoporosis, autoimmune diseases, against the viruses like Hepatitis C, SARS – COV 2 Corona virus, Respiratory syncytial virus, etc. [94].

Use of immunotoxin

Sometimes the monoclonal antibody, immunoglobulin, or cytokine molecules are conjugated with some toxic substances directed to target the tumor cells with specific epitopes. After attaching to the targeted tumor antigen, the tumor cells die or become inactivated due to the effect of the toxin. These are termed as immunotoxins [95, 96, 97]. Many bacterial, fungal, or plant-derived toxins are used in different trials and research related to the use of immunotoxins. In some cancers (such as some breast cancers) and autoimmune disorders, such antibodies can be used [93, 98].

IMMUNOMODULATION BY NATURAL MEANS

Nature-derived materials have been used as a medicinal item from an early stage of human civilization. As a part of nature, people were getting some resources of nature automatically (such as sunlight, water, air, edible plants and fruits, etc.) which were beneficial to their health. From their experiences, they learned the effects of such nature-derived materials and became accustomed to many of them. Many diseases encountered nowadays were not encountered or observed rarely during that period, which may be

due to such reasons [3, 99]. Plant materials are used as medicine for the prevention of diseases at a later stage of civilization. But, for prevention and control of the severity of different diseases, vaccination is perhaps the only form considered in modern medicine [35]. For the treatment of diseases, different drugs of synthetic origin are mainly considered [3, 32]. For re-evaluation of the ancient basic concepts of using nature-derived materials (with which humans are accustomed during evolution) for staying in good health and for exploring some related effective concepts of healthcare, a few important points are analyzed in the light of modern medicine (Fig. 2).

Generally, protein, fat, and carbohydrate are considered the main items of nutrition to the body. The macro and micro minerals and the vitamins are also considered an important part of nutrition for maintaining good health.

But that concept is lacking consideration of the effects of different antioxidants and immunomodulants. To keep the body disease-free, these are very important. Most of such items can be effectively supplied to the body through nature-derived foods. The present trend of supply of some components synthesized chemically to perform the role of the nature-derived antioxidants

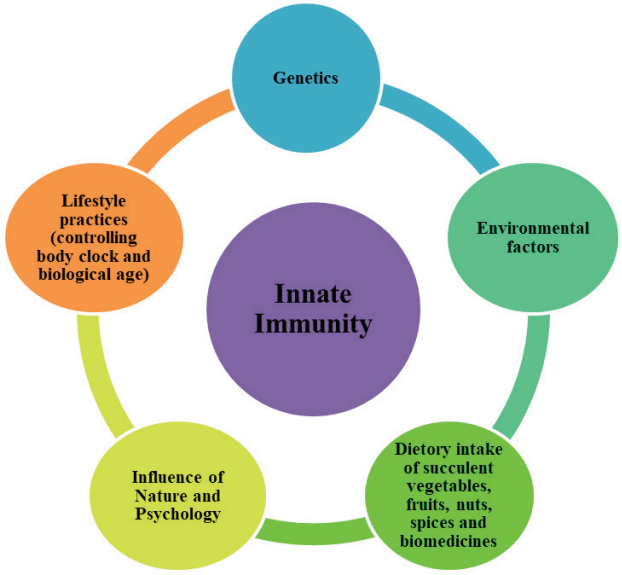

Fig. 2. Innate Immunity factors for immunomodulation (as described in the article).

and immunomodulants may be practically harmful to the health of the individuals [33, 32, 99].

The *Rasayana* concept of *Ayurveda*

In this concept, the rejuvenation of the body system can be performed with some specific medicines available in nature. They can modify the 'rasa's and 'dhatu's (the fluids, secretions, status of metabolic interaction influenced by metallic ions, etc.) of the body and thus can ultimately influence the disease preventive power of the body [100].

The 'Disciplined and Intelligent People's Diet' (DIP diet) concept

A specific diet plan basing mainly on vegetarian food items is advocated in this concept. As per the claims, such a diet practice can supply all essential nutrients to the body and keep individuals disease-free by modulating the immunity status of the body (https://hiims.in/dip-diet).

Use of specific millets in diet for good health - the *Siridhanya* concept

As per this concept, dietary intake of five specific nature-grown millets can control different aspects of body immunity. The unique effects of cleansing of body toxins and healing the important systemic problems of different body systems are the way to show their activities, as per the claim. The five millets advocated are – Foxtail [*Hordeum murinum* L.], Kodo [*Paspalum scrobiculatum* L.], Little millet [*Panicum sumatrense* Roth ex Roem. & Schult.], Barnyard [*Echinochloa esculenta* (A. Braun) H. Scholz], and Browntop [*Urochloa ramose* (L.) T. Q. Nguyen] [101].

The psycho-neuro-immuno-endocrinology concept of disease creation

As per this concept, the psychological status has a very strong relationship with the creation or potentiation of different diseases. The psychological stresses can influence the neuronal, immune, endocrine, etc. systems of the body, and create an environment of catching disease agents or the creation and spread of different diseases [102, 103, 104].

Lifestyle modification and use of succulent biomedicines

In this concept, following a designed lifestyle and practicing specific food habits can prevent most of the diseases.

During the evolution stage, different systems of the body of the individuals are developed with some specific characters to perform some specific functions. Some species become nocturnal, some are diurnal; some are strictly vegetarian, and others are carnivorous or omnivorous. On the other hand, one invisible clock is also working inside the body of every

individual, termed the biological clock or body clock. It is an internal timing mechanism that controls the physiological processes in a 24-hour cyclical manner. The body systems are developed as per the instructions of the biological clock of the individuals throughout the evolutionary stages.

The biological age of an individual is the overall health condition commonly found among individuals of a specific age. The biological age of an individual may not be equal to their chronological age. The lesser the biological age of an individual, the better the actual status of his or her health, and the lesser the chance of catching or suffering from any disease.

As per some recent research, lifestyle practices can influence the biological clock and biological age and thus susceptibility towards almost all diseases of the individuals [33, 99, 105].

Maintenance of the body clock and the near-nature lifestyle can influence the biological age of an individual in a positive direction and can also reduce susceptibility of various diseases [105]. By closing or restricting the entry of different synthetic or non-natural chemicals, micro- and nano-plastic particles, etc. through food, skin and lung absorption can reduce the gathering of them inside the body that can control different important parameters related with disease – from catching of the infective microbes, their growth and multiplication, severity of the diseases, initiation and expression of diseases of non-infectious origin, assisting in expression or suppression of genetic predisposition towards different diseases, etc. [106, 107, 108].

Following a lifestyle designed by considering these important aspects can influence the innate immunity of individuals and can keep them in good health [109, 110].

The addition of succulent vegetable salads, fruit salads, nut mixtures, and spice mixtures in the daily diet can modulate the immune system to a large extent. Along with modification of lifestyle, use of encapsulated biomedicines prepared from nature-derived raw, succulent herbs without addition of any synthetic chemical for control and cure of different diseases can be a good alternative to the chemical based treatment concept followed nowadays. All these procedures influence the innate or non-specific immunity arm of the body to prevent diseases, and so even a single such item may be active against a few diseases together [3, 99, 111].

CONCLUSION

From the early stage of human civilization, efforts have been made to modulate the disease preventive power of the body by different means. The natural substances, such as self or animal urine or the parts of the locally available medicinal plants, were used for such purposes. Afterwards, processes like auto-hemotherapy, auto-vaccine, etc., were developed. Vaccination by the use of parts of the infective organisms or by the use of the knowledge of genetic engineering was initiated afterwards. Not only for the prevention of infectious diseases, but even to reduce the severity of many other diseases, vaccinations are tried. Use of stem cells as some modulating agent for disease prevention and treatment is another new concept. But the parameters like biological age and its effects on expression or suppression of the genetic predisposition towards various diseases, effects of the psychological stressors, etc., of the individuals are now considered as some very important factors behind the initiation and progression of different diseases. Lifestyle-related factors like intake and gathering of different synthetic chemicals inside the body, staying away from nature, non-maintenance of the body clock, etc. are considered some very strong influencing force behind disease creation. Along with following a designed lifestyle and taking items like vegetable and fruit salads, nut mixture, spice mixture, etc., as some regular diet items, the use of disease specific succulent biomedicine capsules can be a good alternative to the chemical-based lifestyle and treatment schedules.

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