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Review Article

SUCCULENT BIOMEDICINES – AN EFFECTIVE WAY OF GETTING PROTECTION AGAINST DISEASES THROUGH IMMUNOMODULATION

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ABSTRACT: Modulation of immunity power of the body is a very strong weapon to combat diseases. Presently, vaccination is considered as the only weapon in this field. Vaccination means introduction of some foreign antigens (generally of infective organisms) inside the body of a human or animal to stimulate the immune system of the body to develop protective power against those antigens in future. Production of protective antibodies along with sensitization of the cells engaged in this process for future fight is the main target of vaccination. The adaptive or acquired immunity section of the individuals is stimulated to perform the work through vaccination. But the other arm of the immunity system, the non-specific immunity can also be utilised to reach the same target. The non-specific defence system of the body comprises different barrier functions of the body, action of phagocytic cells, natural killer cells, T lymphocytes, modification of activities of cytokines etc. The activated non-specific immunity can also protect individuals from catching infection or can assist in reduction of severity of the disease symptoms.

The succulent biomedicines, *i.e.*, the paste, juice or seed-powder of different medicinal plant parts, collected at succulent condition from the plants can be effectively used orally in the capsular form to serve the purpose. As these plant medicines contain much more phytochemicals, both in number and quantity and work together, so expected to be more effective than the dried parts (used in contemporary Herbal Medicines) and without toxicity of isolated phytochemicals (used in research of Modern Medicine). Apart from supply of many important nutraceuticals and micronutrients, these have the ability to act as some immunomodulator by activities like antioxidation, antiviral, antibacterial etc.: protective effects on heart, liver, kidney, ling etc. as well as effects like anti-cancer, anti-diabetic etc. Such 130 reported immunomodulant plants are listed. Different bio-preservatives and bio-encapsulating materials for packaging and transportation of the succulent biomedicines under the cold chain can be arranged for their regular use.

Key words: Immunomodulation, Vaccination, Succulent biomedicines, Prevention of diseases.

INTRODUCTION

The immune system has engaged in identification and destruction of pathogens keeping the damage to the host tissue at a minimum level. So, immunity is an important tool for survival against pathogenic microorganisms by fighting against them. This intrinsic system can be divided into two major components: the innate immune system and the adaptive immune system (Stuart *et al.* 2018, Kasper *et al.* 2015). As like almost all other systems in the body, these two systems are working together with active cooperation and feedback control among the acting weapons and soldiers.

ACTIVITIES OF THE ARMS OF IMMUNE SYSTEM

Innate or non-specific immunity

This section of the immune system generally acts as the first line of defence of the host against almost all kinds of invasion – of physical, cellular or biochemical components inside the body (Singh *et al.* 2011). This defence system comprises of different primary barrier functions of the body (as skin, gut, lacrimal wash, nasal hair filtration etc.), activities of different cytokines, action of different phagocytic cells, natural killer (NK) cells, gamma-delta (gd) T lymphocytes etc. (Nagarathna *et al.*

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2013). So, it generally provides immediate protection against the invading pathogens. In this system, the host cells bearing germline-encoded pattern recognition receptors can recognize pathogens and then trigger a variety of mechanisms to eliminate them (Stuart *et al.* 2018, Kasper *et al.* 2015).

Adaptive or acquired immunity

This arm of the immune system generally takes comparatively more time to develop and act but can bring specific and long-lasting protection. It is considered as different from the innate system as that system can work with specificity along with some power of memory for future.

It can be divided into two parts, cellular immunity and humoral immunity (Singh *et al.* 2011).

Two different types of lymphoid cells perform the main activities in the whole system. These are termed as T and B cells, which practically lead the 'cellular' and 'humoral' immunity, respectively. These two groups of lymphoid cells are found in the circulating blood as well as among the peripheral lymphoid tissues (Nagarathna *et al.* 2013).

Humoral immunity

The humoral immune system deals mainly with antibody production and destruction of the extracellular microorganisms (Singh *et al.* 2011).

The B lymphocytes are converted to the antibody producing plasma cells after getting stimulation by antigen. In this work, macrophage and alike cells are generally represented as an antigen presenting cells to the T lymphocytes. The T lymphocytes, mainly the T helper cells assist the B lymphocytes to produce antibodies.

After stimulation, the plasma cells can secrete different immunoglobulins (Ig) (antibodies). As per the specific conditions, IgM, IgG, IgA, IgD and IgE are secreted by the plasma cells to perform the respective functions. Afterwards, the specific antigens are bound with specific antibodies which lead to inactivation and destruction of such antigens by the phagocytic cells like macrophages (Roshan and Savitri 2013).

Cellular immunity

The lymphocyte cells involved in this system perform basically two important functions: killing of virus infected cells and killing of tumour cells. The Cytotoxic T cells kill the virus infected cells and the Killer T cells kill the tumour cells routinely inside the body system (Singh *et al.* 2011).

Recognition of the specifically identifiable antigen on the targeted cell surface by the T cells of respective subpopulation generally leads to proliferation of these cells and then infiltration of these cells at the site of action to perform their destructive duties (Roshan and Savitri 2013).

The non-specific immune system as well as the whole acquired immune system express their effects with various levels of interactions within them as well as with many other internal and external factors. Genetic predisposition, triggering or masking of such predispositions by different lifestyle and environmental factors are some related important areas (Kasper *et al.* 2015, Stuart *et al.* 2018, Pattanayak 2019b).

MODULATION OF BODY IMMUNITY – A WEAPON TO PREVENT DISEASES

Modulation of body immunity of individuals to prevent different diseases is a century-long practice. Almost during that entire period, emphasis is given on modulation of acquired immunity to achieve the goal. Vaccines are developed to protect individuals from certain infectious diseases. There are different types of vaccines with different advantages and disadvantages. Ideas about types and actions of the available vaccines can assist in understanding of the new concept of immunomodulation by succulent biomedicines, which mainly act on non-specific immunity of individuals.

VACCINES AS IMMUNOMODULATOR

General mechanism of action

A vaccine works by influencing the immune system of the body to recognize and combat pathogens, mainly viruses or bacteria. For this work, certain molecules are to be introduced into the body system to trigger an immune response.

These molecules are named antigens. Antigens are present on all cells, including the viruses and bacteria. These antigens are injected into the body to train the immune system to recognize them as some foreign enemies to produce antibodies and also to remember such fighting events for any future invasion of them. If these invaders (bacteria, virus etc.) reappears, the sensitized immune system will recognize them immediately and will attack aggressively so that they cannot spread and cause any illness (Kindt *et al.* 2007, Publichealth.org).

Commonly used vaccines

There are seven types of vaccines developed for common use. These are live attenuated vaccines,

inactivated vaccines, subunit vaccines, toxoid vaccines, conjugate vaccines, DNA vaccines and recombinant vector vaccines (Kindt *et al.* 2007, Kasper *et al.* 2015).

SUCCULENT BIOMEDICINES AS IMMUNOMODULATOR

Succulent biomedicines

These are the succulent parts of the medicinal plants used as some medicines. Every medicinal plant contains thousands of phytochemicals. In the living plant or at the succulent condition after collection from the plant, all of them are present in the plant parts. If these are used in that condition, they can get the opportunity to show their activity together. But many phytochemicals of the succulent parts of medicinal plants are definitely absent or reduced in quantity in the dry parts of the same plants due to evaporation and chemical changes of the drying procedures.

In the contemporary procedures used for analysis of available phytochemicals for drug development as well as during preparation of medicines used in different codified ethnomedicinal practices (as *Ayurveda*, *Siddha* etc.), the effects of the lost phytochemicals are not available as all of them use only the dry parts of the medicinal plants.

But such lost phytochemicals may have some important effects on our health (Pattanayak 2019a).

Modulation of Non-specific immunity

Modulation of non-specific body immunity of the persons with weak or, in some cases, overactive immunity may also be a weapon to prevent various diseases. It can also be said that persons having sufficient individual non-specific immunity can stay away from many diseases.

The succulent biomedicines can supply important nutraceuticals, micronutrients as well as can prevent many diseases by supplying different other effective phytochemicals at their nature- derived state (Pattanayak 2019b).

The *Rasayana* concept of *Ayurveda*

In the Indian codified healthcare system, *Ayurveda*, one specific therapy in the name of *Rasayana* was described. As per their analysis, this therapy enhances the qualities of rasa (body fluids) and can enriches it with nutrients that can lead attaining the qualities like better longevity, protection from health disorders, increased intelligence and memory power, increased youthfulness, optimum development of body and sense organs etc.

As per the present analysis, it can be said that *Rasayana* is helpful to modulate the body immunity and assist in staying away from diseases (Chulet and Pradhan 2009).

As per *Ayurveda*, *Rasayana* medicines are some wonder drugs that can be taken for a long time even at healthy state without any adverse effects (Chandresh *et al.* 2017).

During analysis, several *Rasayana* medicinal plants exhibit qualities like immunomodulation, antioxidation, anti-inflammatory, hepatoprotective, cardiotonic, hypercholesterolaemia, anti-asthmatic, diuretic, and many other medicinal activities (Kumar *et al.* 2012).

During the phytochemical analysis of dry parts of the *Rasayana* plants, a large number of compounds including polyphenols, flavonoids, carotenoids, curcumin, ascorbate, tocopherol etc. were identified which are having potent immunomodulatory and antioxidant activities (Kumar *et al.* 2012).

Concept of expression of collective effects of phytochemicals

The contemporary system of analysis of phytochemicals to validate claims of medicinal activities of the medicinal plants is criticised for its strong limitations. The contemporary methods used for study of reported effects of medicinal plants by analysis of different solvent extracted portion of dry powder of medicinal plant parts or study of the isolated phytochemicals (active principles) individually is having limitation of not giving any importance to many other phytochemicals actually present in the original plant. Presence of even a few phytochemicals of very minute amounts (volatile, presence at undetectable amounts etc.) may have some strong effects in expression of the medicinal efficacy of the plant parts (Pattanayak *et al.* 2016a, Pattanayak 2019a). There may be events like suppression of toxicity of one phytochemical by another or potentiation of activity at the same manner when a plant part is used as such (Pattanayak 2020).

The conceptual basis behind such debate is that there are some basic differences between the procedures of creation and possible mechanism of action of chemical medicines and that of the herbal medicines. The chemical compounds are developed singly, but even a single herb may contain a huge number of phyto-constituents, all of them always work together. So, there should be some sort of separate mind set to analyse these two systems. The succulent biomedicines contain far greater numbers of phyto-constituents, all of which may not be identified even with the assistance of modern technologies (Pattanayak 2020).

Health benefits of succulent biomedicines

The health benefits of succulent biomedicines may be discussed after dividing them into three categories. But systematic and planned study in that subject is perhaps yet to be initiated, only some ethnomedicinal reports and some reports of study on the diluent extracts of the dry medicinal plant parts are available. Some salient points are added for each category.

1.For control of infectious diseases

In the ethnomedicinal reports on use of medicinal plants in such purposes, the subject is described by the terms like 'antimicrobial effects', 'antiviral effects' etc.

Some study reports on effects of diluent extracts or isolated compounds on some viruses are available. In one review article, antiviral effects of some plant extracts and compounds against eleven types of viruses through different laboratory tests are described (Lin *et al*. 2014). Antiviral activities of diluent extracts of ten plants on three viruses (Herpes simplex, Sindbis and Polio) are reviewed by Mukhopadhyay *et al.* (2012).

Reports on antimicrobial efficacy study of solvent extracts or isolated compounds of a complete Genus of plants are described by Sharifi-Rad *et al*. (2016). In a review article, antimicrobial effects of compounds of 76 medicinal plants are reviewed by Mukhopadhyay *et al.* (2012). The Names of more than 1000 plants with reports for activities against diseases of infectious origin is listed by Pattanayak (2019a).

2. For control of non-infectious diseases

Effects of the isolated phytochemicals to control some non-infectious diseases are available. For control of diabetes, hypertension etc. many such studies are performed. In some good review articles and books, summary of such studies is found (Eddouks and Chattopadhyay 2012, Salehi *et al.* 2019). Flavonoid-rich foods are studied for their activities to control different devastating diseases which can shorten life span (Waheed *et al.* 2020).

Study on many plant-derived compounds and diluent extracts are performed for identification of their potency to control cancers. Many of such study reports are reviewed (Goel 2013, Nwanodi 2017).

3. Effects on different body systems leading to control of diseases

Many types of reports are available related to possible positive health impacts of biomedicines on different body systems and overall activities of the body. Reported activities like anti-ageing (Peng *et al*. 2014), hepatoprotective (Pattanayak *et al*. 2016b), radioprotective (Mukhopadhyay *et al.* 2012) etc. are such examples.

The effects of these three categories are interlinked, and perhaps more than one type of effects may be shown by a single effective succulent biomedicine.

Study on structure identification and possible mechanism of actions of phytochemicals

Various studies are performed to know the chemical structure of the isolated phytochemicals of the medicinal plants. These are available in many review articles and books (Doughari 2012, Olaniyan 2016, Basu *et al.* 2017). Study reports to identify the possible mechanism of actions of the phytochemicals are also found in available literature (Krzyzanowska *et al.* 2010, Doughari 2012, Watson *et al.* 2018).

Study of activities of succulent biomedicines

Medicinal plants have the ability to show various activities related with prevention and cure of many diseases. Among them, immunomodulation activities may be given highest importance for therapeutic use.

According to the established ideas, an individual can acquire immunity against a specific microorganism either through the natural way of getting infection/s and becoming immune after cure or by activated immune system through vaccination.

The third way may be the modulation of non-specific immunity of the individuals which can prevent catching of infections or can reduce the severity of symptoms of the individuals. The succulent bio-medicines can perform that work most efficiently (Pattanayak 2020).

The succulent biomedicines may work inside the body in different ways. Apart from direct action on the invading microorganisms or on the defects of the body systems by the phytoconstituents, they can show their activities through modulation of immunity status of the body. Though the term 'immuno-stimulant' is used in many literatures, many herbal plants mainly perform the work of immunomodulation. The categories like antioxidation, hepatoprotection, cardio-protection etc. can be categorised under the broad umbrella of 'immunomodulation'. But for a better understanding of the subject in respect to the study of activities of succulent bio-medicines, it is discussed under two broad categories – immunomodulation and antioxidation.

As reports on activities of succulent biomedicines are very scarce, the related reports of dry parts of the medicinal plants can be analysed for that purpose.

Immunomodulation by plant-derived medicines

Modulation of the immune responses through the stimulatory or the suppressive activities of the phytochemicals present in the herbal medicines may keep the normal as well as the unhealthy people at a disease-free state (Kumar *et al*. 2012). Immunomodulators can increase resistance of the body against various infections by influencing the soldiers and their weapons engaged in the immune system. The activities may be an increase of the oxidative activity of neutrophils and engulfment power of the phagocytic cells or stimulation of cytotoxic cells to destroy virus infected cells or cancer cells. On the other hand, some of them may modulate the immune system to control excessive activities of some cells of the immune system causing some dangerous diseases (Shahbazi and Bolhassani 2016). Depending on the type of activities, immunomodulators can be classified into three broad categories: Immunoadjuvants, Immunostimulants, Immunosuppressants (Patel 2012).

Activity areas of the succulent biomedicines for immunomodulation

Succulent biomedicines can perform their immunomodulation activities by acting on different parameters of the immune system. Modulation of their activities may have some strong impacts on overall body immunity.

1. Antigen recognition and phagocytosis

Primary binding of antigens, stimulation of phagocytosis, macrophage activation etc. activities are some very important steps. Stimulation of the dendritic cells, the specialised antigen presenting cells capable of directing immune responses after any infection, have tremendous effects on overall body immunity.

2. Lymphocyte proliferation and differentiation

Stimulation of lymphoid cells, modulation of T-lymphocyte function, enhancement of cellular immune function and other modulatory actions on nonspecific cellular immune systems under this section is important.

3. Synthesis of antibodies

Formation of antibody secreting plasma cells from B lymphocytes and then secretion of different types of antibody by the plasma cells in response to antigenic stimulation is the main parameter of humoral immune response that may be influenced.

4. Interactions of antibodies with antigen may also be influenced.

5. Release of biochemical mediators of immune response

Due to modulation of activities of the cells of the immune system, production of different cytokines may also be influenced. The cytokines can work on receptors of cells of the effector organs or on other cells of the immune system.

6. Control of autoimmune diseases may be performed by correction of self and non-self-identification defects of the cells engaged in this work.

7. Modification of target tissue response/target effector organ.

There may be increased nonspecific immunity mediators and natural killer cell numbers for such works.

8. Influence on apoptosis by affecting the programmed cell death.

9. Direct antiviral, anti-bacterial, antifungal, anti-cancer etc. effects.

10. Influence on the Complement system of the body.

(Fu-Huang *et al.* 2008, Patel 2012, Roshan and Savitri 2013).

Examples of immunity modulation activities of some isolated phytochemicals are found in the literature. Immunomodulatory activities of ursolic acid, glycyrrhizic acid, oleanolic acid, nomilin etc. terpenoid compounds are noted (Kumar *et al*. 2012). Saponins are very important phytochemicals as they can take part in many important pharmacological activities like direct antiviral, immunomodulating, cytotoxic, antitumor, antifungal, antiallergic, antiphlogistic, antihepatotoxic etc. activities (Kumar *et al.* 2012).

Anti-oxidation activity of plant medicines

Many fruits and vegetables, commonly used spices as well as succulent parts of many medicinal plants contain antioxidants at their nature-derived condition. By supplying different antioxidants along with important nutraceuticals and micronutrients, these assist us to fight against infectious as well as non-infectious diseases. Expression of the genetic predisposition for many diseases may also be influenced by these antioxidants (Pattanayak 2020).

Activities of antioxidants at cellular level

During respiration, oxygen acts as the terminal electron acceptor. Oxygen splits into single atoms with unpaired electrons, but these single atom oxygens seek other electrons to be in pairs. This scavenging activity of such single atom oxygens, the free radicals, can initiate many detrimental effects inside the body.

The oxygen derived free radicals' formation is a consequence of aerobic metabolism. It can damage or disrupt cellular bio-molecules by producing reactive oxygen species (ROS) during its high reactivity. Different

ROS (superoxide, hydrogen peroxide, hydroxyl, per hydroxyl radicals etc.) can cause damage in the DNA, proteins and lipids of the cell whose actions are not controlled by the anti-oxidants (Sun *et al*. 2011).

The negative activities of the free radicals are seen in creating disturbance in maintenance of normal health as well as initiation of diseases by influencing signal transduction and expression of genes of individuals. They are also involved in bringing inactivation of different receptors, influencing the cells of the immune system of the body for their antimicrobial activity negatively, acting on nuclear transcription factors, cytotoxic actions, ageing etc. Thus, the oxidative stress of the cells has a direct relationship with many patho-physiological conditions of the body (Paur *et al*. 2011, Packer *et al*. 2011).

The antioxidants can either prevent or slow down the process of oxidation of cellular molecules by removing the free radicals. So, the role of antioxidants is actually buffering the overproduction of ROS and keeping them in a tolerable level for normal physiological functioning of the cells. That is termed as redox signaling (Paur *et al*. 2011, Packer *et al*. 2011).

Oxidants vs antioxidants

Antioxidants can act against the oxidants in two ways.

1.By direct scavenging of the free radicals produced inside the cell. These antioxidants are called primary antioxidants.

2. By following other ways excluding direct activities against the oxidants of the cells. A second minor component is required to initiate such type of activities. Antioxidants use these second components and so reduce their availability. The second component may be the binding with some metal ions, scavenging of the oxygen itself, hydro-peroxide conversion to non-radical species, absorbing UV radiation or deactivating singlet oxygen etc. These antioxidants are called secondary antioxidants.

So, formation of active species, gathering of free radicals, availability of metal ions required for overactivity of oxidants etc. are prohibited as well as assistance in repair of cellular damage caused by oxidants and stimulation of bio-synthesis of other antioxidants and defence enzymes are performed by the antioxidants (Paur *et al*. 2011, Packer *et al*. 2011).

Free radicals and disease

Development of disease involves free radicals in many cases. Generally, the free radicals act secondary to the initiation and progression of the disease process. But in some cases, the free radicals take the main role in the disease development process. A direct relation between loss of balance between oxidants and antioxidants and formation of diseases is proved at least in some diseases, but such balance has some strong relation with healthy aging of individuals. Micronutrients have a strong influence in the whole process. So, there is a strong relation between availability of micronutrients inside the cells, regulation of redox signaling and modification of gene expression to either cause or stop of the initiation and maintenance of diseases (Packer *et al*. 2011). Thus, different antioxidants available in the succulent biomedicines can influence the entire series of activities from initiation and maintenance of disease up to healthy ageing of individuals.

Supplying only single antioxidants at large quantities is not profitable to our body system. Dietary intake of different types of antioxidants (as through succulent fruits, succulent biomedicines etc.) on a regular basis is the best way to protect our health (Paur *et al*. 2011).

Common antioxidants of vegetable origin

Many antioxidants are present in the edible vegetable items (like succulent fruits, vegetables, succulent biomedicines etc.). Among them, Carotenoids and Phenolic compounds are considered most important.

Carotenoids

More or less 60 naturally occurring carotenoids are available in our commonly available edible fruits and vegetables (Paur *et al*. 2011). Along with the pro-vitamin A carotenoids, many other carotenoids can be supplied through diet. Among them, α- and β-carotene, and β-cryptoxanthin, lycopene and the hydroxy carotenoids (xanthophylls) lutein and zeaxanthin are common (Paur *et al*. 2011). Among nearly 1000 carotenoids are identified so far, many of them are expected to be present in the succulent parts of medicinal plants. Those may have many other important effects which are not identified (Pattanayak 2020).

Phenolic compounds

These are gatherings of antioxidants of different families with some common basic chemical structure. Benzoic acid derivatives; flavonoids, proanthocyanins, stilbenes, coumarins, lignans, and lignin are important members of this category. Over 400 flavonoids (Cundell 2014) and more than 8000 plant phenols (Paur *et al*. 2011) have been isolated so far. Plant phenols are capable of showing antioxidant activities through their hydrogen-donating properties of the phenolic hydroxyl groups. These can show their antioxidant activities following different ways like scavenging of free radicals; inhibition

of the enzymes like xanthine oxidase, lipoxygenase, myeloperoxidase and cyclooxygenase; interaction with other antioxidants such as ascorbate, chelation of metal ions etc. (Paur *et al*. 2011).

Flavonoids and other polyphenols can show the activities like anti-tumoral, anti-inflammatory, anti-allergic, anti-ischemic etc. (Shi *et al*. 2001).

Plants with immunomodulation and related activities

The names of 50 immunomodulant plants are collected from different sources by Nagarathna *et al*. (2013). Studies on isolated phytochemicals for immunomodulation activities are reported for 35 plants by Roshan and Savitri (2013). Easy preparation of immunomodulant succulent biomedicines without rigid toxicity study is advocated for 31 medicinal plants. Another 47 plants are listed for the same purpose with to some extent rigid toxicity study for control of Covid-19 by Pattanayak (2020).

Considering the available resources and their relevance with the present subject, a comprehensive list of 130 medicinal plants with reported immunomodulation activities has been prepared (Table 1). Among these, some are regularly or even routinely used by some sections of people at various purposes and some others are not used so frequently by the people.

USE OF DIFFERENT SUCCULENT PLANT PARTS AS MEDICINE

In true sense, the fruits, eaten directly as some food item, are some succulent biomedicines. These can supply many important nutrients, vitamins, macro and micro elements as well as many other phytochemicals which are very much important to our health. The boiled, fried or processed products made from different fruits are more delicious than the original fruits themselves in some cases, but always stay far away in comparison to beneficial effects to health.

The same is true for the medicinal plant parts. The dried Amla (*Emblica officinalis* Gaertn) fruit powder or the Amla juice sold in the market after mixing with preservatives and other chemicals are staying far away from the succulent Amla fruit in consideration of getting health benefits from them. In contrast, synthetic chemicals of different categories added during processing of such items may have some detrimental effects on our health (Pattanayak 2019b).

Study on effects of succulent biomedicines

In the available reports of ethnomedicinal use, some broad terms are available for description of the activities of the medicinal plants. Such terms, like 'cure chest affections', 'protect eye from diseases' etc. cannot satisfy the requirement of present-day science.

In some recent study reports, effects of the diluent extracts of the medicinal plant parts are available. These are mainly *in vitro* study reports. Reports of study performed on living laboratory animals by those diluent extracts are not so common. Reports of study of succulent plant parts on living laboratory animals is scarce.

For understanding and validation of actual effects of succulent biomedicines, there is a need for a change in the contemporary concept of related studies. Such conceptual change can act as a basis for further steps required for establishment of the novel system of use of these medicines therapeutically (Diagram 1).

As the metabolic end products of the phytoconstituents available in the succulent biomedicines actually work inside our body system, so more emphasis may be given to the effect of metabolic end products of such medicines, than on the isolated phytochemicals (Pattanayak 2020).

Diagram 1. Change in contemporary pattern required for study of succulent biomedicines (Pattanayak 2020).

The contemporary pattern followed for chemical as well as herbal medicines

Diluent/ Chemical extraction/other source derived materials → primary level efficacy study → active constituent isolation → final safety and efficacy study → proceeding towards development of marketable medicines.

It may be shifted to a new pattern of study for succulent biomedicines

Succulent bio-medicines → *in vivo* or/and in-patient study for validation of efficacy → dose and safety study → chemical composition analysis.

SUCCULENT BIOMEDICINES – PREPARATION, PACKAGING AND TRANSPORTATION

After validation of the claims through *in vivo* or in-patient study, further study of toxicity and then determination of gross therapeutic doses are required before taking decision of bulk production of the medicines. The production center of succulent biomedicines may be established near the cultivation fields of the respective medicinal plant. Aseptic collection of relevant plant parts, their processing (physical), adjustment of doses as per presence of main active constituents at each lot are some initial important areas. Addition of bio-preservatives with the succulent biomedicines, coating with any coating materials of biological origin and then encapsulation of the individual doses by any bio-encapsulating material are the steps to be followed afterwards (Diagram 2). The names of some bio-preservatives and bio-encapsulating materials are added below. Different techniques for their possible use and other important related points like use of spoilage indicators on the packets of succulent biomedicines etc. are discussed in a recent publication (Pattanayak 2019b).

The bio-preservatives and bio-coating materials

Several bio-preservatives are identified by many scientists which may be used for preservation of succulent biomedicines or other bio-materials. Besides common bio-preservative like honey or sugary sap without chemical processing, essential oils of Onion, Clove, Garlic, Cinnamon, Coriander, Mount Atlas mastic, Mint Thyme, *Zizyphus jujuba, Artemisia anomala,* Ginger oil and *Callistemon lanceolatus* are advocated by Cerqueira *et al.* (2015) as bio-preservatives. Essential oils of Basil, Oregano, Rosemary, Sage, Thyme, Coriander, Allspice, Cinnamon, Clove, Mustard, Nutmeg, Vanilla, Bergamot, Eucalyptus and Lemon can also act as bio- preservative (Ebrahimi and Khosravi-Darani 2013). But detailed descriptions of various herbs, herb compounds, spices, essential oils of plants, natural substances etc. are discussed by Pattanayak (2019b). The concentrated juice or the essential oil derived from the same medicinal plant of original succulent bio-medicine may be the best bio-preservative or bio-coating material for succulent biomedicines (Pattanayak 2020).

Diagram 2. Flow chart of preparation and transport of proposed succulent bio-medicines (Pattanayak 2020).

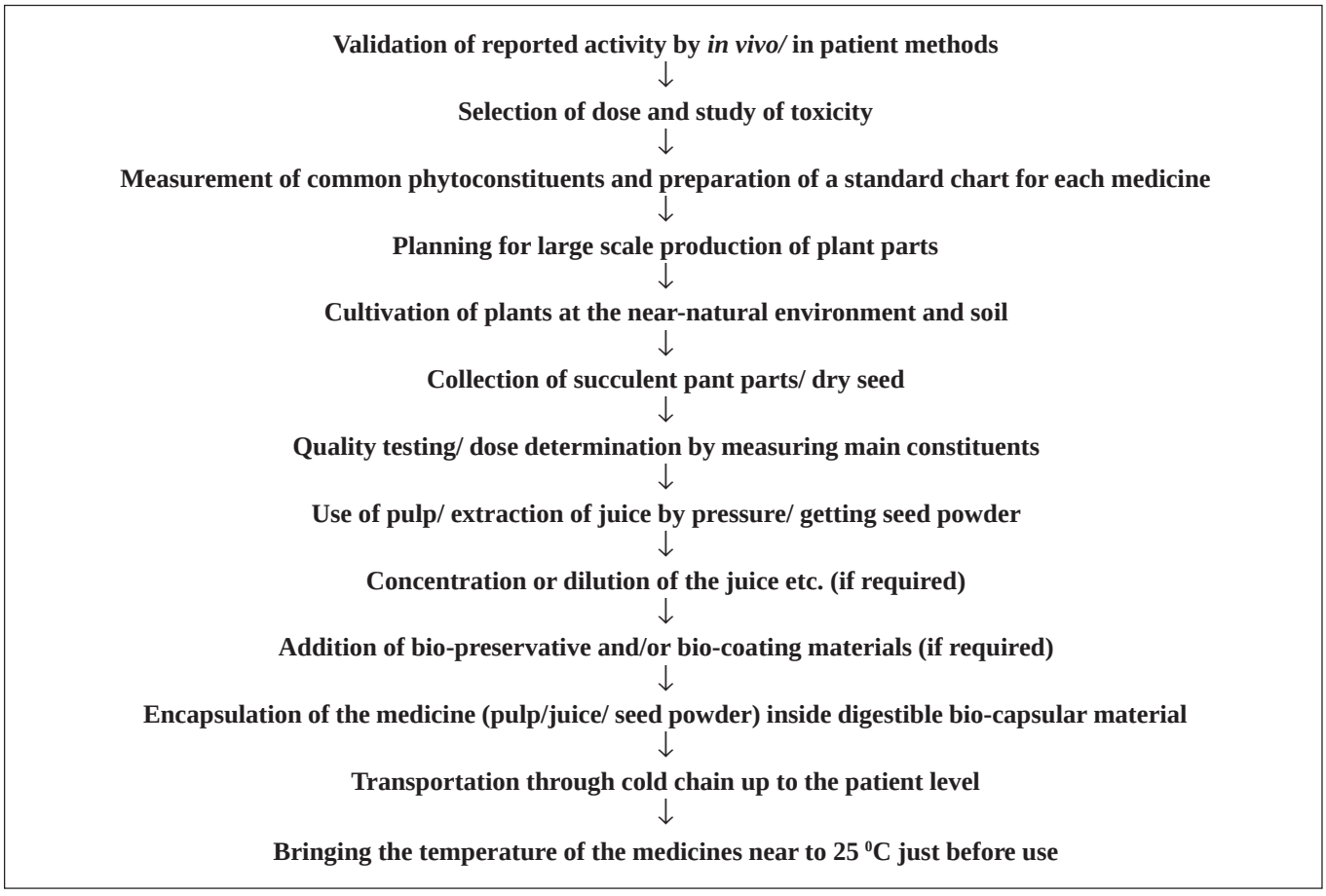

Table 1. Plants with immunomodulation activities (Name of the plant with Family).

Abutilon indicum (Link) Sweet. [Malvaceae]
Acacia catechu (L) Willd. Oliv. [Leguminosae]
Acacia leucophloea (Roxb.) Willd. [Fabaceae]
Acalypha indica L. [Euphorbiaceae]
Acanthospermum hispidum (DC) A. Chev. [Asteraceae]
Actinidia macrosperma C. F. Liang. [Actinidiaceae]
Adhatoda vasica Nees. [Acanthaceae]
Aegle marmelos (L.) Corrêa [Rutaceae]
Aesculus indica Wall. Ex Cambess) Hook [Sapindaceae]
Aframomum melegueta K. Schum. [Zingiberaceae]
Allium sativum L. [Amaryllidaceae]
Aloe vera (L.) Burn,f [Asphodelaceae]
Alstonia boonei De Willd. [Apocyanaceae]
Alternanthera tenella Colla [Amaranthaceae]
Andrographis paniculate (Burm.f.) Nees. [Acanthaceae]
Angelica sinensis (Oliv.) Diels [Apiaceae]
Asparagus racemosus Willd. [Asparagaceae]
Aster squamatus (Spreng) Hieron [Asteraceae]
Astragalus propinquus Schischkin [Fabaceae]
Atractylodes lancea Thunb. [Asteraceae]
Azadirachta indica A. Juss. [Meliaceae]
Bacopa monnieri (L.) Pennell. [Scrophulariaceae]
Balanites roxburghii Planch. [Zygophyllaceae]
Baliospermum montanum (Willd.) Muell-Arg [Euphorbiaceae]
Bauhinia variegata (L.) Benth. [Fabaceae]
Boerhavia diffusa L. [Nyctaginaceae]
Boswellia carterii Birdw [Burseraceae]
Bupleurum chinense DC. [Apiaceae]
Caesalpinia bonducella (L) Fleming [Fabaceae]
Cajanus indicus Speng. [Fabaceae]
Calendula arvensis (Vaill) L. [Asteraceae]
Calophyllum brasiliense Cambess. [Calophyllaceae]
Camellia sinensis (L.) Kuntze [Theaceae]
Capparis zeylanica L. [Capparaceae]
Carlina involucrata Poir. [Asteraceae]
Cassia auriculata L. [Fabaceae]
Catharanthus roseus (L.) G.Don. [Apocynaceae]
Centella asiatica (L.) Urb. [Apiaceae]
Chlorophytum borivilianum Santapau & R.R. Fern. [Asparagaceae]
Cinnamomum verum J.Presl. [Lauraceae]
Cissampelos pareira Linn [Menispermaceae]
Citrous limon (L.) Burm.f [Rutaceae]
Citrus aurantifolia [Christm. et Panz.] Swingle [Rutaceae]
Citrus maxima Merr. [Rutaceae]
Cleome gynandra L.[Cleomaceae]
Clerodendrum phlomidis L.f. [Lamiaceae]
Convolvulus prostrates Frossk. [Convolvulaceae]
Coptis chinensis Franch. [Ranuculaceae]
Coriandrum sativum L. [Apiaceae]
Costus igneus N.E. Br. [Costaceae]
Couropita guianensis Aubl.[Lecythidaceae]
Curcuma longa L. [Zingiberaceae]
Daucus carota L. [Apiaceae]
Dittrichia viscosa (L.) Greuter, [Asteraceae]
Eclipta prostrata (L)L. [Asteraceae]
Emblica officinalis Gaertn. [Phyllanthaceae]
Ephedra sinica Stapf. [Ephedraceae]
Epilobium angustifolium L. [Onagraceae]
Eutrema japonicum (Miq.) Koidz. [Brassicaceae]
Ficus benghalensis L. [Moraceae]
Ficus carica L. [Moraceae]
Galactities tomentosa Moench. [Asteraceae]
Glebionis coronaria (L) Cass. Ex Spach. [Asteraceae]
Glycyrrhiza glabra L. [Fabaceae]
Gmelina arborea Roxb. [Lamiaceae]
Gymnema sylvestre R.Br. [Apocynaceae]
Hemidesmus indicus (L.) R.Br. [Apocynaceae]
*Heracleum persicum*Desf. ex Fisch. [Apiaceae]
Hibiscus sabdariffa L. [Malvaceae]
Hibiscus rosa sinensis L. [Malvaceae]
Hyptis suaveolens (L.) Poit. [Lamiaceae]
Inula crithmoides L. [Asteraceae]
Ipomea pes-caprae (L.) R.Br. [Convolvulaceae]
Ipomoea reptans (L.) Poir [Convolvulaceae]
Laurus nobilis L. [Lauraceae]
Leontodon tuberosus L. [Asteraceae]
Ligusticum striatum DC. [Apiaceae]
Linum usitatissimum L. [Linaceae]
Litsea glutinosa (Lour) C.B. Robins. [Lauraceae]
Lycium barbarum L. [Solanaceae]
Mangifera indica L. [Anacardiaceae]
Matayba elaegnoides Radlk. [Sapindaceae]
Mentha longifolia (L.) Huds. [Lamiaceae]
Moringa oleifera Lam. [Moringaceae]
Morus alba Linn. [Moraceae]
Mucuna pruriens (L.) DC. [Fabaceae]
Nigella sativa L. [Ranunculaceae]
Nyctanthes arbor-tristis L. [Oleaceae]
Ocimum sanctum L. [Lamiaceae]
Origanum majorana L. [Lamiaceae]
Origanum vulgare L. [Lamiaceae]
Paeonia lactiflora Pall. [Paeoniaceae]
Panax ginseng C.A. Meyer [Araliaceae]

Table 1. Plants with immunomodulation activities (contd.).

Picrorhiza kurrooa Royle ex Benth. [Plantaginaceae]	*Sonchus oleraceus* L. [Asteraceae]
Pimenta dioica (L.) Merr. [Myrtaceae]	*Sphaeranthus indicus* L. [Asteraceae]
Piper betel L. [Piperaceae]	*Swertia chirayita* (Roxb.) Buch-Ham. ex C.B.Clarke. [Gentianaceae]
Piper longum L. [Piperaceae]	*Syngium cumini* (L) Skells. [Myrtaceae]
Piper nigrum L. [Piperaceae]	*Syzygium aromaticum* (L.) Merrill & Perry. [Myrtaceae]
Premna integrifolia L. [Lamiaceae]	*Tamarindus indica* L. [Fabaceae]
Prunella vulgaris L. [Lamiaceae]	*Taraxacum officinale* (L.) Weber ex F.H. Wigg. [Asteraceae]
Randia dumetorum Poir. [Rubiaceae]	*Terminalia bellirica* (Gaertn.) Roxb. [Combretaceae]
Rehmannia glutinosa (Gaertn.) Steud. [Orobanchaceae]	*Terminalia chebula* Retz. [Combretaceae]
Reichardia picroides (L.) Roth [Asteraceae]	*Thymus vulgaris* L. [Lamiaceae]
Rhaphidophora korthalsii Schott. [Araceae]	*Tinospora cordifolia* (Thunb.) Miers. [Menispermaceae]
Rheum emodi Wall. Ex Meisn. [Polygonaceae]	*Trachyspermum ammi* (L) Sprague. [Apiaceae]
Rosmarinus offinicalis L. [Lamiaceae]	*Trapa bispinosa* Roxb. [Trapaceae]
Salicornia herbacea L. [Amaranthaceae]	*Tridax procumbens* L. [Asteraceae]
Salvia officinalis L. [Lamiaceae]	*Vaccinium corymbosum* L. [Ericaceae]
Saussurea costus (Falc.) Lipsch. [Asteraceae]	*Vernonia amygdalina* Delile. [Asteraceae]
Schisandra chinensis (Turcz.) Baill. [Schisandraceae]	*Withania somnifera* (L.) Dunal. [Solanaceae]
Sellaginella species P. Beauv. [Selaginellaceae]	*Zingiber officinale* Roscoe. [Zingiberaceae]
Smilax ornate Lem. [Smilacaceae]	

Bio-encapsulating materials

Biological materials of different origin may be considered for bio-encapsulation. Among the plant origin materials, plant exudates (Gum Arabic, Gum karaya, Mesquite gum); plant extracts (Galactomannans, Soluble soybean, Pectin, Cocoa butter); different Starch and Cellulose derivatives, Polysaccharides; proteins like Gluten (corn), Wheat gluten, isolates of Pea or Soy; lipids like Fatty acids/ alcohols, Glycerides, Waxes (Bees wax, Candelilla wax, Carnauba wax), Shellac resin, Phospholipids are important. Among the marine origin products, Carrageenan, Alginate; animal or microbial products like Xanthan, Gellan, Dextran, Chitosan (carbohydrate), Caseins, Collagen, Corn, Whey proteins, Gelatin (protein) etc. are important (Wandrey *et al.* 2010, Cerqueira *et al.* 2015).

Succulent bio-products - a new emerging area of healthcare and agro-industry and the constraints in their immediate arrival

Synthetic chemical free succulent fruit pulp/juice can be prepared following the same technologies of production and transport of succulent biomedicines. Along with supply of important nutraceuticals and micronutrients, these can also assist in further strengthening of the immunity power of the body to resist the invading microorganisms as well as in controlling many dangerous diseases of non-infectious origin – from malnutrition related diseases to cancers. These can also assist to increase disease resistance power of the persons with suppressed immunity power of the body due to various reasons (Pattanayak 2019b).

But that important way of healthcare fails to attract the attention of the researchers, policy makers and industries. A huge number of articles are available with reports of study of diluent extracted portion of the dry plant parts, identification of compounds from them or on so called 'active principles' of many medicinal plants. Availability of such study reports on the succulent parts of plants with reported medicinal activities (fruit, stem, leaf, root etc.) or their pressure extracts (juices) is scarce. Men eat fruits at their succulent condition. But study reports even on the succulent fruits are not easily available. Even for study of the beneficial activities of the green vegetables and legumes on our health, the same procedures of study of their isolated compounds are generally performed (Guaadaoui *et al.* 2015).

This area warrants immediate reconsideration and rethinking for detailed study.

CONCLUSION

The succulent biomedicines may be utilized for immunomodulation to prevent and control different diseases of both infectious as well as non-infectious origin. Many of these plants are having some very

important additional benefits like antiviral, antibacterial, antifungal, anti-diabetic etc. activities. A biomedicine can serve many purposes together and as each of them contain a huge number of phyto-constituents, and so there is nil or negligible chance of development of resistance by the invading organisms against them. The capsules of succulent biomedicines can be used as some regularly usable medicines after performing some adoptive research on them. That may open a new way of serving mankind.

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