Available online at www.sedindia.in/ewijst

ISSN: 0975-7112 (Print)
ISSN: 0975-7120 (Online)

Environ. We Int. J. Sci. Tech. 16 (2021) 53-73

Environment & We
An International
Journal of Science &
Technology

# Key Rasayana Plants of Ayurveda

**Bharti Chaudhry***
Department of Botany, Ramjas College, University of Delhi, Delhi-110 007, India
*Email Id: bhartichaudhry@gmail.com

Article history:
Received 9 September 2020
Received in revised form
06 February 2021
Accepted 21 February 2021
Available online
10 April 2021

Keywords:
Traditional medicine;
Rejuvenation;
Immunomodulator;
Nootropics;
Longevity

**Abstract**

The rising incidence of non-communicable diseases such as cancer, diabetes, hypertension, myocardial infarction, stroke, autoimmune diseases as well as the prevalence of infectious diseases, such as influenza, dengue, malaria, tuberculosis, hepatitis, is increasingly leading to a high rate of morbidity and mortality worldwide. Traditional medicine is becoming popular as a natural and safer alternative to synthetic medicines due to the side effects of modern allopathic medicine, prohibitive cost of treatment, the emergence of drug-resistant bacteria, viruses and parasites, as well as lack of curative treatment for many chronic diseases. Ayurveda is the oldest, holistic, traditional system practised in India that advocates prevention of disease and promotion of longevity. *Rasayana Tantra* or Rejuvenation Therapy is one of the eight disciplines of treatment in Ayurveda. Many medicinal plants used in *Rasayana* therapy are known to replenish the tissues, rejuvenate both body and mind, enhance immunity, restore healthy neuroendocrine functions, promote intellect and delay senescence processes. The review aims to give an update of a few promising *Rasayana* drugs like *Asparagus racemosus, Tinospora cordifolia*, *Curcuma longa*, *Phyllanthus emblica*, *Withania somnifera* that have proved to be powerful antioxidants, anti-inflammatory, antimicrobials, immunomodulators and anticarcinogens; as well as *Medhya-Rasayana* plants like *Bacopa monnieri* and *Centella asiatica* that are potent nootropics and have shown significant clinical potential in attenuation of neuroinflammation, dementia, Parkinson's, Alzheimer's disease and other neurodegenerative disorders.

## 1. Introduction

The incidence of non-communicable diseases, including cancer, metabolic disorders such as diabetes mellitus, hypertension, hypercholesterolemia, myocardial infarction, as well as autoimmune disorders is on a rise globally and posing a major health threat. At the same time, the prevalence of infectious diseases such as influenza, hepatitis, tuberculosis, dengue, malaria as well as zoonotic diseases with pandemic potential, is increasingly leading to a high rate of morbidity and mortality. Medicinal plants have been used since antiquity in traditional cultures all over the world and are increasingly becoming popular as natural alternatives to synthetic medicines. The high cost and side-effects of modern drugs, the emerging drug-resistant microbes and the lack of curative treatment for chronic diseases has rekindled global interest in the alternative traditional systems of medicine. Ayurveda is the oldest, and the most widely practiced traditional healing system, well known for its preventive, restorative, and holistic mode of treatment. Many medicinal plants used in the Ayurveda system of medicine are effective against both common as well as chronic diseases of skin, respiratory system, liver disorders, rheumatoid arthritis, diabetes mellitus, hyperlipidaemia, atherosclerosis, cognitive disorders, cancer and other immunological disorders. The traditional uses of many medicinal plants have been scientifically authenticated by several experimental studies on animal models, cell lines as well as clinicat trials. Medicinal plants have been an important source of drugs in the past like aspirin, digitoxin, morphine, codeine, vincristine, vinblastine, artemisinin and will continue to play an important role in health care for the development of new herbal drugs in future. They can serve as a potential source of new antimicrobials to prevent and mitigate the problem of infection by multi-drug resistant (MDR) bacteria (Badara, 2017). The efficacy of many plant- based medicines in treating a broad spectrum of diseases is usually due to the presence of synergistic interactions of several secondary metabolites.

### 1.1 Concepts and Principles of Ayurveda

The fundamental doctrine of the Ayurveda system of medicine is holistic treatment that takes into account the physical, psychological, social and spiritual well-being of an individual. The philosophy of Ayurveda is based on the theory of *Panchamahabhutas*, according to which all objects in the Universe, including the human body are composed of five basic elements namely *Prithvi* (Earth), *Jala* (Water), *Teja* (Fire), *Vayu* (Air) and *Akash* (Space or Ether). The human body is composed of seven basic body tissues or *dhatus* called as the *Saptadhatus* viz. *Rasa* (plasma), *Rakta* (blood), *Mamsa* (muscular tissue), *Meda* (adipose tissue), *Asthi* (bone or ossiferous tissue), *Majja* (marrow and myeloid tissue) and *Shukra* (reproductive tissue). The three waste products (*malas*) include *Purisha (*faeces), *Mutra* (urine) and *Sweda* (sweat). The tissues of the body constitute structural entities and *malas*, the excretory entities. In addition, there are three physiological entities (*doshas* or biological humors) called as *Tridoshas* (*vata*, *pitta* and *kapha),* that are derived from different combinations and permutations of the five basic elements. *Vata* is the bioenergy that governs muscle and tissue movement, pulsation of the heart, breathing and co-ordination of senses; *Pitta* governs digestion, assimilation, metabolism, endocrine system and body temperature; and *Kapha* forms the body structure, lubricates the joints and maintains immunity. Health in Ayurveda is a manifestation of the balanced state of all *dhatus*, *doshas* and *malas*, both in quantity and quality. An optimum equilibrium among the three humors (*doshas*) is associated with a healthy constitution of the body (Ravishankar and Shukla, 2007; Chaudhry, 2019). Any imbalance due to the accumulation of *doshas* vitiates the structural and excretory entities, affecting the metabolism of the body, and results in disease (*Vikriti*). According to the concept of Ayurveda, every individual has a unique psychosomatic constitution called as *prakriti* which governs the structural and functional attributes of the body and mind, as well as the health and disease patterns of an individual. The genetic constitution of each individual governs the ability to absorb important nutrients from the diet, to cope with toxins as well as predisposition to certain diseases. The balance between *tridoshas* has been correlated with a coordination between the central nervous system (*vata*), endocrine system (*pitta*) and the immune axis (*kapha*).

The whole body is made up of micro and macro channels (*Srotas*) that transport nutrition and excrete metabolic waste products. These biochannels are visible or invisible areas in the tissues of the body that include veins, arteries, capillaries, ducts, passages and spaces inside the body. Any blockage in the biochannels (*srotas*) due to the accumulation of doshas affects the bi-directional flow of nutrients and end products, manifesting in disease. According to Ayurveda, a major cause of illness is a poor digestive system or low digestive fire (*Agni*), due to which food is not digested and nutrients are not absorbed. *Ama* is a unique concept of Ayurveda, which is considered a toxic end product of improper digestion and metabolism, and when accumulated, leads to many diseases. Therefore, eating the right foods, according to the body constitution, is the key to proper digestion and health.The treatment in Ayurveda is individualized and involves the use of purification therapy (*Panchakarma*) and rejuvenation therapy (*Rasayana*) aimed at restoring the balance of disturbed doshas. *Panchakarma* refers to the five types of bio-cleansing therapies, used for elimination of toxins (stagnant *malas*) from the body. *Rasayana* is a therapeutic procedure used to replenish and rejuvenate body tissues, improve immunity and prevent ageing. *Rasayana* therapy includes a combination of herbs, lifestyle interventions, diet, meditation and yoga. Many *Rasayana* drugs used in Ayurveda are potent immunomodulators, adaptogens, antioxidants and nutritive supplements (Patwardhan and Gautam, 2005). *Rasayana* preparations include single herbs or polyherbal formulations. They may be used as decoctions, pills, infusions, powders, tinctures, alcoholic preparations and fractional distillates.

### 2. ***Rasayana*** **therapy with herbs**

*Rasayana* therapy (Geriatrics/ Rejuvenation therapy) is one of the eight branches of Ayurveda that deals with prevention of diseases and promotion of longevity. The word *Rasayana* means the path taken by *Rasa* (*Rasa*: plasma/ primordial tissue/ lymphatic fluids; *ayana*: path). According to Ayurveda, the quality of the *Rasa* affects the health of other tissues of the body and the process which facilitates optimum acquisition, assimilation and circulation of the

essence of food to targeted tissues is *Rasayana* therapy. The plants used as *Rasayana* in Ayurveda are known to enrich *rasa* (replenish the tissues), rejuvenate body and mind, delay old age, promote vitality, vigour, intellect, impart good digestion, lustrous skin and strengthen the immune response of the body. (Puri, 2003). *Rasayana* drugs have been known to act as adaptogens (that enhance the resistance of the body to stress and restore normal physiological functioning); as immunomodulators (that are capable of suppression or stimulation of any components of adaptive or innate immunity), as alteratives (that alter a disease and restore proper functioning of the body through purification of blood, elimination of toxins and increase in absorption of nutrients) and/or as nutritive supplements. They can function as immunostimulators (that activate the mediators or components of the immune system), or immunosuppressants (that suppress the immune response, such as in autoimmune diseases and allergy). *Rasayana* plants also possess the potential to be used as vaccine adjuvants (immunoadjuvants). Immunoadjuvants are added to antigens (vaccines) to increase the production of antibodies without acting as antigens themselves.

Oxidative stress and inflammation are known to play an important role in the pathogenesis of many diseases. Oxidative stress occurs as a result of physiological imbalance between the levels of antioxidants and free radicals (unstable chemicals formed as a byproduct of metabolism) in the body. An over production of free radicals increases the risk of oxidative damage to vital biomolecules like lipids, proteins and DNA, disrupts metabolic pathways and is associated with chronic and degenerative ailments including cancer, arthritis, aging, autoimmune disorders, cardiovascular and neurodegenerative diseases (Pham-Huy *et al.,* 2008). Chronic stress plays a significant role in the disruption of the immune system and has been linked with higher oxidative stress, increased inflammation, lower telomerase activity and shorter telomere length, thus affecting cellular ageing and longevity (Epel, 2009). Supplementation of exogenous (dietary) antioxidants or boosting endogenous antioxidant defences of the body is the key to overcome oxidative stress. *Rasayana* plants are known to act as powerful antioxidants and anti-inflammatory agents. Antioxidants neutralize excess free radicals, protect the cells against oxidative stress and help in prevention of diseases. Plants are known to contain high concentrations of antioxidants like ascorbic acid, polyphenols, carotenoids, glutathione, tocopherols and enzymes with high antioxidant activity. Many *Rasayana* plants have been studied for their free radical scavenging property and immunomodulatory effects in animal models (Govindarajan *et al*., 2005). Antioxidant enzymes (endogenous antioxidants) act as first-line defense against free radicals and enzymes such as superoxide dismutase, glutathione peroxidase, glutathione reductase and catalase have generally been used to assess the antioxidant potential of *Rasayana* drugs (Balasubramani *et al.,* 2011).

*Rasayana* herbs are powerful immunomodulators and are known to modulate the neuro-endocrine-immune system of the body (Farooqui *et al.,* 2018). The interaction between the neuroendocrine and the immune system is essential to maintain the homeostasis of the body. The hypothalamus-pituitary-adrenal axis (HPA-axis) plays a central role in the stress response of the body. The immune response is a complicated interplay of multiple cell types between the innate and the adaptive humoral and cellular immunity, stimulation and suppression of immunocompetent cells and the influence of endocrine and other mechanisms on the immune system (Yamada, 1992). Adaptive (acquired) immunity differs from innate immunity in its antigen specificity and presence of memory cells. The bone marrow, in addition to red blood cells and platelets, produces all cells of the immune system including lymphocytes (B-cells, T-cells, natural killer cells), granulocytes (basophils, neutrophils eosinophils, mast cells), monocytes, macrophages and dendritic cells. The macrophages form an integral component of the innate immunity and play an important role in defence against microbial invasion. Specialized macrophages perform different functions in different tissues like Kupffer cells in liver, osteoclasts in bone, alveolar macrophages in lung and microglial cells in brain. The cells of the innate immune system (including macrophages, dendritic cells, mast cells, neutrophils, basophils and eosinophils) produce cytokines or interact with other cells directly to activate the adaptive immune system. Cytokines are low molecular weight glycoproteins that include interleukins, tumour necrosis factors and interferons. The interferons provide protection against viral infection of cells. The adaptive immunity involves a tightly regulated interplay between antigen-presenting cells and the T and B lymphocytes. The adaptive humoral immunity is regulated by B-lymphocytes that secrete specific antibodies (immunoglobulins). The cellular immunity occurs inside infected cells and is mediated by T lymphocytes. There are three major types of T cells, the T- helper (Th) cells, the cytotoxic T

cells (Tc), and the Regulatory T cells (Treg). The T-helper cells help in activating B cells to secrete antibodies and macrophages to destroy ingested microbes as well as activate cytotoxic T cells to kill infected target cells. The cytotoxic T lymphocytes are involved in direct killing of virus-infected cells, damaged cells and tumour cells by inducing apoptosis. The regulatory T cells (or suppressor T cells) suppress the excessive immune response of other T cells and shut down the T cell-mediated immunity towards the end of an immune reaction, to prevent autoimmunity and chronic inflammation. Th1 and Th2 cells are the subsets of helper T cells that produce important cytokines. Th1 cells drive cellular immunity and help cytotoxic T cells, natural killer cells, and macrophages to fight intracellular pathogens like viruses and bacteria, eliminate cancerous cells and stimulate delayed-type hypersensitivity. Th-2 type cytokines induce humoral immunity and help B cells, in upregulation of antibodies to fight extracellular pathogens. Th1 cells are known to boost antiviral and antibacterial resistance (Kidd, 2003). T-cell homeostasis (immunostasis) requires a fine balance between the Th1-Th2 response. The immunomodulatory activity of *Rasayana* drugs is known to occur mainly via proliferation of lymphocytes, increased activity of macrophages, increased non-specific immunity mediators and natural killer cell numbers, upregulation of interleukin levels, increased antigen-specific immunoglobulin production and reduction of chemotherapy induced leukopenia. Rasayana herbs and formulations are known to stimulate humoral immunity in terms of antibody production and cell-mediated immunity in terms of delayed-type hypersensitivity (Balasubramani *et al.,* 2011).

Inflammation is a biological response by the immune system triggered by pathogens, toxic compounds or harmful stimuli, that initiates a natural defence mechanism and healing process. While acute inflammation is the initial response of the body, uncontrolled chronic inflammation is associated with an impaired innate immune activation and many diseases like atherosclerosis, Alzheimer's disease, Parkinson's disease, diabetes, cancer, allergy and asthma. Chronic or pathological inflammation is common to aging (inflammaging). The dynamic balance of the network of pro-inflammatory cytokines and anti-inflammatory cytokines maintains the physiological function of the inflammation in the body. Elevated levels of pro-inflammatory cytokines play an important role in chronic inflammation, accumulation of senescent cells and age-related diseases (Xia *et al*., 2016; Hardeland, 2019). Vascular inflammation and oxidative stress are major triggers for cardiovascular disease (Steven *et al*., 2019). Inflammatory cytokines cause the oxidation of low-density lipoprotein (LDL) molecules that are known to damage the lining of arteries. Chronic inflammation is also known to play a role in the development of cancer as excessive oxidative stress induces DNA damage and triggers harmful mutations. Immunomodulators are known to alter the activity of immune function through the dynamic regulation of cytokines and other mediators.

The brain is prone to oxidative stress, lipid peroxidation and chronic neuroinflammation has been linked to many neurodegenerative disorders like Alzheimer's disease, Parkinson's disease, epilepsy, as well as psychiatric diseases like anxiety, depression, schizophrenia and bipolar disorders. Cognitive decline and neurodegeneration is usually associated with the ageing process. Alzheimer's disease is the most common form of dementia afflicting old people and involves inflammation, oxidative damage and accumulation of beta-amyloid plaques (Cheignon *et al*., 2018; Teixeria *et al*., 2019). The inflammation is characterized by an increased expression of inflammatory cytokines and over-activated microglia. Parkinson's disease, the second most common age-associated neurodegenerative disorder, is characterized by progressive loss of dopaminergic neurons and the presence of α- synuclein aggregates in the brain. The activation of glial cells and pro-inflammatory cytokines are common features of the Parkinson's disease brain (Wang *et al.,* 2015). The activated microglial cells are known to induce an excessive secretion of neurotoxic factors like nitric oxide (NO), reactive oxygen species (ROS), tumor necrosis factor-alpha (TNF-α) and interleukin-1β which lead to neuronal damage. One of the major factors involved in inflammation is the transcription factor nuclear factor-kappa B (NF-kB), the dysregulation of which is associated with the pathogenesis of various inflammatory diseases. Many plants used in the *Rasayana* therapy have the potential to downregulate the pro-inflammatory NF-Kb levels. Alzheimer's and Parkinson's diseases are usually associated with a deficiency of Acetylcholine (Ach) in the Central Nervous System and increasing the brain Ach levels by inhibition of the enzyme acetylcholinerase (AChE) that hydrolyses Ach into choline and acetate, has been one of the major therapeutic targets. *Rasayana* plants have potent anti-inflammatory properties and those that are specific to the brain are called as *Medhya-*

*Rasayana* herbs (Nootropics). They are used as nervine tonics for improvement of memory and intellect, as sedatives, tranquilizers, as well as for the treatment of neurodegenerative, psychological and psychosomatic disorders.

A significant concept of Ayurvedic medicine aims at prevention of disease and maintenance of health. *Rasayana* herbs are known to exhibit multifarious actions on several body systems and are potent antioxidants, detoxifiers, antimutagens, anticarcinogens and immunomodulators. They can normalize functions of the body, restore healthy neuroendocrine functions, improve non-specific resistance to stress and provide prophylactic treatment. The article attempts to give an update of seven such plants used in Ayurveda with their traditional uses as well as modern experimental and clinical research.

**2.1. Asparagus racemosus Willd. (Family: Asparagaceae)**

**2.1.1. Plant part used**: Dried, tuberous roots

*Asparagus racemosus* (commonly called as Wild Asparagus, Indian Asparagus, Shatavari), is a woody, spinous, much branched under-shrub that bears small, uniform, pine needle-like cladodes (flattened, photosynthetic, modified branches). The roots are numerous, fusiform, fleshy, tuberous and arise as a cluster from the basal end of the stem.

**2.1.2. Traditional Uses:** It is the most popular *Rasayana* drug used in Ayurveda for the treatment of female reproductive ailments as well as a general tonic (Puri, 2003). The root of *Asparagus* is referred as bitter-sweet, cooling, emollient, nervine tonic, galactogogue, aphrodisiac, diuretic, rejuvenating, carminative, stomachic, antitussive and antiseptic. The medicinal properties of the plant are attributed to the steroidal saponins, *Shatavarins* and flavonoids like kaempferol, quercitin and rutin. *Asparagus racemosus* is also known to exhibit beneficial effects in neurological disorders, depression, dyspepsia, diarrhoea, hyperacidity, rheumatism, tumours, inflammation, neuropathy, hepatopathy, cough, bronchitis, and general debility.

**2.1.3. Women Health:** The phytoestogens present in *Asparagus racemosus* roots are responsible for its potential in the treatment of female infertility, curing inflammation of sexual organs, enhancing folliculogenesis and ovulation, preventing miscarriages, and curing hormonal imbalance (Sharma and Bhatnagar, 2011; Kinage and Chaudhari, 2016; Hasan et al., 2016). It has been used for the treatment of leucorrhoea, menorrhagia (excessive bleeding during menstruation), dysmenorrhoea (painful menstruation) and menopausal symptoms. It imparts immunity, prevents ageing, increases longevity, improves mental function, vigour and vitality. It is an effective demulcent for dry and inflamed membranes of the lungs, stomach, kidneys and sexual organs. Traditionally, the plant has long been in use as a galactogogue (which stimulates lactation) as well as in prevention of threatened abortion. Clinical trials on lactating mothers have exhibited significant galactogogue activity in terms of increased prolactin hormone, corroborating its traditional use (Gupta and Shaw, 2011). Psychological stress is common in women and the associated oxidative stress can affect oocyte quality, induce apoptosis and cause female reproductive health disorders, including polycystic ovary syndrome, endometriosis and unexplained infertility (Prasad *et al.,* 2016, Pandey *et al.,* 2018). *Asparagus racemosus* has been implicated to enhance oocyte quality, follicular growth and development by reduction of oxidative stress and increasing the levels of antioxidants in the body (Pandey *et al.* 2018).

**2.1.4. Immunomodulatory:** Several studies have reported the immunomodulatory effects of the root extract of *Asparagus racemosus* by modulating macrophage and lymphocytes activation. It is reported to have a strong impact on murine systemic Th1/ Th2 immunity, by significant upregulation of Th1 (IL-2, IFN-gamma) and Th2 (IL-4) cytokines, suggesting its mixed Th1/ Th2 adjuvant activity (Gautam *et al.,* 2009). The co-administration of aqueous root extract of *Asparagus racemosus* with low immunogenic doses of DPT (Diptheria, pertussis and tetanus) vaccine

is reported to result in higher anti-pertussis antibody titres in experimental animals, indicating its immunoadjuvant potential (Gautam *et al.,* 2004).

**2.1.5. Neuroprotective:** An experimental study has shown the potential of Shatavarin IV in extension of lifespan and alleviation of Parkinsonism in *Caenorhabditis elegans* (nematode) model, by attenuation of oxidative stress. Shatavarin IV has been implicated to alleviate Parkinson's disease symptoms by reduction of alpha-synuclein aggregation, lipid accumulation and enhancement of dopamine level (Smita *et al.,* 2017). The neuroprotective effects of *Asparagus racemosus* root extract and reversal of learning and memory impairment have been reported in ovariectomized adult female Wistar rats. The mechanisms of neuroprotection have been attributed to the enhancement of brain-derived neurotrophic factor and up-regulation of estrogen receptors in the frontal cortex and hippocampus regions of the brain (regions that are associated with the learning and memory process) (Lalert *et al*., 2018).

**2.1.6. Antiulcer and Antioxidant:** The antiulcer and antioxidant activity of *Asparagus racemosus* has been reported in various models of gastric ulcer in rats, resulting in significant reduction of ulcer index, volume of gastric secretion, free acidity and total acidity (Bhatnagar *et al.,* 2005). The study also indicated an increase in antioxidant defense (increase in enzymes superoxide dismutase, catalase, and ascorbic acid) and a decrease in lipid peroxidation. The results were found to be comparable to those of the standard drug Ranitidine.

**2.1.7. Antimicrobial**: The antimicrobial properties of *Asparagus racemosus* have been reported against various pathogenic microbes including *Escherichia coli, Vibrio cholerae, Salmonella typhi, Salmonella typhimurium, Shigella dysenteriae, Shigella sonnei, Shigella flexneri, Pseudomonas pectida, Staphylococcus* and *Bacillus subtilis* (Mandal *et al*., 2000) as well as *Klebsiella pneumonia, Enterococcus faecalis, Clostridium spp.* and *Candida albicans* (Potduang *et al.,* 2008). Crude extracts of the root of *Asparagus racemosus* have also shown significant ovicidal, larvicidal and adulticidal properties against filariasis (C*ulex quinquefasciatus),* dengue (*Aedes aegypti*) and malaria (*Anopheles stephensi)* vector mosquitoes (Govindarajan and Sivakumar, 2014).

**2.1.8. Anticancer**: The root extracts (Shatavarins containing Shatavarin IV) of *Asparagus racemosus* have exhibited significant anticancer activity in human cell lines of breast cancer, colon adenocarcinoma, kidney carcinoma (Mitra *et al,* 2012) as well as human lung adenocarcinoma cell lines (Biswas *et al.,* 2018). Experimental studies have also shown the anticancer potential of *Asparagus racemosus* in *vivo* against Ehrlich ascites carcinoma tumor bearing mice (Mitra *et al.,* 2012).

### *2.2. Bacopa* monnieri (L.) Pennell (Family: Plantaginaceae)

**2.2.1. Plant parts used**: All parts, root, stem, leaf, flower and fruit

*Bacopa monnieri* (commonly called as Bacopa, Indian pennywort, Herb of grace, Thyme-leaved gratiola, Water hyssop, Brahmi), is a small, creeping, perennial herb, that inhabits wetlands and muddy shores. The plant has numerous prostate branches bearing thick succulent, ovate-oblong, sessile leaves. The flowers are pale-bluish in colour, axillary, solitary, arranged on long slender pedicels. The fruits are ovoid or oblong capsules enveloped in persistent sepal-cup and tipped with style base. The major active phytochemicals include triterpenoid saponins (bacosides A-D, bacopasides I–XII, bacopasaponins A-H, betulinic acid).; alkaloids (brahmine, nicotinine, herpestine); phytosterols (stigmastanol, β-sitosterol, stigmasterol) and pseudojujubogenin glycoside. *Bacopa monnieri* possesses nootropic, anxiolytic, anti-depressant, anti-convulsant, adaptogen, astringent, diuretic, sedative, antioxidant, antineoplastic, antimicrobial, refrigerant, anti-inflammatory, anti-ulcer, analgesic, neuroprotective, hepatoprotective and cardiotonic properties.

**2.2.2. Traditional Uses:** The herb is classified as a *Medhya-Rasayana* drug in Ayurveda that promotes healthy longevity, prevents ageing, sharpens intellect and attenuates mental deficits. It has been used traditionally for treating skin diseases, fever, edema, anaemia, indigestion, increased frequency and turbidity of urine, and ulcers. The herb has also been used as a cardiac tonic and is known to improve respiratory functions.

**2.2.3. Neuroprotective and Cognitive enhancement**: *Bacopa monnieri* is implicated in the treatment of anxiety, epilepsy, dementia, cognitive dysfunction, hysteria, amnesia and other neurodegenerative disorders (Russo and Borrelli 2005, Pase et al*.,* 2012; Stough et al*.,* 2015). It has been used as a nootropic drug, to improve mental functions, memory, learning and concentration. Many clinical and *in vitro* studies validating its neuroprotective and cognitive enhancement potential have been documented (Calabrese et al, 2008; Chaudhari *et al*., 2017; Nemetchek *et al*., 2017; Manap *et al.*, 2019). *Bacopa monnieri* has shown significant clinical potential in attenuation of neuroinflammation, dementia, Parkinson's disease, Alzheimer's disease and epilepsy. It is known to protect cells in the prefrontal cortex, hippocampus, and striatum against cytotoxicity and DNA damage implicated in Alzheimer's disease and reduce hippocampal β-amyloid deposition. Bacosides, the primary nootropic phytochemicals, protect the brain against oxidative damage and age-related cognitive decline through several mechanisms. They are known to enhance nerve impulse transmission, repair damaged neurons by upregulating neuronal synthesis and enhance nitric oxide-mediated cerebral vasodilation, resulting in improvement of memory (Chaudhari *et al.,* 2017). A randomized, placebo-controlled, double-blind trial has shown that the extracts of *Bacopa* significantly improved memory acquisition and retention in healthy older Australians (Morgan and Stevens, 2010). *Bacopa monnieri* has been shown to act via antioxidant neuroprotection, acetylcholinesterase inhibition, choline acetyltransferase activation, β-amyloid reduction, increased cerebral blood flow and neurotransmitter modulation (Aguiar and Borowski, 2013). It *has* been shown to have an anti-inflammatory effect on brain microglia and inhibits the release of pro-inflammatory cytokines, tumour necrosis factor-alpha (TNF-α) and Interleukin-6 (IL-6) (Nemetchek *et al.,* 2017). A recent study has shown that the administration of *Bacopa monnieri* in Parkinson's disease animal model, results in suppression of levels of pro-inflammatory cytokines, decreased levels of α-synuclein, and reduction of ROS (reactive oxygen species) in the brain. The study supports the view that *Bacopa monnieri* can limit inflammation in different areas of the brain (Singh *et al.,* 2020).

**2.2.4. Cardioprotective**: The cardioprotective potential of *Bacopa monnieri* has been reported to result in increased rat coronary flow, reduced infarct area and improved cardiac functioning following myocardial ischemia/ reperfusion injury in rat models (Srimachai *et al.,* 2017).

**2.2.5. Anticancer**: Experimental studies have indicated the potential use of *Bacopa monnieri* in cancer prevention and treatment. The plant extracts have been shown to be cytotoxic both *in vivo* as well as *in vitro* in several human cancer cell lines including those of colon, breast, lung and the cervix (Mallick *et al.,* 2017). The anticancer activity has been attributed to the presence of bacosides and cucurbitacin. Bacoside A has been shown to induce cell cycle arrest and apoptosis in human glioblastoma cell lines (Aithal and Rajeswari, 2019).

**2.3. Centella asiatica (L.) Urban (Family: Apiaceae)**

**2.3.1. Plant parts used**: Whole plant, mainly leaves

*Centella asiatica* (commonly called as Asiatic pennywort, Asian coinleaf, Gotu Kola, Centella and Mandukaparni), is a slender trailing herb, rooted at the nodes. It has long, green to reddish-green prostate stems emerging from the leaf axils of a vertical root stock. The leaves are orbicular-reniform, entire, crenate and glabrous. The whole plant/ leaves have been used for their anti-inflammatory, antioxidant, anti-convulsant, anti-depressant, anti-ulcer, wound-healing, sedative, immunostimulant, antidiabetic, neuroprotective, cardioprotective, hepatoprotective, antiviral, antibacterial, antifungal and anticancer properties. The major active phytochemicals include triterpenoid

saponins – asiatic acid, madecassic acid, brahmic acid, isobrahmic acid, thankunic acid, betulic acid, centellic acid; various glycosides-asiaticoside, madecassoside, centelloside, brahmoside; and phytosterols (Stigmasterol, campesterol, Beta-sitosterol).

**2.3.2. Traditional Uses:** In Ayurveda, *Centella asiatica* is one of the main herbs for revitalization of the nerves and brain cells. It is a popular *Medhya-Rasayana* drug widely used for cognitive dysfunction, memory enhancement, nervine disorders, blood purification and promoting longevity (Orhan 2012; Prakash *et al*, 2017). It has been used traditionally for wounds, burns and various skin conditions such as leprosy, lupus, psoriasis, eczema, varicose ulcers, gastrointestinal diseases, renal stones and diseases of the female genitourinary tract.

**2.3.3. Neuroprotective:** Several studies in animal models validate the neuroprotective and neuroregenerative potential of *Centella asiatica*. (Gray *et al*.., 2015; Ceremuga *et al*., 2015; Gray *et al.,* 2016, Gray *et al.,* 2018). It has been shown to protect the neurons from apoptosis and aids in the treatment of many neurodegenerative disorders including depression, anxiety, Alzheimer's and Parkinson's disease. Asiaticoside and Asiatic acid have been shown to have neuroprotective, anti-depressive and anxiolytic effects (Ceremuga *et al.,* 2015).. *Centella* is known to act by providing protection from oxidative stress, inhibition of acetylcholinesterase, enhancement of dendrite arborisation, and protection against Beta- amyloid formation in the brain (Lokanathan *et al.* 2016, Gray *et al.,* 2018). It is known to increase the cerebral levels of GABA (Gamma-Aminobutyric acid), an inhibitory neurotransmitter that counterbalances neuronal excitation and therefore, has the potential to be used as an anticonvulsant for epilepsy treatment (Gray *et al.,* 2018).

**2.3.4. Anti-hypertensive*:*** A recent experimental study in hypertensive animal models has reported the anti-hypertensive activity of *Centella asiatica* in combination with *Curcuma longa,* by decreasing systolic and diastolic blood pressure, increasing urine output (diuretic) as well as improved arterial stiffness (Hasimun *et al.,* 2019).

**2.3.5. Wound healing and treatment of varicose veins** : Many *in vitro* and clinical studies have shown *Centella asiatica* to be effective in the treatment of wounds, burns and post-operative hypertrophic scars by stimulating the synthesis of collagen, inducing angiogenesis, escalating the proliferation of fibroblasts and synthesis of extracellular matrix (Yao *et al.*, 2017; Ahmed *et al.*, 2019). The herb has been found effective for the treatment of patients with signs and symptoms of chronic venous insufficiency that causes leg discomfort, pain and oedema. *Centella asiatica* is reported to improve microcirculatory parameters and help in the treatment of varicose veins (Chong and Aziz, 2013).

**2.3.6. Anticancer**: Asiatic acid has shown growth suppressive and pro-apoptotic potential in several cancer cell lines, including colon cancer (Tang *et al.*, 2009), breast cancer (Hsu *et al.,* 2005)., hepatoma (Lee *et al.,* 2002), melanoma (Park *et al.,* 2005*)* glioblastoma (Kavitha *et al.*, 2015), multiple myeloma (Zhang *et al.*, 2013) and ovarian cancer (Ren *et al.,* 2016). Wang *et al.* (2017) have exhibited the potential of asiatic acid in the attenuation of malignancy of human metastatic ovarian cancer cells. Asiatic acid has also been shown to inhibit lung cancer cell growth both *in vitro* and *in vivo* by apoptosis mediated through mitochondrial damage (Wu *et al*., 2017).

**2.4. Curcuma longa L. (Family: Zingiberaceae)**

**2.4.1. Plant part used**: Rhizome

*Curcuma longa,* commonly known as Turmeric in English and Haldi in Hindi, is a rhizomatous perennial herb, native to tropical South Asia. The plant grows to a height of 3-5 ft and has thickened rhizome bearing a number of cylindrical primary, secondary or even tertiary rhizomes (fingers). The rhizomes are rough, hard, possess many

annulations and are medicinally important. The active phytochemicals include curcuminoids such as Curcumin (diferuloylmethane), demethoxycurcumin, monodemethoxycurcumin, bisdemethoxycurcumin, dihydrocurcumin and cyclocurcumin. The essential oil obtained by steam distillation of rhizome has phellandrene, sabinene, borneol, zingiberenes and sesquiterpenes. Curcumin (a hydrophobic polyphenol) is the most active constituent responsible for the bright yellow colour of turmeric. Turmeric is known to possess potent antioxidant, anti-inflammatory, anticarcinogenic, antidiabetic, antimutagenic, anticoagulant, antiviral, antibacterial, antifungal, anti-protozoal, anti-ulcer, anti-fibrotic, antiasthmatic, hypotensive and hypocholesterolemic properties.

**2.4.2. Traditional Uses**: *Curcuma longa* is widely acclaimed for its multiple health benefits and has been extensively used in the Ayurveda, Siddha and Unani Systems of Medicine. It is known to reduce inflammation, acts as a powerful blood purifier, aids digestion, gives relief from Irritable Bowel Syndrome, and enhances liver function. Turmeric has been used in traditional medicine as a remedy for various diseases, including biliary disorders, anorexia, cough, sinusitis, asthma, rheumatism, diabetic wounds, hepatic disorders, a stimulant of bile duct secretions, healing and disinfection of wounds, jaundice, flatulence, dyspepsia, intermittent fever, eczema, sprains, bruises, inflammatory troubles of joints, conjunctivitis and purulent ophthalmia.

**2.4.3. Antioxidant and Anti-inflammatory**: The therapeutic effects of curcumin against metabolic syndrome, neurodegenerative disorders, cardiovascular diseases, pulmonary diseases, autoimmune and neoplastic diseases are largely attributed to its antioxidant and anti-inflammatory mechanisms (Aggarwal and Harikumar, 2009; Wickenberg et al., 2010; Panahi *et* al. 2016 a,b; Hewlings and Kalman, 2017; Kujundzic *et al.*, 2019*)*. Curcumin is a powerful antioxidant that scavenges free radicals from the body, reduces oxidative stress and improves cognitive functions related to the aging process. It is a powerful anti-inflammatory agent used in all kinds of inflammatory diseases such as osteoarthritis, rheumatoid arthritis, tendonitis, injuries and sprains. Several studies have corroborated the ant-arthritic effects of curcumin in humans and is postulated to offer an alternative to NSAIDs (Non-steroidal anti-inflammatory drugs) for patients with osteoarthritis (Panahi *et al*., 2016 b; Akuri *et al.,* 2017).

**2.4.4. Antidiabetic**: Numerous *in vitro and in vivo* studies have supported the efficacy of curcumin against type 2 diabetes mellitus (Pivari *et al.,* 2019). A meta-analysis study has reported the efficacy of curcumin in significant reduction of glycosylated haemoglobin (HbA1c) in individuals with prediabetes and Type 2 diabetes mellitus (Poolsup *et al*., 2019). The problems associated with oral consumption of curcumin are poor water solubility, limited gastrointestinal absorption, rapid metabolism and elimination. The absorption rate and bioavailability of curcumin is reported to be enhanced when consumed with black pepper (*Piper nigrum).* The efficiency of curcumin with piperine as an adjuvant was found to be more pronounced in mitigating benzo(a) pyrene induced oxidative insult and clastogenicity in mice models (Sehgal *et al.,* 2012).

**2.4.5. Cardioprotective and Hepatoprotective**: The protective effects of Turmeric on the cardiovascular system include lowering cholesterol and triglyceride levels, decreasing susceptibility of LDL to lipid peroxidation, and inhibiting platelet aggregation, thus preventing atherosclerosis. A recent study has shown the potential of *Curcuma longa* aqueous extracts to significantly reduce hyperlipidemia, stabilize cardiac biochemical markers and prevent myocardial injury in hypercholesterolaemic albino rats (Ekeigwe *et al.*, 2019). Several experimental and meta-analysis studies have concluded that curcumin supplementation has favourable effects on metabolic markers and anthropometric parameters in patients with non-alcoholic fatty liver disease. A meta-analysis study concluded that curcumin supplementation is effective in reduction of alanine transaminase (ALT), aspartate transaminase (AST), serum total cholesterol (TC), low density lipoprotein (LDL), fasting blood sugar, serum insulin and waist circumference in patients with non-alcoholic fatty disease, but does not result in reduction of serum triglycerides, high density lipoprotein (HDL), HbA1c, body weight and body mass index (Jalali *et al.,* 2020).

**2.4.6. Immunomodulatory**: The immunomodulatory activity of *Curcuma longa* has been reported in many pre-clinical and clinical studies. The immunomodulation by curcumin is attributed to its effect on the immune cells and the mediators involved in the immune response, such as various T-lymphocyte subsets, dendritic cells, and different inflammatory cytokines (Momtazi-Borojeni *et al.,* 2018; Cantanzaro *et al.,* 2018). Curcumin has been reported to modulate defective immune cells and pro-inflammatory cytokines in systemic lupus erythematosus patients as well as favorably modulate the imbalance in the TH17/Treg ratio observed in such patients (Momtazi- Borojeni *et al.,* 2018). An experimental study in animal models has reported the potential of curcumin to ameliorate ischemia-induced skeletal muscle injury through immunomodulation, suggesting its use for the treatment of peripheral arterial disease (Liu *et al.,* 2016).

**2.4.7 Hypotensive**: The potential of curcumin in regulation of cerebral microcirculatory function and hypertension has been reported in male albino rats. Curcumin treated hypertensive rats have been shown to result in significant reduction of blood pressure, increased blood perfusion, and efficient opening of capillaries (Xia *et al.,* 2016).

**2.4.8. Neuroprotective**: Turmeric has long been known to slow the progression of Alzheimer's disease by removing amyloid-β plaques from the brain. Several *in vivo* and *in vitro* studies support the potential of curcumin in modification of Alzheimer's disease pathology by numerous mechanisms, including inhibiting the formation and promoting the disaggregation of amyloid-β plaques, modification of microglial activity and inhibition of acetylcholinesterase (Tang and Taghibiglou, 2017). Various reports document the beneficial effects of *Curcuma* in dementia and brain aging, attributed to its anti-inflammatory, antioxidant, and antiapoptotic pharmacological properties (Ghosh *et al.,* 2015; Flores, 2017). An experimental study on aged mice, post-abdominal surgery, has shown the potential of curcumin in amelioration of post-operative cognitive dysfunction commonly associated with elderly patients undergoing surgery (Wu *et al.*, 2017). The study suggests that curcumin prevents cognitive impairment via multiple targets, including an increase in the activity of antioxidant enzymes, activation of brain-derived neurotrophic factor-signalling, and neutralization of cholinergic dysfunction.

**2.4.9 Anticancer**: *Curcuma longa* is known to aid in cancer treatment and prevention through induction of apoptosis. Pre-clinical trials involving rats and mice as well as in vitro studies utilizing human cell lines, have demonstrated the potential of curcumin to inhibit carcinogenesis at three stages: tumour promotion, angiogenesis and tumour growth (Labban, 2014). Several *in vitro* as well as *in vivo* studies have demonstrated the potential of curcumin in inhibition of growth of cells from various organs including breast, brain, blood, liver, pancreatic, colon, prostate, ovary and skin cancers (Shao *et* al. 2002; Anand *et al.*, 2008; Labban, 2014; Kunnumakkera *et al.*, 2017; Frassova and Ruda-Kucerova, 2017; Song *et al*., 2019; Tomeh *et al*,. 2019). Curcumin is also known to reduce the side effects of cytotoxic drugs in cancer patients and exerts beneficial effects on cancer treatment associated neurotoxicity, cardiotoxicity, nephrotoxicity and haematotoxicity (Willenbacher *et al.*, 2019). Curcumin has shown promising results in numerous phase I-II clinical trials and the anticancer activity is reported to occur via modulation of multiple signalling pathways in cancer cells (Willenbacher *et al.,* 2019).

**2.5. Phyllanthus emblica L. (Family: Phyllanthaceae)**

**2.5.1. Plant part used**: Mainly fruits, leaves, flowers, bark

*Phyllanthus emblica* (commonly called as Indian gooseberry, Emblic Myrobalan, Amla), is a small to medium-sized deciduous tree with feathery drooping foliage, crooked trunk and spreading branches. The fruit is a fleshy, smooth, globose drupe, light greenish-yellow, with 6 vertical stripes or furrows. It is known to possess numerous therapeutic properties including antipyretic, analgesic, antitussive, adaptogen, anti-atherogenic, antioxidant, anti-carcinogenic, anti-inflammatory, anti-atherosclerotic, anti-anaemic, cardioprotective, gastroprotective, hepatoprotective, nephroprotective, neuroprotective and immunomodulator.

**2.5.2. Traditional Uses:** Amla fruits are acrid, cooling, refrigerant, astringent, diuretic and laxative. The raw fruits are aperient, while dried fruits are useful in haemorrhage, diarrhoea, dysentery, anaemia, jaundice and dyspepsia. The fruit is an excellent source of vitamin C (70-72 %) that is more easily assimilated in the human body than the synthetic vitamin C. It enhances food absorption, balances stomach acid, fortifies the liver, nourishes the brain and mental functioning, supports the heart and blood circulation, strengthens the lungs, acts as an antioxidant eliminating free radicals, acts as a body coolant, detoxifies blood, strengthens vision, reduces macular degeneration, increases skin health, promotes healthier bones, teeth, nails, hair, enhances vitality, immunity and augments intellect. The plant is a powerful *Rasayana* (rejuvenator) drug in Ayurveda that balances both *pitta and vata* and has a unique natural balance of five tastes (sweet, sour, pungent, bitter and astringent) in the fruit. It delays degenerative as well as senescence processes and is effective against diverse ailments like hypertension, neurological disorders, colitis, gastritis, scurvy, ophthalmic problems, diabetes, fever, asthma, hepatic disorders and cancer (Gaire and Subed, 2015; Yadav *et al*., 2017).

**2.5.3. Antioxidant and Cardioprotective**: The potent antioxidant properties of Amla fruit extract are attributed to the presence of abundant phenolic components, especially tannins (gallic acid, ellagic acid, corilagin, pyrogallol, chebulagic acid) and flavonoids (quercetin, rutin). Many clinical and animal studies have demonstrated its potential in the treatment of dyslipidaemia, by bringing about a significant reduction in Total Cholesterol, LDL, Triglycerides, VLDL as well as a significant increase in HDL (Antony *et al.,* 2008; Kumar and Kalaivani, 2011). A recent randomized, double-blind, placebo controlled clinical trial in dyslipidaemic patients has shown that administration of amla extracts results in significant reduction of Total Cholesterol as well as Triglycerides, lipid ratios and atherogenic index of the plasma (AIP). The study also concludes that in contrast to the conventional drug (statins), Amla fruit extracts can reduce cholesterol levels without any concomitant reduction of Coenzyme Q10 (Upadya *et al*., 2019).

**2.5.4. Hepatoprotective**: Amla is a potent *Rasayana* in Ayurveda for hepatic disorders. The hepatoprotective properties of *Phyllanthus emblica* fruits in amelioration of the toxic effects of hepatotoxic agents like ethanol, paracetamol, carbon tetrachloride, heavy metals, antitubercular drugs as well as amelioration of hepatotoxicity resulting from iron overload have been reported in many experimental studies (Thilakchand *et al.*, 2013). A recent study on high fat diet-induced non-alcoholic fatty liver disease in rats shows that the water extract of *Phyllanthus emblica* fruits significantly decreases body weight, peritoneal fat and epididymal fat, enhances the antioxidant enzyme activities, and improves steatosis through elevating adiponectin in adipocytes and PPAR-α (Peroxisome proliferator-activated receptors-alpha) as well as lowering transcription factor SREBP-1c (Sterol regulatory element-binding protein-1c) in the liver of rats (Huang *et al.*, 2017).

**2.5.5. Antidiabetic**: The fruits of *Phyllanthus emblica* and/or its constituents including gallic acid, gallotannin, ellagic acid and corilagin exhibit anti-diabetic effects through their antioxidant and free radical scavenging properties. Amla has been reported to prevent/reduce hyperglycaemia, cardiac complications, diabetic nephropathy, neuropathy, cataractogenesis and protein wasting (D'souza *et al.*, 2014).

**2.5.6. Neuroprotective**: A recent study on animal models has shown significant potential of the extract of unripe fruits of *Phyllanthus emblica* in cognitive enhancement by increase in the levels of brain antioxidant enzymes and decreased levels of thiobarbituric acid reactive substances and acetylcholinesterase activity in rat brain tissue homogenates (Uddin *et al.*, 2016).

**2.5.7. Anticancer**: Several experimental studies, both *in vitro* and *in vivo*, have demonstrated potent tumour repressive properties of *Phyllanthus emblica* fruit extracts against a number of cancer types -breast cancer, colon, cervical, and ovarian cancer as well as leukaemia (Baliga and Dsouza, 2011; Verma et al., 2012; De *et al.*, 2013; Zhao *et al.*, 2015). The flavonoid quercetin has been demonstrated to attenuate tumour growth in several animal models including pancreatic cancer (Angst *et al.*, 2013). The rich amounts of polyphenols and hydrolysable tannin present in amla

extracts are likely to act in synergy to efficiently quench free radicals and impart antiproliferative effects (Zhao *et al.*, 2015).

**2.5.8. Antimicrobial**: *Phyllanthus emblica* fruit and leaf extracts have shown effective antimicrobial properties against many bacteria, viruses and fungi including *Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus, Bacillus cereus, Bacillus subtilis, Vibrio cholera, Salmonella typhi, Salmonella paratyphi A&B, Proteus vulgaris, Enterococcus faecalis, Streptococcus species, Candida albicans,* several *Aspergillus species*, Coxsackle virus, Herpes Simplex viruses, Human immunodeficiency virus, Human papilloma virus and Influenza A virus (Khurana *et al.,* 2019). In a short-term study involving twenty healthy young adults, the use of sugar-free chewing gum containing the fruit extract of amla, was found to be effective in altering the oral microbiome and decreasing the salivary levels of *Streptococcus mutans* and *Porphyromonas gingivalis* (Gao *et al.,* 2018).

**2.5.9. Antiaging**: Amla is an important ingredient of Indian Ayurvedic drug, *Amalaki Rasayana*, and Ayurvedic polyherbal formulations, *Triphala* and *Chyawanprash*. In a study carried out by Guruprasad *et al.* (2017), it was found that *Amalaki Rasayana* administered to healthy aged volunteers (45-60 years), results in a significant increase in telomerase activity in peripheral mononuclear cells of blood samples of the volunteers at 90$^{th}$ day of administration. *Amalaki Rasayana* (prepared from the fruits of *Phyllanthus emblica*) is known to possess potent antioxidant properties, which may be responsible for increase of telomerase activity and maintenance of telomere length. The study suggests the role of *Amalaki Rasayana* in delaying the onset of ageing as decrease in telomerase activity and telomere length have been associated with ageing process and replicative senescence.

### *2.6. Tinospora cordifolia* (Willd.) Miers (Family: Menispermaceae)

#### 2.6.1. Plant parts used: Stems, leaves

*Tinospora cordifolia* (commonly called as Indian Tinospora, Giloya, Guduchi, Amrita), is a large, glabrous, deciduous climbing shrub. The stems are about 6 cm in diameter, with light grey papery bark. The leaves are broadly ovate or orbicular, deeply heart shaped at the base. The pharmaceutical effects of the stems, leaves, and roots of *Tinospora cordifolia* are attributed to the major phytoconstituents including alkaloids (Tinosporine, magnoflorine, berberine, palmatine, choline, Tetrahydropalmatine), terpenoids (tinocordin, tinosponone, tinosporaside, tinocordioside, cordioside, cordifolisides A to E, tinocordifolioside) ; and steroids (ecdysterone, β- sitosterol).

**2.6.2. Traditional Uses:** *Tinospora cordifolia* is widely used as a *Rasayana* drug in Ayurvedic system of medicine for its adaptogenic, immune-stimulating and rejuvenative properties. It is a powerful antioxidant, antidiabetic, anti-tumour, antipyretic, anti-arthritic, anti-allergic, anti-hyperlipidaemic, antimalarial, anti-inflammatory, antineoplastic, hepatoprotective, osteoprotective, neuroprotective and immunomodulator. The drug is prescribed for intermittent fevers, malaria, liver damage, respiratory tract infections, tuberculosis, gout, diabetes, jaundice, dyspepsia, urinary problems, AIDS, chronic diarrhoea, dysentery and skin diseases. It is also useful in the treatment of heart diseases, leprosy, helminthiasis, osteoporosis, rheumatoid arthritis, and for strengthening the immune system. The stem is bitter, stomachic, stimulates bile secretion, lowers serum cholesterol and cures urinary, liver, respiratory and skin diseases. The plant is also a source of essential micronutrients like copper, calcium, phosphorus, iron, zinc and manganese (Rahal *et al.*, 2014). Ethnobotanical uses also include eye disorders, antidote to snakebite, and scorpion stings.

**2.6.3. Analgesic**, **Antipyretic and Anti-inflammatory:** The analgesic, antipyretic and anti-inflammatory properties have been experimentally validated in albino mice models (Hussain *et al.*, 2015). The methanolic extract of *Tinospora cordifolia* exhibited therapeutic effects in different models of pain, inflammation and pyrexia in a dose-dependent manner. The alkaloid berberine has been shown to improve vascular health by reduction of endothelial inflammation, even in patients already affected by cardiovascular diseases (Cicero and Baggioni, 2016).

**2.6.4. Antimicrobial and Immunomodulator**: The immune-stimulatory and antimicrobial properties of *Tinospora cordifolia* have been reported against a variety of microorganisms, including *Mycobacterium tuberculosis* (Gupta *et al.*, 2016), *Salmonella typhimurium* (Alsuhaibani and Khan, 2017) and *Streptococcus mutans* (Agrawal *et al.*, 2019*).* Treatment with methanolic extract of *Tinospora cordifolia* has been shown to result in an increased survival and reduced bacterial load in *Salmonella typhimurium*-infected mice. It is also reported to have reduced the liver inflammation (reduction in the levels of Alanine transaminase (ALT) and Aspartate transaminase (AST) enzymes) and rescued the levels of antioxidant enzymes in *Salmonella typhimurium*-infected mice (Alsuhaibani and Khan, 2017). The leaf extracts of *Tinospora cordifolia* have also exhibited *in vitro* anti-HIV activity and may have the potential for protection and treatment against various viral diseases in human beings (Estari *et al*., 2012). Many experimental studies have shown the extracts of *Tinospora cordifolia* and its compounds to modulate phagocytosis, activate macrophages and various cytokines (Salkar *et al.,* 2017). The aqueous extract of *Tinospora cordifolia* has been found to enhance phagocytic and pinocytic activity of murine macrophages *in vitro,* supporting the immunomodulatory potential of the plant (More and Pai, 2017).

**2.6.5. Antidiabetic**: Several studies validating the therapeutic potential of this plant for treatment of endocrine and metabolic disorders have been documented. (Kinker and Gopal, 2015; Chakraborty, 2016; Dhama et al., 2017). The extract of *Tinospora cordifolia* has shown significant anti-diabetic activity in streptozocin-induced diabetic rats (Pathak *et al.*, 2016) and has been found to possess β cell regenerative potential (Rajalakshmi and Anita, 2016).

**2.6.6. Hepatoprotective**: The hepatoprotective potential of *Tinospora cordifolia* as single or polyherbal formulation is extensively documented (Dhama *et al*., 2017). A study on healthy, asymptomatic moderate alcoholic volunteers, has shown significant hepatoprotective effects of *Tinospora cordifolia.* It has been shown to reverse the urinary excretion of vitamins, associated with alcoholism, and amelioration of the effect of alcohol on vitamin metabolism in alcoholic men by decreasing oxidative stress, increasing intestinal absorption, regenerating liver and modulation of lipid metabolism (Sharma and Dabur, 2016).

**2.6.7. Anticancer**: Several experimental studies in human cancer cells and animal models have reported cytotoxic effects of *Tinospora cordifolia* and its phytochemicals (like palmatine and berberine) via multiple mechanisms including induction of DNA damage, apoptosis, antioxidant activity, inhibition of topoisomerase, Nf-kB, COX-2 and Nrf2 (Jagetia, 2019). The pro-apoptotic effects of chloroform fraction of *Tinospora cordifolia* on breast cancer cells have been attributed to the compounds rutin and quercetin (Ansari et al., 2017). Significant antioxidant activity of the ethanolic extract of *Tinospora cordifolia* has been reported on Diethylnitrosamine induced liver cancer in male Wister albino rats. The extract has been shown to have reverted the levels of lipid peroxidation as well as enzymic and nonenzymic antioxidants to near normal in cancer affected animals (Jayaprakash *et al,.* 2015).

**2.6.8. Neuroprotective**: Recent studies have shown the neuroprotective potential of *Tinospora cordifolia* by suppression of neuroinflammation and protection of dopaminergic neurons in mouse models with Parkinson's disease (Kosaraju *et al.*, 2014; *Birla et al*., 2019). An analysis of the effects of *Tinospora cordifolia* (Guduchi) churna in the model organism, *Drosophila melanogaster* has revealed that the life span of *Drosophila* is enhanced in both parent and F1 generation (Pathak *et al.,* 2016), corroborating the rejuvenation effects of *Tinospora cordifolia*.

**2.7. Withania somnifera (L.) Dunal. (Family: Solanaceae)**

**2.7.1 Plant part used**: Dried roots

*Withania somnifera* (commonly called as Indian winter cherry, Indian ginseng or Ashwagandha), is an erect, evergreen, tomentose shrub that grows up to two feet in height. The roots are stout, fleshy and whitish brown. The dried roots are pharmacologically important and the main phytochemicals include alkaloids (withanine, withananine,

somniferine, somniferinine, somninine, nicotine, visamine); Steroidal lactones (Withaferine-A, withanone, withanolides) Steroids (cholesterol, β-sitosterol, stigmasterol, diosgenin); Flavonoids (kaempferol, quercitin) and saponins.

**2.7.2. Traditional Uses**: *Withania somnifera* is known to possess numerous therapeutic properties including an adaptogen, antioxidant, anticancer, anti-epileptic, neuroprotective, anti-stress, antimicrobial, anti-inflammatory, anti-arthritic, hypoglycaemic, hypolipidaemic, anticoagulant and immunomodulant. It is an important immune-boosting, *Rasayana* drug in Ayurveda used as a general tonic to rejuvenate the body, relieve mental and physical fatigue and increase longevity. (Singh *et al*., 2011; Dar *et al.,* 2015). Ashwagandha has been compared with *Panax ginseng* (Chinese or Korean ginseng) in its adaptogenic properties and therefore popularly known as Indian ginseng. The drug is prescribed as an analgesic for musculoskeletal disorders like arthritis and rheumatism, as well as a nervine tonic for neurodegenerative disorders like Parkinson's disease, Alzheimer's disease, epilepsy, nervous exhaustion, anxiety, multiple sclerosis and senile dementia. It has long been used as an aphrodisiac and is useful in the treatment of bronchitis, asthma, cystic fibrosis, hypertension, cancer, neoplasia, diabetes, ulcers, debility from old age, irritable bowel syndrome, dropsy, impotence, sexual and genital weakness, and spermatorrhoea. A clinical study on 46 oligospermic males has revealed the potential role of root extract of *Withania somnifera* in the treatment of male infertility, by increase in the sperm count, semen volume and serum hormone levels (Ambiye *et al.,* 2013).

**2.7.3. Anti-inflammatory**, **anti-arthritic and antioxidant**: An experimental study has revealed potent anti-inflammatory and anti-arthritic effects of the aqueous extract of *Withania somnifera* roots in collagen- induced arthritic rats. Oral administration of the extracts at a dose of 300mg/ kg.wt. attenuated the levels of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) and oxidative stress markers in arthritic rats, resulting in a significant reduction in bone/ cartilage damage (Khan *et al.,* 2019). In a clinical study, the efficacy and tolerability of *Withania somnifera* was investigated in sixty patients with knee joint pain and discomfort. Significant reduction in pain, stiffness and disability was observed at the end of twelve weeks, as assessed by Visual Analogue Scale. The therapeutic response was found to be dose-dependent and free of any gastrointestinal disturbances (Ramakanth *et al.,* 2016). The anti-inflammatory and antioxidant properties of *Withania somnifera* and its components Withaferin- A and Withanolide- A have been demonstrated in murine immortalized BV-2 microglial cells, by inhibition of lipopolysaccharide- induced nitric oxide and reactive oxygen species production in microglial cells, downregulation of NF-kB pathway and upregulation of Nrf2 pathway (Sun *et al.,* 2016). The antiplatelet, anticoagulant, and profibrinolytic activities of Withaferin-A have been reported by Ku and Bae (2014) in human umbilical vein endothelial cells.

**2.7.4. Neuroprotective and Anti-stress**: Many experimental studies in animal models and human clinical trials have been documented substantiating the neuroprotective, anxiolytic effects and improved cognitive functions of *Withania somnifera* (Bhattacharya and Muruganandam, 2003; Pratte, 2014; Farooqui *et al*., 2018; Lopresti *et al*., 2019; Birla *et al*., 2019). A clinical study has demonstrated significant improvement in both immediate and general memory after treatment with Ashwagandha root extract in adults with mild cognitive impairment. The treatment group also demonstrated improvement in executive function, attention and information processing speed (Choudhary *et al.,* 2017). The efficacy of *Withania somnifera* root extract as a neuroprotective agent has been shown in cultured model neurons (human neuroblastoma cells) exposed to an *in vitro* injury system designed to mimic mild traumatic brain injury. Treatment with the extract resulted in an increased length of neurites and reduced cell death, indicating its potential to improve neuronal connectivity and enhance neuronal survival after injury (Saykally *et al.,* 2017). *Withania somnifera* root extract has been shown to reverse β-amyloid and HIV induced neuro-pathogenesis in human neuronal cells (Kurapati *et al.,* 2013). The neuroprotective role of *Withania somnifera* root extract in maneb-paraquat induced mouse model of Parkinsonism has been reported to counteract oxidative stress and improve behavioural, anatomical and biochemical deformities (Prakash *et al.,* 2013). Administration of the root extract of *Withania somnifera* has been shown to ameliorate the levels of Bisphenol A (BPA) induced oxidative stress and cognitive dysfunction in Swiss albino mice. It has been shown to regulate the level of endogenous antioxidants and provide neuroprotection

against oxidative damage and memory impairment induced by BPA, a potent endocrine disruptor (Birla *et al.*, 2019). The anxiolytic potential of *Withania somnifera* has been shown in a randomized, double-blind, placebo-controlled trial of mildly anxious, 60 healthy adults by Lopresti *et al.* (2019), via its moderating effects on the hypothalamus-pituitary-adrenal axis. The supplementation of Ashwagandha extract has been shown to result in a reduction of cortisol and dehydroepiandrosterone-sulphate as well as increased testosterone in men. The protective effects of *Withania somnifera* extracts and/or its major constituents are known to be mediated by restoration of mitochondrial and endothelial function, mitigation of apoptosis, inflammation and oxidative stress mechanisms (Dar and Ahmad, 2020).

**2.7.5. Antibacterial and Antiulcer**: Antiulcer and antioxidant potential of *Withania* in reducing stress-induced gastric ulcer is reported in animal models (Bhatnagar *et al.,* 2005). Antibacterial activity of *Withania somnifera* has been reported against Gram-positive isolates from pus samples, including pathogens such as methicillin resistant *Staphylococcus aureus* and Vancomycin-resistant *Enterococcus* species (Bisht and Rawat, 2014).

**2.7.6. Anticancer**: Numerous studies have shown the anticancer efficacy of *Withania somnifera* in human cancer cell lines and in murine models. Withaferine-A, is a potent inhibitor of angiogenesis and protective against lung, prostate, breast, colon, renal, pancreatic cancer and leukaemia. (Hahm et al., 2013; Kapoor, 2014; Palliyaguru et al., 2016; Lee and Choi, 2016; Dutta et al., 2019).

**2.7.7. Thyroid function**: The efficacy and safety of *Withania somnifera* root extract has been studied in subclinical hypothyroid patients and eight weeks of treatment with Ashwagandha improved serum Thyroid stimulating hormone (TSH), serum triiodothyronine (T3), and thyroxine (T4) levels, indicating its potential benefits in thyroid dysfunction. (Sharma *et al*., 2018).

## 3. Future Prospects and Conclusions

With the progression of non-communicable diseases due to unhealthy lifestyle and mental stress, as well as an increase in the emergence of multi-drug resistant pathogens including microbes with pandemic potential, herbal drugs can prove to be natural therapeutic agents to enhance immunity, delay senescence processes and provide preventive, curative health care. The concept of *Rasayana* therapy is unique to Ayurveda and the plants used as *Rasayana* can regulate multiple biological events within the body. They are known to possess a wide spectrum of pharmacological properties, including antioxidant, anti-inflammatory, cardioprotective, neuroprotective, hepatoprotective, detoxifiers, antimicrobials, anticarcinogens and immunomodulators. The traditional uses of these plants have been validated by many experimental studies on animal models, human cell lines and clinical trials. *Curcuma longa, Phyllanthus emblica* and *Tinospora cordifolia* have proved to be powerful anti-inflammatory agents, antioxidants and immunomodulators that have exhibited significant clinical potential against endocrine and metabolic disorders. *Bacopa monnieri* and *Centella asiatica* are potent nootropics and have shown significant clinical potential for neurological health and attenuation of dementia, Parkinson's, Alzheimer's, epilepsy and other neurodegenerative diseases. *Tinospora cordifolia* and *Phyllanthus emblica* are hepatoprotective and powerful antimicrobials that can provide protection against bacterial and viral infections. *Curcuma longa*, *Withania somnifera*, *Centella asiatica* and *Phyllanthus emblica* have potent anticancer properties. Adaptogens like *Asparagus racemosus* and *Withania somnifera* are anxiolytic, neuroprotective and can restore endocrine, nervous and the immune system. Inclusion of such *Rasayana* herbs in our lifestyle can prevent chronic inflammation, strenghthen the immune system, enhance mental and physical performance, restore healthy neuroendocrine functions and protect against stress-induced damage. They can therefore, play a significant role in the management of diseases affecting longevity, including hyperlipidaemia, atherosclerosis, diabetes mellitus, hepatic disorders, asthma, cognitive decline and neurodegenerative disorders associated with the ageing process. The traditional wisdom of Ayurveda needs to be integrated with scientific advances based on experimental and clinical research for the development of commercially viable phytomedicines and synergistic polyherbal formulations to enhance immunity and to provide prophylactic and curative treatment. However, safety,

quality, efficacy, optimized dosage, lack of good manufacturing practices as well as inadequate large scale clinical trials, still remain major challenges in the promotion of herbal drugs.

***Author's contribution:*** *Bharti Chaudhry (Associate Professor) wrote Conceptualization, Reviewing and final Editing and also corresponding author.*

**Conflict of Interest:** The author declares that there is no conflict of interest.

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