

## IMMUNOSTIMULANT EFFECTS OF NATURAL SUBSTANCES: PROSPECTS FOR USE IN THE ELDERLY

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### INTRODUCTION

Ever since Antiquity, the therapeutic properties of many plants have been used as alternative or complementary treatments for different types of pathologies. Plants have been, and continue to be, an object of continuing study in the search for new substances with therapeutic activities. Starting from their traditional use through phytochemical and biological screening, research, in time, has endeavoured to obtain positive, concrete and safe therapeutic results.

The use of herbs in the treatment of diseases, a very ancient tradition and was of greatest interest between the 16th and 18th centuries, when we have evidence, through important experiments and discoveries, of a more specialized botanical culture. Furthermore, thanks to chemistry, in that period, the secrets of the constitution of plants began to be penetrated, extracting and isolating, although not in completely pure form, some of their active ingredients, first of all salicene, isolated from willow bark, which Hippocrates himself, the father of modern medicine, extracting its sap, had identified as having febrifuge and analgesic properties, although unaware of its active ingredient.

The therapeutic activity of plants therefore depends on their chemical constituents and these constituents, although having a very similar chemical structure, can give plants different pharmacological activities.(1)

Herbal medicines, according to the European laws currently in force, are drugs of botanical origin, medicinal products having exclusively medicinal plants or preparations of medicinal plants as their pharmaceutically active ingredients.(2)

These preparations may be made up of the pulverized drug, i.e. the part of the plant that contains the active ingredients or, as is

the case more frequently, from standardized extracts or Galenic preparations of the drug. Standardization is fundamental as it gives the botanical drug constant characteristics of qualitative and quantitative composition, therefore it has a constant and reproducible therapeutic effect.

Before being put on the market, herbal medicines are subject to pharmacological, toxicological and clinical studies that prove their effectiveness and safety of use. Today, the globalization of markets and the growing interest of multinational corporations are increasingly investing the herbalist sector, consequently leading to increased use of the plants, or better, of the botanical drugs, understood as leading elements of natural medicine, alternative medicine and dietary supplements.

The rediscovery of natural substances is a social fact that increasingly involves both the producer and the consumer; suffice it to say that about 80% of the world's population prefer using natural medicine.(1)

### BOOSTING THE IMMUNE SYSTEM

The term 'immunostimulation' indicates a preventive or therapeutic approach which has the aim of boosting the stimulation of the humoral and cellular immune system. As the organism is in continuous contact with the external environment and is attacked by exogenous agents, some of which are also pathogens, such as bacteria, viruses, fungi and protozoa, the immune system is continuously solicited to protect the integrity of our body and defend it, as well as to provide for the elimination of the waste products of the metabolism.(5)

Numerous studies have shown that the immune responses can be boosted by a series of factors of a different nature and origin. Immunostimulants or immune boosters, are substances that act mainly through non-specific stimulation of the mechanisms of immune defence. These include cytokines, such as interleukin-2 and interferon, widely used clinically in different types of pathologies. As far as medicinal plants are concerned, as early as 1980 Drews proposed the use of immunostimulants phytotherapeutic ingredients as an alternative possibility to therapy with antibiotics and the prophylaxis of infections, especially when the defence mechanisms of the organism have to be activated in conditions in which the immune system is weakened. Chronic stress and depression represent some of the conditions that provoke a lowering of the immune defences.(4)

Another important condition in which there is a variation, often characterized by a reduction, of the immune defences, is ageing, a period in life when natural immunostimulant agents can represent an effective aid to prevent some age-related pathologies.

### AGEING AND THE IMMUNE SYSTEM

Gerontology and Evolutionary Biology consider ageing as a continuous, universal, progressive, intrinsic and detrimental process, which gradually reduces the capacity of adaptation of the organism to environmental stimuli, therefore increasing the proba-

bility of falling ill. Ageing can therefore be outlined as a process which converts healthy individuals into fragile ones, with the reduction of the reserves in many of the organism's systems, and with an exponential increase in the vulnerability to many illnesses and to death. Over time, very many studies have focused on identifying the biological events to which the progressive deterioration which takes place at the same time as ageing could be attributed. Ageing can be considered a multi-factor process, the result of the interaction between genetic and environmental factors and life style. Although it is not yet possible to define exactly to what extent the structural and functional modifications of the organism, with reference to senescence, must be related to genetic constitution and to what extent to exogenous factors of an environmental nature, the latter certainly have greater importance and strategies based on them have to be adopted for ageing well. A balanced diet, regular physical exercise and keeping the organism under control through periodic tests definitely represent the main factors at the basis of ageing in good health.(5)

The main role of defence of the organism against pathogenic agents is carried out by the immune system which implements and regulates all those processes of recognizing antigens, recognition of responses of various types - specific or specific - against extraneous antigens in order to neutralize and eliminate them.

It is now widely confirmed that at an advanced age the immune system is progressively reshaped (immune senescence) concerning both specific and non-specific immunity. Not all the components of the immune system are concerned in the same way by age-dependent alterations, as some immunological functions are considerably compromised whilst others maintain an efficient action even in the elderly. Both in man and in animals, cellular immunity mediated by T-lymphocytes represents the component of the immune system that is most sensitive to the ageing process. The decline of the function of the T-cells is closely correlated with the anatomical and functional involution that appears at the level of the thymus gland after puberty, which is followed by a reduced proportion of thymus hormones which control the maturation and differentiation of T-lymphocytes.

The altered function of cellular populations consequently causes an altered regulation of inflammatory processes, as well as of the capacity of immune response in discriminating between extraneous or endogenous molecules.(6)

As far as the alteration of the regulation of the inflammatory processes is concerned, with ageing the levels of pro-inflammatory cytokines increase and, independently of the presence of pathologies, many studies have documented the increase of concentrations in the serum of elderly individuals with respect to young individuals.

In the elderly subject, the altered capacity of regulating the immunological reactions causes a tendency to produce more self-antibodies with a consequent appearance of arthritis, psoriasis and other self-immune pathologies.

Furthermore, it has now been established that the immunological functions are the result of a complex cooperation between different cellular typologies, and within the same lymphoid system, between different sub-populations of lymphocytes. Experimental evidence has shown that the thymus has an important regulating action on these cellular typologies; and further experimentation has shown that thymic involution is an age-dependent type of phenomenon. Thymic involution is not described as an intrinsic and irreversible phenomenon but depends on micro-environmental factors and in the first place on the neuroendocrine modifications that accompany ageing.

This evidence is based on the fact that the thymic function, as well as that of various leukocyte populations, may be at least partially corrected by appropriate treatment.

It is for this reason that it is very important for the elderly to protect and keep their immune systems healthy, and a possible aid in this context could come from immunostimulant natural substances, in order to boost and prevent the reduction of immune responses associated with age.(7)

### IMMUNOSTIMULANT ACTION OF NATURAL SUBSTANCES

Ingredients with capacities of stimulating the immune system have been described in many types of natural substances. Immunostimulation through the use of natural substances has the aim of treating infectious diseases, mixed diseases, viral infections, syndromes related with being bedridden, chronic infectious diseases, persistent infections and their immunopathogenic consequences and resistant bacterial infections. Another field of application for immunostimulants is the adjuvant use in the treatment of cancer.

The biological activity of immunostimulants can address both the specific and the aspecific immune system. Non-specific and non-antigen dependent immunostimulants do not act at the level of the cells of the immune memory; in addition, considering that their pharmacological action decreases relatively quickly, they must be administered cyclically.

The aspecific immune system is mainly made up of phagocytes, granulocytes, macrophages, monocytes, Natural Killer cells and various soluble factors, such as the complement system and cytokines, and not being antigen-specific, it does not have a memory and is involved in the defence mechanisms that are activated immediately after infection.(3) Differently, the specific immune system requires longer periods of time to reach a sufficiently high title.

The immunostimulant activities of some of the most important medicinal plants are shown here below.

### ACEROLA

Acerola is a plant originating in Central America and the Caribbean. Its immunostimulant action is due to its high content of Vitamin C. The main function of Vitamin C is its part in the reduction of metals, like copper and iron which, in turn, act as co-factors in hydroxylation reactions, in which

molecular oxygen takes part. Hydroxylation reactions are those catalyzed by dioxygenase, in the case of the intervention of iron by synthesis of the connective tissues, of the metabolism of tyrosine and the synthesis of carnitine, whilst those catalyzed by monooxygenase include the intervention of copper, in the synthesis of catecholamines and the synthesis of peptide hormones. Another important role of ascorbate is linked to its antioxidant effect which leads to the elimination of free radicals, preventing oxidative cellular damage.(8)

The other elements that take part in the protection of the organism react with ascorbate, forming the ascorbyl radical, capable of reacting directly with the reactive radicals of oxygen.

### ASTRAGALUS

Astragalus is a leguminous plant originally from Asia, which has been used in China for thousands of years for medicinal purposes. The long, yellow and fibrous root is used. Astragalus has primarily an immunostimulant activity: it reinvigorates, heals and stimulates the immune system. This system is certainly one of the most recommended in the case of a damaged or depressed immune system. It also has anti-bacterial, anti-inflammatory, tonic and diuretic properties. Some studies have also shown that astragalus helps the heart in the prevention against the Coxsackie B2 virus.(9)

### ECHINACEA

This plant, typical of North America, belongs to the family of Compositeae Tubiflora. Its name comes from the Greek, "echinos" which means hedgehog, recalled by the shape of the flowers placed in the centre, which are each protected by a stiff acuminate bract. The dry extract is obtained from the root.

In the organism, its immunostimulant

action appears with increased activity of the phagocytes of the immunocompetent cells, the macrophages and the white cells, and the consequent increase in the resistance by the organism to attack by pathogenic agents. Numerous clinical studies have shown that giving Echinacea to patients affects by a flu syndrome or pharyngitis, can reduce both the symptoms and the duration of the illness. Other studies have confirmed the efficacy of this plant in promoting phagocytosis by white cells, i.e. their capacity to incorporate and destroy germs, viruses, fungi and other foreign bodies, and the increase of these cells in the blood. In particular, Echinacea has been shown to be capable of accelerating the natural anti-viral response through an effect stimulating the production of cytokines, such as interleukin-7, essential to boost the activity of the T-helper lymphocytes against viruses of influenza, and the action of interferon-gamma. In vitro tests have also documented an increase of 20-40% of the mechanisms of phagocytosis and in vivo the proliferation of macrophages. Lastly, through the inhibition of the enzyme hyaluronidase, produced by bacteria to penetrate the mucous membranes of the organism and evade the blood circulation, Echinacea contributes to keeping the natural anti-infectious barriers, rep-

### ELEUTHEROCOCCUS

This is an adaptogen plant, of which the root is used. Its action is to boost the capacities of adaptation of the organism in situations of stress. Its active ingredients are eleutherosides, coumarine, triterpenes and isoflavones. In particular, the eleutherosides can be distinguished into adaptogen active ingredients: eleutherosides A,B,B1,C,D/E and oleanoligosides: eleutherosides I, K, L, M. The adaptogens can optimize the secretion of hormones. Taken regularly, Eleutherococcus reinforces and stimulates the immune system. Other active ingredients present are the glucoside Beta-sitosterol, the coumarinic glucoside of isofraxidine, ethylgalactoside, heterosides of syringasterol, derivatives of oleamic acid, polysaccharides, phenolic compounds such as coumarine, lignans and phenylpropanoic acids. Glucosides are compounds of a glucidic nature in which the free oxirid of the carbonic group of sugar is bonded, through a semi-acetalic bond, to the oxirid of another molecule of a different nature, i.e. not glucosidic, called aglycone.

There are also the terpenes, which can be said to represent perhaps the largest and most complex class of natural products. They are hydrocarbons, often of oxygenated skeleton compounds (alcohols or ketones) containing 10, 15, 20 or 30 atoms of carbon. The majority of these compounds are in the plants, but some of the more complex ones (squalane, lanosterol) are in animals. In terpenes, various functional groups are present, making classification difficult.(10) However, terpenes contain a characteristic carbonaceous skeleton: they appear to be formed of a variable number of units of isoprene (isopentane). As far as the isoflavonoids or Vitamin P are concerned, these are intensely coloured substances, which act in synergy with Vitamin C, boost its action, improve its absorption and preserve it from oxidation.(10)

Their action is mainly to reinforce the blood vessels, especially the capillaries, boost the immune defences and fight the action of free radicals.

### GINKGO BILOBA

The dry extract of Gingko Biloba and its leaves are characterized by a wealth of flavonoids and terpenes, which carry out important biological actions. Quercetin is the essential metabolite of the flavonoid fraction and has a considerable anti-phlogistic activity, due to the direct inhibition of multiple initial causes of inflammations. For example, it limits both the production and the release of histamine, and other allergic-inflammatory factors. According to a recent study, quercetin is an antioxidant that is present in some foods, with an important role on the immune system, to the extent of being able to play an adjuvant function and improving the efficacy of antitumour drugs. Research states that this natural mol-

ecule has a potential chemopreventive activity, namely that it has the capacity to block the process of transformation of a normal cell into a tumoural one, or to convert it if already in course.(9)

One of the systems that the body uses to free itself of pre-cancerous cells, which are generated at the start of the degenerative process, is programmed "cellular suicide" or apoptosis. In this way, the organism is freed of its irreversibly damaged cells to be able to guarantee the survival of the individual. Many new generation antitumour drugs act on the mechanisms that activate cellular apoptosis. Another study on this bioflavonoid has also highlighted neuroprotective properties of the antioxidant molecule, proving that the neurons exposed to quercetin resist damage far better than neurons which are not treated.(8) Researchers have exposed mouse neurons to quercetin or to Vitamin C, which are both antioxidant molecules. The cells were then exposed to hydrogen peroxide, a highly reactive radical, to imitate the type of oxidative cellular damage that is believed to occur in the case of Alzheimer's disease. The cells that had been treated with quercetin suffered significantly less damage than those treated with Vitamin C and those not treated with antioxidants.

#### LICORICE

The liquorice plant grows wild in the regions of the Mediterranean. Already known to ancient Chinese doctors, mentioned by Hippocrates as a remedy for coughing and found in stick form in the funeral accoutrements of Tutankhamen, liquorice takes its name from two Greek terms, "glykys" which means sweet and "rhiza" which means root. Its name of sweet root is due to the sweetish taste that allows it to be used in sweets or sweeteners for tisanes. Since the 1980s, the efficacy of the active ingredients in liquorice has been shown on various typologies of viral infections. The most important active ingredient of liquorice is glycyrrhizine which gives it an anti-inflammatory and anti-viral action and it is 50 times sweeter than saccharose. Glycyrrhizine or glycyrrhetic acid is the main constituent of liquorice, a triterpenic saponin, together with flavonoids and phytosterols.(9) Modern research is trying to obtain advantages from liquorice for new therapeutic prospects: the treatment of ulcers, chronic liver diseases, herpes and the prevention of serious self-immune diseases.

The other active ingredients present are: triterpenic saponins, starch, D-glucose, sugars, saccharose, amines, rubbers, waxes, volatile oil, a bitter ingredient, lignin, amino acids, flavonoids (liquiritin). The anti-inflammatory activity of glycyrrhetic acid is caused by the inhibition of two enzymes that catalyse the degradation of two cytoprotective prostaglandins (PGE and PG 12). Glycyrrhetic acid also inhibits 11-hydroxysteroid dehydrogenase which increases the percentage of corticoids in tissues with sodium retention, excretion of potassium and increased blood pressure. Recent studies conducted on animals have shown that the anti-viral effects can be indi-

rect and at least in part due to the stimulation of the production of interferon by the tumoural cells. When mouse tumoural cells are exposed to the influenza virus, 100% of the cells treated with glycyrrhizine survive, whilst those not treated die.(8) The transfer of the treated cells offered greater resistance to the infections of the Herpes simplex virus.

#### FERMENTED PAPAYA (FPP)

Papaya, the fruit of the so-called "melon tree" is increasingly sought after and appreciated. It is very rich in vitamins, minerals and amino acids. However, its most important active ingredient is papain, the enzyme that stimulates the digestion of proteins, so that it is an irreplaceable remedy after large and hasty meals. In addition, papaya can be of great help in the case of infections of the urinary tract, inflammations and problems of the joints.

Its percentage composition of micronutrients and otherwise, can be broken down as follows: 86,5% water, 12,8% carbohydrates, Vitamin E, Vitamin C, Vitamin A, riboflavin, niacin, thiamine, calcium, phosphorus and iron. Vitamin C is important for its antioxidant, anti-free radical and immune system stimulating properties.

Its content in the fruit of the papaya is equivalent to 84 mg/kg. Another important constituent of the papaya is α-tocopherol (Vitamin E). It has a protective value for multiple pathologies: cardiovascular, cutaneous, otorhinolaryngiatric and neoplastic pathologies. Vitamin E protects the cellular membranes from the processes of degradation (lipoperoxidation), with anti-oxidant and anti-free radical activities which the organism encounters with the advancing age.

All the parts of the plant contain a latex which contains enzymes, the so-called cystein-proteinas, belonging to the family of Class II chitinases. Of these, the main one is papain which appears as a grey powder, soluble in water and with a marked proteolytic action.

In addition, the shoots of papaya are rich in some types of flavonoids (1264 mg/kg), polyphenols which act favourably on the immune system thanks to their anti-oxidant and anti-free radical, anti-inflammatory, anti-platelet aggregating, anti-thrombotic and anti-allergic properties. They also inhibit the synthesis of numerous enzymes involved in the processes of tumoural genesis, such as lipoxygenases and cyclooxygenase, as well as representing a great reserve of vitamins.(8)

Fermented papaya has proven to be an excellent anti-oxidant, and an excellent nutraceutical adjuvant in various therapies, especially in those of the immunostimulant type. As a functional food, FPP stimulates the systems of adaptation of the oxydoreductive regulation and immunomodulation. FPP has a beneficial effect on the general functioning of the immune system, i.e. on the activation of macrophages. Research has shown how FPP stimulates the production of the superoxide anion radical in leukocytes and in macrophages; this radical is recognized as essential in the destruction of the invader micro-organisms through a

process of phagocytosis, known as oxidative explosion.

It has also been shown that a month of taking FPP orally leads to an increase in the production of Interferon-gamma, through which the immune system can better fight infections and disease.

#### ROYAL JELLY

Royal Jelly is produced by worker bees through their hypopharynx and mandibular salivary glands; it appears in a gelatinous form and is collected with non-metal tools and filtered to remove impurities. Its essential components are at least 66% water, followed by sugars (14% divided between glucose, fructose and sucrose), then proteins (13%), lipids (4.5%), and vitamins, especially B1, B2, B3, B5, B6, and, to a lesser degree, Vitamins A, B12, C, D and E.

Royal jelly also contains calcium, copper, iron, phosphorus, potassium, silicon and sulphur.

It is for this reason that it is particularly suitable for those who are in situations of stress or immunodepression. Royal jelly, thanks to the considerable presence of Vitamin B5, is a powerful "anti-ageing" agent: it delays the effects of ageing of the skin and also works well in some pathologies, such as against lupus erythematosus.(8) The most valuable component of royal jelly is, however, 10-hydroxydecanoic acid, which has anti-bacterial and antimicrobial activities. This highly important organic ingredients is present in the fresh jelly and reaches its greatest concentration during the phase of processing the royal jelly which takes place in the pharynx glands of the worker bees and decreases as the product ages. The immunomodulating activity of Royal Jelly mainly concerns the stimulation of the production of antibodies.(9) In the past few years, some studies on rats have shown that Royal Jelly has an anti-microbial effect on many species of bacteria, such as *Bacillus subtilis*, *Staphylococcus aureus*, *Streptococcus hemolyticus* and *Enterococcus*.

#### DOG ROSE

A shrub belonging to the family of the Rosaceae. The dog rose is one of the very many species of wild rose and is common throughout Europe (excluding the extreme northern regions), north Africa and western Asia. In Italy, it can be found (up to 1500 metres above sea level), at the edges of woods, in Mediterranean scrub, in clumps of shrubs, in meadows, in vineyards and in fields; it can form impenetrable hedges, growing up to three metres in height. The parts used are the cynorrhodons, i.e. the false fruit which can be seen on the plant, made up of a red and fleshy oval-shaped receptacle, containing the real fruit (achenes) which are a darker colour. The cynorrhodons, which are collected between September and October, are very rich in Vitamin C (100 grams of flesh contain up to 3 grams), the inner part, without hairs, is used to make jams, jellies and tisanes. The high content of Vitamin C and other vitamins (A, B1, B2, E, P, K, PP), makes the dog rose an excellent vitaminizing agent and

very suitable: in the cases of general fatigue, in states of convalescence, against colds and viral diseases, to fight free radicals and to improve the immune defences. In addition to vitamins, the active ingredients with an immunostimulating activity are mainly flavonoids, riboflavin, carotenoids, and anthocyanins. Flavonoids are polyphenolic compounds, secondary metabolites of the plant. They are mainly hydrosoluble, and are usually present in the plant as glycosides and in the same plant an aglycone can exist in combination with different sugars.(8) The term is completely interchangeable with bioflavonoids, the name by which these nutrients are usually known. Sometimes they are grouped together under the name Vitamin P. Their name comes from flavus (= yellow) and refers to the role they play as botanical pigments. The colouring they give to fabrics depends on the pH. Blue pigments are formed by chelation with certain metal ions. Anthocyanins are a specific group of Flavonoids.(10) Anthocyanins are another class of pigments, which vary from red, to violet and blue, according to the chemical variations that the plant undergoes, for example changes in the pH. Carotenoids are a groups of red, yellow and orange pigments, which are very much present in the plant world. Carotenoids can be considered polyenes and be distinguished into four groups: hydrocarbon or carotenes; tonic or oxydrylic derivatives, for example lutein, or xanthophyll; carotenoids; xanthophyll esters, for example crocetin, better known as the colouring of saffron. Carotenoids also have marked antioxidant effects. Riboflavin is the other name of Vitamin B2, a hydrosoluble vitamin synthesized in small quantities by the intestinal bacterial flora. Riboflavin is an important cofactor, as it takes part in the cellular oxydoreductive reactions. Dog rose is recommended in cases of influenza, colds, and inflammations, in particular if cutaneous, in the form of packs (9).

#### UNCARIA

Uncaria is a climbing shrub that grows wild in the Amazon forests, where it is known as "Uña de Gato" (cat's claw). Brazilian and Peruvian "Curanderos" use the leaves of Uncaria by infusion, but above all the bark, in decoctions in the prevention and treatment of inflammatory rheumatic diseases and allergic diseases, in the inflammation of the first part of the digestive tract (gastritis and ulcers) and in the degenerative neoplastic pathologies. At present, this plant has been recognized as having anti-inflammatory, anti-viral, anti-mutagen and immunostimulant properties.(9)

Uncaria has a fairly complex chemical composition and its many compounds carry out the different actions it has been recognized as having, but the studies conducted confirm the superiority of the extracts of the whole plant, with respect to the individual purified fractions; it is therefore preferable to use the plant as a whole, in the filtered and standardized extractive form, also in consideration of the extensive botanical and seasonal variability of this plant. Consequently, in the light of these studies, Uncaria is indicated as an adjuvant in

(2000) Vol.3 no.1, January  
(4) F. Mearrelli, F.Pescari,  
"Immunostimulation e Piante Medicinali"  
Edizioni Planta Medica (2002)

(5) M.Provinciali, A.Smrilevi  
"Immunoprevention and Immunotherapy of  
cancer in ageing" Cancer Immunol.  
Immunother. (2005) 54:93-106 DOI  
10.1007/s00262-004-0539-3

(6) P.Albanese, E.Meral Inelman  
"L'Invecchiamento e la Medicina Anti-Aging",  
Università degli Studi di Padova, Scuola di  
Specializzazione in Geriatria (2000);55(7):48-  
58

(7) A.Ciaramella, P.Bossi, C. Caltagirone "I  
processi biologici nell'invecchiamento e ruolo  
dell'inflammazione" Clinica Neurologica  
Università di Roma Tor Vergata  
(2003);38(6):669-72

(8) N.Fabris, E.Mocchegiani, M.Muzzoli,  
M.Provinciali "Interazioni Immuno-  
Neuroendocrine nello Sviluppo e nel  
nell'Invecchiamento" Giornale di Clinica  
Medica PICCIN - (1989) 11:679-686

(9) G.Arienti "Le Basi Molecolari della  
Nutrizione" Seconda Edizione PICCIN  
(2003):978-88-299-1666-5

(10) Fitoterapia di qualità e prodotti naturali -  
Pharbenia -Plant Informazioni August 2005

(11) Frank.C.Lu "Elementi di tossicologia-  
Principi generali" EMSI (2005)

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