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Ageing and osteoarticular system for healthy ageing on behalf of Integrative Medicine Research Group (IMRG)

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Abstract. – Integrative Medicine Research Group (IMRG) presents a new conference scene about the "Ageing and osteoarticular system for healthy ageing" within a multidisciplinary approach of Integrative Medicine.

Key Words:
Ageing, Bone disease, Medicine, Cancer, Patients, Mushrooms, Integrative medicine.

Introduction

Aging refers to the physiological changes that occur in the human body from adulthood attainment and ending in death. These changes involve a decline of biological functions and are accompanied by psychological, behavioral, and other changes. Some of these changes are quite obvious, while others are subtle as bone decay.

Bones undergo a lifelong remodeling process – mature bone tissue is removed, and new bone tissue is formed. Bone remodeling is a highly regulated process that maintains a balance between bone resorption and formation, thus maintaining skeletal integrity.

This balance changes with increasing age, resulting in loss of bone tissue. The ageing bone has reduced mineral content and is prone to osteoporosis – a condition in which bones are less dense, more fragile, and prone to fractures.

Another aspect involving the integrity of the osteoarticular system is cancer disease due to the presence of bone metastases, that are responsible for high morbidity in patients[1].

The aim of this Conference scene within Integrative Medicine Research Group (IMRG) is to focus on the use of complementary medicine[2-8] as support to ageing and osteoarticular system for healthy aging and in the context of Integrative Medicine[9].

Here, we highlight the most relevant discussion presented by speakers in the conference *"Ageing and osteoarticular system for healthy ageing"*, with the aim to improve the knowledge about this topic within a multidisciplinary approach including Integrative Medicine.

Oral Session

Curcumin Boswellia and Osteoarthritis

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Natural compounds, such as curcumin and *Boswellia serrata,* have been studied for their antioxidants and anti-inflammatory properties showing benefits in the treatment of osteoarthritis[10].

Turmeric took its origin from the plant *Curcuma longa* (Zingiberaceae family), in particular from its rhizoma[11]. It is a golden spice containing active compounds called curcuminoids, such as curcumin, demethoxycurcumin and bisdeme-

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thoxycurcmin[12]. Turmeric demonstrated antioxidant activity in several *in vitro* and *in vivo* models. Curcumin, which is the main active compound, is able to reduce oxygen radical species (ROS), such as superoxide anion ($O2^{-}$), hydroxyl radicals (OH), H_2O_2, singlet oxygen, nitroxide, peroxynitrite, and peroxyl radicals (ROO). It has also been shown to reduce the expression of several pro-inflammatory cytokines, including TNF-α, Vascular Endothelial Growth Factor (VEGF), and interleukins 1, 2, and 6[13]. Several clinical studies on the effect of curcumin in osteoarthritis have been performed demonstrating the ability to alleviate the symptoms[14].

Boswellia serrata gum resin extracts have also shown anti-inflammatory properties in tissue levels of TNF-α and IL-1β in experimental models[15]. The active components responsible for the anti-inflammatory action are six major boswellic acids, namely keto-*β*-boswellic acid (KBA), 3-O-acetyl-11-keto-*β*-boswellic acid (AKBA), *α*-boswellic acid (*α*-BA), *β*-boswellic acid (*β*-BA), 3-O-acetyl-*α*-boswellic acid (*α*-ABA), and 3-O-acetyl-*β*-boswellic acid (*β*-ABA). LI13019F1 is a formulation containing both the acidic and non-acidic fractions of *Boswellia serrata* gum resin. Results demonstrated the anti-inflammatory properties of this compound by the inhibition of 5-LOX activity, the leukotriene B_4, and the prostaglandin E_2 production[16]. A randomized clinical trial reported that the administration of patients with *Boswellia serrata* for eight weeks was able to reduce the pain in the osteoarthritis of the knee[17].

Therefore, both *Boswellia serrata* and turmeric in various *in vitro* and *in vivo* studies have shown anti-inflammatory activity at the osteoarticular level. However, curcumin is unstable and easily degraded or metabolized into other forms posing limits to its clinical development. Pharmacokinetic studies revealed that curcumin is poorly absorbed and rapidly eliminated[18]. Thanks to new delivery systems such as phytosome, we are able to improve bioavailability by increasing their effectiveness. In particular, phytosomal technology could overcome the limitations of traditional delivery systems and it has been shown to increase curcumin absorption and bioavailability. Phytosomal curcumin has a chemical formulation different from liposomes, allowing a better oral absorption and stability profile. Results of a randomized clinical trial showed that total curcuminoid absorption from Meriva (phytosomal curcumin) was 29 folds higher compared with the non-phytosomal curcuminoid mixture[19,20]. In addition, both the safety and efficacy of phytosomal curcumin have been studied in several diseases, such as inflammatory disorders or cancer[20]. *Boswellia serrata* is another natural compound with low oral absorption. Thus, the use of phytosome delivering *Boswellia serrata* could be a good strategy. A new delivery system based on lecithin (Casperome) has been developed and results reported a higher absorption and higher systemic availability of *Boswellia serrata* compared with the *Boswellia serrata* alone. In particular, Casperome has been studied for inflammatory conditions, such as musculoskeletal pathologies. Results showed diminished pain and enhanced function[21,22].

The Role of Nutraceutics in the Control of Osteoarticular Inflammaging

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Inflammaging is a low-grade chronic inflammatory process that increases with advancing age and much faster when the person does not implement a correct lifestyle in its fundamental aspects. They are proper nutrition, proper physical activity, and stress management. The rhythms imposed on us by the current lifestyle do not facilitate these activities; furthermore, the environment in which we live is a source of further stress, just think of atmospheric, environmental, electromagnetic pollution, etc. to which we are subjected. All these conditions lead to a chronic inflammatory state, a source of cellular oxidative stress, an altered neurotransmitter response with excess adrenaline and noradrenaline and relative activation of the orthosympathetic system with consequent inhibition of the parasympathetic system, which is fundamental in controlling inflammation. This is followed by a response of the hormonal system with excess cortisol and a state of insulin resistance and its consequences, overweight, metabolic syndrome, etc. A transcription factor, the NF-kB, was highlighted as responsible for initiating the proinflammatory response[23]. It is involved in the activation of a huge number of genes in response to situations of stress, infections, and inflammation. It is responsible for activating soluble endothelial adhesion molecules such as ICAM 1 and VCAM 1, which are ligands for leukocyte integrins, responsible for the mechanisms of adhesion and migration of leukocytes in the extracellular matrix and tissues during the inflammatory process. It also

stimulates macrophages and endothelial cells to produce chemokines such as Interleukin-18 (IL-18), which stimulates the migration of leukocytes from blood to tissues and is found in high quantities in the tissues and synovial fluids of patients with rheumatoid arthritis (RA) and stimulates angiogenesis[24].

In particular, NF-kB stimulates some cytokines highlighted as major responsible for the chronic inflammatory state such as Interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF-a) in addition to Interleukin-1, (IL-1), Interleukin-2 (IL-2), and Interleukin-12 (IL-12).

IL6 and TNF-a are predictors of a chronic inflammatory state which, if present in high quantities in the elderly, are associated with disease, disability and increased mortality[25]. In addition, IL-6 activates osteoclasts and thus predisposes to a state of early osteoporosis, activates PCR and consequently VES, which are found high in rheumatoid arthritis (RA), in systemic lupus erythematosus (SLE) and in scleroderma.

TH2 innate immunity induces differentiation of B lymphocyte cells into plasma cells for the production of IG, activates the TH17 system and inhibits the Treg system (TGF-b). Furthermore, a dysregulation or overproduction of the TH17 system leads to autoimmune diseases such as multiple sclerosis (MS) and rheumatoid arthritis (RA)[26].

As a result of all this, there is, therefore, an inflammatory state which, if not countered, will lead to tissue and organic damage. We think of an inflammation and premature wear of the cartilages, at the origin of osteoarthritis processes and inflammation of the soft tissues, like tendons, ligaments, joint capsule in capsulitis, bursitis, etc. and their wear. Early sarcopenia, osteopenia and early osteoporosis are also linked to inflammatory phenomena. In addition to the fundamental rules for restoring a correct lifestyle, the main and indispensable road to pursue, nutraceuticals offer numerous aids to limit this inflammatory state and the subsequent oxidative stress that underlies degenerative phenomena.

Another fundamental element in the control of inflammation and its consequences must be aimed at controlling the bacterial proliferation of intestinal origin, endotoxemia. The gram-negative intestinal bacteria, in their cell wall contain lipopolysaccharides (LPS) which following their breakdown are released into the circulation and are intercepted by some innate immunity receptors capable of recognizing even non-protein structures such as LPS. In particular, Toll Like Receptor 4 are specific for bacterial LPS (endotoxin) which, once coupled, stimulates the transcription factor NF-kB which in turn activates the pro-inflammatory cytokine cascade. A nutritional and microbiota rebalancing is required, and it may be useful to support glutathione with nutraceutical remedies. All enteric circulation, which may contain LPS, passes through the liver before entering the systemic circulation. here the LPS can be intercepted thanks to hepatic glutathione which must be supported by specific nutrients such as N acetylcysteine, S adenosyl Methionine, Zinc and induced by specific substances of vegetable origin such as Silymarin from *Sylibum Marianum* and Curcumin from *Curcuma Longa*[11]. N acetyl cysteine also has a direct role in inhibiting TNF-triggered NF-kB activation and suppresses induction of IkappaB phosphorylation, degradation and nuclear translocation of NF-kappaB[27]. On the existing inflammatory state and its consequences, nutraceuticals allow to act on numerous etiological agents such as the reduction of the impact of environmental and atmospheric pollution. Numerous substances that we breathe every day such as Pm10 and especially Pm2.5, heavy metals, etc., they are able to penetrate into our body and trigger a particularly damaging inflammatory response even in the osteoarticular structures[28]. Also, for the elimination of these substances it is essential to keep the levels of the substances that eliminate them correctly through the Phases I, II, and III of the liver. Basically, the Glutathione Phase, the Sulphation phase, the Glucuronation phase, and the Methylation phase. The nutrients necessary for the conjugation of environmental and atmospheric pollutants as well as heavy metals are the precursors of glutathione as already seen for LPS, and another important substance is alpha lipoic acid (ALA). ALA contains the SH group which also has an intracellular chelating action of xenobiotics and is also an inhibitor of the proinflammatory transcription factor NF-kB. ALA has proven useful in joint inflammation such as rheumatoid arthritis[29] and in chondroprotection[30]. ALA also plays a powerful antioxidant role both intra and extracellular useful in the prevention of tissue damage induced by inflammatory phenomena.

Also, worth mentioning is *Zingiber officinalis*, a plant with anti-inflammatory properties, inhibitor of COX2 and 5 Lipoxygenase, of the production of PGE2, IL-1, IL-2, IL-6, IL-12, TNF-a and which inhibits the function of NF-kB[31]. It also has

an anti-allergic action, modulates the Mast cells and inhibits the release of histamine, stimulates the hepatic Phase II enzymes (Nrf2), has antihypertensive action, hypoglycemic action, anti-nausea action and is also an "herbal biohenancer", which improves the bioavailability of substances that are taken simultaneously (drugs, vitamins, minerals, phytotherapeutic products). It has proven useful in arthritis, osteoarthritis, rheumatoid arthritis, muscle pain, asthma, diabetes mellitus. Therefore, proper vitamin-mineral integration and the use of herbal extracts offers valuable and valuable help for the osteoarticular system.

Nutrition and Ageing: the Role of "Hericium Erinaceus"

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The properties of *Hericium erinaceus (H. erinaceus)* on the central nervous system have been investigated thanks to a collaboration among the Department of Biology and Biotechnology of the University of Pavia, the Department of Preventive Medicine of the IRCCS Fondazione Policlinico di Milano and the Department of Earth and Environmental Sciences of the University of Pavia. We focused on the effects of *H. erinaceus* standardized extracts on cognitive aspects, mood disorders, such as anxiety, depression and sleep disorders. Starting from a preclinical model of wild-type mice, applying a translational approach, we arrived at overweight and obese patients.

Hericium Erinaceus

H. erinaceus (Bull.:Fr.) Pers. (Hericiaceae, higher Basidiomycetes) is one of the edible and medicinal mushrooms distributed in Asia, Europe and North America. The nutritional and medicinal properties of *H. erinaceus* grown in low temperature conditions are well known and documented in Europe, China and Japan[32].

H. erinaceus consists of several components, including polysaccharides, proteins, lectins, erinacol and terpenoids, some of whose biological activities have been studied. Hericenone and erinacine have been isolated from the fruiting body and mycelia of *H. erinaceus,* respectively, and hericenone C-H and erinacine A-I have been shown to stimulate nerve growth factor (NGF) synthesis in cultured astrocytes[33]. Thanks to a collaboration with Professor Hirokazu Kawagishi of the Research Institute of Green Science and Technology of the Shizuoka University, we were able to quantify the contents of erinacine A, hericenone C and D in our extract[34].

The potential neuroprotective effects of *H. erinaceus* in neurodegenerative diseases, including dementia and motor dysfunction, have attracted considerable attention because both hericenone and erinacine are low-molecular weight, relatively lipid soluble compounds that are able to pass the blood-brain barrier.

Effect on Hippocampal Neurotransmission

We recorded in hippocampus CA3 pyramidal cells spontaneous and evoked glutamatergic excitatory post-synaptic currents in mice treated for two months with oral supplementation or with dextrin (as placebo control) or with *H. erinaceus* by using whole-cell voltage-clamp technique[35,36]. In treated mice, a statistically significant increase in the frequency and amplitude of both spontaneous events was recorded[37]. As regards evoked synaptic currents, mossy fiber-CA3 synapse synaptic excitatory current (EPSCs) in treated mice were increased in amplitude. Paired pulse experiments suggest that the synaptic mechanism, responsible for these changes, was an increase in presynaptic mechanism of release[37].

Effects on Recognition Memory

Researchers have long been interested in the mechanisms underlying recognition memory, one of the main features of the human personality. Current consensus agrees that recognition memory is the sum of two distinct cognitive processes, knowledge and remember. Knowledge can be defined as the process used to identify when something (i.e., object, person, environment) has been encountered previously; remember is the spatial and temporal context of the event (Figure 1).

However, it remains debatable whether knowledge and remember reflect anatomically and functionally distinct, dissociable memory processes (i.e., the dual-process model) or whether these processes constitute a single expression of memory traces of different strengths in the context of a unitary declarative memory system (i.e., the unitary strength model). Answering this question is pivotal to understanding recognition memory function[38].

H. erinaceus improved recognition memory and increase the novelty exploration behavior of a new environment[37,38]. *H. erinaceus* does not affect object location function so the mushroom has no effect on the spatial working memory. There-

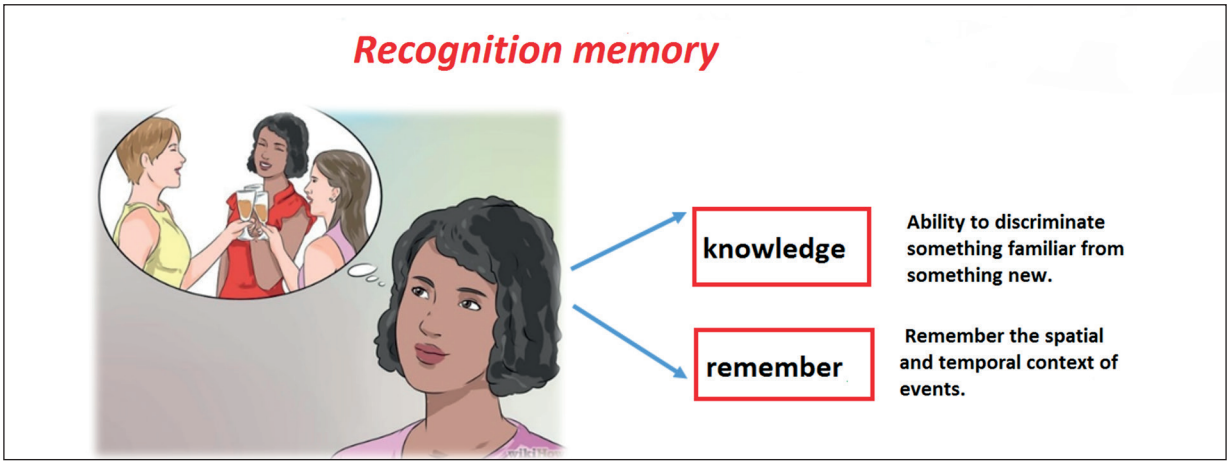

Figure 1. The figure illustrates the two components of recognition memory: knowledge and remember.

fore, the results obtained support the hypothesis that recognition memory can be modeled as a dual process. Specifically, in this model perirhinal cortex is involved in the recognition of individual items encountered previously (familiar object), while hippocampus recollected associations and relationships between stimuli[38].

Then, we evaluated the effects of the *H. erinaceus* supplementation in a physiological preclinical model of aging in wild-type mice. Specifically, we addressed how the mushroom can influence cognitive and locomotor frailty in elderly. Frailty is a syndrome associated with cognitive impairments and locomotor dysfunctions that lead to a poor quality of life and negative health outcomes[36]. Using spontaneous behavioral test such as Novel Object Recognition (NOR) and the Emergence tests, we evaluated locomotor activity and knowledge component of recognition memory of wild type mice from 11 months (adult stage) to 23.5 months (senescence stage). Locomotor activity and recognition memory were evaluated on the base of different locomotor and cognitive parameters and were monitored during the physiological aging of the mice. Starting from 21.5 months old (senescence stage) the frailest mice were treated for two months with *H. erinaceus*. We demonstrated that *H. erinaceus* partially recover recognition memory in frail mice by inducing hippocampal and cerebellar neurogenesis[36].

Effects of H. erinaceus on Mood and Sleep Disorder In Humans

Many articles described the bidirectional relationship between obesity and mood disorders. Obesity patients have a greater risk to develop major depressive disorder, sleep disorders and anxiety than normal weight people; however, on the other hand, depressed patients have a higher risk of overweight or obesity. Our translational approach applied to *H. erinaceus* studies, allow us to apply our knowledge to a human clinical trial. Vigna et al[39] demonstrated that oral supplementation with a standardized extract of *H. erinaceus* for eight weeks in overweight or obesity patients improved moods and sleep disorders.

Our data demonstrate that oral supplementation with a standardized extract oral of *H. erinaceus* increases recognition memory, partially reverts cognitive decline during aging, and improves moods and sleep disorders in overweight obese patients.

Role of Intestine in Chronic Inflammatory Process and in Aging-Related Disease

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Ageing is a complex process that combine genetic, epigenetic and environmental factors. A chronical phlogosis status represents a risk for the morbidity and the mortality in the elderly[40]. Chronical inflammation is related to cellular ageing (inflammaging) that, if perpetuated, can led to an uprising of a series of pathological conditions such as sarcopenia, characterized by a progressive and generalized loss of mass and muscular skeletal strength, strictly related to a physical impairment and poor quality of life[41].

In this context the intestine and, in particular microbiota, have a primary role. Intestinal microbiota is a complex system than can modulate the host physiology in general, but in particular the skeletal muscular tissue[42]. Intestinal microbiota is the complex of the microorganisms (bacteria, viruses, fungus and protozoa) which live inside a host, meanwhile the microbiome or metagenome represents his genetic heritage. Intestinal microbiota comprises several microbial species (estimated today at least 1500) in different variable proportions and in steady-dynamic balance. Its composition is strongly influenced by the host lifestyle, nutrition, health condition and the environment in which it lives, the medicine it takes, especially in the first three years of life. An altered balance with predominance of useless stock, pathogenic microorganisms, and reduction of biodiversity, characterizes the intestinal dysbiosis, which if becomes persistent and chronic can led to an onset and a subsistence of a low chronical inflammation[43].

The geriatric population is frequently affected by an intestinal microbial dysbiosis, which contributes to a local inflammation status of the intestine and a reduction of protective mucus and tight junction damage with increasing of epithelium permeability. As a consequence, it occurs a transition in the systemic circulation of food macromolecules and antigens, usually present in the intestinal lumens, among which the LPS (part of the external membrane of the Gram-bacterial), a bacterial endotoxin, able to activate and sustain, in the tissues where it goes, a chronic phlogistic process[44]. A non-balanced nutrition can influence the intestinal microbic population, leading to an onset of dysbiosis and to the consequent local and systemic phlogistic reaction. Recent research demonstrated that feeding young mice with an inflammatory diet with high fat level, lead to the uprising of a low-grade chronic inflammation, identified by the elevation of TNF-a and IL-6[45]. Another experiment estimates the increasing of circulating levels of LPS, up to 3 times higher in the mice fed with high fat level diet in comparison with the ones belonging to the control group[46].

Inflammation aged-related has an important role in the uprising of the muscular pathology, because it seems to be associated to muscular mass reduction and functional impairment of the skeletal muscle. Inflammatory and high fat diet can directly compromise the tight junction, other than the mechanism sustained by dysbiosis. Obesity is often related to an intestinal dysbiosis in which is possible to observe an altered comparison Bacteroidetes-Firmicutes and a progression of sarcopenia because increases the inflammatory load and oxidative stress damaging DNA and altering immunity and endocrine processes[47].

An extreme model of inflammation induced by bacterial endotoxins is represented by sepsis, that can be deadly but also cause a serious muscular atrophy caused by the growing proteolytic degradation and by the protein synthesis reduction. In a context of skeletal muscular inflammation in the aged patient, we can observe, as seen before, an increase of TNF-a and IL-6, induced by the LPS circulating[48]. It has been demonstrated that the TNF-a, produced by macrophages, induces proteins degradation and promotes cellular apoptosis, while the macrophagic IL-6 represses the protein synthesis. These researches demonstrate that high levels of bacterial LPS could change the already precarious balance of protein synthesis – degradation in geriatric patient causing a muscular mass reduction. As a confirm of the ability of the intestinal microbiota to influence the skeletal muscular size, Bindels et al[49] in 2012 showed an intestinal dysbiosis in mice with neoplastic cachexia that reduced *Lactobacillus* spp. With a selective integration through an oral formulation of *Lactobacillus gasseri*, it was observed a reduction of inflammatory cytokine, especially IL-6 and MCP-1, with a muscular mass growing of the anterior tibial muscle. These effects seem to be bacterial specific. As a matter of fact, same results haven't been found with the administration of an oral formula made of *Lattobacillus acidophilus*, not able to change the inflammatory and atrophic markers[49].

Valuated altogether, those studies on mouse models suggest a possible correlation between the Lactobacillus species and the size of the skeletal muscle. Microbiota is involved in the intestinal absorption process of the nutrients and the consequent synthesis of the aminoacids, necessary for the wellness of the muscular tissue, is not of less importance.

Several investigations describe the strict relationship between the intestinal dysbiosis and the metabolic imbalance that confirm the important role of microbiota in the digestive process and in nutrient absorption. It's possible to suppose a correlation between the intestinal microbiota and the low-grade chronic inflammation, because a growing number of investigations confirms that some species could promote it; instead others,

through different mechanisms, could contrast it. Recent research demonstrates how an overrepresentation of bacterial species such as *Roseburia, Akkermansia,* and *Faecalibacterium*, through the production of fat short-chain acids (acetate, lactate, butyrate, propionate), is capable of promoting health.

To conclude, the link between fitness and microbiota is still uncertain, because of several factors among which diet, physical exercise, pharmacotherapy and concomitant pathologic conditions. The relationship between intestinal microbiota and skeletal muscle remains very interesting.

The researches on mouse models, designed to manipulate microbial ecology to reach the skeleton muscular health, are finalized to improve the geriatric patient quality of life. This goal can be reach by modifying the food habits and administering specified formulation based on prebiotic and probiotic. The objective of research is to find a medical integrative strategy which considers the geriatric patient and his fragilities, which sarcopenia remains one of the most important and invalidating problem.

Ageing and Osteo-Oncology

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The discovery of cellular senescence in 1961 by Hayflick and Moorhead[50] represented a groundbreaking finding since it was the first demonstration that normal cells are not immortal, as believed at the time, and provided the basis for a scientific demonstration of the evolutionary theory of ageing initiated by Peter B. Medawar in 1952. Cellular senescence can impact on multiple physiological and pathological processes such as wound healing, fibrosis, cancer and ageing. We can consider ageing process and cancer disease as two sides of the same coin. To date, due to the improvement made in cancer diagnosis and treatment, the survival of cancer patients has dramatically increased in all setting, type and stage of disease[51-55]. In this context, for example, the approach to bone metastasis (BMs) is growing so much that today we talk about "Osteoncology". Bone is the third most common site of metastasis after liver and lung. In the USA, about two thirds of patients who die from cancer each year have evidence of bone disease[56,57]. It is now clear that the incidence of BMs is distributed differently among primary cancer types: in particular, breast and prostate cancers represent the majority of tumors that metastasize to bone tissue. As well described in literature, BMs can manifest with two different kinds of lesions[58]. Specifically, breast, lung, melanoma and kidney cancers generally cause osteolytic lesions where osteoclast activity is increased leading to disruption of tissue architecture; whereas, prostate cancer is usually linked to osteoblastic lesions in which "activated osteoblasts" alter the physiological bone formation/resorption turnover. The skeletal related events (SREs) about BMs are various and include pain (75% of patients), pathological fractures, spinal cord compression, and hypercalcemia[59], all symptoms that influence negatively prognosis and quality of life. The treatment approach to BMs is always multidisciplinary involving a team of specialists in the areas of oncology, palliative care, radiotherapy, orthopedics, nuclear medicine, radiology, and physiatrics with the aim to obtain an effective management in this setting of patients. More recently, according to English literature, an integrative approach (IA) is also contemplated, suggesting treating cancer patients[3]. The IA is based on practices and substances that are used together with conventional medicine (CM) and recent data on use of integrative approaches have demonstrated that around 49% of cancer patients combined these remedies with their cancer treatment and that in 67% of cases the interventions are self-prescribed[60-62]. Discussion on IA interventions and guidance on potentially beneficial therapies and potential toxicities is a task that physicians should undertake. Extensive research is required to assess actual IA use in different patients and to work towards an integrated model of healthcare provision, which could also inform appropriate EU legislation.

Protection of Osteoarticular System by Cordyceps spp and Cordycepin

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Parasitic Cordyceps fungi, such as *Cordyceps sinensis* and *militaris*, is a parasitic complex of fungus and caterpillar, which has been used for medicinal purposes for centuries particularly in China, Japan and other Asian countries.

The most know is caterpillar fungus Cordyceps *sinensis (Ophiocordyceps sinensis, Hirsutella sinensis*), a fungus parasitizing on a range of ghost moth larvae of the *Thitarodes (Hepialus armoricanus*) genus, which lives in alpine grassland ecosystems of the Tibetan Plateau and the

Himalayas in an altitude between 3300 to 5000 meters beyond the tree line, during the asexual cycle. It is a club-shaped fruiting body, which use and collection dates back at least a thousand years in Tibet where it is called *Yartsa Gunbu*. The earliest known written documentation of *Yartsa Gunbu* is found in a Tibetan text authored by Nyamnyi Dorje (a Tibetan physician and lama who lived from 1439 to 1475), "An Ocean of Aphrodisiacal Qualities — A special work on *Yartsa Gunbu*" which has been translated by Jakob Winkler (http://mushroaming.com/Nyamnyi_Dorje_on_Cordyceps)[63].

In Traditional Chinese Medicine (TCM), *Cordyceps sinensis* is commonly known as "*dong chong xia cao*" meaning "winter-worm summer-grass". The Latin name of the mushroom *Cordyceps sinensis* means "Chinese club head" (cord = "club", ceps = "head", and sinensis = "from China"). Similar properties are described for a related mushroom, *Cordyceps militaris*, which is much easier to cultivate artificially.

The medicinal value of both *Cordyceps militaris* and *sinensis* has been recognized for more than 2000 years in Tibet, China and the Orient. Oriental folklore calls for their potency, strength giving effect, plus willpower and stamina. In a recent treatise on Tibetan medicine, *Ophiocordyceps sinensis* (referred to as *Yartsa gunbu*) is placed in the category of *tsi men*, the "medicinal essences", which includes several tonics[64].

Cordyceps sinensis and *Cordyceps militaris* contain a great number of bioactive compounds such as sterols, alkaloids, polysaccharides, nucleosides, cordycepin, ergosterol, mannitol, adenosine, amino acids, inorganic elements, vitamins, fatty acids, ketones, aldehydes, ether, phenols and other minor compounds[65].

Cordycepin, a derivative of the nucleoside adenosine that lacks an oxygen in the 3' position of its ribose moiety, is the main bioactive compound studied in *Cordyceps* both *sinensis* and *militaris*[66].

The isolation of Cordycepin (3'-deoxyadenosine) dates back to 1950 and was first discovered in *Cordyceps militaris*[67].

A large body of literature indicates that cordycepin indeed has biological activities and pharmaceutical potential. In tissue culture, anti-inflammatory properties and anti-tumor effects are especially well established[68,69]. In addition, it has been shown to be effective in numerous animal models of disease, including models for osteoarthritis, inflammatory lung disease, cerebral ischemia, kidney failure and cancer[69-77].

The production of cordycepin in Cordyceps is coupled with the production of pentostatin, an adenosine deaminase inhibitor[71], by a single gene cluster. Pentostatin protects cordycepin from deamination to 3-deoxy-inosine. Dual production of these two adenosine analogs is following a bacterial-like protector-protégé' strategy of purine metabolism. The safeguarded cordycepin can be deaminated to 3-deoxyinosine once the former reaches a self-toxic level in fungal cells. The co-production of cordycepin and pentostatin is the result of the evolutionary pressures on this insect-infecting fungus.

As for cordycepin bioavailability, little is known about the absorption pathways of adenosine and its analogues following oral administration. Recently, it has been discovered thar 3′-deoxyinosine, considered to be inactive, is absorbed into the systemic blood circulation and that cordycepin 5′-triphosphate, the active metabolite of cordycepin, can be formed not only from cordycepin, but also from 3′-deoxyinosine. This novel nucleoside rescue metabolic pathway might be responsible for therapeutic effects of cordycepin following oral administration.

Cordycepin is a polyadenylation inhibitor that has been shown to inhibit inflammation[72].

Cordycepin has been studied in models of osteoarthritis proving that it acts as a novel type of anti-inflammatory painkiller, reducing pain and osteoarthritis progression in animal models. Cordycepin treatment reduced monosodium iodoacetate-induced changes in pain behavior and mechanical allodynia, reduced synovial macrophage infiltration, thus reducing established knee joint pain and synovial inflammation. It also reduced induced subchondral bone changes, showing a protective effect on cartilage, also by inhibiting the expression of cartilage proteolytic enzymes.

The mechanisms by which cordycepin attenuates pain behavior are a result of an inhibition of inflammatory signaling, and/or direct effects on the primary afferent nociceptors. Cordycepin mediated prevention of the activation of a range of pro-inflammatory mRNA translation which may contribute to the effects of cordycepin on osteoarthritis pain responses. The data demonstrate that cordycepin is orally effective and functions as a polyadenylation inhibitor.

Cordycepin reduced pain behavior, synovial inflammation and joint pathology in osteoarthritis models, and it may hold promise as a compound for a novel class of orally available anti-inflammatory and analgesic drugs in patients

with high synovial inflammation, and potentially also for other conditions associated with pain and inflammation.

However, if we take into account that the evolution of natural compounds is likely to have led to synergistic mixtures, there appears to be a case for initially testing mixtures rather than pure compounds, as activity may be lost by purification of single compounds.

Nutritional and Supplementation Strategies for Prevention and Recovery in the Sportsmen Injuries

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The pathogenesis of the injuries on the sportsmen is multifactorial and related to both external causes (weather conditions, game surface, kind of shoes, etc.) and intrinsic causes (age, postural aspects, training, stress, lifestyle, and diet). The majority of the injuries are muscular, followed by stress fractures, ligamentopathies and tendinopathies[73].

For a perspective focused on the sportsman with the purpose of reducing the risk of his muscular injury, we should consider several aspects such as the hydration status, micronutrients deficiencies, vitamin D levels, and oxidative stress[74-78].

It's strongly recommended to avoid reducing the caloric intake under certain limits. Low caloric intake enhances the fatigue, has immunosuppressive effect and sets up the injuries. Caloric restriction can cause deficiencies of micronutrients, some of which – iron, calcium and D vitamin, are very common on sportsmen and athletes, especially on the female ones. It's pivotal to guarantee a correct hydration: it does exist a straight correlation between the weight reduction caused by dehydration and deterioration of the performance, other than an increasing risk of muscular injuries[79,80].

The contemporary western nutrition is characterized by omega 6 and omega 3 ratio biased toward the first, causing, as a consequence, a major production of proinflammatory molecules effect. For the sportsmen is necessary to rebalance this relation by focusing on the food habits and avoiding the excessive use of food rich in omega 6, preferring the omega 3, both through the diet and the supplementation[81].

An integration with antioxidant aimed to reduce muscle damage effect caused by training is only suggested for people with a proved deficiency of one micronutrient, for people in caloric restriction for a long-time interval, in subjects that personally decided to limit or totally exclude food that provides vitamins. In all other cases, it is more advisable to revisit the food habits with a good number of fruits and vegetables. Even in case of injuries recovery, as during the immobilization phase than the rehabilitation phase, it's possible to increase nutritional and supplementation strategies aimed to accelerate the coming back to the sport practice.

Conclusions

We believe that ageing and osteoarticular system for healthy ageing represent a new challenge in all area of medicine and a multidisciplinary and integrative approach is the right interpretation to improve the clinical results and quality of life in our patients. In the next future, our wish is to propose and organize prospective studies, within IMRG, with the aim to improve the knowledge in these setting of patients, treated within a program of multidisciplinary and integrative approach.

Conflict of Interest

Dr. Stefania Cazzavillan, Dr. Alessandro Scorba and Daniele Santagà are scientific consultant for AVD Reform.

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