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INTEGRATIVE MEDICINE IN ONCOLOGY, MILAN OCTOBER 19TH, 2019

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Abstract – *Complementary and Alternative Medicine (CAM) interventions are widely used by patients with chronic disorders, including cancer, and may interact with cancer treatment. Physicians are often unaware of this, probably due to poor patient-physician communication on CAM.*

The purpose of this study was to evaluate the physician knowledge, attitudes and practice patterns regarding CAM in a survey conducted in Italy among physicians.

KEYWORDS: *CAM, Medicine, Cancer, Patients, Mushrooms, Microbiome, Integrative medicine.*

INTRODUCTION

Over 30% of Europe's cancer patients are using some form of Complementary or/and Alternative Medicine (CAM), yet, not even one out of five of these patients has received advice from his/her doctor about the CAM therapy, with the vast majority acting on the basis of information from the Internet, media, friends and family.

In the United States (US), the use of CAM is constantly increasing with the largest practice being among the non-Hispanic whites and in the rural areas, compared with the cities; in terms of geographical areas, the highest use was observed in the Mountain regions and in New Mexico[1].

Nevertheless, the literature about CAM occurrence/use in cancer patients is not mainly rich, especially if we consider the European drafts only, and the prevalence is probably under valuated. Nonetheless, the literature on CAM use by cancer patients is not an accurate snapshot of the situation, especially considering European papers only, as CAM use is probably being underrated.

Many patients do not declare that they involve in this practice, on the one hand b ecause they undervalue the relevance of the products they take, considering them 'natural', unable to interact with conventional drugs and devoid of side effects; on the other hand, because they are somehow reluctant to admit the use of an unconventional treatment, worrying that such behavior may be interpreted as reflecting a loss of trust in their oncologist and the treatment he/she has prescribed. Furthermore, most clinicians are unfamiliar with these kinds of treatments[1] and hence do not pay enough attention to this aspect of the anamnesis at the time of the assessment/examination; usually, they do not explicitly ask about this topic, as they do for all other health matters, such as comorbidities or conventional drugs[1,2]. This paper gives the highlights of the most relevant discussion held by the speakers in the *"Oncologia Integrata"* meeting, with the aim to improve the knowledge about CAM and its potential and possible role inside traditional medicine in a new care dimension: integrative medicine in oncology.

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ORAL SESSION

COMPLEMENTARY AND ALTERNATIVE MEDICINE IN ONCOLOGY: BETWEEN HOPE AND REALITY

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According to the National Center for Complementary and Alternative Medicine (NCCAM), USA, Complementary and Alternative Medicine (CAM) is an umbrella term comprising very different practices: nonbiological interventions (e.g., prayer, meditation, music therapy, massage) and biological interventions (e.g., herbs, also known as botanicals, vitamins, minerals, probiotics and traditional Chinese medicine), which are outside mainstream Western medicine (Figure 1). Such practices or substances are defined as 'alternative' when they are used *in place of* Conventional Medicine (CM) and 'complementary' when they are used together with CM[1,2]. Interest in CAM has grown quickly in the last decade. Some of the reasons for the increased interest include massif internet marketing diffusion, dissatisfaction with mainstream medicine and a desire of patients to have more control over medical decisions.

Recent data indicates that CAM is used to treat a wide range of late-life health conditions, especially chronic or long-term ailments such as arthritis and pain, diabetes, hypertension, depression, anxiety, sleep disorders, infections and cancers[3].

In a recent Italian multicenter study[2], we found that 49% of cancer patients combined CAM remedies with their cancer treatment and that, in 67% of the cases, the interventions were self-prescribed. Their main sources of information were the Internet and the media (48%), while only 6% of the patients had received information on CAM by physicians. Critically, 85% of patients were not aware of the risk of side-effects of CAM remedies and of potential interactions with TM treatments. The latter issue raises disturbing questions and highlights the need for greater patient-physician communication on CAM. Although oncologists generally discuss treatment options with patients (choice of treatment, therapeutic targets, side-effects), they largely ignore CAM. A study performed at the University of Texas MD Anderson Cancer Center in Houston has found limited communication and discordant views among physicians with regard to CAM therapies[4]. Insufficient patient-oncologist communication on CAM has also been reported.

In the collective mind, CAM are considered to be "natural" and, therefore, associated with low risk of toxicity and/or interactions. The risk associated with any health care is generally separated into direct and indirect risk.

Direct risk is caused by the treatment itself and is directly linked to the intervention. This dimension includes traditional adverse effects from a treatment, such as gastritis as adverse effect, due to FANS assumption. Indirect risk is related to adverse effect of the treatment context, e.g., CAM use, rather than the intervention. A patient may be harmed by a care context which prevents the patient from receiving the best possible treatment relevant to her or his health needs, e.g., when patients seek a complementary provider for their health complaints which may be effectively treated by CM (i.e. cancer), and the complementary provider, often unwittingly, causes a delay of conventional treatment.

Unpublished recent data about Physician attitudes and perceptions about CAM, in an Italian survey, demonstrates that oncologists and hematologists have better knowledge of CAM than other specialists (geriatrics, infectiologists, surgeons and internists) and physicians that were involved also in

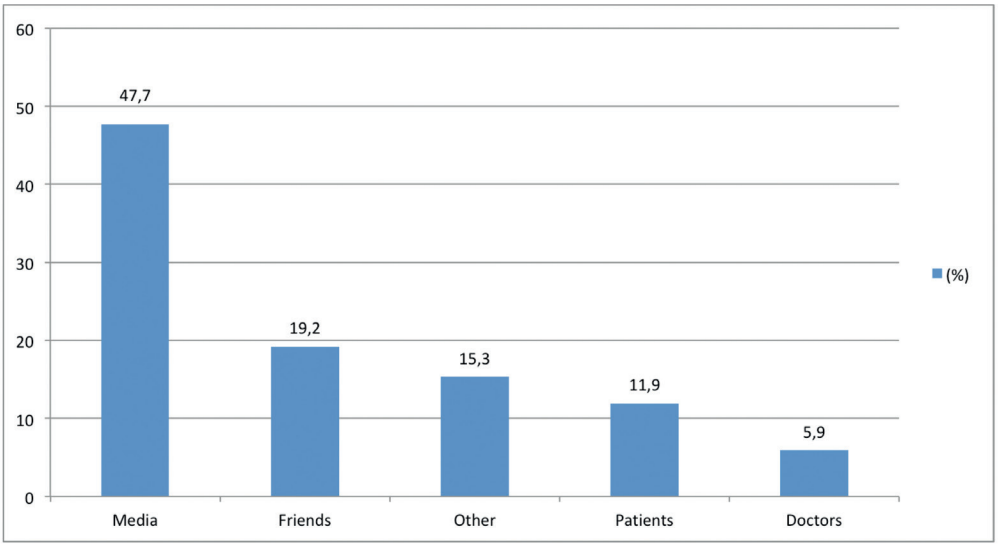

Fig. 1. Source of knowledge about CAM.

research had better knowledge of CAM than those who were not (p<0.003).

Discussion of CAM interventions and guidance on potentially beneficial therapies and potential toxicities is a task that physicians should undertake. Extensive research is required to assess actual CAM use and dosage in different patients and to work towards an integrated model of healthcare provision, which could also inform appropriate EU legislation.

TOXICITY PREVENTION OF THE NUTRACEUTICAL-ANTIBLASTIC DRUG INTERACTIONS BY CHECKING INDIVIDUAL GENETIC METABOLIC PROFILE

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Drug-drug interactions between antineoplastic drugs (ADs) and others have been extensively investigated. Conversely, little is known of the effect of ADs co-administration with nutraceuticals/dietary supplements (N/DSs). This is an emerging problem because N/DSs are often self-prescribed by cancer patients[2]. N/DSs encompass a wide range of products, such as herbs, nutrients, vitamins, minerals and probiotics. Any assessment of their interactions with cancer drugs, particularly ADs, is hindered by the difficulty in knowing the amount of active substances patients actually take. Moreover, there is no agreement on which approach should be used to determine which N/DSs are most likely to influence the efficacy of ADs treatment[5]. At the "Oncologia Integrata" meeting held in Milan, the author presented a comprehensive review and recent developments in the metabolic routes of the main ADs and their possible interactions with N/DSs. To date, the PubMed and Cochrane databases contain papers describing the metabolic routes of the main ADs and N/DSs and 133 studies recommend a diagnostic step to detect the expected AD-N/DS interactions based on properly metabolization pathways. ADs and N/DSs sharing the cytochrome P450 pathway are at risk of severe interactions in patients with specific CYP450 deficit. Well known is the drug interaction of St. John's worth in patients who received sorafenib, imatinib, etc., due to CYP3A4 deficit[6]. In conclusion, recent advances in pharmacogenetics offer exceptional opportunities to identify prognostic and predictive markers to enhance the efficacy of individualized AD treatments[7]. Table 1 affords a guide to genotyping patients who are due to receive ADs and is a promising tool to prevent occult AD-N/DS interactions in poor metabolizers. N/DS use by cancer patients receiving ADs is a topical problem requiring urgent attention from the scientific community.

TABLE 1. Same example AD-N/DS metabolic pathways.

Agents	*Effect on metabolic pathway*	*Interaction with anticancer drugs*
Pineapple (Bromeline)	CYP2C9 inhibition	Risk of over dosage with paclitaxel
Turmeric	CYP1A2, CYP2B6, CYP2C9, CYP2D6 weak inhibition	Risk of over dosage with Bendamustine, risk of inefficacy of pro-drugs (Cyclophosphamide, Tamoxifen etc.)
Cannabinoids	CYP2C9 induction	Risk of over dosage of prodrugs (Cyclophosphamide, Tamoxifen etc.)
Echinacea	CYP3A4 induction	Improved pharmacokinetic (weak) of Cyclophosphamide dasatinib, docetaxel, erlotinib, imatinib, sorafenib, vinca alkaloides
ESSIAC*	CYP3A4 inhibition	Risk of over dosage with bortezomib, dasatinib, docetaxel, erlotinib, imatinib, sorafenib, vinca alkaloids
Green Tea	CYP3A4 inhibition	As for Essiac
Gingko Biloba	CYP3A4 CYP2C19, inhibition	As for Essiac
Grape Fruit	CYP3A4 inhibition	As for Essiac
Licorice	CYP2B6, CYP3A4 weak inhibition	As for Essiac (weak)
Milk thistle	CYP2C8, CYP2C9 weak inhibition	Risk of over Dosage with cyclophosphamide, paclitaxel
St. John's worth (Hypericum)	CYP3A4 induction	Improved pharmacokinetic of Cyclophosphamide dasatinib, docetaxel, erlotinib, imatinib, sorafenib, vinca alkaloids

MEDICINAL MUSHROOMS AS AN INTEGRATIVE SUPPORT IN ONCOLOGY

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Medicinal mushrooms have been used in traditional folk medicine and ethno-pharmacology for prevention and as support against diseases since ancient times. However, translating traditional Eastern practices into acceptable evidence-based Western therapies is difficult[8,9]. The concepts are different. Western Evidence Based Medicine focuses on the mechanisms of action of standardized molecules, while traditional medicine deals with the whole mind-body system, with a concept that is now recognized as adaptogenic.

Various compounds from numerous mushroom species have been extracted and studied *in vitro* and in animal models, and many of them have been demonstrated to have curative properties[10] (Figure 2). However, while a novel compound may prove effective against the tumor cells *in vitro*, it does not mean that it will translate into a useful compound *in vivo*. Moreover, different manufacturing standards, criteria of purity and under-powered clinical trials make the assessment of efficacy and toxicity by Western standards of clinical evidence difficult. When specific compounds are extracted and concentrated, the risk of drug interference is always present; so, even though purified bioactive compounds derived and standardized from medicinal mushrooms are a potentially important new source of anticancer agents[11], there might be another way to consider the use of medicinal mushroom. Whole (not extracted) medicinal mushroom may be considered "*superfoods*" with lots of different compounds in non-pharmacologic concentrations, which act synergistically without interfering with drugs.

In the latest years, plenty of attention has been paid on the interference of the gut microbiota and the tumor microenvironment on the efficacy of cancer drugs.

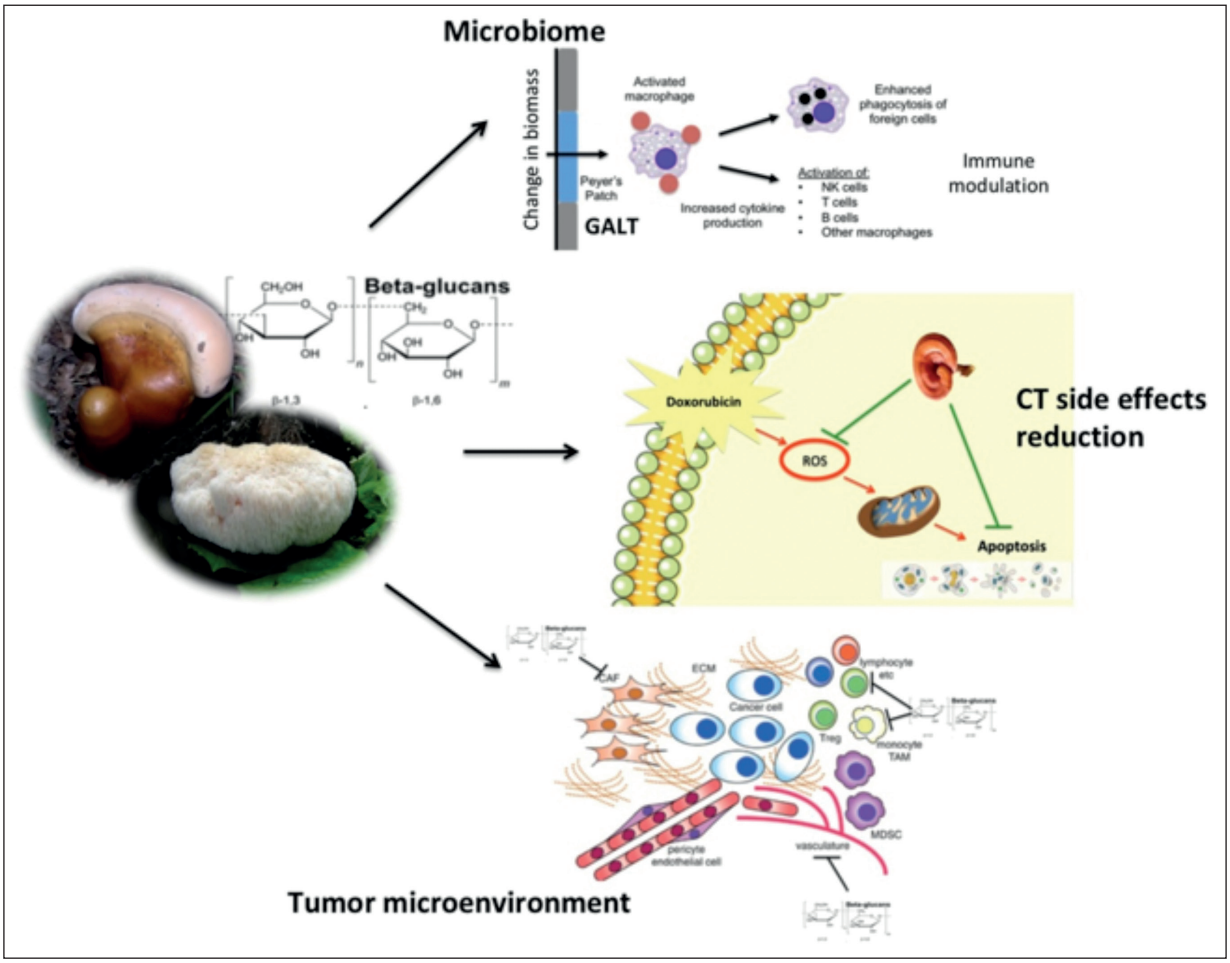

Fig. 2. Mushrooms activity.

Many recent scientific papers have been focusing on the action of mushroom on the qualitative and spatial composition of gut microbiota[12-14]. Not only indigestible beta-glucans (soluble and insoluble), but also other bioactive compounds, such as the polyphenolic fraction[15], seem to exert a potential effect on microbiota. These data, obtained from many studies on different culinary and medicinal mushroom, have led to the hypothesis that most of the described beneficial effects of their use depend on their action on microbiota[16-18].

Growing scientific evidence has demonstrated a possible role of an altered microbiota in the dysregulation of several inflammatory/immune processes involved in tumor initiation and progression by promoting the specific composition and activation of the tumor microenvironment[19,20]. Emerging data on the use of mushroom β-glucans suggest that the tumor microenvironment might be actively manipulated by the use of β-glucans and β-glucan-based nanoparticles suggesting a novel combination strategy to improve the effect of immunotherapy[21].

These new trends in research offer a rationale for the study and use of medicinal mushroom as a synergistic complement in integrative oncology (Figure 2).

EFFECTS OF A NOVEL MEDICINAL MUSHROOMS DIETARY SUPPLEMENT IN A MOUSE BREAST CANCER METASTASIS MODEL

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Breast cancer (BC) is the greatest widely invasive cancer in women and the second main cause of cancer death in women, after lung cancer. In the last years, substantial advances in the diagnosis and treatment of breast cancer have improved survival rates dramatically. Earlier detection thanks to advances in screening, new personalized approaches to treatment and better understanding of the molecular mechanisms involved in the disease, have generated a steadily decline in the number of deaths.

In the United States (U.S.), the estimated number of BC survivors is about 3 million.

About 10-20% of BCs are triple-negative. Triple-negative BC does not express estrogen receptors, progesterone receptors, and the human epidermal growth factor type II receptor (HER2). For this reason, triple-negative BC does not respond to hormonal therapy medicines or drugs that target HER2 protein receptors. For researchers, there is intense interest in finding new drugs or substances that can treat triple-negative BC. One of the most furthermost hopeful sources for new drug discovery in cancer therapy are medicinal mushrooms that display anticancer, oncoimmunological, and immunomodulating activity[9,22].

We studied the effects of a novel medicinal mushroom dietary supplement in a mouse BC metastasis model. "Mic. U-care" is a novel supplement provided by A. V. D. Reform s.r.l. (Noceto, Parma, Italy) consisting of mycelium and sporophores extracts of *Agaricus blazei, Cordyceps sinensis, Ganoderma lucidum, Grifola frondosa*, and *Lentinula edodes.*

We used the cellular line 4T1, a BC cells triple negative derived by mouse.

The experimental plan consisted of 3 arms with randomized control, 4T1 tumor bearing, and 4T1 tumor bearing and supplemented mice (Table II). Animals of the supplemented group were pre-treated with "Mic. U-care" at an oral dose comparable to that normally used in humans. After 2 months of "Mic. U-care" supplementation, we injected 4T1, animals were monitored for all the experimental time in weight, water consumption, locomotor performances (by emergence test), and echography. At the end, mice were euthanized and all organs were isolated, and a tissue library has been established. We start studying the effects of "Mic. U-care" on metastasis development, on oxidative stress, and inflammation markers on the lung. In particular, we measured three markers of oxidative stress by immunocytochemistry, namely inducible nitric oxide synthase 2 (NOS2), superoxide dismutase 1 (SOD1) and cyclooxygenase 2 (COX2); for inflammation the transforming growth factor (TGF-beta) and interleukin 6 (IL6) were also measured. Transmission Electron Microscopy (TEM) was used for the morphological ultrastructural analysis.

We monitored the Quality of life (QoL) during all the experimental time, by tuning a quality of life score and a significant improvement was recorded in the supplemented animals. In conclusion, "Mic. U-care" has the ability to reduce the density of metastases in the lung, and induces a significant improvement in oxidative stress, inflammation and QoL. These experimental data, obtained in the pre-clinical animal model of BC triple negative, are the necessary premise for translating the research into humans and thus we hope that it can lead to future clinical trials.

TABLE 2. Experimental plan. MM is the medicinal mushroom blend provided by AVD reform: "Mic.U-care".

T0 n= 34 mice randomized to:		
Control mice n=4	**4T1 mice n= 14**	**4T1 MM mice n= 16**
• 1st Ultrasound • Measure of body weight • Emergence Test	• 1st Ultrasound • Measure of body weight • Emergence Test	• 1st ultrasound • Measure of body weight • Emergence Test
2 months	2 months	2 months + MM
T1		
Control mice n=4	**4T1 mice n= 14**	**4T1 MM mice n= 16**
PBS Injection	4T1 cells Injection	4T1 cells Injection
• Measure of body weight	• Measure of body weight	• Measure of body weight
20 days	20 days	20 days + MM
T2		
Control mice n=4	**4T1 mice n= 14**	**4T1 MM mice n= 16**
• 2ND Ultrasound • Measure of body weight • Emergence Test	• 2ND Ultrasound • Measure of body weight • Emergence Test	• 2ND Ultrasound • Measure of body weight • Emergence Test
15 days	15 days	15 days + MM
T3		
Control mice n=4	**4T1 mice n= 14**	**4T1 MM mice n= 16**
• 3TH Ultrasound • Measure of body weight	• 3TH Ultrasound • Measure of body weight	• 3TH Ultrasound • Measure of body weight
1 day	1 day	1 day
Sacrifice		

CORRELATION BETWEEN MICROBIOTA AND IMMUNE SYSTEM IN THE MANAGEMENT OF CANCER PATIENTS

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Microbiota is the set of all the micro-organisms (bacteria, virus, fungal and protozoal) of an organism, whereas the microbiome represents their genetic heritage. The gut microbiota of a single individual comprises many different species (currently estimated as being at least 1500) present in varying proportions. Its composition is strongly influenced by many elements, such as diet, health conditions, lifestyle, infections and antibiotic therapies. Changes in microbiota, which alter the balance between the host organism and microbes, are called dysbiosis[23].

The role of the microbiota in the origin of some types of cancer and as a modulator of the immune response towards cancer cells has aroused the scientific community's deep interest. Inflammation, oxidative stress and gut microbiota conditions can be added to the already known fundamental causes of cancer (genetic predisposition, lifestyle and immune system)[24].

It is well known that cancer manifests itself in chronically inflamed tissues and this is especially evident in the gastrointestinal tract. Classical examples include gastric cancer associated with *Helicobacter pylori*, hepatocellular carcinoma and colorectal cancer associated with inflammatory bowel disease. Growing evidence suggests that this association is no coincidence, but could actually be causal[24,25].

Many bacteria accountable for dysbiosis contribute to the onset of immune and inflammatory processes, which are involved in cancer etiology. Production of bacterial genotoxic endotoxins and other inflammatory mediators could lead to an alteration of the intestinal permeability with the onset of inflammatory processes, both local ones (which induce and sustain the forming of neoplastic clones) and systemic ones, which can alter the immune response.

Chronic dysbiosis is considered one of the causes triggering the development of low-grade chronic inflammation, induced by lipopolysaccharides LPS (powerful endotoxins located at the outer membrane of gram negative bacteria).

It is well known that low-grade chronic inflammation is one possible co-factor in the pathogenesis of cancer, even after induced damages to DNA[26-28].

It is also estimated that 15% of tumours are caused by infective agents. On top of the already known correlation between infection with some strains, such as *Helicobacter pylori,* and gastric cancer, *Fusobacterium nucleatum* could be related to higher incidence of colorectal cancer and *Escherichia coli*, which could induce DNA changes through the release of genotoxic toxins, could increase the risk of Crohn disease and tumorigenesis[29,30].

It is important to study also the genetic profile of every bacterial species that is part of the microbiome, because the bacterial genome produces metabolites that can generate effects, either deleterious or therapeutic ones. In fact, it is possible to improve the efficacy of oncologic treatments intervening on the patient's intestinal bacterial populations. The bacterial genome has high potential, not only in the oncologic field. The microbiome comprises millions of genes that do not belong to the human genome and that encode many proteins, opening the possibility to modulate the response to drugs acting directly on the microbiota.

Manipulating the microbiota, through the use of antibiotics, probiotics or faecal transplant, it is possible to increase the response to the new immunotherapeutic drugs in oncology[31]. Recent research has shown the ability of the microbiota to influence the patient's response to oncologic therapies. Studies published in the last few years have demonstrated that the alteration of the intestinal microbial populations caused by repeated antibiotic therapies can impair the efficacy of anti-PD-1 immunotherapy, especially if there is a deficiency in the *Akkermansia muciniphilar* bacterium. A preclinical study made by the University of Texas demonstrated that the patients affected by metastatic melanoma whose intestine showed more bacterial diversity had a better response to immunotherapy[32]. Researchers found a correlation between microbiome composition and cancer progression under anti-PD-1 drugs treatment. Preliminary data demonstrate that anti-PD-1 drugs responders have higher gut microbiome biodiversity than non-responders. As a matter of fact, also the bacterial community changes: in the former, a larger presence of Clostridiales has been found, whereas, the latter showed a prevalence of Bacteroidales.

MINDFULNESS-BASED STRESS REDUCTION (MBSR) IN INTEGRATIVE ONCOLOGY

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Mindfulness-based stress reduction (MBSR) is the method designed by Jon Kabat-Zinn, US physician of Indian origin, founder and director of the clinic for stress reduction at Massachusetts University.

CISM is an Italian Association whose primary purpose is the dissemination and promotion of mindfulness, through the development of specific mindful qualities that Kabat-Zinn cultivated through this kind of practice. He applied MBSR in different clinical conditions, such as in patients with chronic pain in multiple syndromes, anxiety, depression, sleep disorders and cardiovascular diseases. In 2007, McCracken, Vowles and Eccleston found the Mindful Attention Awareness Scale (MAAS) related to multiple measures for pain management[33].

In addition to pain measure, mindfulness has helped limit mood disorders like depression, anxiety, physical and psychological pain related, also improving the level of acceptance and reducing catastrophic thinking. There has been extensive research on the effectiveness of MBSR in patients with various types of cancer since 2007[34].

Most of the experimental work was conducted by Carlson and Canadian colleagues, who started with a randomized trial of 89 patients with different types of cancer. Patients were divided into two groups and randomly assigned to the MBSR group and to the control group (Speca, Carlson, Goodey et Angen, 2000). Patients randomized to the MBSR group experienced a 65% symptomatic improvement in their mood and a 35% in stress symptoms compared with the control group[35].

Intention, attention and non-judgmental attitude (IAA model proposed by Shapiro et al[36]) are the mindful qualities associated with psychological and biological improvement. The functionality of the autonomic nervous system is also very interesting as the patients that survive the cancer are at high risk of cardiovascular disease and HRV dysfunction. Studies on emotions performed by Candace Pert and the Polyvagal theory have confirmed the close relationship between cancer biology, emotional behaviour and patient outcome. A 2017 systematic review had a broader scope including 13 studies of all cancer types[37]. This review reported that 9 out of 13 studies had most consistent positive effects about measures of stress, mood disturbance, anxiety, depression, quality of life, cortisol profile and blood pressure. The largest study to date randomly assigned 322 and 336 women with breast cancer to treatment or care controls group, respectively. Greater improvements were reported on overall distress as well as sleep, anxiety, fatigue, fear of cancer recurrence in the mindfulness groups compared with control[38].

Therefore, to date, there has been an exponential growth in mindfulness training for psycho-physical well-being.

NUTRACEUTICS TO SUPPORT THE LIVER IN ITS DETOXIFICATION ROLE FROM POTENTIALLY CARCINOGENIC SUBSTANCES (Pesticides, heavy metals, endocrine disruptors, environment pollutants)

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Nowadays, our body is flooded by toxins from many sources: pesticides, heavy metals, bisphenol A, parabens, food additives, preservatives, colorants, environment pollutants (pm 10, pm 2.5), drugs, etc.

Many of these substances are potentially carcinogenic[39], they can interfere with the endocrine system and they can behave like estrogens[40-42].

Many scientific studies now agree that lifestyle, understood as diet, physical exercise, weight control, reducing alcohol consumption and smoking cessation[42-44], on the one hand, and the interaction with the environment and genetics, on the other, can be considered the major triggering factors of cancer disease.

In particular, the environment toxic substances[45] interact with our DNA altering it and damaging cell functions.

Under these environmental influences, cancer disease can develop in our body. The liver is the main organ responsible for deactivating and removing these substances from the body.

Among its fundamental functions, the liver also operates detoxification, a process where the exogenous and endogenous toxins (xenobiotic) can be rapidly deactivated, so that they cannot trigger any reaction from our immune system. By doing so, they protect it, so that it cannot start any pro- inflammatory impairment (TH2 type) and, at the same time, inhibition of defences, which provide protection from carcinogenic cells and devious viral agents (TH1 type).

This happens when the liver accomplishes his functions, in a balanced way, without triggering any immunologic alterations, but simply removing

correctly the inactivated toxins with the bile and intestinal flux or through kidney excretion. These complex operations are carried out by particular enzymes called of Phase I, II and III, which work in sequences; in order to function properly, they need specific vitamins, minerals and amino acids. In this regard, correct nutraceuticals integration, designed by expert therapists case by case, represents a very good strategy for preventing cancer disease development. Moreover, nutraceutics has proved to be a very important support for protecting the liver from the side effects of chemotherapy drugs, such as the non-alcoholic fatty liver disease (NAFLD) or the chemo/radio therapy induced mucositis, providing that the galenic formulation of the used plants does not interfere with the metabolism of traditional drugs. Therefore, it is important to consider, as an add-on therapy, the use of phytosomal or liposomal extracts, with a highly absorbing power and processed with soy lecithin (non GMO), so that no interferences with liver cytochromes occur, as it can conversely happen with the same extract (curcuma longa and piperine) in a non phytosomal form[46].

CONCLUSIONS AND FUTURE OUTLOOK

The use of CAM by cancer patients is an outstanding issue that requires greater attention by the scientific community and physicians.

We believe that physicians should expand their knowledge of CAM interventions, their beneficial effects and potential toxicity. Discussion of CAM interventions and guidance on potentially beneficial therapies and potential toxicities is a task that physicians should undertake. Extensive research is required to assess actual CAM use and dosage in different patients and to work towards an integrated model of healthcare provision, which could also inform appropriate EU legislation.

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Conflict of Interest:

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

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