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# Nutraceuticals and diet in human health and disease. The special issue at a glance

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## ABSTRACT

This first Special Issue collects fifteen original research and up-to-date review articles addressing the beneficial properties of herbal products, nutrient supplements, dietary regimens, and functional food for the complementary therapy of human pathologies. In these articles, renowned scholars present and discuss the curative effects and the molecular mechanisms of action of nutraceuticals, medicinal herbs, and dietary regimens that have been proven effective in the treatment of cancers, metabolic syndrome, fatty liver disease, heart arrhythmia and neurodegenerative disorders.

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## 1. Introduction

Nutraceuticals, medicinal herbal products, and diet regimens have been shown to elicit health promoting, preventive and curative effects toward many different pathological conditions, such as cardiovascular diseases,<sup>1</sup> the metabolic syndrome,<sup>2</sup> and age-related frailty<sup>3</sup> including cognitive decline and neurodegenerative disorders.<sup>4,5</sup> A variety of nutraceuticals have shown potential anticancer activity via multiple pathways.<sup>6,7</sup> Additionally, specific diet regimens such as ketogenic diet and caloric/protein restriction diet have been shown to benefit cancer patients undergoing radio- and chemotherapy and to prevent cancer cachexia.<sup>8–12</sup>

Taken together, the whelm of data supporting the benefits of such complementary medical strategies strongly supports their integration in the protocols for the treatment of human pathologies.

## 2. The special issue at a glance

The Journal of Traditional and Complementary Medicine is committed to providing the community of biomedical scientists and clinicians with a platform for the publication of articles covering a wide range of medical practices, including the use of natural dietary supplements, that are effective in treating diseases as part of an

integrative approach.<sup>13</sup> In this Special Issue we have collected fifteen original research and up-to-date review articles addressing the historical/traditional use and the beneficial properties of herbal products, nutrient supplements, dietary regimens, and functional food in preventing and combating human pathologies (Table 1).

**The ketogenic diet**, i.e., a high-fat, low-carbohydrate and amino acid rich diet, has been shown to reflect differently on the cellular metabolism of normal and cancer tissue, sensitizing the latter to killing therapies.<sup>14,15</sup> Here, **R Klement and collaborators** studied the impact of the ketogenic diet on the body composition of cancer patients undergoing radiotherapy. They show that a ketogenic diet in association with amino acid supplementation may reduce the fat mass while preserving the skeletal muscle mass in rectal and breast cancer patients. The authors conclude that the ketogenic diet along with ample amino acid intake is safe and can improve the fat-free body mass during radiotherapy in cancer patients.

**Free fatty acids (FFAs)** have been shown to play a role in the pathogenesis of **prostate cancer** by altering the metabolism and the proliferation and invasive behavior of prostate cancer cells.<sup>16</sup> Accordingly, the serum of patients with prostate cancer features abnormal levels of FFAs.<sup>16</sup> Interestingly, there is a continuum of increased levels of serum FFAs along with progression from prostatitis to benign prostate hyperplasia and prostate cancer. This suggests that inhibition of *de novo* FFA synthesis could be a valuable strategy to prevent the pathogenesis and progression of prostate cancer.<sup>17,18</sup> Here, **S V Singh and collaborators** studied the molecular mechanisms through which the ethanol extract of *Withania somnifera* root (WRE), a medicinal plant used in Ayurvedic medicine, inhibits the

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**Table 1**  
The selected articles at a glance.

TOPIC	AUTHORS	TITLE	TYPE OF ARTICLE	FOCUS ON
Ketogenic diet	RJ Klement, G Schäfer, RA Sweeney	A ketogenic diet exerts beneficial effects on body composition of cancer patients during radiotherapy: An interim analysis of the KETOCOMP study	original	Body mass composition in cancer patients undergoing radiotherapy
Prostate cancer	S–H Kim, KB Singh, E–R Hahm, BL Lokeshwar, SV Singh	<i>Withania somnifera</i> root extract inhibits fatty acid synthesis in prostate cancer cells	original	Inhibition of lipidogenesis in cancer cells by <i>Withania somnifera</i>
Colorectal cancer	H–J Shin, D–H Kim, X Zhong, H–W Yum, S–J Kim, K–S Chun, H–K Na, Y–J Surh	Preventive effects of Korean red ginseng on experimentally induced colitis and colon carcinogenesis	original	Inhibition of inflammation and colon carcinogenesis by <i>Korean Red Ginseng</i>
Ovarian cancer	JH Ha, M Jayaraman, R Radhakrishnan, R Gomathinayagam, M Yan, Y–S Song, C Isidoro, DN Dhanasekaran	Differential effects of thymoquinone on lysophosphatidic acid-induced oncogenic pathways in ovarian cancer cells	original	Inhibition of cell migration by <i>Thymoquinone</i>
Ovarian cancer	L Vallino, A Ferraresi, C Vidoni, E Secomandi, A Esposito, DN Dhanasekaran, C Isidoro	Modulation of non-coding RNAs by resveratrol in ovarian cancer cells: In silico analysis and literature review of the anti-cancer pathways involved	original	Non-coding RNA profiling in <i>Resveratrol</i> -treated cells
Cholangiocarcinoma	S Thongchot, M Thaneer, W Loilome, A Techasen, T Boonmars, P Sa–Ngiamwibool, A Titapun, P Yongvani, C Isidoro, N Namwat	Curative effect of xanthohumol supplementation during liver fluke-associated cholangiocarcinogenesis: Potential involvement of autophagy	original	Autophagy-mediated cancer cell death induced by <i>Xanthohumol</i>
Non-Melanoma Skin Cancers (NMSC)	RR Prasad, S Paudel, K Raina, R Agarwal	Silibinin and non-melanoma skin cancers	review	Inhibition of UVB-induced NMSC by <i>Silibinin</i>
Metabolic syndrome	MA Khatuna, S Sato, T Konishi	Obesity preventive function of novel edible mushroom, Basidiomycetes-X ( <i>Echigoshirayukidake</i> ): Manipulations of insulin resistance and lipid metabolism	original	Basidiomycetes X powder reduces the adipose tissue and restores insulin sensitivity in obese mice.
Metabolic syndrome/PCOS	M Caputo, E Bona, I Leone, MT Samà, A Nuzzo, A Ferrero, G Aimaretti, P Marzullo, F Prodham	Inositols and metabolic disorders: From farm to bedside	review	Dietary Inositol improves hormonal disequilibrium and insulin sensitization
Non-Alcoholic Fatty Liver Disease (NAFLD)	S Panyod, L–Y Sheen	Beneficial effects of Chinese herbs in the treatment of fatty liver diseases	review	Herbal medicine to prevent and counteract fatty liver diseases
Non-Alcoholic Fatty Liver Disease (NAFLD)	V Musolino, M Gliozzi, E Bombardelli, S Nucera, C Carresi, J Maiuolo, R Mollace, S Paone, F Bosco, F Scarano, M Scicchitano, R Macrì, S Ruga, MC Zito, E Palma, S Gratteri, M Ragusa, M Volterrani, V Mollace	The synergistic effect of <i>Citrus bergamia</i> and <i>Cynara cardunculus</i> extracts on vascular inflammation and oxidative stress in non-alcoholic fatty liver disease	Clinical trial	Polyphenol extracts from <i>Bergamot</i> ( <i>Citrus bergamia</i> ) and <i>Cynara cardunculus</i> improve NAFLD in diabetic patients
Cardiac arrhythmias	A Beik, S Joukar, H Najafipour	A review on plants and herbal components with antiarrhythmic activities and their interaction with current cardiac drugs	review	Herbal compounds with anti-arrhythmic properties
Multiple Sclerosis	AD Fuzimoto, F Brigo	The “Treatise on the spleen and stomach” ( <i>Pi Wei Lun</i> ) as the first record of multiple sclerosis in the medical literature – A hypothesis based on the analysis of clinical presentation and herbal medicine	review	Herbal remedies for inflammatory autoimmune neuro-demyelination
Neurodegenerative diseases	A Prasansuklab, JM Brimson, T Tencomnao	Potential Thai medicinal plants for neurodegenerative diseases: A review focusing on the <i>anti</i> -glutamate toxicity effect	review	Herbal products protecting from glutamate neuronal excitotoxicity
Neuroplasticity, neurodegeneration, glioblastoma	L Colucci–D’Amato, G Cimiglia	<i>Ruta graveolens</i> as a potential source of neuroactive compounds to promote and restore neural functions	review	Neuroprotective function of <i>Ruta graveolens</i> : potential beneficial effects in neurodegeneration and in glioblastoma

lipidogenesis in human prostate cancer cells. They show that WRE can reduce the intracellular levels of acetyl-CoA, total free fatty acids, and neutral lipid droplets in prostate cancer cells by decreasing the expression of several key enzymes involved in fatty acid metabolism.

**Colorectal cancer** is among the most common and deadliest cancers in Western countries; its pathogenesis has been linked to life-style diet and chronic inflammation, besides genetic predisposition.<sup>19,20</sup> Particularly, chronic inflammatory bowel disease poses a risk of developing colitis-associated cancer, which can be prevented by inhibiting the COX-2 downstream signaling.<sup>21</sup> Here, **Y-J Surh and collaborators** show that *Korean Red Ginseng* (KRG) can prevent the progression from colitis to colitis-associated colorectal cancer through multiple mechanisms. At molecular level, KRG inhibited the expression of cyclooxygenase-2 (COX-2) and of inducible nitric oxide synthase (iNOS) in experimental models of colitis and colitis-associated colon carcinogenesis. Based on these data, the authors propose KRG as an adjuvant chemopreventive agent for preventing inflammation-associated colorectal cancer.

**Ovarian cancer** ranks as the fifth most common and as the most lethal gynecologic tumor in women worldwide. The metabolic cross-talk between cancer and stromal cells in the tumor microenvironment (TME) plays a pivotal role in determining the malignant behavior of ovarian cancer cells.<sup>22,23</sup> Lysophosphatidic acid (LPA), a lipid growth factor present in high concentration in the TME of ovarian cancer, has been shown to regulate multiple oncogenic pathways<sup>24</sup> in ovarian cancer cells and to corrupt the glucose metabolism and the phenotype of cancer associated fibroblasts.<sup>25</sup> Here, **D N Dhanasekaran and collaborators** investigated the ability of *Thymoquinone* (TQ), a phytotherapeutic from *Nigella sativa* with anticancer properties, to inhibit LPA-induced oncogenic activation in ovarian cancer cells. TQ was unable to attenuate LPA-stimulated proliferation or metabolic reprogramming in ovarian cancer cells, yet it potently inhibited the basal and LPA-stimulated migratory and invasive capabilities of ovarian cancer cells.

**Resveratrol** (RV), a polyphenol abundant in grapes, berries, and nuts, is a caloric/protein restriction mimetic and a well-known nutraceutical with anticancer properties.<sup>26</sup> RV has been shown to be a strong inducer of autophagy, a homeostatic lysosomal degradation process, in ovarian cancer cells.<sup>27</sup> Previous study showed that RV inhibits the migration-response to the inflammatory cytokine IL-6 in ovarian cancer cells via micro-RNA-mediated activation of autophagy.<sup>28</sup> Here, **C Isidoro and collaborators** report the **profiling of microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) in ovarian cancer cells** exposed to RV. They employed Diana tools and Gene Ontology (GO) pathway analyses along with Pubmed literature search to identify the biochemical pathways and functional processes potentially modulated by the dysregulated miRNAs and lncRNAs. Globally, RV increased the expression of tumor suppressor non-coding RNAs and downregulated the expression of oncogenic non-coding RNAs. The authors concluded that RV could exert its anticancer activity via non-coding RNAs epigenetic modulation of the pathways governing cell homeostasis (including glucose metabolism and autophagy), cell proliferation, cell death and cell motility.

**Cholangiocarcinoma** arises from the malignant transformation of cholangiocytes, the epithelial cells lining the bile ducts. Its pathogenesis and aggressiveness have been associated with the desmoplastic stroma of the hepatobiliary tract, characterized by intense fibrosis and high content of pro-inflammatory cytokines. Previous data showed that Resveratrol can interrupt the release of IL-6 by cancer associated fibroblasts and by doing so it can restore autophagy and limit the proliferation and invasive capabilities of cholangiocarcinoma cells.<sup>29</sup> Drugs modulating autophagy have been shown to promote cell death, reduce invasiveness capacity and sensitize cholangiocarcinoma cells to chemotherapy.<sup>30,31</sup> Here, **N Namwat and collaborators** show that *Xanthohumol* (XH), a

flavonoid found in *Humulus lupulus*, exerts antitumor activity in an experimental animal model of liver fluke cholangiocarcinogenesis by inducing autophagy. On dissecting the molecular mechanisms, it was found that XH induced autophagy-dependent apoptosis in cholangiocarcinoma cells.

**Ultraviolet B (UVB) radiation** causes DNA aberrations (such as thymine photodimerization), oxidative stress, inflammatory responses, and altered cellular signaling that ultimately contribute to the development of skin cancers, among which **Non-Melanoma Skin Cancers** (NMSCs) are the most prominent.<sup>32</sup> A variety of herbal-derived products have shown the potentiality to protect skin cells from UVB damage.<sup>33–35</sup> In this review article, **Agarwal and collaborators** summarize the experimental data on the protective and preventive potential of milk thistle plant-derived *silymarin* and/or *silibinin* against UVB-induced NMSC in pre-clinical settings. Particularly, silibinin was shown to prevent UVB-induced thymine dimerization, to promote DNA repair, to induce p53-mediated apoptosis in DNA-unrepaired damaged cells, and to trigger an anti-inflammatory response, thus supporting its potential use to prevent and/or manage NMSCs.<sup>36,37</sup>

**The metabolic syndrome** refers to a complex pathophysiological condition characterized by obesity and inflammation of visceral adipose tissue, insulin resistance and hyperglycemia, dyslipidemia with atherosclerosis, and hypertension that associates with increased risk of cardiovascular disease and type 2 diabetes mellitus.<sup>38,39</sup> Such a complex and interconnected comorbidities could be targeted by nutraceuticals and/or functional food able to impinge simultaneously on multiple biochemical pathways.<sup>40–42</sup> Here, **T Konishi and collaborators** present original data showing that the edible Japanese mushroom *Echigoshirayukidake* (classified as *Basidiomycetes* X, BDM-X) counteracts typical features of metabolic syndrome such as insulin resistance, Type 2 diabetes, obesity, and adipose inflammation. The experiments were conducted in a genetically defined obese model rat (OLETF, Otsuka Long Evans Tokushima Fatty) supplemented with the BDM-X powder extremely rich of antioxidant polyphenols and of  $\beta$ -glucan. The treatment reduced the adipose tissue, restored insulin sensitivity, and reduced plasma adiponectin. Based on these data, the authors propose BDM-X as a new resource applicable to the functional foods or the complementary biomedicines to prevent metabolic syndrome leading to type 2 diabetes.

Another natural molecule that has shown promises for the management of the metabolic syndrome is **Inositol (or myoinositol)**, which is abundantly found in many fruits.<sup>43</sup> In their review article, **F Prodam and collaborators** point to the role of inositol in the regulation of several hormones with a focus on its dietary intake and the role of the gut microbiota in the intestinal uptake. Inositol acts as an insulin-sensitizing agents and free radical scavengers, and thus improves insulin-resistance and inflammation. To be noted, inositol deficiency may also underlie the **Polycystic ovary syndrome (PCOS)**, characterized by defective oocytes maturation, infertility and menstrual irregularity, which often associates with the metabolic syndrome. Accordingly, supplementation with the isoform *D-chiro-inositol* helps to manage the metabolic alterations associated with PCOS.<sup>44</sup>

Linked to the metabolic syndrome is the **Non-Alcoholic Fatty Liver Disease (NAFLD)**, which represents an additional risk factor for cardiovascular diseases.<sup>45</sup> Consumption of so-called “Junk food” rich of fat and sugar increases the risk of developing fatty liver disease. Plant-derived polyphenols and flavonoids may represent an ally in the treatment of NAFLD.<sup>40</sup> For instance, the essential oil from garlic or from ginger has been shown to improve lipid accumulation, inflammation, and fibrosis in the liver of obese mice fed with high-fat diet.<sup>46,47</sup> **S Panyoda and L-Y Sheen** have reviewed the literature and here list the herbal medicines with the potential to prevent NAFLD.

**Insulin resistance and type 2 diabetes mellitus (T2DM)** along with adipose inflammation worsen non-alcoholic steatohepatitis

further stimulating the fibrotic processes toward **NAFLD**, and bergamot polyphenols can prevent such progression.<sup>40,48–50</sup> **V Molace and collaborators** conducted a randomized, double blind, placebo-controlled clinical study to evaluate the antifibrotic effect of *Bergacyn*, an innovative formulation combining Bergamot (*Citrus bergamia*) Polyphenolic Fraction (BPF) and extract of *Cynara cardunculus* (CyC). The study showed that concomitant administration of BPF and CyC reduced the serum markers of oxidative stress and inflammation while improving liver fibrosis and function in T2DM patients. These preliminary data support the inclusion of this polyphenol formulation in the therapeutic strategy to counteract vascular inflammation and fibrosis in patients suffering from T2DM and NAFLD.

**Cardiac arrhythmias** (including bradycardia, tachycardia, flutter, fibrillation) are responsible for at least half of sudden cardiac arrests. In their article, **H Najafipour and collaborators** have reviewed the literature on the plants and herbal compounds with anti-arrhythmic properties. They found thirty-six herbs or their derivatives that showed potentially effective in the treatment of arrhythmias in animal and cellular models, and for which the mechanism of action had been investigated. The most promising ones were *dauricine*, an alkaloid from *Asiatic Moonseed Rhizome*, and *sophocarpine*, an alkaloid from *Sophora flavescens*, that inhibit cardiac transmembrane Na<sup>+</sup>, K<sup>+</sup>, and Ca<sup>2+</sup> ion currents thus prolonging the action potential duration and effective refractory period.<sup>51,52</sup> The authors also warn on the possible synergistic interaction of certain herbal components (e.g., Hawthorn, Licorice and Ginseng) with cardiac glycosides.

**Multiple sclerosis (MS)** is an inflammatory autoimmune-mediated neurological disorder characterized by axon demyelination in the central nervous system. The pathology was well described in details with histological and clinical correlates by Jean-Martin Charcot in 1868, who introduced the term “la sclérose en plaques” for the focal damages in the white and gray matter tissues caused by infiltration of immune and inflammatory cells.<sup>53,54</sup> Here, in their interesting review article **A Fuzimoto and F Brigo** trace the history of the description of the disease and make an interesting comparison with the first description of MS-related symptoms given by the Chinese physician Li Gao (who lived in 1180–1251, during the Jin dynasty). The authors made an excellent search on the effective curative potential and the molecular mechanisms of action of the herbal remedies (the ones more effective are *Astragal radix*, *Ginseng radix*, *Glycyrrhizae radix*, and *Berberine*) proposed by Li Gao in his treatise *Pí Wèi Lùn* (脾胃论 “Treatise on Spleen and Stomach”) to manage this invalidating neurological disorder.

Chronic and age-related **neurodegenerative diseases** (e.g., Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, fronto-temporal dementia, others) are associated with progressive neuronal loss in the central nervous system. Excitotoxicity and pro-oxidant free radicals may lead to neuronal cell death through inhibition of the autophagy-lysosomal clearance of damaged mitochondria and of abnormally folded neuroproteins that eventually accumulate in the cells.<sup>55–57</sup> A variety of nutraceuticals and herbal-derived compounds have been shown neuroprotective activity in experimental *in vitro* and *in vivo* models of neurodegenerative diseases.<sup>58,59</sup> As glutamate is a major excitatory neurotransmitter in the brain, oxidative stress linked to excessive glutamate is believed to play a major role in neurotoxicity and neurodegeneration.<sup>60</sup> Here, **Tencomnao and collaborators** present a comprehensive review of the medicinal plants with *anti*-glutamate toxicity properties. In particular, they focus on six candidate plant species of Thailand (namely, *Acanthus ebracteatus*, *Cleistocalyx nervosum*, *Pueraria mirifica*, *Rhinacanthus nasutus*, *Streblus asper*, *Bacopa monnieri*) that could be a promising resource for prevention and complementary therapy of neurodegenerative diseases, describing their active constituents and mechanism of action against glutamate toxicity-mediated neuronal cell death.

Promoting **neuroplasticity** is another therapeutic strategy to

slow down age-related neurodegeneration,<sup>61</sup> and a variety of nutraceuticals have been shown promising in restoring brain function after neuronal injury.<sup>62</sup> In this contest, *Ruta graveolens* is gaining attention because of its content of neuroactive compounds potentially able to promote neuroprotection. Here, **L. Colucci-D'Amato and G. Cimaglia** have reviewed the neuroprotective properties and the mechanisms of action of *rutin*, the most abundant bioactive component of *Ruta graveolens*, in a variety of experimental settings of neurodegeneration.

### 3. Concluding remarks

Nutraceuticals are natural compounds found in dietary aliments that have nutritional and therapeutic potentials to prevent or cure pathological conditions as well as to improve health and longevity, and to promote the quality of life.<sup>63</sup>

The articles collected in this Special Issue of the Journal of Traditional and Complementary Medicine add to our knowledge on the health benefits provided by specific dietary regimen, nutrient supplements, herbal nutraceuticals and edible mushrooms for the cure of cancer, metabolic syndrome, fatty liver disease, cardiovascular diseases and neurodegenerative diseases.

These studies provide the scientific ground for and encourage the implementation of preventive and curative strategies based on the inclusion of nutraceuticals, dietary regimens, and a healthy lifestyle in an integrative approach to treat the disease and, overall, the patient.

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