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Verbanac, Donatella; Maleš, Željan; Barišić, Karmela

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Mini-review

Nutrition – facts and myths

DONATELLA VERBANAC[1,*]
ŽELJAN MALEŠ[2]
KARMELA BARIŠIĆ[1]

[1] *University of Zagreb Faculty of Pharmacy and Biochemistry Department of Medical Biochemistry and Hematology, HR-10000 Zagreb, Croatia*

[2] *University of Zagreb Faculty of Pharmacy and Biochemistry Department of Pharmaceutical Botany HR-10000 Zagreb, Croatia*

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Taking responsibility for your life, among other factors, means also considering what to eat and which nutrition pattern to follow. Everyone needs to think about what they put on the plate and which ingredients should be avoided. Food, as such, will never be a drug or medication, like a painkilling tablet relieving pain in a short amount of time, for example. However, proper nutrition is our ally in the prevention of diseases, maintaining balance in our body and our mind. By following the main principles of a healthy diet, the physiological homeostasis can be managed, as well as faster recovery from disease achieved.
This review is aimed at summarizing basic principles of nutrition recommendations and at empowering stakeholders (pharmacists, medical biochemists, physicians) to be able to communicate to their patients and customers healthy and sustainable nutrition choices through the personalized advice.

Keywords: nutrition, personalized approach, biologically active substances, Mediterranean diet, liquid biopsy, microbiota

Food and nutrition are the key issues challenging today's humankind. Ignorance in human nutrition results in a series of modern illnesses (most known is metabolic syndrome, characterized by elevated blood pressure, diabetes, atherosclerosis, and cardiovascular disease in general). Asked what, how and why we eat, each of us will give an answer that will seem to be justified and acceptable. Nevertheless, if we ask questions about how healthy our eating habits are, many of us will be confused because it is not easy to answer that question. Today's nutritional trends are changing very rapidly. For example, the study led by Canadian researchers' shows that moderate saturated fat consumption may lower risk of stroke (1), which opposes previously widely accepted recommendations for avoiding food rich in these ingredients (2). Recent systematic evaluation of dietary consumption patterns across 195 countries published in Lancet (3) reveals that inappropriate, poor dietary habits are responsible for more deaths than any other risks globally, including tobacco smoking (4). Namely, millions of people are dying around the world from poor, processed diets, often high in sodium and lacking in whole grains and fruits, according to

* Correspondence, e-mail: dverbanac@pharma.hr

a study published (5). The report states that one on five deaths (about 11 million/year) is linked to unhealthy eating habits, which could also be attributed to the lack of nutrients. A study of 2017 (6) concluded that the majority of the population does not consume enough nuts, seeds, milk and whole grains while it consumes too much of processed meat, with high sodium content, sugary meals and drinks. All over the world, about 10 million people annually die due to cardiovascular disease; 913.000 from cancer and almost 339.000 from type 2 diabetes (3). Ironically, the contrary behaviour of taking over-care on nutrition and deliberately, by purpose, avoiding necessary food and nutrients from the everyday diet is taking its toll. Eating habits leading to continuous dietary restrictions are responsible for the increase in the incidence of anorexia nervosa (7), as well as nutritional deficiencies in children on a restricted diet. These nutrition patterns are self-chosen by children with some types of social, behavioural disorders or selected by their parents; and are mainly due to nutrition misrepresentation, alternative nutrition treatments, cultural inclinations or misunderstandings regarding food tolerance (8).

Healthy nutrition can be an ally in combating some still unmet medical needs. Everyone needs to think about what he or she puts on the plate and which ingredients should be avoided in order to have a relatively good metabolism and maintain the physiological and psychological balance. Nowadays, people tend to adopt some of the nutrition habits of their predecessors. This is probably due to the fact that we are plagued by the epidemic of chronic diseases such as obesity, type 2 diabetes, atherosclerosis, heart attacks, stroke and different types of malignancy. Moreover, getting back to the ancestors' style of nutrition is encouraged by the benefits received when following an equilibrated diet, which is primarily observed through the growing popularity of the Mediterranean diet. It is based on the extensive use of seasonal fruits and vegetables, providing varied, but straightforward menus that include low processed ingredients with high nutritional value (9).

What type of nutrition to recommend to an individual depends on their physiological condition, age, biochemical and haematological findings, and is related to the personal lifestyle (10), so the diet regimen should reflect person's daily physical and mental activities.

Finally, a large number of factors affects our diet. We eat to meet the basic physical, physiological and emotional needs. The main reason we eat is to satisfy the sense of hunger, but we often eat because of happiness, the feeling of pleasure and joy provided by the food we eat. It is also happening that we eat because of despair, sadness or because we have encountered "insolvable" situations, so we are looking for comfort in food. Each individual has certain eating habits that have developed mainly during childhood (11). These habits may change over the years, primarily due to a change of a way of life, but certain eating--related rules remain with us forever.

What are the nutrition myths?

Usually, dietary myths are related to concepts on nutrition that are poorly supported or contradicted by scientific evidence (12). Nowadays, we are provided more than ever with the commercials and advice that wealthy and less affluent people are willing to follow in order to ensure a healthy, good quality life and well-being. Here, the irrational situation has taken place in which people become addicted to so-called healthy food, bioproducts, organically produced fruit and vegetables and very often are putting themselves on restricted calorie intake. These self-selected diets are mainly based on nutrition misinfor-

mation, cultural preferences, alternative nutrition therapies, or misconceptions regarding food tolerance. Health care providers must be involved in monitoring both growth and feeding patterns particularly in children and younger people to identify inappropriate dietary changes that may result in nutritional deficiencies (8).

We are also witnessing a big movement towards the macrobiotic diet, particularly among severely ill patients (13). Very often, this happens without understanding the real origins, means and purpose of this diet that represents a basis of far-east nutrition pattern, which is quite different from the western-based civilization. Specifically, in 1897 Japanese physician Sagen Ishizuka, published in Japanese "A Chemical Nutritional Theory of Long Life" describing a new type of diet based on integral grains and vegetables that can eliminate many health-related issues. Hundred years later, at the beginning of the twentieth century, the American writer of Japanese origin, George Ohsawa, claimed to have cured tuberculosis thanks to this diet. Ohsawa dedicated himself to the goal of popularizing Ishizuka's diet. He elaborated ideas almost two centuries old, believing that such a diet provides greater resistance to disease and enables a better quality of life, with total health, both body and mind. Ultimately, Ohsawa believed that such a diet can greatly extend life expectancy, hence giving it the name of a macrobiotic diet, forming the name of the original Greek word "macros", meaning big, and "bios", which means life (14).

Since the macrobiotic diet is basically a low calorie, low in saturated fats and rich in plant fibers, minerals and complex carbohydrates, it makes it possible to significantly reduce the risk of developing degenerative diseases associated with obesity, increased fat and cholesterol levels, high blood pressure and digestive disorders (15). Although there was initially a doubt as to whether the man of Western civilization is to follow such a diet, today macrobiotics is rapidly penetrating the western lifestyle, especially among higher educated people, who are increasingly developing an awareness of health and nutrition. Many characteristics of presently popular dietary recommendations (eating fresh, in-season, locally grown, organic foods) are reflected in macrobiotic diet and lifestyle (16).

Vegetarian nutrition pattern

People become vegetarians for different reasons. In the past, these were guided by religious rules, and today they are ecological, ethical, philosophical and economic reasons. Of course, many people become vegetarians for the sake of better health, since numerous studies have shown that there is a correlation between the vegetarian type of diet and the reduced occurrence of metabolic diseases, particularly insulin resistance diabetes type 2 (17). Obesity and associated complications such as vascular disease, elevated blood pressure, diabetes, and oncological diseases are among the first in this group. The main features of the vegetarian diet are reduced total fat content, saturated fatty acids and cholesterol, and increased overall nutritional content of the meals. The last few are useful for regulating intestinal function and maintaining "reasonable" glucose and blood cholesterol levels (17, 18). Most importantly, such nutrition ensures increased intake of fruits and vegetables – ingredients that, due to their high antioxidant, fibers and minerals content prevent the development of some forms of malignancies, vascular diseases, and degenerative diseases, and at the same time increase endurance (19, 20).

If a vegetarian diet is varied and well balanced, it can certainly be a basis for good health, as well as for environmental sustainability (21). However, this is not applicable to

more restrictive vegetarians – vegans, who also feed on foods of plant origin but opt for only certain species. It is immediately apparent that nutrition that escalates to exclude a large number of foods can hardly ensure the intake of all necessary nutritive components. Therefore, if strict dietary management is associated with unbalanced and deficient intake of nutrients, the potential dangers of such a diet should be known. This is especially true for calcium, vitamin D and vitamin B12 deficiencies, but also some amino acids, zinc and iron, which should be monitored closely, especially in children (22).

As far as protein is concerned, *i.e.* amino acids as their basic building blocks, it is possible to meet the daily needs by supplying only plant food, by combining certain foods, which should also provide an appropriate intake of total calories to meet the daily energy needs (18, 20). However, if the foods are not adequately combined to assure such amino acid complementarity, there is a risk of various disorders associated with certain nutritional deficiencies, as already mentioned (7, 8).

Proteins and amino acids – new perspectives

Many nutrition myths are also related to the daily protein intake. Proteins are named from the Greek word meaning "the first" or "πρωτεο» and since our body is subjected to a daily struggle for life, we need a "dependable power supply" of protein in order to "fix" the damaged structures in the body, at any time. Recommended daily protein intake for healthy adults is 0.8–1.0 grams per kilogram of body weight (23). Sometimes conventional wisdom is that an adult needs a daily amount of more than 1 gram per kilogram of body weight, referring to the organisms in an intense growth and development, and persons who are engaged in intense physical or intellectual work (24). Intake of over 1.2 to 1.5 g kg^{-1} body weight is recommended for athletes during the preparation and process of building muscle mass, but this intake should be supervised by a professional (25). For professional "body-builders", the amount of input protein depends on the phase of preparation for competition; a daily intake ranges from 2 to 2.5 g kg^{-1} body (26). Such high amounts of protein cannot be taken and ingested through the regular 5–6 daily servings. In this case, only exceptionally, athletes can drink shakes as an additional portion of protein, and take amino acids and their mixtures as supplements. It is important to take these within 2 to 3 hours after meals to ensure efficient utilization of the consumed protein to build muscle (27).

Very popular types of diets today, such as high protein/low carb diet and ketogenic diet can be beneficial in some diseases, such as epilepsy (28), but in the long-term result in acidosis and potential intoxication of the body. Outside its application as an epilepsy therapy, the ketogenic diet has been considered a potential treatment for a variety of other neurological and metabolic disorders such as Alzheimer's disease, Parkinson's disease, and glaucoma (29). Studies on an experimental animal are showing promising results in these areas (30). However, many issues such acidosis, gastrointestinal system disturbances, reduced appetite are associated with ketogenic nutrition patterns are still subject of debates and myths associated with them can be dispersed only when the evidence-based, long-term human studies will be completed (29).

Mediterranean diet

We are witnessing a breakthrough of new products which, until recently, did not exist in our everyday lives. Many of them find their way to our table, bringing along new flavors

and changing our dietary habits gradually. Unfortunately, such nutritional changes are not always appropriate for our health. In today's modern world, more and more people might be heading in the wrong direction concerning their nutrition. Lack of time, combined with a principle of saving money, accounts for the enormous popularity of fast food. It is cheap, prepared instantly and full of strong flavors, but disturbingly imbalanced concerning nutritional value. We are using too much protein of animal origin in the form of meat products which are often a source of "bad" animal fats (which are usually "hidden"). Many times if vegetables are on our menu, they are often frozen or canned. This type of food, for the most part, does not compare with fresh food. Technological food processing, consumption of fast food and changes in tastes and habits are inevitably leading to negative consequences on people's health and often resulting in metabolic disorders and diseases such as pathological obesity, gastroenterological diseases, cardiovascular diseases, type 2 diabetes, *etc*. (31).

Is there "a salvage pathway"? The answer to this question is: yes there is, and the name of the "pathway" to follow is the "Mediterranean diet". The term Mediterranean diet refers to dietary patterns originated in the areas of the Mediterranean region. They were first described in nutrition-related literature in the 1960s (32). There are several variants of this diet (mainly due to the geographical location), but some common components can be identified (33): high consumption of olive oil; moderate wine consumption (red in particular); high consumption of vegetables, fruits, legumes, and grains; high consumption of fish; moderate consumption of milk and dairy products, mostly in the form of cheese, and low consumption of meat and meat products.

Many studies have so far demonstrated the health benefits of the Mediterranean diet (33–35). This evidence is strongest for coronary heart disease, but it also applies to some forms of cancer, mainly those associated to the digestive tract (36), prostate (37) and breast (38) and for the majority of chronic inflammatory diseases (34, 35). Recently, the Mediterranean diet has been ranked as the best nutrition patterns for 2019 according to the U.S. News Report (39). The evidence-based data recently collected report that by introducing the Mediterranean diet the overall health benefits can be achieved. The measurable outputs have shown that the levels of inflammatory markers (CRP, fibrinogen, homocysteine and LDL cholesterol) decrease, regardless of weight loss (35).

Studies concluded recently, reported that the well-balanced diets, such as the Mediterranean diet, bring four sustainable benefits: (*i*) major health and nutrition benefits; (*ii*) lower environmental impacts and richness in biodiversity; (*iii*) high sociocultural food value; and (*iv*) positive local economic returns (40).

Should we approach the Mediterranean diet by examining the impact of a dietary culture and synergistic effects of all ingredients rather than isolating single nutrients found in some foods? Presumably, the answer would be affirmative since the examination of single nutrients ignores the important and complex interactions between components of a diet. The discovery of oleochantal active component from olives, a compound capable of the inhibition of COX enzymes that exhibit the anti-inflammatory properties (41), resulted in extensive discussions on mutual synergistic properties among different compounds found in Mediterranean food concept of (42–44). Therefore, dietary recommendations to the population regarding the Mediterranean diet should include a whole-diet approach along with general lifestyle changes (45).

'Eat the Rainbow'

When it comes to healthy eating, this would be the best advice. That is because munching a variety of colorful ingredients gives us many different phytonutrients. There are thousands of these compounds in plants (and some are illustrated in Table I). They may fight disease, especially when they work together in synergy. Although most of them are not well absorbed by the body (46), there are data showing that they may help fight inflammation, some forms of cancer by clearing the body of free radicals before they damage the cells (47). However, additional research on these is needed.

Overweight and obesity – new insights

Overweight and obesity represent a growing medical and socioeconomic problem of modern society with numerous consequences on human health. Overweight individuals are at increased risk for developing chronic and degenerative conditions, from metabolic, cardiovascular and malignant diseases to increased susceptibility to infections and higher mortality rates (57). Apart from being energy storage, fat tissue also has numerous endocrine and immune functions. Fat tissue can induce insulin resistance, development of metabolic syndrome and, by secreting adipokines, directly contribute to inflammatory processes that make obesity a chronic inflammatory disease (58).

The human body is home to a large number of distinct microbial communities, with the thickest population in the distal gut – representing gut microbiota. Gut microbiota has an important role in obesity development since they perform important metabolic functions in nutrients digestion, absorption and metabolism. Also, the specific development of gut epithelia and the immune system are under the direct influence of gut microbiota. By inducing metabolic endotoxemia, microbiota contributes to the development of inflammatory processes in the organism. Along with pharmacological and surgical treatments, controlled weight loss in obesity can also be achieved by a balanced diet and by modulating gut microbiota with probiotics and prebiotics (59).

The dramatic rise of overweight and obesity levels in the population is associated with an increase in unhealthy diets and poor physical activity, which in turn increases the incidence of non-communicable diseases. Diet is one of the key modifiable health determinants. However, there is no "one best" and it is difficult to say which is the best diet for each one of us and it is not simple to engage people to take responsibility in changing their habits and maintain their personalized diets (60).

Microbiota as an inevitable player in diet selection

The vast array of gene products provided by resident microbes is known to diversely supplement the host's own metabolic processes. This includes the generation of energy from dietary components, an association that is, for example, essential with regard to polysaccharides and lipids. Further influences of the gut microbiota include modulation of neuro-hormones and gut-derived lipids, short-chain fatty acids, triglyceride clearance, vitamin biosynthesis and mucosa-associated immunity. Evidence from experimental animal models and human subjects indicate that changes in the gut microbiota (with prebiotics and/or probiotics) may participate in the control of the development of metabolic diseases associated with obesity and chronic degenerative diseases (59).

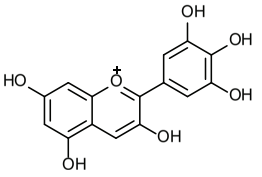
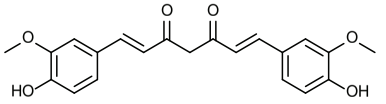
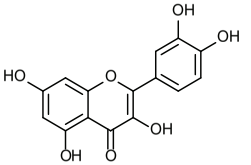
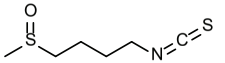
Although the majority of the population consumes half of recommended fermentable fibers intake, a diet that consists of high intake of fermentable fibers and plant polyphenols, appears to regulate microbial activities within the gut. These support regulatory guidelines and encourage increased consumption of whole-plant foods (fruit, vegetables and whole-grain cereals), and provide the scientific rationale for the design of efficacious prebiotics (61). Similarly, recent human studies with carefully selected probiotic strains show that ingestion of viable microorganisms with the ability to hydrolyze bile salts can lower blood pressure, a recognized risk factor in cardiovascular disease (CVD) (62). Taken together, such observations raise the intriguing possibility that gut microbiome modulation by whole-plant foods, probiotics and prebiotics may be at the base of healthy eating pyramids advised by regulatory agencies across the globe. Dietary strategies aimed at modulating gut microbiota or their metabolic activities are emerging as efficacious tools for reducing CVD risk (61), as well as inflammatory bowel disease (IBD) (63). The metabolic activities of gut microbiota facilitate the extraction of phosphorylated nucleotides (representing chemical energy) from indigested dietary substances, afterward stored in host adipose tissue for later use. Different mechanisms to explain the metabolic shift towards energy storage have been suggested: (1) the gut microbiota can increase the capacity to harvest energy from food and (2) the gut microbiota can modulate plasma lipopolysaccharides levels that activate the inflammatory tone and the onset of obesity, type 2 diabetes, and other chronic inflammatory diseases. Moreover, it has an additional activity on digesting and utilizing many biological polyphenols (64). The research on the gut microbiota is starting to give new interesting results.

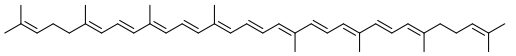
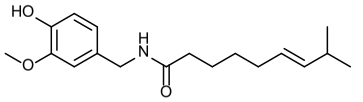
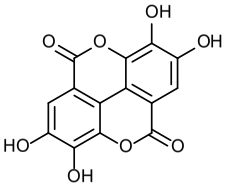
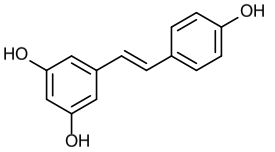
Substantial inter-individual variation in the response to diet and new analytical and diagnostics tools and methods development

Despite scientific, technological, and economic progress over the last century in eradicating issues of widespread food shortage and nutrient deficiency in the world, we are faced with a new set of nutrition challenges related to energy imbalance and metabolic disease, which require new approaches in solving them. Recent developments in the area of new analytical tools and methods (65) enable us to systematically study large quantities of detailed and multidimensional metabolic and health data, providing the opportunity to address current nutritional through the approach of precision nutrition (10). This approach integrates various sets containing big data on genes, transcripts, proteins, metabolites, microbiome composition, to expand our understanding of the complexity and diversity of human metabolism in response to diet. With the tools, we can get better insights into each individual's phenotype, health status, as determined through the interfaces between biochemistry, behaviur and environment. Diets serving allergies are particularly sensitive in this respect. The increase in the prevalence of food allergy (both physician-diagnosed and patient suspected) has led patients to pursue a variety of other alternative diagnostic procedures for suspected food allergy. These approaches include different methods from the IgG, electro-dermal and cytotoxicity testing to the provocation/neutralization and applied kinesiology. Many of these have largely been unproven and may lead to unnecessary elimination diets (66). More reliable and accurate methods are still to be developed.

The continuous search for new metabolic biomarkers that would replace the old ones has yielded a promising non-invasive and repeatable procedure called liquid biopsy,

Table I. Some food that contains pharmacologically active compounds, the chemical structure of these compounds and some beneficial effects known so far

Source/Ingredient	Active compound	Structure	Beneficial effects
blueberries, grapes, cranberries, cherries, red cabbage, and eggplant	anthocyanin		could help lower blood pressure and protect against diabetes, possesses antioxidative properties, helps in restoring gut microbiota and prevents malignant transformations (46)
turmeric	curcumin		may protect against type 2 diabetes, reduce inflammation, and fight depression (48)
apples, onions, berries, and red wine	quercetin		might ease asthma symptoms, lower cholesterol levels, fight obesity and exhibits immunomodulatory activity (49)
cruciferous veggies like broccoli, Brussels sprouts, cabbage, cauliflower, and kale	sulforaphane		helps in preventing the formation of several types of cancer (42, 44)

Source/Ingredient	Active compound	Structure	Beneficial effects
tomatoes, watermelon, and pink grapefruit	lycopene		possesses potential to help fight pathological proliferation and cancers, particularly prostate cancer (50, 51)
cayenne and other spicy peppers	capsaicin		helps in relieving pain from arthritis, fibromyalgia, and some types of nerve damage, as well as psoriasis itching. It's also being studied in cancer prevention; helps with weight loss (52, 53)
raspberries, strawberries, pomegranates and walnuts	ellagic acid		acts as fat burner and inhibitor of enzymes responsible for epigenetic transformations, claims are based on studies obtained on experimental animals, clinical studies on humans are yet to be performed (54, 55)
peanuts grapes, some berries red wine	resveratrol		has shown promise as a tumor suppressor, exhibit anti-inflammatory and brain booster properties (54, 56)

which involves sampling peripheral blood for diagnostic screening as well as determining response to therapy and evaluating the outcome of the disease (67). It was applied in cancer research, since peripheral blood can contain circulating tumor cells, circulating tumor DNA, and vesicular structures, the so-called exosomes, which are released into the circulation by the tumor cells (68), but also contains the whole variety of human and bacterial metabolites released in circulation by eukaryotic and prokaryotic cells living in the organism. Thus, in a non-invasive way, through the analysis of peripheral blood, the molecular profile of the disease can be established, the degree of affected tissue can be determined, and the response to the therapy can be estimated. Thereby, one of the essential ideas of precision medicine, accentuated almost ten years ago by the founder and establisher of new principles and ways of cure, Leroy Hood (69), comes true. In his lectures, Hood has persistently pointed out that in the new era of personalized approaches undertaken while assessing different conditions and diseases, "blood becomes a window through which we observe what is happening in the body" (70). The same idea was accepted and maintained by the other biomedical disciplines, from genetics to the personalized nutrition.

New tools of personalized nutrition include among genomics, proteomics, metabolomics, microbiomics, phenotyping, high-throughput analytical chemistry techniques, longitudinal tracking with body sensors, informatics, data science, and sophisticated educational and behavioral interventions. The role of experts working in biomedicine becomes crucial. The mission set by the scientists and scientific community, conveying scientific papers to educate the general public in all generation segments. For us, researchers in biomedicine, the mission is primarily oriented towards the people suffering from different medical conditions. In particular, this assumption is imposed when it comes to eating habits and nutrition because scientific knowledge in this area is rapidly changing. All these measures will allow the development of better personalized and predictive nutrition recommendations and interventions that have the potential to transform the way people make nutrients selections and finally improve the overall population health.

CONCLUSIONS

A new era will offer a new way to formulate and provide nutrition recommendation, as it combines approved concepts of customized, healthy nutrition with a high level of personalization and with consumer engagement and motivation elements. However, a detailed guideline that considers the most relevant personal factors to provide a scientifically grounded personalized diet is still needed. Customized support should also be integrated to help in adopting long-term healthy nutrition habits and to facilitate a personalized/precise food intake assessment and informed purchasing food choices. These would clearly contribute to the society in which very soon the consumers will be empowered to make a habit of healthy living by making sustainable, healthy dietary choices that fit their personal needs, health and behaviors, thereby preventing the development of chronic, no communicable diseases.

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