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BIOLOGICALLY ACTIVE INGREDIENTS FROM FOOD WITH ANTI-OBESITY PROPERTIES

Donatella Verbanac[1], Mihaela Perić[1], Hana Čipčić-Paljetak[1], Mario Matijašić[1] and Višnja Stepanić[2]

[1] University of Zagreb School of Medicine, Center for Translational and Clinical Research, Department for Intercellular Communication, Šalata 2, 10000 Zagreb, Croatia

[2] Laboratory for Epigenomics, Division of Molecular Medicine, Ruđer Bošković Institute, Bijenička 54,, 10002 Zagreb, Croatia

Summary

Despite the fact that almost all food possesses some pharmacological properties, there are food ingredients that due to their unique composition and mechanisms of action, exhibit moderate but still well recognized therapeutic effect. The ingredients that are responsible for this effect became gradually more interesting study topics in numerous academic and private research laboratories.

Obesity has already been recognized not only as an aesthetic, but also as a public health issue for several decades, while in the last ten years it has been classified as a disease. Number of obese people and subsequent obesity-related conditions is inevitably growing. The lack of effective drugs currently present at the market is highly evident. This directs the research into the new sources, such as the natural ones. Food is one of the most promising options that could be readily applied in searching for the new medicines for the prevention and treatment of obesity.

In addition to this, high importance is placed also on studying the relationship between the host and its microbiota, as this coexistence is responsible for the metabolic and physiological equilibrium, as well as bioavailability of some important nutraceuticals.

Application of tailor-made, personal approach in the prevention and treatment of obesity and parallel study of life-style impact on human epigenome, might significantly contribute to combat obesity - this growing issue of our civilization.

Key words: obesity; biologically active compounds; nutraceutical; drug discovery; microbiota; personalized medicine.

List of abbreviations:

AMPK – AMP-activated protein kinase; ATP – adenosine triphosphate; CCK – cholecystokinin; C/EBP-α – CCAAT/enhancer-binding protein alpha; CYP450 – cytochrome P450; DNMT1 – DNA (cytosine-5-)-methyltransferase 1; EGCG – epigallocatechin-3-gallate; FAS – Fas cell surface death receptor; FOXO3a – forkhead box O3 transcription factor; GLP-1 – glucagon-like peptide-1; IL-6 – interleukin 6; LPS – bacterial lipopolysaccharide; MnSOD – manganese superoxide dismutase; NF-kB – nuclear factor kappa-light-chain-enhancer of activated B cells; Nrf2 – nuclear factor erythroid 2 [NF-E2]-related factor 2; OXM – oxyntomodulin; P4 – prevention, prediction, patient's participation and personalization; PP – pancreatic polypeptide; PPAR-γ – peroxisome proliferator-activated receptor gamma; PYY3-36 – polypeptide PYY3-36; R&D – research and development; ROS – reactive oxygen species; SAM – S-adenosyl methionine; SIRT1 – sirtuin (silent mating type information regulation 2 homolog) 1 (*S. cerevisiae*); SREBP-1 – Sterol regulatory element-binding protein 1; TNF-α – tumor necrosis factor alpha

INTRODUCTION

From the molecules within the food ingredients towards new medicines

Although modern pharmaceutical drugs are commonly accepted as a miracle of the 20th century, the importance of food for achievement and maintenance of health should not be underestimated. Biologically active compounds present in food can have beneficial pharmacological effects on our organism and can promote wellbeing and health throughout the lifetime. However, we can never consider them equally efficient, effective and important as drugs since their therapeutic potential cannot be readily achieved through dietary regimens, as their healing properties are only visible in the long run. They are active, safe and available as synergistic element if used regularly for the prolonged period of time. Dietary intake can enhance our possibilities to reduce symptoms, heal faster and minimize disability.

The popularization of healthy diet design is no new phenomenon and yet the average consumer can be easily overwhelmed by the diversity of available approaches. Fortunately, medical professionals with a firm understanding of the basic nutritional principles common to any diet regimen can help guide their patients toward their best-suited options based not only on personal preferences but also on the emerging understandings of expected health implications of specific dietary choices [1].

On drug discovery…

Research and development (R&D) of a new drug product with targeted and precise therapeutically relevant response is very demanding, complex and expensive endeavor. The overall R&D process resulting with market launch of the new drug lasts up to 13.5 years, with an average cost of $1.8 billion that progressively increases. This is due particularly to the more demanding regulatory requirements and increasingly cost-constrained healthcare systems [2].

New marketing possibilities

Changing demographics and life expectations will generate 'new' patient populations and 'new' conditions. In order to develop and launch drugs in the most lucrative way, pharmaceutical industry needs to explore new areas of science and include targeted customer groups at the early phase of drug research and development process. The industry has to recognize where added value for patients, beyond just providing drugs, can be profitably achieved. After deciding on the main focus, they need to identify, retain or build specific capacities necessary to achieve their goals and gain significant advantages over the competitors [3].

The newly emerging market opportunities are mainly concentrated around the following segments – prevention, prediction, patient's participation and personalization (P4) of medical approach and therapies. New therapeutic options that are being developed in the last decade comprise small molecules, biologicals (e.g. recombinant proteins, gene therapy, stem cells-based approach), as well as nutraceuticals.

Obesity – threat and challenge

Obesity is a nutritional disorder that can only be considered as an epidemic with devastating health implications. Despite this, it has been mainly regarded in the public eye as merely an aesthetic apprehension. Currently, the number of people worldwide who are obese is equal to the number of those who are starving. According to the current trajectory, majority of the United States population will be obese by the late 2040's [4]. Obesity represents a heavy financial burden on the healthcare system in developed countries. Strum [5] estimates that an added $395 or 36% of annual medical expenditures is spent on adults with obesity as compared to normal weight adults with costs increasing as obese adults age into obese elderly. In 2008, 9.1% of the United States national health expenditure or $147 billion was ascribed to the direct and indirect costs of obesity [6] and it is estimated that it will increase up to 17.6% by 2030, meaning that 1 in every 6 dollars spent on healthcare will be attributed to obesity [4].

Obesity is also an emerging issue in Mediterranean countries (Croatia included) especially amongst children which represents a great concern [7]. This trend is attributable to an increasingly sedentary lifestyle, as well as to excess sugary and salty snacks. In our era of globalization, geographic distribution is no longer a key determinant of dietary choices and it is, in fact, the availability of Western-style cheap foods and large chain stores that are taking their toll on dietary choices [8,9].

Obesity is now understood to be a chronic inflammatory disease [10] largely influenced by the adipose tissue metabolic activity [11]. In order to make the best use of the Mediterranean diet anti-inflammatory properties, the pro-inflammatory impact of excess adipose tissue must be reduced. Specifically, increased inflammation in the adipose tissue appears to be, at least in part, promoted by elevated levels of bacterial-associated lipopolysaccharide (LPS) in the gut [12,13], thus furthering the incentive to explore the relationship between the gut microorganisms and food as a means of intervention in this metabolic disorder.

Changes in lifestyle and the increase of chronic diseases

Increased affluence and urbanization led to a lifestyle of daily routine characterized by less physical activity and more readily available foods with higher energy densities having as a consequence an increase in overweight individuals. In 2008, across the 27 countries of the EU, 59% of adult men and 48% of adult women were either overweight or obese [9]. Furthermore, the prevalence of chronic non-communicable diseases such as cardiovascular diseases, high blood pressure and type 2 diabetes has increased, leading to concerns about the reduced quality of life. Modern lifestyles and longer life are also linked to various mental health issues such as depression, poor concentration and loss of memory [9]. For much of its history, nutrition science has focused on the role of essential nutrients in preventing metabolic deficiencies. However, there is now a need to ensure not only the necessary levels of key nutrients but also of functional components in the context of lifestyle changes and declining energy expenditures.

Food and metabolism

Basic equation of metabolism

All metabolic processes ideally adhere to one basic law: food and oxygen provide for the production of carbon dioxide, water and energy. Half of the produced energy, in the form of heat, maintains the body temperature necessary for optimal chemical reactivity. The remainder of the energy provided

from food takes the form of energy-dense compounds such as ATP. It is worth remembering the vital role of oxygen in allowing the optimal processing of foods and that a deficiency of oxygen, hypoxia, is a contributing step toward inflammation [14].

Definition of food

In addition to the macronutrients (proteins, carbohydrates and lipids) essential dietary intake also includes micronutrient minerals and vitamins. Nutritional supplements ensure a complete intake of micronutrients [15] since their quantities in foods are declining due to soil depletion and food processing [16]. Water is also considered to be the essential nutrient assuring the crucial media in which our biochemical and metabolic reactions can take place [17]. Although these fundamental components are required by all humans, precisely how each individual processes these nutrients is determined by the interplay of many components, some of which can be directly influenced by lifestyle and dietary choices.

Functional food and nutraceuticals

Many definitions for functional foods exist worldwide but there is no official or commonly accepted one. Some authors consider any food as indeed functional because it provides nutrients and has a physiological effect. So, functional food can be considered a marketing term for a food whose attraction lays in its health claims and the way the product is perceived. Some even believe that, any food, if marketed appropriately and accompanied with particular health claim, is a functional food. Some foods deemed to be functional are actually natural whole foods where new scientific information about their health qualities can be used to proclaim benefits. Many, if not most, fruits, vegetables, grains, fish, and dairy and meat products contain several natural components that deliver benefits beyond basic nutrition. Examples include lycopene in tomatoes, omega n-3 fatty acids in salmon or saponins in soy. Even tea and chocolate have been noted in some studies as having functional attributes, i.e. attributes beyond the provision of elementary nutrients.

Others think that only fortified, enriched or enhanced foods with a component having a health benefit beyond basic nutrition should be considered as functional. Most definitions suggest that a functional food should be, or look like, a traditional food and must be a part of our regular diet. A functional food can be targeted at the whole population or at particular groups, which may be defined, for example, by age or genetic constitution.

Working definition

The European Commission Concerted Action on Functional Food Science in Europe (FUFOSE) (ftp://ftp.cordis.europa.eu/pub/fp7/kbbe/docs/functional-foods_en.pdf) proposed the following working definition of functional food:

"A food that beneficially affects one or more target functions in the body beyond adequate nutritional effects in a way that is relevant to either an improved state of health and well-being and/or reduction of risk of disease. It is consumed as part of a normal food pattern. It is not a pill, a capsule or any form of dietary supplement."

Chemical classes of nutraceuticals

Biologically active compounds come from the wide variety of chemical classes (Fig. 1.) ranging from simple minerals and amino acids, to more complex ingredients such as isoprenoids, phenolic compounds or microbe related nutraceuticals. These ingredients can provide means to address the increasing burden on the health care system by promoting health through prevention rather than treatment.

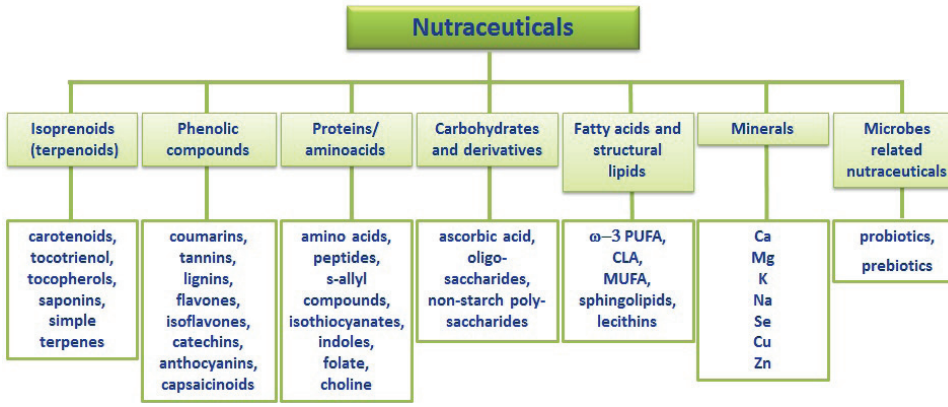


Figure 1. Nutraceuticals are currently divided into different classes of chemical compounds (phenolic and isoprenoids), as well as constituents from the macro and micro nutrients and finally into the class of microbial derived metabolites.

Plant derived polyphenols

Plant polyphenols are compounds abundant in vegetables, fruits, cereals, wine and tea, particularly green and black. However, they generally have been

found in low- / sub- μM concentration in the blood when there are applied as pure substances [18]. There are two reasons for their poor oral bioavailability. First, polyphenols which are redox-active molecules, such as quercetin and epigallocatechin-3-gallate (EGCG), are prone to auto-oxidation which modifies their structures and reduces their bioavailability. Second, as xenobiotics, polyphenols are extensively metabolized by intestinal bacterial enzymes as well as by various human metabolic enzymes. These transformations change their structure and thus affect their biological activities. To compensate for such properties, much effort has been invested in the development of nano-formulations that would prevent their (bio)chemical transformations and would enable efficient delivery to the desired place of action.

However, there is also a parallel effect of food polyphenols towards microbiota [19]. Polyphenols, in the form of glycosides, are present in the ingested food and as such are able to modify the composition of the gut microbiota. These glycosides are cleaved at the glycosid bonds by the microbiota, thus liberating glycans subsequently used for microbiota survival. Additionally, released glycans modify the relative proportions of various bacterial strains in the gut, e.g. they increase the relative proportion of *Bacteroidetes* known to be reduced in obese people. Thus, a supplementation with polyphenols through or in combination with food rich in polyphenols (e.g. apples, grapefruit, kiwi, onion, green tea) may contribute to body weight reduction in obese people and maintenance of the healthy body weight.

Plant polyphenols can contribute to both prevent and cure obesity. Obesity has been associated with inflammation and oxidative stress. Adipose tissue produces adipocytokines (shortly adipokines) like leptin, IL-6 and TNF-α which induce production of reactive oxygen species (ROS). Polyphenols, on the other hand, have been known for their antioxidative and anti-inflammatory activities, directly scavenging various ROS. For example, quercetin and EGCG are particularly strong antioxidants, while polyphenols which are weaker radical scavengers (e.g. apigenin) contribute to the maintenance of homeostatic ROS levels by inhibiting ROS generating enzymes and/or inducing expression of antioxidant and detoxifying enzymes. In the context of obesity, polyphenols have been found to suppress fat absorption from the gut and uptake of glucose by skeletal muscles, inhibit various uptake transporters and CYP450 isoenzymes and also inhibit anabolic pathways and stimulate catabolic pathways in adipose tissues [20].

Polyphenols generally show hormetic dose-response curves with the U- or J-shape, meaning that they primarily act as pro-oxidants and are cytotoxic at high concentrations (>50 μM), while demonstrating antioxidant and anti-inflammatory effects at low concentrations [21-23]. Polyphenols modulate activi-

ties of various transcriptional factors particularly redox-sensitive ones such as NF-kB (the main inflammatory mediator), Nrf2 (the main regulator of antioxidant and detoxifying molecules) and PPAR-γ (the nuclear hormone receptor acting as adipogenic transcription factor). Some polyphenols have also been found to modify epigenome by direct targeting epigenetic enzymes or indirectly through effecting concentrations of their co-factors, like S-adenosyl methionine (SAM) [18]. By regulating genome transcription polyphenols are able even in small doses impact various signaling pathways and biological processes.

At low doses, polyphenols suppress adipocyte differentiation and proliferation. Quercetin exerts anti-adipogenesis activity by activating the AMPK signal pathway [22]. Its treatment (10-100 μM) of 3T3-L1 pre-adipocytes reduced the expression of adipogenic transcription factors and enzymes like SREBP-1, C/EBP-α, PPAR-γ and FAS at the protein level by activating the AMPK signaling pathway. Similar effects have been observed for EGCG [24].

Expectation from the new generation of functional food

The motivation for development of functional foods has arisen from the growing interest in the relationship between diet, specific food ingredients and health. Healthy eating can make a key contribution to human health and well-being, but busy consumers may not have the time to access their optimal diet. Functional foods can provide health enhancing ingredients in a convenient form (Fig. 2).

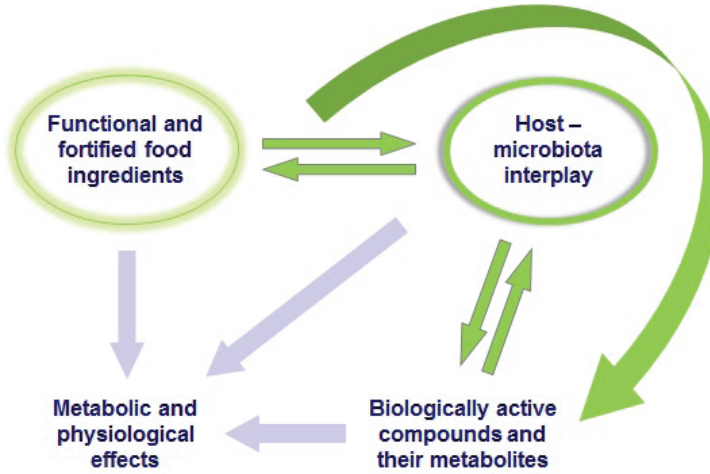


Figure 2. Functional and fortified food has influence on host-microbiota relationship and their equilibrium. Additionally, generated metabolites and pharmacologically active compounds provoke subsequent effect on our metabolism and physiology in general.

Awareness of associations between food and health continually increases as the evidence of their interplay accumulates. The importance of a healthy lifestyle, including the diet and its role in reducing the risk of illness and disease has now become a common knowledge. Alongside growing affluence across Europe, this knowledge has allowed easier access to a safer, more varied diet, all of which should promote longevity. Most recent advances in food and nutrition sciences have highlighted the possibility of modulating some specific physiological functions through food intake [25].

Strategies to control obesity with nutraceuticals

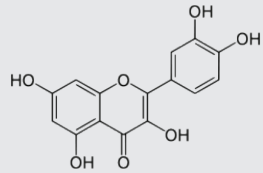
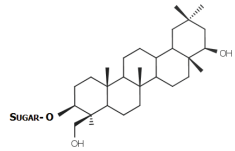
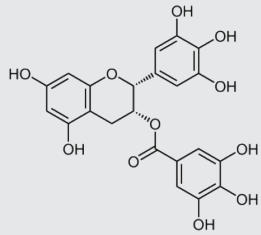
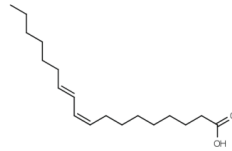
The development of functional foods for weight control involves the knowledge of the body weight control system. There are several approaches reported for the body weight control by incorporating functional ingredients into the food [26]. Observed effects of particular biologically active molecule(s) could be mainly explained by the following suggested mechanisms of action:

1. Inhibition of food intake (by inhibiting orexigenic signals or enhancing anorexigenic signals);
2. Controlling and retreating the bioavailability of nutrients (by suppressing the digestive enzymes and/or interacting with them to physically prevent their absorption);
3. Increasing stimulation of energy expenditure (EE) (thermogenesis); and
4. Modifying the composition of the gut microbiota.

Molecules with proven activities and promising results

There are number of biologically active compounds from different types of food and food ingredients which have triggered increased attention by scientific and industrial sectors. Some of them are currently considered as promising hits/leads for the further developed as new therapeutics are provided in Table 1. Briefly, quercetin (although possessing many pleiotropic effects) and black soys saponins are investigated additionally as digestive enzymes (amylase and lipase) inhibitors. They are often called "natural tetrahydrolipstatin or natural Orlistat" referring to the currently used drug produced by Roche which acts locally in the intestine as pancreatic lipase inhibitor. Polyphenolic catechines and xanthines although possessing mild effect in enhancing thermogenesis and reducing obesity, if used constantly for a longer period of time can have highly beneficial effects on maintaining desirable body weight. Finally, conjugated linoleic acid(s) represents an interesting lead since among other effects, it also decreases leptin levels in serum, halting and diminishing down-regulation of receptors in the obese individuals.

Table 1. Selected biologicaly active compounds with promising anti-obesity activity

Name/ Source	Basic structure	Activity/Mode of action	Literature	Remarks
Quercetin/ onion, apple, kiwi, artichokes		- additive and/or synergistic effect via transcription mechanisms mediated by NF-κB, AMPK, PPARγ, PGC-1α, Nrf2 - inhibition of digestive enzymes (amylase) - decreasing adipogenesis	Lo Piparo 2008 27; Aguirre 2011 21 ; Del Rio 2013 28; Zamora–Ros 2014 29; http://europepmc.org/abstract/MED/16802696	- as a isolated compound exhibits low bioavailability
Black soy saponins/ beans, souses, milk, cheese		- inhibition of pancreatic lipase - weight loss in animals proven	Han 2001 30; Kim 2009 31; Kim 2013 32.	- obesity in human - not yet assessed
Cathechins and xanthines/ green tea, black tea, coffee, white layer below the citrus' peel		- thermogenesis enhancement - adipogenesis decrease - decrease of fat accumulation in obese animals - potential to reduce obesity in human, however the effect is short lasting and mild	Kovacs 2004 33; Westerterp-Plantenga 2005 34 ; Huang 2009 35.	- effective only if used regularly for longer period of time
Conjugated linoleic acid (CLA) mixture/ ruminant's meat, seed oil		- inhibition of lipoprotein lipase - stimulation of enzymes associated with the fatty acids β oxidation - decrease of leptin in serum - decrease of weight in obese animals - decrease of weight in obese humans	Nagao and Yanagita 2005 36 Silveira 2007 37.	- effects in human have not been completely assessed yet

What is next and how to proceed in fighting obesity epidemics?

Follow our metabolism and consider epigenetics

The overall metabolic regulation should be considered with regard to intrinsic, external and epigenetic contributors.

The intrinsic components include the hypothalamus, the neuroendocrine control center for most metabolic processes. While hypothalamic function generally remains within predictable ranges, the variable quantity and composition of adipocytes between individuals are most significant in their role as metabolically active tissue. Fat/adipose tissue needs to be recognized not only as having insulation and storage function but also as being the main site for production of leptin, adiponectin and resistin and other proteins and peptides which collectively influence the balance of intake and expenditure coordinated by the hypothalamus [38,39].

In addition to the hypothalamus and adipocytes, a third intrinsic component, having been widely accepted as such since the late 1990's publication of "The Second Brain", is the gastrointestinal (GI) tract [40]. This massive system of digestion and absorption is connected to metabolic regulation as the location for 90% of the body's serotonin receptors, a neurotransmitter well known to modulate mood, satisfaction, pleasure and affect.

The GI tract plays a key role in sensing and signaling food intake to the brain [41] *via* gut hormones. Therefore a number of peptides synthesized in the GI tract have been investigated as potential drug targets for the appetite metabolic regulation. The possibility of developing active ingredients that modulate the secretion and/or signaling of these peptides made this field an attractive drug discovery platform. So far, relatively few gut hormones have been completely investigated for their effects on fine-tuning of appetite and energy expenditure. Those found to affect food intake are peptide YY3-36 (PYY3-36), pancreatic polypeptide (PP), glucagon-like peptide-1 (GLP-1), oxyntomodulin (OXM), ghrelin, amylin, and cholecystokinin (CCK) [41,42]. Ghrelin stimulates appetite and food intake, in contrast to all other known gut hormones that promote "satiation" (cause meal cessation) and/or promote "satiety" (delay the initiation of the next meal) [43].

Obesity arises as a result of interplay between the individual behavior and unhealthy environmental factors, genetic background and epigenetic factors. Epigenetics studies the heritable changes in gene expression that do not involve changes of the DNA sequence. Epigenome denotes heritable chemical modifications of DNA and histone molecules, such as DNA methylation and histone acetylation and methylation, which all together determine a way of chromatin folding and thus gene activity. Based on the presence of a specific epigenetic modification, so-called epigenetic marks, the chromatin becomes less or more condensed, that is more and less active, respectively. Dietary behavior is found to considerably modify the human epigenome [44]. Epigenome is greatly determined *in utero* and at an early age, but can be altered during life, particularly through diet and related food ingredients.

Considerable part of polyphenols' cancer chemopreventive potency is related to their effects on epigenome [18] by means of reversing aberrant gene methylation patterns. For example, EGCG is an inhibitor of methylation activity of DNMT1 as well as down-regulator of its expression. Quercetin and resveratrol are known activators of mutually dependent key enzymes in regulating metabolism - AMPK (its phosphorylation) and SIRT1 (its expression) [45].

SIRT1 deacetylates transcriptional factor FOXO3a what leads to up-regulation of manganese superoxide dismutase (MnSOD) [46]. The MnSOD has been connected with the elderly obesity [47]. It is interesting that a threefold increase in the expression of MnSOD gene has been associated with a decreased CpG methylation comparing a vegetarian with an omnivore group what may be ascribed to the influence of plant polyphenols on epigenome [44].

Microbiota – our allies in fighting obesity

The human body is home to a large number of distinct microbial communities, with the densest population in the distal gut (the gut microbiota). The vast array of gene products provided by resident microbes is known to diversely supplement the host's own metabolic processes [48]. This includes the extraction of energy from dietary components, an association that is, for example, essential with regard to polysaccharides and lipids [12]. Further influences of the gut microbiota include modulation of neurohormones and gut-derived lipids, short-chain fatty acids, triglyceride clearance, vitamin biosynthesis and mucosa associated immunity [48]. 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 [49].

The metabolic activities of gut microbiota facilitate the extraction of phosphorylated nucleotides (chemical energy) from indigested dietary substances, afterward stored in host adipose tissue for later use [50]. Cani et al. [51] suggested different mechanisms to explain the metabolic shift towards energy storage: (1) gut microbiota can increase the capacity to harvest energy from the food and (2) gut microbiota can modulate plasma lipopolysaccharides levels which activate the inflammatory tone and the onset of obesity and type 2 diabetes.

Targeting and modulating microbiota composition and functionality is becoming an increasingly widespread investigational therapeutic strategy. Such approaches are applying specific antibiotics, introducing food supplements in the form of probiotics and prebiotics and modifying the dietary components to achieve required and significant health benefits. Probiotics are live microorganisms which when administered in adequate amounts confer a health benefit on

the host, while prebiotics are selectively fermented ingredients that allow specific changes, both in the composition and/or activity in the GI microorganisms that confer benefits upon host well-being and health, whereas their mixture is called a synbiotic [10]. Interventions aimed at improving health parameters through microbiota modifications with adjusting the diet and using pre- and probiotics supplements have already shown some promising results on several clinical indications, including obesity [52]. Nevertheless, progress in understanding the mechanisms by which the gut microbiota interact with the host and knowledge about the long-term health effects of microbiota modulation will provide new opportunities for additional pharmacological or dietary intervention [53].

Personalized approach

World-wide changes in today's attitudes, information management, science and technology are all evolving on a converging course with one thing at the center – the individual. Taken separately each of these forces is important. Taken together, they synergistically change the health sector towards personalized medicine approach. Personalized medicine primarily involves an individual approach to the patients aiming at better predicting, preventing and treating diseases as well as monitoring them in their daily life. The principle of personalized medicine is the assumption that the disease is treated on the basis of the patient's specific individual characteristics and needs. This requires a high level of understanding of all available data and using the knowledge of molecular biology, physiology and clinical features of diseases as well as transferring this knowledge to patients and the community at large (see: www.epma.com).

The biggest potential of the personalized approach to medicine lies in the ability to seek solutions which are, from the very beginning, better fitted to different groups of patients compared to the so-called 'one size fit all' approach. Of course, the huge impact that the use of so-called general or universal drugs (particularly antibiotic therapy) has played on people's health, cannot be completely dismissed [54].

Application of tailor-made, personal approach in prevention and treatment of obesity and parallel study of epigenome-modifing life - style associated factors, might significantly contribute to combat obesity - this growing issue of our civilization. The physicians of the future will be surely more aware of the important role the diet and dietary ingredients play in the disease progression but at the same time will hopefully have at hand the extended therapeutic arsenal, including functional foods and nutraceuticals, in the battle against obesity.

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Biološki aktivne sastavnice hrane kao saveznici u borbi protiv debljine

Sažetak

Iako gotovo sva hrana posjeduje određena farmakološka svojstva, postoje namirnice koje zahvaljujući sastavu i jedinstvenom djelovanju imaju umjereni, ali i opće priznati terapijski učinak. Sastojci koji su odgovorni za takav učinak, sve važniji su predmet izučavanja brojnih istraživačkih laboratorija u društvenim i privatnim institucijama. Debljina je već više desetljeća prepoznata ne samo kao estetski, već i javno zdravstveni problem, a unatrag desetak godina dobila je i kvalifikaciju bolesti.

Trend porasta pretilosti i s njom povezanih kroničnih bolesti i stanja neminovno raste, a nedostatak učinkovitih lijekova sada prisutnih na tržištu utječe na to da se iz prirodnih izvora, posebice hrane nastoje iznaći nove terapijske opcije koje bi se primijenile u prevenciji i liječenju debljine. Osim tih izvora, veliki značaj stavlja se i na izučavanje međusobnog odnosa domaćina i njegove mikrobiote, budući je taj suživot odgovoran i za metabolizam naših stanica, ali i za uspješno metaboliziranje i bioraspoloživost brojnih biološki aktivnih spojeva iz hrane koji su kao zasebne molekule slabo bioraspoloživi.

Osim toga izučavanje utjecaja epigenetskih čimbenika i primjena personaliziranog pristupa u prevenciji i tretmanu debljine uvelike može doprinijeti uspješnijem i učinkovitijem suočavanju s ovim rastućim problemom današnje civilizacije.

Ključne riječi: debljina; biološki aktivni spojevi; nutraceutici; istraživanje lijekova; mikrobiota; personalizirana medicina.

Adresa za dopisivanje / Corresponding author:
Doc. dr. sc. Donatella Verbanac
University of Zagreb School of Medicine,
Center for Translational and Clinical Research,
Department for Intercellular Communication,
Šalata 2, 10000 Zagreb, Croatia
donatella.verbanac@mef.hr
tel. +385 1 4566972
fax. +385 1 4566724