

## Editorial

# Medicinal Diets: From Molecules to Nutrients to Foods: Basic and Clinical Implications

Nutrients are digested and absorbed in the body at different locations in the gastrointestinal tract, and diet plays a key role in bringing fats, proteins, carbohydrates, fiber, micronutrients including vitamins, and antioxidants in close contact with the intestinal mucosa where absorption occurs.

The human intestinal microbiota, through its diversity and functions in health and disease, is greatly involved by providing substrate metabolism of branched-chain and aromatic amino acids, components of diet, drugs, bile acids, xenobiotics, biosynthesis of short-chain fatty acids, steroid hormones, neurotransmitters, and vitamins [1-4]. A great deal of evidence has shown that nutrients act as mediators contributing to the pathophysiology of biological processes, including oxidation, inflammation, and organ dysfunction. Moreover, their synergistic mechanisms result in greater effects, thus highlighting the importance of focusing on food groups, in addition to nutrients [5]. In this respect, diet can be regarded as a type of beneficial agent, and currently much attention is given to the contribution of diets to health maintenance as well as to the complex pathogenesis of diseases [6].

Thus, nutrition should be placed at the forefront of public health programs as a cost-effective means to prevent a number of chronic diseases, which include metabolic disorders (obesity, type 2 diabetes), cardiovascular diseases (coronary heart disease, hypertension and stroke) [7-9], cancer [10, 11], liver disorders, dental diseases and osteoporosis [12-14].

With this scenario in mind, the Editors of the present issue of *Current Medicinal Chemistry* have gathered valuable evidence from a large number of experts worldwide in order to focus on “Medicinal” diets and their role in health and disease. From a basic science perspective, this area provides opportunities to advance our understanding of related pathophysiological mechanisms. From a clinical perspective, this opens new avenues to provide patients with an active and empowering role in health maintenance, with numerous positive repercussions.

### **In Section 1, the Basic Implications are Examined.**

**Teixeira *et al.*** discuss the role of four dietary polyphenols – resveratrol, curcumin, epigallocatechin-3-gallate (EGCG) and quercetin – in molecular pathways regulated by mitochondria and their potential impact in human health. The mechanisms underlying the polyphenols’ beneficial effects include, among others, the attenuation of oxidative stress, the regulation of mitochondrial metabolism and biogenesis and the modulation of cell-death signaling cascades, among other mitochondrial-independent effects.

**Wang *et al.*** focus on the complex molecular mechanisms linking the neurohormonal response of the gallbladder to the gastrointestinal hormone cholecystokinin (CCK), which, under food stimulation, initiates gallbladder contraction and bile secretion, thus preventing the precipitation of excess biliary cholesterol and gallstone formation. Gallbladder-specific CCK-1R-selective agonists may provide an efficacious novel strategy for preventing gallstone formation by promoting gallbladder emptying, particularly in subjects with gallbladder contractile dysfunction, e.g. patients with celiac patients as well as patients on total parenteral nutrition.

**Silva & Jones** review the effect of “functional foods” on metabolic control, and potential implications in health and disease. Given the high and increasing incidence of glucose intolerance and type 2 diabetes related to over-nutrition in Westernized societies and the potentially significant role of diet and food awareness in preventing or reversing this condition, the review will focus on those food components or supplements that specifically improve glycemic control.

**Vergani** focuses on free fatty acids (FA) which are the major mediators of hepatic steatosis; patients with NAFLD have elevated levels of circulating FA which correlate with disease severity. Steatosis is a reversible condition that can be resolved with changed behaviors, or that can progress towards more severe liver damage such as steatohepatitis (NASH), fibrosis and cirrhosis. Thus, excess of fatty acids, an essential component of digested foods,

might initiate the mechanisms leading to intra-hepatocyte incorporation and accumulation of triglycerides, an essential step in the onset and perpetuation of liver steatosis.

**Cataldo *et al.*** describe the subtle mechanisms linking the function of Aquaporins (AQPs), a family of membrane channel proteins widely expressed in the human body, to the beneficial action played by some food nutrients and phytochemical compounds. The authors provide an overview of what is known regarding the AQP modulation exerted by healthful dietary patterns and plant polyphenols.

### **In Section 2, the “Clinical Implications” are Reviewed.**

**Di Ciaula *et al.*** discuss the close connection between overweight, obesity, dyslipidemia, insulin resistance and altered cholesterol homeostasis to increased gallstone occurrence. A number of specific nutrients acting as risk factors with respect to gallstone formation include increased energy intake with highly refined sugars and sweet foods, high fructose intake, low fiber contents, high fat, consumption of fast food and low vitamin C intake. On the other hand, high intake of monounsaturated fats and fiber, olive oil and fish (rich in  $\omega$ -3 fatty acids) consumption, vegetable protein intake, fruit, coffee, moderate alcohol consumption and vitamin C supplementation exert a protective role.

**Stokes *et al.*** place the burden of non-alcoholic fatty liver disease (NAFLD) into clinical perspective with a focus on the impact of nutrition and cite examples of short-term interventions that assess direct effects of dietary-related components on hepatic steatosis. The main focus is on the three macronutrients, i.e. dietary carbohydrates, fats, and proteins.

**Surdea-Blaga *et al.*** summarize current knowledge regarding food and gastroesophageal reflux. For example, fat intake increases the perception of reflux symptoms. Regular coffee and chocolate induce gastroesophageal reflux and increase the lower esophageal exposure to acid. Spicy foods might induce heartburn, but the exact mechanism is not known. Beer and wine induce gastroesophageal reflux, mainly in the first hour after intake. For other foods, such as fried food or carbonated beverages data on gastroesophageal reflux is scarce. Similarly, there is limited data on the type of diet and gastroesophageal reflux. Mediterranean diet and a very low carbohydrate diet, by contrast, appear to protect against reflux.

**Portincasa *et al.*** discuss a frequent functional gastrointestinal disease, namely irritable bowel syndrome (IBS), which can be influenced by foods. Dietary education is essential to deal with foods that are potential triggers for the onset or worsening of symptoms. However, further studies are required to link the ultimate role of diets in different IBS subtypes.

**Ferri *et al.*** provide evidence that healthy diet and improved dietary practices contribute to reduced chronic disease risk among shift workers. A possible role of education programs on eating behavior as preventive strategies in this group of workers should incorporate several important lifestyle changes.

**Carbone *et al.*** discuss the role of ethanol as a potential direct cardioprotective agent and update current knowledge on the intracellular mechanism underlying the cardioprotective effects of polyphenols and ethanol. The need for randomized clinical trials able to clarify the potential role of red wine consumption in reducing cardiovascular risk is also discussed.

**De Angelis *et al.*** address the issue of diet, benefits to human health and activity of gut microbiota. Habitual diet (Western, Agrarian and Mediterranean omnivore diets, vegetarian, vegan and gluten-free diets) drives the composition of the gut microbiota and metabolome. Specific relationships between diet and microbes, microbes and metabolites, microbes and immune functions and microbes and/or their metabolites and some human diseases are being established.

**Garruti *et al.*** report on nutritional factors, other lifestyle components including excess body fat in interfering with female reproduction and fertility. In an attempt to define “the optimal fertility diet”, the authors will consider the role played by a Mediterranean lifestyle and specific macronutrients (animal and vegetable proteins) on ovulatory disorders and female fertility.

**Ezquerro *et al.*** discuss the effects of diets on adipose tissue. In obesity, dietary changes should be individualized, tailored to food preferences and allow for flexible approaches to reducing caloric intake in order to increase the motivation and compliance of overweight and obese patients. The review summarizes compelling evidence

showing body composition changes, impact on cardiometabolism and potential adverse effects of very-low calorie, low- and high-carbohydrate, high-protein or low-fat diets.

**Almeda-Valdes *et al.*** discuss the role of diet in patients with the metabolic syndrome, a very common metabolic disorder. The goal of treating metabolic syndrome is to reduce the risk of coronary heart disease and the development of type 2 diabetes. Lifestyle modification therapy combines specific recommendations on diet alone or combined with other strategies.

**Di Ciaula and Portincasa** focus on the dangerous link between diet and contaminants in driving the rise of obesity epidemics. Indeed, maternal diet, intestinal microbiota and chemicals introduced as contaminants with food, are all factors able to increase the risk of obesity. Widely diffused toxics are able to promote obesity in children and adults, mainly by acting on the differentiation pathway linking multipotent stromal stem cell to mature adipocyte, modulating epigenetic factors and influencing a series of mechanisms finally leading to altered dietary habits, increased adipocyte formation and fat storage. The efficacy of primary prevention strategies acting on all these factors might contribute to reversing the continuous rising of the obesity epidemic.

**Badimon *et al.*** underscore the importance of the link between diet and cardiovascular disease (CVD). Current research places the Mediterranean dietary pattern, rich in fruits and vegetables, as the most cardioprotective, because of its high concentration of bioactive compounds such as unsaturated fatty acids, polyphenols, fiber, phytosterols, vitamins and minerals, which exert antioxidant, anti-inflammatory and anti-thrombotic effects contributing to the delay of CVD initiation and progression.

**Mastronuzzi and Grattagliano** examine the problem of adequate caloric intake as a major determinant of health status especially when degenerative conditions become a predominant risk for difficult-to-treat diseases, as in aging. The maintenance of nutritional status is the best measure to counteract the risk of protein-caloric malnutrition and its complications which often affect elderly populations and frail patients. Attention is placed on certain aspects associated with malnutrition as an indicator of disease severity and health costs in the elderly population. The impact of nutritional interventions and nutrient supplementation on general indices of malnutrition is also discussed as a promising strategy.

**Altomare *et al.*** review the topic of cholecystectomy, as a condition which can have nutritional and metabolic consequences in the short-term (diarrhea, abdominal pain and bloating) and in the long-term (increased body mass index with metabolic syndrome, gastritis, liposoluble vitamin deficiency). Pathogenic mechanisms behind these disturbances are reviewed and the need for an early post-operative nutritional intervention based on a low-lipid, high-fiber diet, is highlighted.

In conclusion, the continuously evolving field of nutrition with respect to prevention and treatment, as well as induction and perpetuation of chronic diseases, is central in modern clinical medicine with a myriad of translational implications. We as Editors believe that undergraduate and postgraduate students, residents, researchers, clinicians and nurses alike will enjoy and take advantage from reading the following chapters in *Current Medicinal Chemistry*. All contributions have been reviewed, include updated bibliographies and current guidelines, and are enriched with concise tables and figures, dealing with the key pathophysiological mechanisms and chemical formulas.

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