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Review

Nutraceuticals: A paradigm of proactive medicine

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ABSTRACT

Nutraceuticals define a new category which shades the frontier between drugs and food. As per its definition, a nutraceutical is "a food or part of a food that provides benefits health in addition to its nutritional content". Active substances either way extracted from plants (phytocomplexes) or of animal origin, when extracted, concentrated and administered in a suitable pharmaceutical form, can create a very promising toolbox useful to prevent and/or support the therapy of some pathologic conditions given their proven clinical efficacy. It is worldwide recognized that diet and lifestyle are essential to promote and maintain well-being and nice-being condition, other than help to prevent diseases possible onset. Both non-correct dietary habits and lifestyle can in fact determine pathological conditions. The metabolic syndrome, a worldwide epidemic threat, can be named an outstanding example. This syndrome is characterized by a cascade of cardio metabolic risk factors which include obesity, insulin resistance, hypertension, and dyslipidemia. Prevention is the key strategy for an effective proactive medicine, in which efforts are addressed to prevention and, consequently, to lower the risk connected to some lifestyle related diseases reducing, at the same time, any National Health Systems cost needed to guarantee the proper therapeutic approach based on pharmaceuticals. Nutraceuticals use in prevention is a proactive reverse approach tool to preclinical health conditions. They can be effectively used, by including in the daily diet, in an area which shades in the range "beyond the diet, before drugs", since they combine both nutritional and beneficial healthy properties of food extracts with the healing properties of natural active compounds.

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1. Nutraceuticals

> "*Nothing exists in the world that, given the appropriate conditions and situations, cannot be used for a therapeutical scope*".

[Charaka Samhita, Sutrasthana, XXVI, 12]

The term "nutraceutical", has been coined in 1989 by Stephen DeFelice, founder and chairman of the Foundation for Innovation in Medicine (DeFelice, 1989), and it is a *portmanteau* of the words "nutrition" (indicating a nourishing food or food component) and "pharmaceutical" (with reference to a drug). It identifies a food or part of a food, which can be of vegetal or animal origin, that has a beneficial pharmaceutical activity beyond its nutritional value. The rationale behind their use is becoming the millennium challenge (Volpe and Sotis, 2015).

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Traditional medicine, as well as the pure holistic approaches, extensively used since centuries plants, vegetal and animal origin derivatives to alleviate and/or cure many pathological conditions. In general, any food, due to its content of active compounds, has the potential to go beyond its nutritional value as a source of macro and micronutrients, and can also be used as a drug depending on the dose. Nevertheless, attention should be paid to potential risk factors related to the use of vegetal matrixes, e.g. safety of the starting material, absence of allergenic compounds, absence of toxicity, absence of exogenous and endogen contaminants, possible presence of toxic secondary metabolites and/or environmental pollutants that can potentially cause an health threat.

Contradictory information exists about food derived products available as over the counter products (OTC) in pharmacies as well as available on the market. Many of them belong to the food supplements category which includes also herbal products. All of them claim beneficial effect on human health. Dietary supplements are widely used and offer the potential to improve health if appropriately targeted to those in need. Compared to dietary supplements, pro- and pre-biotics, as well as herbal products differ very much from nutraceuticals. The adopted administering form (e.g. pills, tablets, capsules, and liquids) can be the same, but, while nutraceuticals must have a proven clinical efficacy beyond their nutritional value, the other above mentioned products do not necessarily have a specific proven action on a health condition.

In particular, pro-biotics and pre-biotics are, respectively, live bacteria used in general to help gastrointestinal conditions, and specialized plant fiber that nourishes the good bacteria already present in the large bowel or colon (gut microbiota). Both do not have specific effect on pathological health condition, but can however be effective in helping "good" bacteria to grow (McCarville et al., 2016).

Food supplements are often confused with "functional food": as per their definition, they are food derived products (or food added with one or more active compounds) that are to be included as a part of the usual diet with the aim of obtaining beneficial effects for health. These supplements as well as the functional foods can compensate and/or can have a beneficial effect due to the addition of specific components, in presence of a lack, if any, of one or micro or macro nutrient in the body. They do not have necessarily any proven pharmacological effect (Rautiainen et al., 2016).

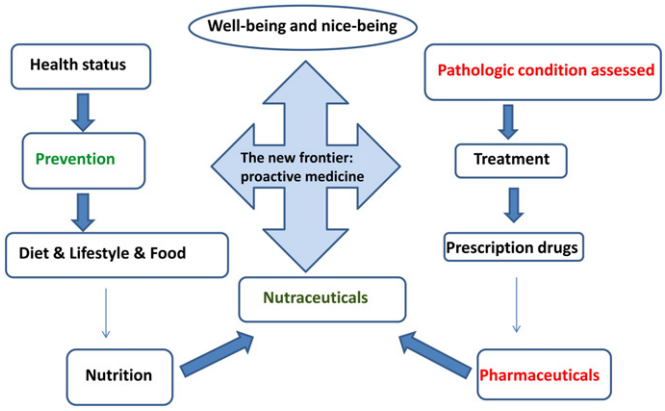
Nutraceuticals, on the opposite, are formed by many active substances extracted from vegetal (as phytocomplex) or from animal origin food, which are concentrated and administered in the suitable pharmaceutical form, and must have a pharmacological effect in addition to their nutritional value. They can be effectively used to prevent and even cure some pathologic conditions when they have proven safety, better bioavailability and clinically proven beneficial health properties.

The area where nutraceuticals can be adopted to support or prevent a therapeutic pharmacological based therapy, lays "beyond diet, before drug", as stated by Ettore Novellino in 2012 (Santini, 2014). Their inclusion to the daily diet to prevent the onset of pathologic conditions allows to avoid or delay the need to use pharmaceuticals. Nutraceuticals for this reason can become key players and be a proper paradigm of proactive medicine for subjects who qualify for an alternative non-pharmacological approach to a health condition.

In many cases, in fact, drug based approach is addressed to cure the symptoms deriving from the onset of a chronic health condition following an organ damage which is already present.

In the traditional approach, which can be named watchful medicine, the subject waits till the symptoms of a disease become evident (often following a clinical screening test since many health conditions are asymptomatic, e.g. hypercholesterolemia), then gets a prescription from a medicine doctor and starts a pharmacologic therapy.

Scheme 1 summarizes this approach as well as the area where nutraceuticals can position themselves challenging watchful medicine with proactive medicine, the new frontier which is focused on prevention and uses nutraceuticals together with lifestyle change and proper use of food.



Scheme 1. The frontier between drugs and nutrition in proactive medicine.

The use of nutraceuticals, in some conditions, can be effective in preventing the onset of the pathological condition and hence saving the well-being condition before the organ damage become evident adopting a proactive medicine approach to reach the goal of maintaining a well-being and nice-being status at any age (Scheme 1).

Even if nutraceuticals are experiencing a growing interest among both consumers and medicine doctors (MD), so far a shared regulatory definition has not been assessed. The current European regulations consider nutraceuticals the same way as the food supplements (see the EC Regulation n. 1924/2006 of the European Parliament and Council, recently updated by the UE regulation 2015/2283). This recent regulation focused on "novel foods", defines the foods categories and completes the definition of food supplements. In this new regulation, the term "nutraceutical", however, is still not officially recognized or mentioned. According to this vision, the European Food Safety Authority (EFSA) does not make any distinction between food supplements and nutraceuticals. In a similar way, the Dietary Supplement Health and Education Act (DSHEA, 1994), defined dietary supplements as a category of food, and the United States Food and Drugs Administration (FDA) which regulates dietary supplements according to the Food, Drug and Cosmetic Act (FD&C Act, 2014) as per the Section 413 (d) of the FD&C Act, 21 U.S.C. 350b (d).

The aim is to ensure their safety, wholesomeness and their labeling to be truthful and not misleading. The term nutraceutical is accepted even if not officially recognized indicating a lack of regulation in the area. Due to these reason, nutraceuticals are often assimilated to food supplements in both perception of MD and in the collective imagination, notwithstanding the major differences existing between these two food derivatives.

2. Nutraceuticals and proactive medicine

The millennium challenge is nowadays more and more focusing on prevention more than on diseases cure and therapy. When considering that life expectance has been extended due to the possibility to cure the majority of the health conditions, people requirements are now addressed to maintain a well-being status as well as a nice-being status. Current progresses in both medicine and pharmacological approaches to diseases have been tremendous. At the same time, the cost for any National Health System is increasing in a parallel way to the progress of the so called lifestyle diseases, connected to both wrong dietary habits and wrong lifestyle. For these reasons and for a better sustainable health management, there is a growing interest in alternative and more "natural" approaches to preventive actions with respect to pharmacologic therapy, as in the collective imagination drugs are considered often, like chemicals, a source of potential risk other than a cure (Maddi et al., 2007). The proactive medicine focuses on prevention, and represent an alternative which is also capable to reduce the onset

of health conditions reducing the cost of long-term chronic therapies other than increasing the well-being and nice-being of people, who is more and more looking for better life quality and health status. National Health Systems, which are in charge and take care of the population health conditions, are challenged by the growing cost of long-term chronic pathological conditions.

Among the main reasons for the worldwide growth of attention to dietary supplements and nutraceuticals, there is in fact the increasing desire of keeping an healthy status, the well-being and nice-being preservation, and, last but not least, the health trends (Das et al., 2012; Rautiainen et al., 2016).

At the same time, the greater availability of convenience foods, combined with less physical activity, determined both an increase of consumption and the onset of new dietary habits that privileged refined food and reducing the amount of fruits and vegetables in daily diet possibly causing dysmetabolism and other health conditions (Caplan, 2013).

The traditional way of handling a disease with an appropriate treatment has been for centuries centered on a static approach: the patient, often unaware of a potential health risk, waited till the clear signs of the disease onset appeared (watchful waiting or active surveillance medicine). This was followed by a diagnosis from a MD and by the starting of the proper pharmacological treatment which used a prescription drug to ease the symptoms till the apparent disappear of the pathologic condition. Fig. 1 summarizes this traditional approach to health issues.

The pharmaceutical approach is the only realistic way to face an illness since the symptoms usually appear when the organ damage is already ongoing. This is the case of hypercholesterolemia, hypertension, hyperglycemia, hypertriglyceridemia, etc., all conditions where symptoms become visible when it is too late and the organ damage is already present.

On the other hand, the proactive medicine approach to health, well-being and nice-being, is the best tool to prevent the illness onset. Proactive medicine, or "initiative medicine", is a dynamic approach which consists in taking preventive action before the onset of a disease instead of waiting for the disease to become evident.

Fig. 2 summarizes the overall picture of the nutraceutical approach to health issues and prevention. Potentially useful nutraceuticals belong to different chemical classes, ranging from cathecolic and resorcinic derivatives to polyphenols, and are obtained from different sources such as plants, fruits and vegetables, fungi, algae, and microalgae. When compared to drugs, nutraceuticals are, in general, safer, have less unwanted side effects, and a higher bioavailability (Espin et al., 2007). In the following, some examples of proactive medical approach using nutraceuticals for the prevention of chronic health conditions, will be exploited. The choice of references selection for the present review has been centered on data available on the different databases with reference to the different pathologic conditions where nutraceuticals are or have been used as support therapy or as therapeutic agent. The searched databases include Cochrane Library, Web of Science, CAS, EMBASE, PubMed, MedLine, PubChem, Scopus, etc. The main criteria to sort the references focused on the available clinical data and/or reports on the use/effect relationship for the evaluated nutraceuticals. The available data and meta-analyses, where available, have been sorted out in first place based on chronological order and then the latest evidences have been taken into account and commented based on the relevance of the reported data in the overall general context.

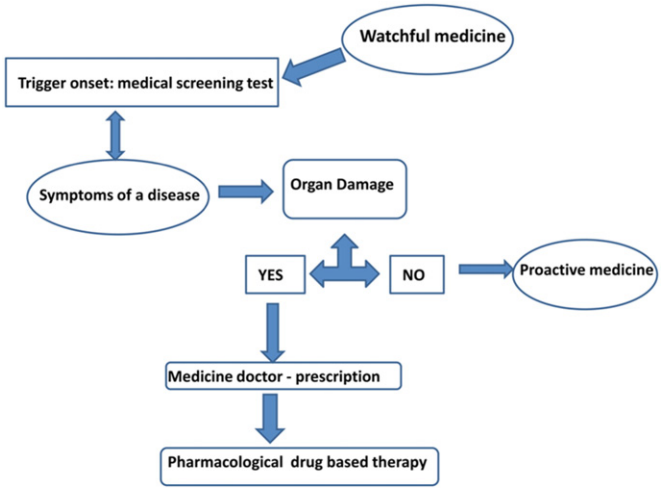


Fig. 1. Traditional pharmacological approach.

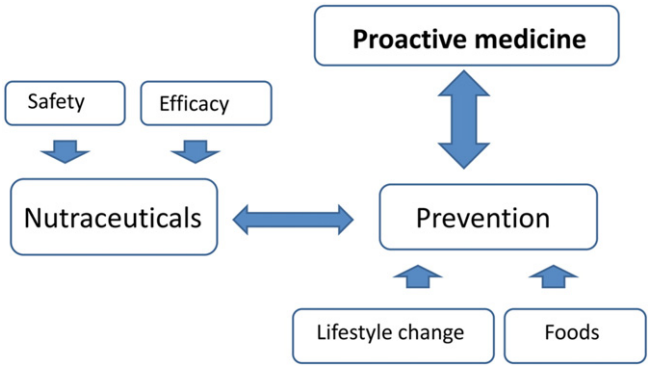


Fig. 2. Proactive medicine nutraceutical approach.

3. Hypertension

Beyond the well-known effects on blood pressure of the dietary approaches, lifestyle changes and the beneficial effect of adopting the Mediterranean diet, a large number of studies have investigated the possible blood pressure lowering effect of different nutraceuticals, most of which are antioxidant agents with a high tolerability and safety profile. In particular, a relatively large body of evidence supports the use of potassium, magnesium, L-arginine, vitamin C, cocoa flavonoids, beetroot juice, coenzyme Q10, controlled-release melatonin and aged garlic extract. The effect seems to be dose related and the absence of unwanted side effects represent a good indicator for their safe use and inclusion in the diet as per a recent analysis of literature data which analyzed the published studies (in the range 1990 to 2015) on nutraceuticals with a clinically demonstrable blood pressure lowering effect on human (Borghi and Cicero, 2016).

Berberine, extracted from *Coptis root* (dried root and rhizome of *Coptis trifolia*) and *Phellodendron amurense* (a tree belonging to the Rutaceae family), has been frequently used for the adjuvant treatment of type 2 diabetes mellitus, hyperlipidemia, and hypertension. Safety and efficacy studies in terms of evidence-based medical practice have become a prevalent application of the Chinese herbal medicine. A recent meta-analysis examined twenty-seven randomized controlled clinical trials including a total of 2569 patients. In the treatment of hypertension, berberine showed a good lowering effect on blood pressure more than the lifestyle intervention alone or placebo.

The same occurred when berberine combined with oral hypotensor was compared to the same hypotensor. No serious adverse reaction was reported indicating that berberine can be considered safe in its use also in combination with drugs and that berberine has good therapeutic effect on hypertension. Considering the relatively low cost compared with other first-line medicine and treatment, berberine based nutraceuticals might be a good alternative to treat hypertension (Lan et al., 2015).

Garlic (*Allium sativum*) is a species of the onion genus native to central Asia, and it is rich of phytonutrients with therapeutic effects on cardio vascular diseases, mainly in hypertension, making its extracts an

useful tool for prevention and control of hypertension (Mota, 2016). Garlic based nutraceuticals containing *S*-allylcysteine and organosulfides as the bioactive sulfur compound have shown promising results in the treatment of hypertension (Frankel et al., 2016).

A recent study using aged garlic extract examined this effect allowing to determine a lowering blood pressure by about 10 mm Hg and 8 mm Hg, systolic and diastolic, respectively, similar to the standard medication. Aged garlic extract is standardizable, highly tolerable, with little or not documented harmful interaction when taken in combination with drugs which have the same effect or with blood-thinning medication. The possible mechanism of action has been described as involving the stimulation of the vascular small molecules of endogenous hydrogen sulfide (H_2S) producer capable to enhance the endothelial nitric oxide (NO) regulation, which induce smooth muscle cell relaxation, vasodilation, and blood pressure reduction. Dietary as well as genetic factors may influence the efficiency of the hydrogen sulfide and nitrogen oxide signaling pathways and may contribute to the hypertension onset (Ried and Fakler, 2014).

The beneficial nutraceutical potential has also been connected to the presence in garlic extracts of organoselenium compounds, steroid saponins and sapogenins (e.g. β-chlorogenin). Garlic also contains vitamin B_6 and B_{12} flavonoids, lectins and *N*-fructosyl-amino acids, which may contribute, along with organo-sulfur compounds, to the biological effects in preventing cardiovascular diseases (Charu et al., 2014).

4. Hypercholesterolemia

Among the main health threat connected with metabolic syndrome, dyslipidemia is among the most relevant ones. This pathological condition determines an abnormal amount of lipids in the blood. Prolonged elevation of insulin levels as well as a high level of O-GlcNAc transferase can also cause dyslipidemia. Most dyslipidemia cases observed in developed Countries are often due to both wrong diet and lifestyle. Pharmaceutical treatment is the primary choice when dyslipidemia is already in advanced stage, and statins are at the forefront strategies to manage it although they are not always well tolerated. It has been observed that 6–7 months after starting statin therapy, discontinuation rates average 30%. For this reason the interest both from pharmaceutical research and from patients requesting supplementary and/or alternative treatments is growing, especially when patients do not tolerate well the pharmacological therapy. A nutraceutical preventive approach could help to better face the metabolic syndrome for patients who do not qualify for statin treatment or are intolerant to this therapy. Moreover this could help to reduce any unwanted side effects caused by the statins (Afilalo et al., 2008).

Within the widely marketed nutraceuticals with clinically demonstrated effects on hyperlipidemias as well as on one or more components of the metabolic syndrome, omega-3 fatty acids, psyllium, soluble fibers, red yeast rice, berberine, and apple phytocomplex are among the most studied.

Recently Krill oil as a source of n-3 fatty acids has been considered for hyperlipidemia. Krill oil is obtained from shrimp-like small crustaceans of the Euphausiacea order, namely *Euphausia superba*, which are found in all the world's oceans. Krill oil is a relatively new marine n − 3 fatty acid supplement, and it has been widely associated to beneficial effect on different health conditions showing interesting metabolic effects, among which on inflammation, glucose tolerance, triglycerides and lipid lowering. Krill oil has been accepted as Generally Recognized as Safe by the American FDA and recently obtained the Novel Food status by the European Union.

Notwithstanding the use of a Krill oil based nutraceutical for different health conditions would need a more in deep assessment and more clinical data substantiating the claimed healthy beneficial properties, its lipid lowering ability has been more studied.

Its beneficial action has been related mainly to a fatty acids content similar to fish oil. Krill contains two marine n-3 polyunsaturated fatty acids, EPA and DHA, mainly bound in phospholipids. Whereas the EPA and DHA in fish oils are bound in triglycerides, Krill oil, reported as mostly well tolerated (Kwantes and Grundmann, 2015), is a rich source of phospholipid-derived EPA and DHA, and the difference between the chemical binding of EPA and DHA seems to affect their bioavailability in favor of the krill oil. EPA and DHA bioavailability in krill oil has been shown to have a 72 hour higher bioavailability compared to fish oil, supporting the hypothesis that phospholipids are better absorbed than triglycerides (Köhler et al., 2015). A recent double-blind, randomized clinical trial (on 25 moderately hypertriglyceridemic subjects with triglycerides in a range between 150 and 500 mg/dL), compared the effect of n-3 (administering 1000 mg twice a day) and Krill oil lipid-lowering effects (administering 500 mg twice a day) for 4 weeks. The results indicate comparable results. The observed TC, HDL-C, LDL-C and TG levels variation were −3.8%, +4.5, −3.7, −55.7% respectively for Krill oil, and −2.1, +1.4, −1.9, −72.8 for esterified n-3 treatment, respectively (Cicero et al., 2016).

Berberine can be obtained from plants of the *Berberis* species, and it is usually found in the roots, rhizomes, stems, and bark. Chemically, it is an alkaloid drug which has a tetracyclic skeleton derived from a benzyltetrahydroisoquinoline system incorporating an extra carbon atom provided by *S*-adenosyl-methionine via an *N*-methyl group. A recent meta-analysis examined twenty-seven randomized controlled clinical trials based on 2569 patients divided in subgroups administered berberine by alone versus placebo or combined with oral hypoglycemic or lipid lowering drugs or hypotensive medications. It has been observed that berberine obtained a better lipid lowering effect compared with drugs alone. In particular, a total cholesterol (TC) and low density lipoprotein (LDL-C) lowering, and high density lipoprotein (HDL-C) level raising was observed, with no unwanted side effect (Lan et al., 2015).

A study on high cholesterol induced hyperlipidemic hamsters treated with berberine (46.7 mg/kg/day for 140 days) allowed to assess the lowering effect on serum of TC and LDL-C, and also an increasing effect on the HDL-C. It has been observed that the excretion of bile acids with feces was increased by berberine. This observation suggested as a possible mechanism of action a retard the synthesis of cholesterol by down regulating the mRNA expression of 3-hydroxy-3-methyl glutaryl coenzyme A reductase and accelerating the clearance of lipids by upregulating the low-density lipoprotein receptor, cholesterol 7α-hydroxylase, and uncoupling protein-2 expression (He et al., 2016).

Red yeast rice, the fermentation product of the mold *Monascus purpureus* has been extensively studied for its cholesterol lowering ability. The identification of bioactive components, e.g. polyketide pigments (statins) allowed the red yeast rice to obtain the nutraceutical status. Hypercholesterolemic effect of this compound, however, has been validated as due to monacolin K (lovastatin) which has been recognized as the key component in cholesterol reduction. Moreover, the possible presence of secondary toxic metabolites, e.g. mycotoxin citrinin, and the variable statin content is generating a disputable scenario, where dose inconsistency and co-occurrence of toxin citrinin hampers its dietary supplementation prospect (Patel, 2016).

A systematic recent analysis of ten randomized controlled trials involving 905 Chinese subjects with dyslipidemia, compared the use of red yeast rice (monacolin K) and simvastatin. The results confirmed the above mentioned observation since no statistically significant difference in any of the outcomes examined was observed, suggesting that the use of red yeast rice as an alternative to simvastatin is not supported on current evidence excluding the patients intolerant to the statins (Ong and Aziz, 2016).

Recently, the German Federal Institute for Drugs and Medical Devices warned on the use of red yeast rice. According to the food safety requirements as set by the European Regulation for the use of food supplements with high doses of active compounds (EU, 2002), the content of monacolin K, should be considered a drug at levels higher than 5 mg/day due to existing scientific data supporting a pharmacological effect at this dose (BVL/BfArM, 2016).

EFSA in 2011 was asked to provide a scientific opinion on health claims with reference to the maintenance of normal blood LDL cholesterol concentrations pursuant to Article 13 of Regulation (EC) No. 1924/2006 in relation to monacolin K from red yeast rice and determined in 10 mg of monacolin K from fermented red yeast rice the amount to be consumed daily to obtain the claimed effect (EFSA Scientific opinion, 2011).

This value has been accepted in many European Countries. Pure lovastatin (monacolin K) can cause unwanted side effects, e.g. kidney problems or muscle issues. Red yeast rice products can cause the same health issues depending on the amount of active compound contained due the higher bioavailability of the red yeast rice compared to pure lovastatin (Childress et al., 2013).

As outlined in a recent report of the Conseil Superior de la Sante of Belgium (Avis Du Conseil Superieur De La Sante, 2016) the exact amount of monacolin K in red yeast rice is highly variable, ranging from 3 to 30 mg daily depending on the brand. The variability of this active principle content is an health risk, due to the lack on appropriate information for the customers. The Food and Drugs Administration (FDA), issued a warning since 2007, outlining that red yeast rice products contain lovastatin, an unauthorized drug (FDA, 2014). Considering this, the current regulatory framework may not be adequate to ensure consumer safety representing a risk for health (Venhuis et al., 2016).

The hypothesis that polyphenolic compounds from apple extracts, e.g. quercetin, (−)-epicatechin, (+)-catechin, procyanidins, anthocyanins, dihydrochalcones (phloridzin), phenolic acids, play a key role in cholesterol metabolism led recently to study polyphenolic extracts from apples with the goal to develop a new nutraceutical effective against hypercholesterolemia.

Apples varieties differ in their polyphenolic composition: an in vitro study showed that Annurca apple, the only cultivar native to Campania region (Southern Italy), has the highest polyphenolic concentration and an uncommon polyphenolic profile compared to the other cultivars available on the Italian market (Tenore et al., 2013). The Annurca variety resulted richer in dimers and oligomers with $6 < n < 8$. Annurca polyphenolic extract resulted in a high capacity of increasing Apo-A1 levels (2 times), and of decreasing LDL-C concentrations (−48%), in HepG2 cell medium (Tenore et al., 2014).

Procyanidin dimers (procyanidin B2) are the most effective in decreasing low density lipoprotein, LDL-C (−60%), and increasing Apo-A1, the main membrane protein constituent of nascent discoidal HDL-C (+85.7%), while the oligomers $6 < n < 8$ are the main responsible for the TC increase (almost 9 times the control) in the cell culture medium (unpublished results). The mechanism of action for lowering the cell cholesterol content, seems to involve the activation of Sterol Regulatory Element Binding Proteins (SREBP-1) transcription factor, which caused a considerable LDL receptors up-regulation (Christina and Paul, 2006). Annurca apple catechins, as well as statins, the first-line lipid-lowering drug therapy, can indirectly increase the sterol regulatory element binding protein (SREBP-2) expression which in turn lead to the LDL-receptor over expression, the event mostly responsible for the effective lowering of plasma LDL-C (DeBose-Boyd et al., 2001). It can be reasonably hypothesized that dimeric procyanidins from apples have a statin-like LDL-lowering effect, but, differently from statins, which do not substantially rise the high density lipoprotein plasmatic level (values on the average below 10%), the apple dimeric procyanidins are fully able to increase the apolipoprotein A1 (APO-A1) protein concentration in the cell medium (+71.4%) of an HepG2 cell culture.

The unique distribution of the polyphenolic fraction in Annurca variety (28.5% procyanidin B2 and 10.9% of oligomers with $6 < n < 8$) can be associated to the high effect in lowering the low density lipoprotein and in rising the Apo-A1. Both these fractions seem to be responsible, with different mechanisms of action, of the plasma cholesterol-lowering effect. Dimers are readily absorbed in gut, quickly reaching the liver where they act indirectly by increasing the number of LDL-C receptors (Yasuda et al., 2011); the oligomers, on the other hand, which are confined in the gut, would locally act with a β-cyclodextrin like mechanism, trapping the cholesterol molecules, this way reducing its absorption (Leifert and Abeywardena, 2008).

A recent in vivo, twelve weeks clinical trial study on humans, indicate that Annurca apples (200 g/day) fed to patients with mild hypercholesterolemia (in a range between 210 and 250 mg/dL) had a good hypocholesterolemic effect with a TC reduction of −8.3%, to be compared with Granny Smith and Red Delicious varieties, which resulted in a total cholesterol, TC, reduction of −4.4% and −3.1%, respectively. Fuji and Golden Delicious resulted in a TC reduction level of −2.0% and −1.3%, respectively. Annurca apple induced also a reduction of LDL-C of −14.5%, and an increase of HDL-C of +15.2% (Tenore et al., 2016). Based on these data, a nutraceutical containing Annurca polyphenolic extract (phytocomplex), has been developed from our research group. Preliminary results indicate that administering two 400 mg/day capsules of Annurca phytocomplex polyphenolic extract, resulted, on the average, in a TC reduction of −25%, an HDL-C levels increase of +49.2%, an LDL-C lowering of −37.5%. No alteration of both triglycerides or sugars level compared to baseline has been observed.

This is further outlined by the ratio LDL-C/HDL-C in the plasma samples of patients treated with the nutraceutical, which decreased from 6.26 to 2.30, indicating a reduction of the cardiovascular risk which is considered relevant if this value is around 3 (Millán et al., 2009). While the use of the hydroxymethyl-glutatil-CoA reductase inhibitors may come along with well-established unwanted events e.g. myopathy, and diabetes, a nutraceutical containing Annurca apple polyphenolic extract, did not show any adverse effect, better bioavailability and high efficacy.

5. Type 2 diabetes

Type 2 diabetes mellitus is a metabolic disorder due to relative or absolute lack of insulin, resulting in elevated blood glucose levels and it is characterized by persistent high blood sugar which can produce long-term cardiovascular and renal disorders, retinopathy, etc. Despite the availability of many anti-diabetic medications on the market, diabetes and its complications are considered among the main medical challenges also due to adverse effects both in the short and long run due to the use of the hypoglycemic drugs. The delay on these pathological conditions in subjects with impaired glucose tolerance can be obtained with a lifestyle change or the use of drugs (Ros et al., 2015).

As an alternative proactive approach, many phytocompounds obtained from plants or of a microbial origin, e.g. galegine (similar to metformin) isolated from *Galega officinalis* can be adopted as therapeutic and/or preventing agents. The mechanisms of action of many natural products as anti-diabetics can be related to the glucosidase and amylase inhibition, with effect on glucose uptake and glucose transporters, implying the modification of the mechanisms mediated by the peroxisome proliferator-activated receptor, inhibition of protein tyrosine phosphatase 1B activity, and activities of hormones involved in glucose homeostasis. Among the most studied nutraceuticals candidates as potential sources as anti-diabetics are: amorfrutins, *Morus alba*, fatty acids, and phlorizin.

Amorfrutins are isoprenoid-substituted benzoic acid derivatives, and form a family of natural products extracted from edible parts of two legumes of the Fabaceae family, namely *Glycyrrhiza foetida* and *Amorpha fruticosa*, which are able to bind to and activate the nuclear receptor peroxisome proliferator-activated receptor gamma (PPARγ). This results in selective gene expression and physiological profiles different from activation by current synthetic PPARγ drugs. PPARγ plays a central role in lipid and glucose metabolism; however, current PPARγ-targeting drugs are characterized by undesirable side effects. To fight possible unwanted side effects of thiazolidinediones, among the mainstay PPAR full agonists drugs for the treatment of type 2 diabetes, recently selective PPAR modulators as safer alternatives to PPAR full agonists have been evaluated. In diet-induced obese and diabetic mice,

amorfrutin treatment strongly improved insulin resistance and other metabolic and inflammatory parameters without any concomitant increase of fat storage or other unwanted side effects e.g. hepatoxicity (Weidner et al., 2011).

Morus alba L. leaves have been used for the management of diabetes and to improve health condition as natural traditional olistic remedy since centuries. Their effect on type 2 diabetes has been associated to the potential of the extract in the high inhibition of Cytochrome P450 enzymes, suggesting a possible nutraceutical use of the plant extract due to its bioactive compounds content and negligible other drugs interactions and safety in diabetes management (Kar et al., 2015).

A recent study aimed to evaluate the hypoglycemic effect of aqueous extract of *Morus alba* leaves in Alloxan induced diabetic albino rats, has been conducted in comparison with animals treated with Glibenclamide. The use of *Morus alba* extract (600 mg/kg) significantly reduced blood glucose levels as compared to control group, and comparable results when compared to Glibenclamide, confirming the hypoglycemic activity of *Morus alba* leaves (Madalageri et al., 2016). The beneficial effect has been attributed to the 1-deoxynojirimycin, an alpha glucosidase inhibitor contained in the phytocomplex. This substance proved to be effective on liver injury and hepatic glucose metabolism in diabetic mice. 1-deoxynojirimycin can increase hepatic insulin sensitivity via strengthening of the insulin-stimulated PKB/GSK-3 signal pathway and by modulating glucose metabolic enzymes (Liu et al., 2016). These results suggest a possible beneficial use of a nutraceutical based on this substance to help in maintaining physiologic sugar level in the blood.

Among the other possible alternatives, also dietary lipids, e.g. n − 3 and n − 6 fatty acids, which can act as peroxisome proliferator-activated receptors ligands and transactivate them, have been considered as nutraceuticals for type 2 diabetes treatment, focusing on the interactions between dietary lipids and PPARs (Itoh et al., 2008). These receptors respond to several exogenous and endogenous ligands by modulating genes related also to insulin homeostasis. PPARγ, expressed in adipose tissue and liver regulates, among others, glucose metabolism, and it is the target of type 2 diabetes drugs like thiazolidinediones. These drugs revealed toxicity, prompting the search for alternatives to replace their use. Structure-function studies evaluated the binding efficiency of the dietary lipids with PPARs by comparing them to these drugs (Itoh et al., 2008). Dietary lipids were able to bind to the ligand binding domain and cause conformational changes to activate the receptor, but they revealed to be weak PPARγ ligands due to their low physiological concentration (Xu et al., 1999). This observation however, allows to make the hypothesis that a nutraceutical based on concentrated n-3 and n-6 fatty acids, in the proper balance, could be effective in type 2 diabetes treatment.

6. Inflammation and oxidative stress

Inflammation causes the activation of cellular and systemic components of the immune system (Weiss, 2008), and it is an adaptive response which, in general, is triggered by a chemical or physical injury. The first step involves immune system cells including macrophages, mast cells, and dendritic and natural killer cells, which converge at the site of injury. Chemical mediators, e.g. cytokines and reactive oxygen species, prompt leukocytes to reach the area of injury or infection, and lead to the elimination of pathogens and/or tissue repair (Ferguson and Laing, 2010). The pharmacologic approach to these disorders uses extensively anti-inflammatory agents, including non-steroidal anti-inflammatory drugs and anti-rheumatic drugs. There can have several unwanted side effects, e.g. dose dependent side effects and difficulty of use for primary prevention.

Proper lifestyle and correct dietary habit have a key role in inflammatory responses and have no unwanted side effect compared to conventional pharmacological treatment. The higher availability of food, following the Industrial Revolution, determined in industrialized Countries an increased dietary intake of red meat, sugar, salt, high-fat foods, partially hydrogenated fats, trans fats, refined grains, and, at the same, the diet was lowered in fresh fruits, vegetables, fibers and n − 3 and n − 6 fatty acids (Galland, 2010).

Nutraceuticals extracts from vegetal matrices represent a powerful tool to prevent and cure the inflammation as an alternative to the pharmacological treatment. As an example, clinical trials have addressed the pharmacokinetics, safety, and efficacy of *Curcuma longa*. Turmeric is a rhizomatous perennial plant belonging to the Zingiberaceae family and it is used as a spice in cuisine (curry powder) other than as a remedy in traditional medicine. Promising effects have been observed in patients with various pro-inflammatory diseases. The mechanism of action of curcumin has been correlated to its ability to mediate the upregulation of peroxisome proliferator-activated receptor-gamma activation (Jacob et al., 2007).

The relative absence of unwanted side effects and dose related studies have confirmed curcumin safety for >3 months use at doses as high as 12 g/day of curcuminoids, which include curcumin (diferuloylmethane), the main component, demethoxycurcumin, and bisdemethoxycurcumin. The biological activity has been related to the ability of the spice to modulate signaling molecules like, among the others, pro-inflammatory cytokines, apoptotic proteins, NF–kB, cyclooxygenase-2, 5-LOX, STAT3, C-reactive protein, prostaglandin E_2, adhesion molecules, transforming growth factor-β (Gupta et al., 2013).

In clinical trials, curcumin has been used either alone or in combination with other substances. Various formulations of nutraceuticals based curcumin, including nanoparticles, liposomal encapsulation, emulsions, capsules, tablets, and powder, have been examined to maximize the bioavailability (Liqiang et al., 2015).

Nevertheless, unwanted side effects associated with curcuma intake have been reported when determining the dose response and safety. Thirty three volunteers were given curcumin (dose in the range 500–12,000 mg/day) and safety was assessed for 72 h after administration. In seven cases minimal toxicity was observed and symptoms like diarrhea, headache, rash, and yellow stool were reported (Lao et al., 2006). Similarly, a dose administered in the range 0.45 to 3.6 g/day for 1–4 months on subjects in a previous clinical study, was associated with nausea and diarrhea and caused an increase in serum alkaline phosphatase and lactate dehydrogenase contents (Sharma et al., 2004).

Among the most interesting nutraceutical candidates to act as anti-inflammatory, polyphenols are another outstanding example. The benefits of using polyphenols are mainly associated with their high antioxidant capacity that slows down the oxidative stress rate. They are a class of vegetal natural origin substances which are able to modulate human cellular signaling and gene expression. These compounds include phenolic acids, flavonoids, catechins, hydroxycinnamates, coumarins, anthocyanins, ellagic acid, lignans, ellagitannins and isoflavones. In a similar way to amides and carotenoids, polyphenols predominantly act as antioxidants, by scavenging free radicals and chelating metal ions. Some polyphenols also increase the levels of glutathione and the expression of antioxidant enzymes such as glutathione peroxidase, catalase, and superoxide dismutase. All are able to reduce the oxidative stress, which has been associated to the occurrence of chronic diseases and is believed to promote cell proliferation and causing, among others, malfunctions in heart disease, diabetes, and autoimmune disease (Yahia, 2010).

Flavonoids, the largest group of grape polyphenols, are considered to have important biological properties, including anti-inflammatory activity. Grape polyphenols have been shown to decrease chronic inflammation either by modulation of inflammatory pathways or by reducing the reacting oxygen species (ROS) levels. As natural compounds, grape flavonoids and proanthocyanidins can target multiple pathways to overcome chronic inflammation, and are more effective compared to synthetic mono-targeted anti-inflammatory drugs (Sung et al., 2012).

Even if their absorption ability is quite low, grape polyphenols can have direct positive impact on gut mucosa notwithstanding a low

intrinsic activity since they are poorly absorbed by the intestine, highly metabolized and quickly eliminated (Manach et al., 2004). Nonetheless, experiments based on oral administration of wine to rats showed that poorly adsorbed grape polyphenols may decrease the oxidative damage exerted on DNA in caecal mucosal cells suggesting that dietary flavonoids can have a positive effect regardless their poor absorption (Scalbert et al., 2002).

The low concentrations of naturally occurring polyphenols and their very rapid metabolism once ingested prompts the study of nutraceuticals to be administered in form of pills, capsules, etc., where these molecules can be concentrated and used in a suitable pharmaceutical form and in a dose effective form (Bernal et al., 2010).

7. Combined nutraceutical formulation

The search for alternatives to drugs stimulated interest for combining nutraceuticals to test their possibly higher efficacy with the aim of obtaining safer and more effective formulations for humans. Among the widely marketed nutraceuticals with clinically demonstrated effects on hyperlipidemia, red yeast rice, soluble fibers, n-3 fatty acids, and berberine, are among the most studied (Kong et al., 2004). Beyond red yeast rice and n-3 fatty acids, whose use has been related to a reliable decrease in cholesterol, only a few evidence is available to assess a preventive/therapeutic cholesterol-lowering effect due to combined nutraceuticals. For berberine and soluble fibers, the evidence of a positive multimetabolic effect is growing, contributing to a better control of both glucose and lipids values that consequently could be useful in the management of metabolic syndrome (Cicero et al., 2015). A complete assessment of this aspect is still to be cleared, as well as their mechanism of action. A recent study on primary prevention clearly addressed the key role played by nutraceuticals in improving lipid profile in patients with low to moderate cholesterol levels (Mazza et al., 2015). In this study sixty six patients (average age 56 years) without an history of cardiovascular diseases or organ damage, were administered for six months one tablet per day of a nutraceutical containing red yeast rice, policosanol, berberine, folic acid and coenzyme Q10. Serum total cholesterol, LDL-C, HDL-C and triglyceride values were determined and compared. A reduction of total cholesterol (−19.2%), LDL-C (−17.4%) and triglycerides (−16.3%) was observed, while HDL-C remained unchanged. As an evidence, no difference was observed in the control group (Mazza et al., 2015).

Another recent analysis study reports data on two nutraceutical combinations, namely A and B, administered alternatively for 8 weeks to a cohort of 23 randomized patients, 52% of which were women (average age 59 years). Nutraceutical A was made of policosanol and red yeast rice monacolin K, 3.0 mg, berberine 500 mg, plus astaxanthin, folic acid and coenzyme Q10. Nutraceutical B was made of red yeast rice containing monacolin K 3.3 mg, berberine 531 mg and *Morus alba* leaf extract. Total cholesterol level changed from 246 to an average value of 213 and 198 mg/dL (−13% and −19%); HDL-C from 47 to 51.8 and 52 mg/dL (+10% and +10%), and LDL-C from 176 to 142 and 127 mg/dL (−19% and −28%), for nutraceutical combinations A and B, respectively. These data suggested that an increased content of berberine and monacolin K with *Morus alba* extract improves the effect on plasma cholesterol (Trimarco et al., 2015).

Nutraceutical use in combination with reduced dose of statin has been also tested with the aim of reducing the unwanted side effects due to pharmacological therapy. In a six months study conducted vs placebo on 137 dyslipidemic subjects with previous adverse events to statins at high doses, 2 tablets/day of *Berberis aristata*/*Silybum marianum* made using 588 mg/105 mg, respectively, were used and statin dose reduced to one half. Lipidic profile did not change substantially with statin at half dose and nutraceutical addition. No relevant adverse events were recorded, but the TC, LDL-C and HDL-C, compared to start of the study, did not change significantly: observed values were +4%, +2% and +5%, respectively. Considering the results, based on the one hundred twenty eight subjects which completed the program, the nutraceutical used can be considered as an addition to statins in patients not tolerating high dose of these drugs (Derosa et al., 2015).

8. Conclusions

The main issue regarding the proper and effective use of nutraceuticals in prevention and therapy is connected to the lack of clinical data substantiating in full their efficacy. Nutraceuticals bioavailability affects their efficacy as disease-preventing agents, and it is another open challenge for further studies. The oral bioavailability of a nutraceutical is defined as the fraction of the ingested nutraceutical that can reach the systemic circulation in an active form and depends mainly on the food composition and structure (Parada and Aguilera, 2007). Only nutraceuticals which reach and distribute to the tissues and organs where they can exert their beneficial health effects are effective. Barriers preventing ingested nutraceuticals from reaching the systemic circulation in an active form, are chemical instability during digestion, poor solubility in fluids, slow absorption from the gastro intestinal tract, and first-pass metabolism. Some strategies to improve this aspect have been outlined recently, e.g. the use of nanotechnology to encapsulate nutraceuticals in presence or absence of lipids as the major components of the delivery systems (McClements and Xiao, 2014; Yao et al., 2014).

Nutraceuticals delivery is a wide open challenge for producers, dealing with solubility issues. Systems currently being studied for labile and poorly permeable hydrophilic nutraceuticals include nanoparticles, intestinal permeation enhancers, and mucolytics (Gleeson et al., 2016). The bioavailability profile of nutraceuticals, e.g. hydrophobic substances, may be due to a limited bioaccessibility, poor absorption, or chemical transformation within the gastrointestinal tract. It can be improved, for example, using oil–water emulsions, core-shell (zein-pectin) nanoparticle delivery system (Huang et al., 2016), nanoencapsulation (Neves et al., 2016), and also nanoemulsions (Aboalnaja et al., 2016). Studies on nutraceuticals as single or combined phytocomplexes are hence very much needed, as well as the need of assessing their mechanism of action. At the same time, there is need of clinical data substantiating any health related claim. This aspect is becoming a major issue as well as the assessment of their safety and the total absence of unwanted side effects other than the presence of possible interactions with prescription drugs or with food usually included in daily diet. Nevertheless, considering the low cost of the starting food matrices, often side products of other agrifood chain production, nutraceuticals represent a tool for expanding a proactive medicine approach to prevent diseases onset and a money saving tool for the National Health Systems facing with long-term chronic health conditions which require pharmacological therapy. The efforts addressed to develop nutraceutical based proactive approach are going to be the priority as per the quote “prevention is better than therapy of a disease”.

The lack of shared regulation on this topic is another severe barrier for their proper use. Nutraceuticals are actually categorized as food supplements, and the same regulations are currently applied. This causes confusion among consumers and lack of proper information on the market. A shared regulatory framework for nutraceuticals does not exist. The key issue is mostly related to the health claim status and whether a nutraceutical or the phytocomplex itself could be defined “a medicinal by function”. Nutraceuticals seem to belong to this last category. The Foods for Particular Nutritional Uses (PARNUTS) regulatory frameworks that include foods for special medical purposes and food intended for particular nutritional uses (Directive 2009/39/EC) could be adopted. In July 2016, the Directive 2009/39/EC on PARNUTS has been replaced by the Regulation EU n. 609/2013 with the aim of providing a new concept of dietetic food and a new framework for defined categories of food that are considered as essential for certain vulnerable groups of the population e.g. food for special medical purposes or total diet replacement for weight control.

Nevertheless, a pioneer vision of a complete assessment of nutraceuticals, has been proposed since 2002 with the Nutraceutical Research and Education Act (NREA) by the Foundation for Innovation in Medicine guided by Stephen DeFelice. NREA foresaw the setup of a Nutraceutical Commission (NUCOM) dedicated to the review and approval of nutraceuticals and also to develop programs specifically addressed to encourage the clinical research in the area. The realization of this perspective plan could trigger new actions and stimulate the proper worldwide information on nutraceuticals as well as the research in the field, encouraging the onset of a prevention proactive medicine based mechanism which adopts in full nutraceuticals to prevent better than cure pathological conditions arising from wrong diet and lifestyle, and acting, consequently, "beyond the diet before the drugs".

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