Special characteristics of non-nutritive food constituents of plants - Phytochemicals.

Wilfried Andlauer[1] and Peter Fürst

formerly: Institute for Biological Chemistry and Nutrition, University of Hohenheim, D-70599 Stuttgart, Germany

Introduction

„The scientist to be successful must be a sort of Janus looking at the same time to the future and the past"
Francisco Grande

Throughout history, civilized societies have devoted a deep interest in, and concern about, the integrity of food supply. Long before the development of the distinct scientific discipline of nutrition, philosophers and later physicians paid close attention to the role of the daily diet in individual and public health. Interestingly, during the last 2000 years, from the time of Hippokrates (460-377 BC) to the dawn of modern medicine, there was little distinction made between food and drugs. The practice of medicine itself consisted largely of the wise choice of natural food products.

Hippokrates clearly recognized the essential relationship between food and health and emphasized that „...differences of diseases depend on nutriment" [1, 2]. Pliny the Elder (23-79 AD) found widespread adulteration throughout food and drug supply outlined in his Natural History „... so many poisons are employed to force wine to suit our taste - and we are surprised that it is not wholesome!" Pliny, also reflected the layperson's distrust of medical practice that has existed throughout the ages: „Physicians acquire their knowledge from our danger by considering poisons as ... food constituents in our daily nutrition, though the greatest aid to health is moderation in food. Only a physician can commit homicide with complete impunity [3]. In contrast, Galen (131 - 201 AD), a physician, reflected confidence in the knowledge and ability of physicians to establish sound diets that would advance public health [4].

Overstated beliefs in the effects of aliments upon health and disease, appear to be based on magical thinking about food. Utilizing the primeval principle that like makes like, the alchemists pursued their search for the „elixir vitae". Modern successors of the alchemists employed the same concept. Casimir Funk discovered in the shell of rice grain a nitrogen-containing amine-base (amine); since he thought that this substance is „life-essential" for the human being, he defined the idiom „Vitamin" from „Vita = life" and „amine" [5]. He also reviewed evidence concerning the etiology of several food-related diseases and proposed that the absence of „vitamins" caused those diseases. Indeed, it is fascinating that the power we today attribute to vitamins is not unlike that one described to „elixir vitae" [6].

What are Phytochemicals?

Phytochemicals are to be found both among nutrients and non-nutrients. The non-nutrient phytochemicals refer to every naturally occurring chemical substance present in plants, usually in small amounts especially to those phytochemicals that are biologically active.

Phytochemicals occur in all higher plants and in all parts of plants - wood, bark, stems, pods, leaves, fruits, roots, flowers, pollen and seeds [7].

Occurance and dietary intake

The major phytochemicals are phenolic compounds like flavonoids, phenolic acids and phytoestrogens.

[1] Corresponding author: PD Dr. Wilfried Andlauer, Haute Ecole Valaisanne, Route du Rawyl 47, CH-1950 Sion, Switzerland, *Tel.: +41 (0) 27 606 86 59; FAX: +41 (0) 27 606 85 15, anw@hevs.ch*

Flavonoids are ubiquitous in plants; almost all plant tissues are able to synthesize flavonoids. The number of flavonoids may be close to 5.000. The most important flavonoids are quercetin, kaempferol, myricetin and chrysin, found in most fruits and vegetables. In fresh vegetables like onions, kale, broccoli and french beans a high share of quercetin is found (30-486 mg/kg). Kaempferol could only be detected in kale, endive and turnip tops in significant amounts (31-218 mg/kg). In general, flavonoid levels in processed food are approximately 50 % lower than in fresh products [8]. The content of flavonoids in various beverages like tea and wine is very high [9]. Black tea infusions prepared with tea bags (4,0 or 5.0 g) contain 17-25 mg/L quercetin, 13-17 mg/L kaempferol, and approximately 3 mg/L myricetin [10]. The contents of catechins ranges 3-10 % (wt/wt solids) [11]. Green tea contains up to 30 % polyphenols with the catechins being the most prominent polyphenol fraction; among these epigallocatechin gallate represents 50-60 % of the total catechin content corresponding to 30-42 % (wt/wt solids) [12] or 10-133 mg/L [9]. The highest content of flavonoids in wines was found especially in Chianti and in some red Bordeaux and Riojas [10, 13]. In contrast, white wines revealed only tracer quantities [14].
Phenolic diterpenes include carnosol in rosemary leaves [15] and curcumin in turmeric, curry and mustard. Carnosol and carnosoic acid have been isolated and purified and shown to account for over 90 % of the antioxidant properties of rosemary extract in vitro [16].
Phenolic acids like ferulic acid, p-cumaric acid and caffeic acid are found in fruits, vegetables and cereals [17, 18]. Edible plant material contains numerous weekly oestrogenic diphenolic compounds termed phytoestrogens. They are the lignans, isoflavones, coumestans, and resorcylic acid lactones. The precursors of these compounds are to be found in fiber-rich unrefined grain products, various seeds, cereals, legumes and tea. In **Table 1** isoflavone and lignan concentrations are given in selected cereals compared to soy and linseed [19, 20].

Table 1: Isoflavone and lignan concentrations (mg/kg) in selected cereals as compared to soybean and linseed

Rye	2-8
Wheat	5
Oat bran	7
Oat meal	2
Soybean (textured)	1100
Linseed meal	600-800

The only known estimates of total phytochemical intake adopted from modern literature, is in the range of 1-1,5 g/d as calculated from a mixed diet including vegetables, fruits and beverages such as tea and red wine [21]. The daily flavonoid supply in The Netherlands is reported to yield about 25 mg, with a range of 4-46 mg [22]. More recently the mean flavonoid intake in Finnish diet was estimated to be 3.4 mg/d ranging 0-41.4 mg/d, much lower than the Dutch consumption [23].
Even moderate tea consumption can contribute to a substantial quantity of catechins to the diet. Since polyphenolic catechins are 20-30 % of the dry solids in tea extract, total phenolic catechin ingestion in humans is in the range of 0.3 to 1 g/day. Heavy drinkers of green tea in Japan may consume 1 g of epigallocatechin gallate per day. [24]. Modern technologies are in progress to develop an increase and standardization of the levels of active catechins in tea preparations and to improve the overall performance of green tea extracts.

Epidemiologic evidence for chemoprevention

Recent epidemiologic studies promote the notion that an increased consumption of plant products is an important factor in reducing the risk of degenerative diseases like coronary heart diseases and cancer [25-28]. These findings are supported by a recent epidemiological review based on 15 American and European case control and prospective studies showing that there is a striking consistency in reduced risk for colorectal and gastric cancer associated with intake of whole grain [29]. Accordingly, it has been demonstrated that high intake of various soy products, rich in isoflavonoids and lignans, protects against breast cancer and prostatic cancer. This claim is supported by the fact that subjects with breast cancer or at high risk of breast cancer excrete low amounts of lignans and isoflavonoids, but subjects living in areas with low risk of hormone-dependant cancers have higher levels [30, 31].
The pleiotropic effects of dietary flavonoids have been emphasized especially related to degenerative diseases [32]. Several epidemiologic studies suggest that black tea consumption is associated with a reduced risk of degenerative diseases such as cardiovascular disease [33, 34]. It has been reported that the incidence of coronary mortality and lung cancer is higher among population with low dietary intake of flavonoids [23, 35]. A design for a diet rich in fruits, vegetables and legumes has been proposed [36].

In 1992 a fascinating hypothesis was postulated: the s.c. “French Paradox” [37]. It claims that French subjects who have similar intakes of saturated fatty acids, similar risk factors and comparable plasma cholesterol levels exhibit a much lower incidence of death from CHD than US or West European subjects with comparable intakes of fat. It could be demonstrated that consumption of red wine was the only dietary factor that showed a negative correlation with CHD. In subsequent reports the remarkable effects of red wine have been confirmed and possible underlying mechanisms discussed [38].[39-41] It is to emphasize that in recent communications similar effects were observed with grape extracts only [42]. The essential question remains still unanswered: whether alcohol per se [40, 43] or the nonalcoholic fraction of wine (grapes), represented mainly by phenolic compounds, are the primary factor responsible for the protective effect. Indeed, the current report, showing impressive effects of antioxidant capacity with alcohol-free red wine, is an actuating notion in this respect [41].

In conclusion, there is little doubt that the preventive effects of plant products are intrinsically related to the presence of phytochemicals. Indeed, some of them have been considered previously as needless, useless or even toxic dietary compounds [19, 44]. Longitudinal dietary changes indicate that increasing share of population respond positively to current health manage with regard to diets containing more fruits and vegetables [45]. Currently positive associations of exercise and fruit consumption with cardiovascular health has been reported in female adolescents and adults [46]. All available data confirm and reinforce the advantages for human health of a balanced diet containing plenty of fruits, vegetables and cereals and of reducing the amount of fat in the diet. Based on the available epidemiological studies, the US Government recommends a consumption of 400-600 g of vegetables and fruits daily, which comprises three to five portions of vegetables, and two to three pieces of fruit [47].

Preventive action of phytochemicals

During the last 30 years, research in the field of nutrition and chronic disease causation has led to exciting, significant progress in providing an understanding of specific risk factors and chemopreventive agents. The major health problems considered are cardiovascular diseases and the nutritionally linked cancers. One aspect involved in initiation and development of both cardiovascular diseases and the cancers noted are abnormal oxidative processes, leading to the generation of hydroxyl radicals and peroxyl compounds. In part, the protective role of vegetables, fruits, and tea is thus to provide antioxidant vitamins and specific phytochemicals that display a powerful inhibition in oxidative reactions. Epidemiological studies (*vide supra*) as well as laboratory experimentation have yielded sound data and evidence in support of the fact that vegetables, fruits, and tea and specific antioxidants therein account mechanistically for inhibition [48].

It is to remember that with a normal diet the intake of phytochemicals is about 1-2 g a day [21]. This represents a chemical cocktail of 5 000-10 000 substances, not taken into account that they can also influence each other in their effects [21].

Antimicrobial, antiinflammatory action

For thousands of years, spice and food plants have been purposely used against bacterial and fungal growth. Egyptians were known to have treated infections with garlic and also during the two World Wars it was used against wound infections. Horseradish, nasturtium and cress as well as cabbage, cauliflower and brussel sprouts contain large amounts of antimicrobial mustard oils. They exhibit remarkable antimicrobial and antiinflammatory activities [49, 50]. Antiinflammatory action of phytochemicals is attributed to their ability to inhibit the catalysis of prostaglandin formation from n-6 fatty acids [51].

Antioxidative action

Free radicals can play an important part in the development of various degenerative diseases. There is growing body of evidence that the chemopreventive effects of phytochemicals contribute to inactivate “reactive oxygen species”, thereby ellicit antioxidative action [52-54]. The mode of action is according to one or more of the following functions: a) as free radical scavengers, b) as reducing agents, c) as potential chelators of pro-oxidant metals, and d) as quenchers of the formation of singulet-oxygen.

As mentioned, red wine possesses potent antioxidative capacity and reduces the oxidation of human low density lipoprotein (LDL) [38, 55, 56]. Actually, the wine phenolics were more effective than α-tocopherol in reducing LDL-lipid oxidation (cf. French Paradox) [37, 38]. Resveratrol, present in most red and white wines, is assumed to protect against atherosclerosis by reducing the peroxidative degradation of LDLs, probably due to its capacity to chelate copper [55].

Although black and green tea are powerful antioxidant beverages, they are apparently lacking effect on lipid peroxidation [57-59].

Carnosic acid, carnosol, and rosmarinic acid, present in various spices exhibit dose-dependent inhibition of LDL oxidation in human aortic endothelial cells [16].
The wide mixture of phytochemicals with varying redox potentials in plant foods may interact in a synergistic manner, enabling effective protection against lipid oxidation at low concentration levels [60].

Antithrombotic action
Not only metabolic disorders but also the diet may influence blood coagulation. Modulation of platelet aggregation was demonstrated for many flavonoids derived from wild garlic and garlic, for wine and grape juices. Similar effects were reported for isoflavones from soy, gingerol from ginger and carnosol from rosemary [51, 61, 62].
The modulation of cyclooxygenase and lipoxygenase has been suggested as possible underlying mechanisms for the antithrombitic action [51, 63, 64].

Blood-pressure regulating action
Particularly alkaloids are claimed to have a blood pressure regulating effect; enhancing activity of caffeine in coffee and tea as well as theobromine in cacao is well known [65]. Black and green tea also contain flavonoids, which have a blood pressure decreasing effect, in contrast to glycyrrhizin, a saponine from liquorice root. Glycyrrhizic acid, the active component of liquorice, acts by inhibiting 11-β-hydroxysteroid dehydrogenase, which catalyses the reversible conversion of cortisol to cortisone [66]. Plant substrates with a blood pressure lowering effect have also been identified in garlic, but their mechanism is not clarified yet.

Blood-glucose influencing action
Myricetin, commonly found in tea, berries, fruits, and medicinal plants mimics insulin in stimulating lipogenesis and glucose transport in rat adipocytes in vitro [67]. Myricetin-stimulated glucose uptake is possibly due to a change in the intrinsic activity of the glucose transporter, caused by alterations in membrane fluidity or transporter-lipid interactions, as a result of the insertion of myricetin into the membrane bilayer. Thus, myricetin may have therapeutic potential in the management of non-insulin-dependent diabetes mellitus by stimulating glucose uptake, without the presence of fully functional insulin receptors [67].
Inhibitors of starch splitting enzymes like tannins (polyphenols) are also important glucose regulating substances. They attach to starch and/or enzymes and as a result slow down starch digestion resulting in a slower rise of the blood glucose concentration. The phytic acid in grains and legumes also seem to have unidentified inhibitory effect on starch digestion.
A fascinating reappraisal of traditional treatment of diabetes refers to the antihyperglycaemic, insulin-releasing and insulin-like activity of Agrimony [68].

Cholesterol-lowering effect
Excessive amounts of cholesterol has been linked to the development of cardiovascular diseases and atherosclerosis. Therefore a decrease of cholesterol is desirable in many cases. A cholesterol decreasing effect has been attributed to compounds with structural similarity, like phytosterines (plant sterols) [69, 70]. These compounds, consumed at levels of 200-400 mg/day in Western diets [71], may effect cholesterol absorption in the gut [71]. Garlic-containing drugs have been used in the treatment of hypercholesterolemia [61] even though their efficacy is not generally established [72].
Consumption of diets rich in soy protein has been claimed to protect against the development of atherosclerosis. Potential mechanisms include cholesterol lowering and inhibition of lipoprotein oxidation by soy proteins or soy-isoflavones [73].

Anticancerogenic action
Several phytochemicals are claimed to limit or to inhibit cancer progression [74-76].
The mechanism of phytochemicals can be demonstrated at a well known model for oncogenesis, the initiation – promotion model [74, 76]. The initiation – promotion model, allowing a tentative classification of phytochemicals according to the stage they impact the carcinogenesis.
To *category 1* belong substances which block the formation of cancerogens from precursor substances like amins and nitrits [54].
In *category 2* are substances which inhibit the cancerogenesis by preventing cancerogenic substances to approach and react with the target tissue [77, 78].
Category 3 contains substances like carotenoids, which become effective only after biological irreversible destruction has taken place by suppressing the neoplasia [79].

Substances in *category 4* stimulate the immune system (stimulating T-helper cells and cytokines), thereby impairing the already proliferating tumor cells [80].
Category 5 comprises substances, which effect the oncogen expression. These anticarcinogenic mechanisms are related to inhibitory actions of tyrosine kinases and other enzymes [81-83] that are associated with the transmission of signals from cellular growth factor receptors and expressed at high level in transformed cells.
Category 6 consists of antioxidative compounds (cf. *antioxidative action*), scavanging free radicals and preventing oxidative damage of DNA.
Interesting data concerning phytoestrogenic isoflavones and lignans as potential cancer-preventive substances are currently emerging. The phytoestrogenic compounds are classified as *category 7*. The weakly estrogenic isoflavonoids influence sex-hormone production, metabolism and biological activity, intracellular enzymes, protein synthesis, growth factor action, malignant cell proliferation and differentiation [30, 84]. Due to the structural similarity, phytoestrogenic compounds compete with the physiologic estrogens for the estrogen receptor binding sites [85, 86].

Conclusions

Public health authorities consider prevention and treatment with phytochemicals as a powerful instrument in maintaining health and to act against nutritionally induced acute and chronic diseases, thereby promoting optimal health, longevity and quality of life.
The current knowledge of the beneficial effects of phytochenicals will undoubtedly have an impact on nutritional therapy. At present, phytochemical based products – many designer foods, functional foods and nutraceuticals - represent the fastest growing segment of today's food industry. The market is estimated at 30 billion US $ growing at 5% per annum. The correct balance is struck between the exploitation of lucrative business (irresponsible market entrants) and adequate consumer protection (Hardy 2000).
Although it may be many years before the new designer foods will be stocked on supermarket shelves, the ongoing program will lead to a new generation of foods, which will certainly cause the interface between food and drug to become increasingly permeable. Thus, in the future we will see the emergency of phytochemical soups, phytochemical processed meat, bread and sausage. And many of these foods might be genetically produced. A horror vision for one - a fantastic fulfillment, indeed, for others.

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