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SHORT COMMUNICATION

The co-evolutionary perspective of the food-medicine continuum and wild gathered and cultivated vegetables

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Abstract Accumulated evidence suggests that our genes are still adapted to a pre-agriculturalist diet, which was devoid of refined sugars and dairy products and that our modern dietary behaviour is in great part responsible for several modern life style diseases. Especially the consumption of fruits, spices and vegetables, cultivated or gathered from the wild, are perceived as being healthy or endowed with a prophylactic effect and therefore many of these dietary items are regarded as both at the same time: food and medicine. I argue that green leafy vegetables began to contribute substantially to the human diet only with the beginning of agriculture, when the ecological niche of weeds began to prosper. Wild gathered vegetables added to the agriculturalists' dietary need in form of a back-up resource in times of shortage and in form of micronutrients and allelochemicals promoting the development of the modern pharmacopoeias. Similarly to wild gathered foods are cultivated staples recently getting more attention by phytochemists and pharmacologists. Especially local cultivars and agro-ecotypes may present interesting opportunities for phytochemical and pharmacological analysis in the attempt of identifying bioactive dietary allelochemicals. Chemical and biological characterization of local crop cultivars serves for the selection of varieties with specific nutraceutical properties. Germplasm can be obtained from several local organizations, which arrange easy access to seeds and products of rare crop cultivars, foster their commercialization and secure catering through the conservation of agro-biodiversity.

Keywords Agro-biodiversity · Beta-caryophyllen · Cannabinoid receptor · Falcarinol · Glucosinolates · Neolithic diet · Nutraceuticals

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Introduction

Throughout the ages, and at least since Hippocrates' [ca. 480–377 BC] proclamation "let food be your medicine, let medicine be your food", physicians recognized the impact of food on ageing, disease and well-being (Schäfer 2005; Heinrich and Prieto 2008). Also do nutritional deficiencies occur in both, populations of poor as well as affluent societies (Johns 1990). This short review tries to connect the co-evolutionary aspects between weeds, vegetables and agriculture with the permanent and ongoing adaptation to phytochemicals in human nutrition, integrating food chemistry as well as the protection of agro-biodiversity.

It is argued that our genome did not have enough time to completely adapt to the profound changes in diet and lifestyle occurring since the Neolithic

Revolution (for a recent review see: Carrera-Bastos et al. 2011). On the other hand, it is widely acknowledged that dietary products, especially spices, fruits and vegetables, either wild-gathered, semi-domesticated or cultivated, are used for both, food and medicine, representing both aspects at the same time (Etkin and Ross 1982; Johns 1990; Etkin and Ross 1991; Etkin 1996; Moerman 1994; Bonet and Vallès 2002; Pieroni et al. 2002; Etkin 2006). The continuum between these overlapping and blurred aspects can be exemplified with the well-diffused meme "an apple a day keeps the doctor away". While some might argue that this saying refers to the vitamin content and vague disease preventive and healthy nature of fruits in general it has become clear that diet and especially plant foods contain secondary metabolites exerting specific pharmacological and physiological effects (cf. Johns 1990; Etkin 2006; Gertsch, 2008; Lindeberg 2010; Carrera-Bastos et al. 2011; Valussi 2011). These authors adopt a perspective on diet and health from an evolutionary biology point of view inspired by the seminal paper by Eaton and Konner (1985): "Paleolithic nutrition—A consideration of its nature and current implications". Lindeberg (2010, p. 221) points out that humans and animal species in general are genetically adapted to the array of foods available in the ecological niche where great part of their evolution took place. At the same time did the plants and animals considered as food by humans develop strategies (e.g. allelochemicals, flight behaviour) to support the pressure exerted by herbivores and carnivores, securing a successful spread of their genes (Lindeberg 2010, p. 221). It is argued that with respect to the Palaeolithic dietary regime our present agriculturalist diet resulted in an alteration of several major functional dietary factors such as glycaemic load, fatty acid balance, macronutrient balance, trace nutrient density, acid–base balance, sodium–potassium ratio as well as fibre content, which are influential parameters in the progress and development of Western life-style diseases (Eaton 2000; Mann 2004; Cordain et al. 2005; Carrera-Bastos et al. 2011). The Palaeolithic diet is described as bereft of grains, refined sugars and dairy products consisting mainly and to varying extents of meat, fish, shellfish, insects, and wild plant foods such as nuts, roots, carbohydrate rich tubers as well as fruits and vegetables (Eaton et al. 2002; Cordain 2002; Lindeberg 2010). Harlan (1992, p. 12–14), however, reviews literature reporting evidence for a dietary role of seeds from wild grasses in hunter-gatherer as well as agriculturalist societies. This suggests that grains may have contributed to a certain extent to human diet also prior to agricultural practices. Among the vegetables used by hunter-gatherer societies as food according to Harlan (1992, p. 14–17) feature above all leaves and young shoots of legumes (Fabaceae) as well as fruits from the Solanaceae and Cucurbitaceae.

Vegetables in agricultural societies and medicine

We are adapted to deal with certain types of plant phytochemicals, ranging from basic requirements for essential nutritional co-factors (e.g. vitamins, folic acid, linoleic acid) to enzymatic detoxication systems and the possibility of transformation by gut bacteria (Johns 1990). The highest concentration of allelochemicals such as plant lectins (carbohydrate-binding proteins), protease inhibitors (inhibitors of protein degrading enzymes), endocrine disruptors (e.g. phytoestrogenes such as isoflavones), cyanogenic glycosides, pyrrolizidine alkaloids and phytic acids can be found in young plants as well as in the most vital parts such as sprouts, seeds, beans and roots (Lindeberg 2010). Johns (1990, pp. 210–250) hypothesizes that plant allelochemicals became part of a healthy digestive ecology and beneficial constituents in a balanced nutrition exerting a disease controlling effect and an essential prophylactic role in the changing sanitary conditions the Neolithic life style brought along. The increasing use of weeds for dietary purposes gave way to the perception of more subtle pharmacologic properties of this allelochemical rich ecological group of species and promoted the development of the modern pharmacopoeias (Logan and Dixon 1994; Stepp and Moerman 2001; Leonti et al. 2006). *De Materia Medica*, written by Dioscorides [ca. 40–90 AD] and one of the most influential herbals ever written, testifies to the importance of gathered and cultivated vegetables as well as crop species in general, used for both, medicine as well as food (Leonti et al. 2010a). In a cross-cultural analysis with a historical focus and including data from Spain, Italy and Greece we have argued that especially the role of gathered leafy green vegetables in the Palaeolithic diet might be overestimated and that this category of food began to play a crucial role in human nutrition only with the beginning of the Neolithic era (Leonti et al. 2006).

Most of the wild relatives of our cultivated vegetables are weeds, which found their ecological niche prospering only with the beginning of agriculture and the establishment of permanent settlements (Maurizio 1927; Harlan 1992; Zohary and Hopf 2000). Many of our weeds we know today did not exist in that form prior to the invention of agricultural practices but co-evolved together with the harvest techniques and land management systems of Neolithic societies (Willerding 1986; Jacomet et al. 1989; Harlan 1992, p. 89). Thus, habitats and growing conditions for wild gathered vegetables were limited before the onset of the Neolithic era. Therefore, we proposed that the Neolithic economy experienced an intensification and diversification in the use of leafy green vegetables in form of a backup resource in times of shortage and by satisfying agriculturalists' need for micronutrients and allelochemicals. Furthermore, we suggested that wild-gathered vegetable species might contribute to a diversification of vegetables in city markets, which, thanks to the high content of nutrients and allelochemicals would at the same time contrast non-adaptive food habits (Leonti et al. 2006).

But Europe also holds a rich heritage of cultivated crops as well as a rich gene pool of many wild crop relatives (Heywood and Zohary 1995). Around 180 cultivated plant species with a European cultivation history are grown in Europe (Heywood and Zohary 1995). Roughly 100 of these species are cultivated for dietary purposes including grain crops, fruit trees, vegetables, oil crops, as well as potherbs and condiments (Heywood and Zohary 1995). Meanwhile, landraces, adapted to the different agro-ecological conditions across Europe are affected by genetic erosion because they are progressively displaced by high-yielding varieties (Hammer and Laghetti 2005; Montesano et al. 2011). Etkin and Ross (1991) noted a paucity of pharmacological interest in staple foods and argued that the few existing studies on medicinal properties of staple foods is grounded on the reduced diversity and content of herbivore repelling allelochemicals plant domestication brought along, which makes staple food at fist glance unattractive to phytochemists. Etkin and Ross (1991) specified, that "the pharmacologic banality of domesticates has been exaggerated" and that we would benefit from pharmacological inquiries into staples. Also Brandt et al. (2004) pointed out, that only "few studies focus on the identification of new types of health promoting compounds from vegetables and fruits". Especially bitter, pungent and aromatic functional foods such as artichoke (*Cynara cardunculus* L. ssp. *cardunculus*, Asteraceae), dandelion (*Taraxacum officinale* G.H. Weber ex F.H. Wigg; Asteraceae) and chilli pepper (*Capsicum anuum* L.; Solanaceae) are used in the treatment of digestive disturbances around the globe and there exists a growing body of clinical evidence corroborating their efficacy (e.g. Meghvansi et al. 2010; Valussi 2011). Ginger (*Zingiber officinale* L.), which is used in diet and medicine contains potent inhibitors of inflammation and their mechanism of action was recently elucidated (cf. Nievergelt et al. 2011), while flavonoids, which are poorly bioavailable but widespread in food plants, may generate bioactive metabolites that act on the central nervous system (Vissiennon et al. 2012). There are, however, also clinical studies with food derived compounds, such as curcumin obtained from *Curcuma longa* L. (Zingiberaceae). Several trials have shown reliable evidence for the positive effect of curcumin in patients with inflammatory conditions such as rheumatoid arthritis and inflammatory bowel disease (White and Judkins 2011). Recently the European Food Safety Authority (EFSA) approved the health claim "reduction in platelet aggregation" for a lycopene-free, water-soluble tomato (*Lycopersicon esculentum* L.; Solanaceae) concentrate (EFSA 2009). After in vitro and *ex vivo* platelet aggregation studies (O'Kennedy et al. 2006a; O'Kennedy et al. 2006b) the tomato concentrate was standardized on the total quantity of 37 characterized constituents (EFSA 2009).

Generally, however, domestication of crop plants led to a decrease of secondary plant metabolites, the potentially noxious as well as the potentially beneficial ones. This affects the co-evolutionary relationship between plant chemicals and human receptors and molecular targets.

Some allelochemicals in human diet, their co-evolutionary aspects and molecular targets

Beta-caryophyllene (BCP)

BCP is one of the most common sesquiterpenes and widely distributed across the plant kingdom (Knudsen et al. 1993; Cai et al. 2002). It is a constituent of the essential oil of numerous spice, medicinal and food plants such as cloves (*Syzygium aromaticum* (L.) Merrill et Perry, Myrtaceae), origano (*Origanum vulgare* L., Lamiaceae) black pepper (*Piper nigrum* L., Piperaceae), cinnamon (*Cinnamomum* spp.), rosemary (*Rosmarinus officinalis* L.), cannabis (*Cannabis sativa* L., Cannabaceae), hops (*Humulus lupulus* L., Cannabaceae) and basil (*Ocimum* spp., Lamiaceae).

Recently, we found that this bicyclic sesquiterpenoid selectively binds to the cannabinoid receptor type 2 (CB_2 receptor) acting as a full agonist at dietary relevant concentrations able to imitate the physiological effects of the endogenous ligands 2-AG and anandamide (Gertsch et al. 2008). Agonistic interactions with the CB_2 receptor, part of an ancient lipid-signalling network (endocannabinoid system) transmit cellular signals, which lead to an attenuation of inflammatory processes (for a review see: Guindon and Hohmann 2008).

But also staple crops like maize (*Zea mays* L.) and rice (*Oryza sativa* L.) are able to synthesize BCP. Intriguingly herbivore attack in maize and rice induces the production of BCP, which serves as an attractant of entomopathogenic nematodes below ground and parasitic wasps above ground (Rasmann et al. 2005; Cheng et al. 2007; Köllner et al. 2008). This indirect plant-defence interaction is, however, not mediated by the endocannabinoid system since insects and some nematodes lack endocannabinoid receptors, probably due to secondary loss (McPartland et al. 2006). During the breeding process, however, did North American maize cultivars lose the ability to produce and release BCP upon herbivore attack, which leads to increased application of pesticides (Rasmann et al. 2005; Köllner et al. 2008). From an ecological perspective are sesquiterpenes such as BCP bio-signalling molecules emitted by plantae participating in plant–plant as well as plant-animal communication (Rasmann et al. 2005; Kim et al. 2009). BCP is one of the atmospherically most prevalent sesquiterpenes and beta-caryophyllinic acid, its degradation product, can be detected in environments as diverse as the tropics and the arctic. Since sesquiterpene emission occurs prevalently during the day, ozonolysis occurring in the troposphere is the main degradation pathway keeping the BCP level in equilibrium with its biome (Chen et al. 2012). Similar to the insect-plant interaction mediated by complex volatile mixtures Gertsch et al. (2010) hypothesize that exposure to CB_2 receptor active plant metabolites, such as BCP, may have led to co-evolutionary adaptations also in mammals. Curiously, BCP is also a FDA approved food additive and unlike hydrophilic compounds (e.g. polyphenols) readily bioavailable.

Falcarinol

Another example of a highly bioactive dietary constituent targeting the endocannabinoid system is the polyyine falcarinol occurring in a range of cultivated Apiaceae vegetables such as carrots (*Daucus carota* L.), parsley (*Petroselinum crispum* (Mill.) Nym. ex A.W. Hill), celery (*Apium graveolens* L.) fennel (*Foeniculum vulgare* L.) as well as pastinake (*Pastinaca sativa* L.). Falcarinol binds to the CB_1 receptor mediating an inverse agonistic effect. Flacarinol, which in susceptible humans acts as a moderate skin irritant, aggravated histamin-induced oedema on human forearm skin when applied together (Leonti et al. 2010b). This pro-allergenic activity of topically applied falcarinol seems to be linked to its antagonistic action on CB_1 receptors in keratinocytes, which impedes that the constitutively present anandamide tone exerts its anti-inflammatory action (Leonti et al. 2010b). Subjects showing positive patch test towards carrots, however, are able to eat and digest falcarinol-containing vegetables without showing sings of allergic reactions (Murdoch and Dempster 2000) although CB_1 receptors are expressed throughout the gastrointestinal tract (Izzo and Camilleri 2008). This particularity suggests that the subtypes of CB_1 receptors present in the gastrointestinal tract may have adapted to falcarinol exposure through diet. Falcarinol uptake though carrot consumption might constitute the missing link in the paradoxal picture showing high concentration of natural carotenes in human serum associated with a decreased incidence of cancer, while dietary supplementation with pure carotene does not show any positive effect (Zidorn et al. 2005). Similar to BCP, whose production may be elicited in plant tissue upon herbivore attack falcarinol is considered a phytoalexin since its production may be increased after fungal infections (Christensen and Brandt 2006). Apart from polyacetylenes, dihydroisocoumarins, chromones and beta-carotene, purple carrot varieties additionally contain more that 40 phenolic acids as well as 5 major acylated cyanidin glycosides

(Kammerer et al. 2004; Kurilich et al. 2005). To the functional food and dietary supplement industry the phytochemical diversity across carrot varieties poses a major challenge in the attempt of maximizing health benefits from carrots (Metzger et al. 2008; Christensen 2011).

Glucosinolates

Brassica vegetables, one of the most important leafy crops around the globe, produce a range of aliphatic, indolic and aromatic, sulphur and nitrogen containing glucosinolates (Carlson et al. 1987; Rosa et al. 1997; Yang and Quiros 2010). Although the occurrence of glucosinolates is explained with their anti-nutritional properties this class of compounds and their characteristic organoleptic properties was one reason for the domestication of Brassicaceae as vegetables, salads, spices and herbal remedies (Mithen 2006, p. 25). The enzymatic breakdown product of the glucoraphanin glucosinolate leads to sulforaphane, an isothiocyanate that has been shown to induce the detoxication enzymes quinone reductase and glutathione transferase (Zhang et al. 1992). This finding led to the conclusion that the anticarcinogenic effect of broccoli (*Brassica oleracea* L. var. *italica* Plenck) might be related to this inductive effect (Zhang et al. 1992). Gamet-Payrastre et al. (2000) report data suggesting that in addition to the activation of detoxifying enzymes the prevention of cancer by sulforaphane is also due to a specific apoptosis inducing effect towards cancer cells, while the metabolite 3,3′-diindolylmethane, which is generated upon ingestion of indole-3-carbinol and widespread in *Brassica* vegetables, has been shown to weakly interact with the CB_2 receptor (Yin et al. 2009).

The study by Kushad et al. (1999) evidenced that not only the glucosinolate content of the five analyzed *B. oleracea* groups varied greatly but that also within the varieties var. *italica*, var. *gemmifera* DC., var. *capitata*, var. *botrytis* and var. *acephala* the glucosinolate profiles differed significantly. Principal component analysis of 24 Chinese cabbage (*Brassica rapa* L. subsp. *pekinensis* (Lour.) Hanelt) varieties from Korea showed considerable differences among the glucosinolate contents and profiles of the cultivars tested (Kim et al. 2010). In another survey of glucosinolate variation in *B. rapa* crops including 82 different varieties Young and Quiros (2010) on the other hand observed similar profiles of the Chinese cabbage accessions, while the other *B. rapa* groups studied showed high variation. The same study evidenced that two Japanese turnip accessions (var. *rapa*) differed qualitatively by their characteristic and considerable 2-methyl-2-propenyl-glucosinolate and *n*-butyl-glucosinolate content. Both, 2-methyl-2-propenyl-glucosinolate and n-butyl-glucosinolate, are not commonly found in *Brassica* species (Young and Quiros 2010). Such differences in glucosinolate content across genotypes clearly suggest differences in nutritional and health-promoting properties and a potential for breeding "designer" Brassicaceae (Rosa et al. 1997; Kushad et al. 1999).

Discussion

Agricultural practices have intensified human dietary dependence on vegetables and herbs. This relationship has led to co-evolutionary adaptations in both, human requirements for plant derived allelochemicals, and crop cultivars with health promoting qualities. Phytochemical and pharmacological analyses of landraces and local cultivars are more rewarding with respect to globally traded varieties in the attempt of selecting for nutraceutical vegetables. With respect to globally traded brands landraces (agro-ecotypes) and local cultivars, apart from being richer in taste and smell, show also a higher amount and greater variety in allelochemicals. This facilitates the physical detection of minor compounds and the characterization of their pharmacologic potential. Once the antagonistic and synergistic effects of allelochemicals have been elucidated the health promoting properties of plant foods may be optimized (Christensen 2011).

Access to systematic and botanically characterized collections of landraces, however, is rare. Genebanks aiming at the long-term preservation of agricultural biodiversity generally concede access to their collections. Such access is granted only in accordance with the terms and conditions explained in the "International Treaty on Plant Genetic Resources for Food and Agriculture" (2012) (http://www.planttreaty.org/) and is generally confined to seeds, which are only rarely the plant part a pharmacological and phytochemical investigation is focusing on. Notable exceptions are provided by some genebanks (e.g. in Italy, Hammer et al. 1999) and a rising number of NGOs, e.g. the

Austrian "Arche Noah" association (http://www.arche-noah.at/etomite/), the German "Verein zur Erhaltung der Nutzpflanzenvielfalt" (http://www.nutzpflanzenvielfalt.de/) the French Association "Kokopelli" (http://kokopelli-semences.fr/who_are_we), and the Swiss "ProSpecieRara" foundation (www.prospecierara.ch), amongst others.

ProSpecieRara is a non-profit organization that was launched in 1982 pioneering the protection of crop varieties and farm animals. The aim of ProSpecieRara is the safeguarding of agricultural biodiversity, to gather, conserve and communicate the knowledge and cultural values of traditional cultivars and landraces, to arrange easy access to seeds and farm animals for everyone, to sustain the endangered cultivars and landraces by fostering the commercialization of specialities, and ultimately to provide an important contribution to the security of our catering through the conservation of the diversity of crop plants and farm animals. ProSpecieRara has achieved to conserve 26 races of farm animals, ca. 1000 crop varieties as well as ca. 450 berry and 1800 fruit tree cultivars. The inventory of agro-biodiversity in Switzerland was published in a series of textbooks (e.g. Borbach et al. 2002; Bartha-Pichler et al. 2005; Bartha-Pichler et al. 2006; Heistinger 2010; Szalatnay et al. 2011). The handbook "Samengärtnerei" gives instructions on the preservation of cultivars, on how to increase diversity, how to produce seeds to propagate cultivars and how to crossbreed (cf. Heistinger 2010). Today, ProSpecieRara products, inclusive their seeds are sold by the most common supermarket chains throughout Switzerland offering dietary diversity and promoting *in situ* cultivation. Another initiative by ProSpecieRara is the collaboration with animal and horticultural farms, which provide the possibility for educational visits about agricultural diversity and species-appropriate farming (see: www.prospecierara.ch).

Conclusions

Allelochemicals occurring in vegetables and shaped by co-evolutionary interplay with microorganisms and herbivores such as insects have receptor binding capacity also in humans. Considering the huge variety of endangered crop cultivars, which with respect to wild gathered species are fully adapted to farming systems, local initiatives aiming at the protection of these varieties are a straightforward and practicable approach in the attempt of contrasting non-adaptive food habits. Promoting non-domesticated as well as cultivated vegetables in the attempt to diversify assortments of crops with a nutraceutical potential in city markets does of course, not exclude each other. Chemical profiling and pharmacological characterization of local crop cultivars serves for the selection of varieties with specific nutraceutical properties.

It is generally acknowledged that ethnobotanical field-research and studies on traditional knowledge systems should provide a feedback to the local communities and society in general (e.g. Heinrich et al. 2006; Rivera et al. 2006; González et al. 2011). The diversification of vegetables and fruit varieties in home gardens and city markets together with the wealth of literature on local crop cultivars published by the organization presented above might serve as a model for ethnobotanical field studies.

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