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Plant chemistry and food web health

Author for correspondence:
Klaus Schlaeppi
Email: klaus.schlaeppi@unibas.ch

Klaus Schlaeppi^{1,2} , Josef J. Gross³ , Siegfried Hapfelmeier⁴  and
Matthias Erb¹ 

¹Faculty of Science, Institute of Plant Sciences, University of Bern, Bern 3013, Switzerland; ²Department of Environmental Sciences, Faculty of Science, University of Basel, Basel 4056, Switzerland; ³Veterinary Physiology, Vetsuisse Faculty, University of Bern, Bern 3012, Switzerland; ⁴Faculty of Medicine, Institute for Infectious Diseases, University of Bern, Bern 3001, Switzerland

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Contents

Summary	957	V. Conclusion: phytochemicals modulate food web health	960
I. Introduction: phytochemical connections in the food web	957	Acknowledgements	961
II. Glucosinolates in soil, animal and human health	958	References	961
III. Benzoxazinoids in soil, animal and human health	959		
IV. Direct and indirect microbiome-mediated health effects	960		

Summary

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Plants are systemically relevant to our planet not only by constituting a major part of its biomass, but also because they produce a vast diversity of bioactive phytochemicals. These compounds often modulate interactions between plants and the environment, and can have substantial effects on plant consumers and their health. By taking a food web perspective, we highlight the role of bioactive phytochemicals in linking soils, plants, animals and humans and discuss their contributions to systems health. The analysis of connections among food web components revealed an underexplored potential of phytochemicals to optimize food web health and productivity.

I. Introduction: phytochemical connections in the food web

Current frameworks such as ‘One Health’, ‘One Medicine’ or ‘Ecosystem Health’ apply integrative systems thinking to understand and improve environmental, animal and human health (Zinsstag *et al.*, 2011). They have also been broadened to include soils and plants (van Bruggen *et al.*, 2019). Common to these frameworks is the recognition that different components of a system are connected and collectively determine global wellbeing. Here, we apply this integrative ‘One Health’ thinking to the food web and explore how plants in general, and plant chemistry in particular, contribute to their health.

A food web is such a system, where the cycling of plant material connects the different components. The connecting material consists mainly of biologically accessible organic molecules made

by plants from inorganic matter using solar energy, so called phytochemicals (Fig. 1). Phytochemicals account for up to 90% of the continuous production of organic molecules on our planet (Bar-On *et al.*, 2018). Despite recent advances in food (bio-) technology, we heavily depend on plant-derived organic molecules to feed the growing world population. Even plans to colonize Mars rely on plants as primary extra-terrestrial food source (McKay, 2004). In general terms, phytochemicals present a large share of the energy and matter that travels from producers to consumers and back. The cycling starts with phytochemicals being consumed by countless micro- and macro-organisms, with domesticated animals converting them into food products. Consistently, our human body is largely made from plant-derived organic building blocks. The consumed phytochemicals and their transformation products cycle then back to the environment as detritus, i.e. organic material from faeces or dead organisms. Plants also directly provide the

environment organic molecules by secreting root exudates, thereby feeding the surrounding rhizosphere microfauna and macrofauna (Fig. 1; Sasse *et al.*, 2018). Generally, the plant-derived carbon, mainly from decomposition, presents a major allocation to the global soil organic matter stocks that are key for climate homeostasis (Schmidt *et al.*, 2011). However, life on our planet is not simply maintained by providing plant-derived chemical building blocks to consumers, but the vast diversity of plant compounds also shape many organismal interactions and thereby environmental health.

Phytochemicals are broadly classified into primary and secondary metabolites. Primary metabolites account for only a small fraction of the diversity of chemicals and include carbohydrates, amino acids, fatty acids and vitamins among others. They mainly serve as building blocks and energy-carrying carbon resources and thereby, they are essential for plant growth as well as for animal and human diets. Plants also produce a staggering diversity of secondary metabolites. Although boundaries between primary and secondary metabolites are blurry, the latter often modulate interactions

between plants and the environment, and can have substantial effects on consumers and their health (Erb & Kliebenstein, 2020). For instance, plant alkaloids have evolved to protect plants from herbivorous animals and can also be harmful to humans. Many other secondary metabolites, as in essential oils or superfoods (e.g. goji or acai berries), are promoted for their beneficial effects on our health. However, for many secondary metabolites, the effects on consumer physiology and health remain unknown.

Below, we put forward that phytochemicals other than well-known nutrients and vitamins represent important proximal links between food web components and function as mediators of food web health (Fig. 1). We do this with two well-studied examples, glucosinolates and benzoxazinoids, and illustrate their journey and discuss mechanisms by which they mediate food web health.

II. Glucosinolates in soil, animal and human health

Glucosinolates form a large group of structurally diverse sulphur containing secondary metabolites commonly found in *Brassicaceae*

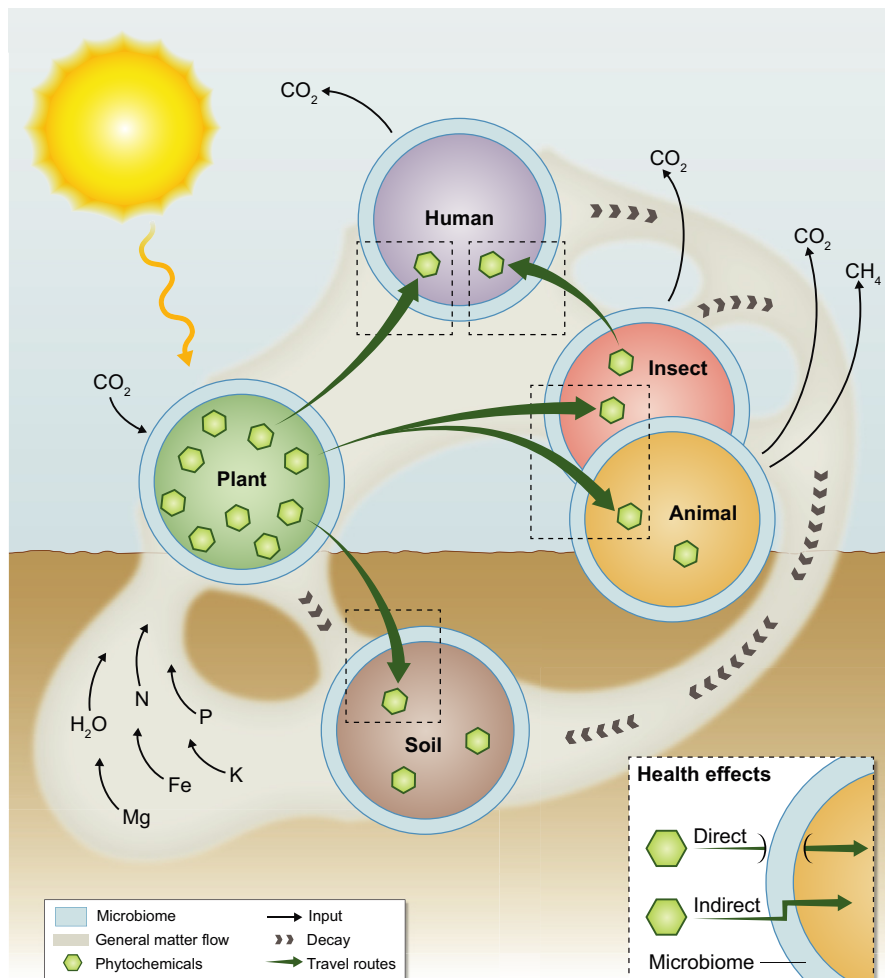


Fig. 1 Matter flow and phytochemical connections in the food web. This simplified food web consists of humans, animals and insects that consume matter produced by plants growing in soil. The general matter flow is indicated by the grey shading. Plants use solar energy to convert CO₂, H₂O and micronutrients into a broad diversity of biologically accessible phytochemicals. Green arrows illustrate the 'routes' where and name the 'vehicles' how the phytochemicals travel the food web. Every food web component has its specific microbiome (light blue) that interacts with phytochemicals and its health effects. The inset illustrates that health effects can be caused directly by the phytochemicals or indirectly through changes in the microbiome.

plants including broccoli, cabbage, cauliflower, rapeseed and mustard (Blažević *et al.*, 2020). These β -thioglucoside N-hydroxysulphates function as a two-component system, where they become activated by glucohydrolases, known as myrosinases. The aglucones rearrange to different compounds such as isothiocyanates, thiocyanates or nitriles that are responsible for the sharp taste and typical odour of *Brassica* vegetables. For plants, glucosinolates primarily have a defence function against pathogens and pests, but also operate in regulation, growth and development (Erb & Kliebenstein, 2020). This health function is mainly attributed to the antimicrobial capacity of the glucosinolate hydrolysis products, which are effective against (soil-borne) plant pathogens as well as against animal and human pathogens (Romeo *et al.*, 2018; Poveda *et al.*, 2020).

Glucosinolates travel down the food web to soil (Fig. 1) when released by *Brassicaceae* into the rhizosphere (Mönchgesang *et al.*, 2016; Sasse *et al.*, 2018). Due to their antimicrobial properties, glucosinolates likely establish a pathogen and pest suppressive zone in the rhizosphere. Glucosinolates also reach soils when *Brassica* inter- or cover crops are used in rotations and their glucosinolate-containing residues are incorporated into soil by tillage (Gimsing & Kirkegaard, 2009). The latter cropping method is referred to as biofumigation, which successfully controls fungal and oomycete pathogens, plant-parasitic nematodes and other pests on a field scale (Brennan *et al.*, 2020; Poveda *et al.*, 2020). Hence, glucosinolates function as natural biocides to improve soil health.

Upward travel of glucosinolates in the food web (Fig. 1) occurs when, e.g. insects, ruminants or humans consume glucosinolate-containing plant material. Specialized insect herbivores can ingest glucosinolates as they have evolved the capacity to detoxify them (Halkier & Gershenzon, 2006). Some insects even accumulate glucosinolates and activate them by their own myrosinases, which increases their resistance to natural enemies and their capacity to recruit mating partners (Beran *et al.*, 2014). When animals consume glucosinolate-containing forages, phytochemicals are partly degraded by the rumen and intestinal microflora and then absorbed by the digestive tract (Mandiki *et al.*, 2002). Glucosinolates such as 5-vinyl-1,3-oxazolidine-2-thione or thiocyanates were detected in products such as milk, eggs, muscular tissue and visceral organs like liver, lung and kidney (Mabon *et al.*, 2000; Zhu *et al.*, 2018), suggesting that glucosinolates will travel further up the food web with human consumption of these products (Fig. 1). Glucosinolates often negatively affect livestock performance and health (reviewed by Tripathi & Mishra, 2007). Negative effects include retarded growth, reduced feed intake, lower egg and milk production. Systemic effects are manifested by iodine deficiency, hypertrophy of kidney, liver and the thyroid gland followed by an elevated secretion of thyroid hormones (Tripathi & Mishra, 2007), which is associated with an increased digesta efflux and consequently reduced rumen retention time (Barnett *et al.*, 2012). Despite the overly negative effects on animal physiology, the use of glucosinolates-containing fodder can improve environmental health by mitigating methane emissions by ruminants (Dillard *et al.*, 2018; Sun, 2020). Mechanistically, glucosinolates do not directly inhibit the methanogenic microbes, but are supposed to alter the microbial community and rumen fermentation

parameters (Kumar *et al.*, 2018; Sun, 2020). Hence, together with the aforementioned indirect effect of reduced rumen retention time, methane production decreases and interestingly, seems to persist when dairy cows continue to feed on pastures (Storlien *et al.*, 2017).

In contrast to predominately negative health effects on animals, glucosinolates account for many health promoting effects on humans when consuming raw or cooked brassica vegetables. While glucosinolates are activated by glucohydrolases in plants, these enzymes are often denatured during cooking. Glucosinolates still function in a pro-drug-like manner where after ingestion they are activated by the intestinal gut microbiota. Hydrolysis of glucosinolates to isothiocyanates by a commensal gut bacterium was recently uncovered as an underlying mechanism (Liou *et al.*, 2020). Activated glucosinolates have beneficial health effects in humans including anti-inflammatory, antimicrobial and antioxidant functions as well as being cancer preventive agents (Narbad & Rossiter, 2018). For instance, diets rich in brassica vegetables are associated with a decreased risk of gastrointestinal cancer (Herr & Büchler, 2010). Health claims are underpinned by detailed mechanistic studies of indole-3-carbinol (I3C), the activated hydrolysis product of glucobrassicin, a glucosinolate found in broccoli and other crucifers. I3C when supplemented in the human diet, functions as a strong agonist of the arylhydrocarbon receptor (AHR) and effectively complements dietary AHR ligand deficiencies (Li *et al.*, 2011). AHR agonists are essential for normal intestinal immune development and associated host-microbial mutualism. More specifically, dietary AHR agonist deficiency leads to profound intestinal mucosal immunodeficiency in mice (Schiering *et al.*, 2017). This evidence attests a clear health promoting potential to at least one commonly consumed glucosinolate, although it remains to be demonstrated whether consumption of cooked or raw broccoli significantly effects AHR activation in humans (Koper *et al.*, 2020).

These examples highlight that glucosinolates, as they travel up and down the food web, function as important health modulating phytochemicals connecting the food web across soils, plants, animals and humans.

III. Benzoxazinoids in soil, animal and human health

Benzoxazinoids are a structurally diverse group of indole-derived, nitrogen containing secondary metabolites that are mainly produced by major monocotyledonous crops such as maize, wheat and rye (Frey *et al.*, 2009). Benzoxazinoids typically accumulate as glucosides in intact plant cells (Glauser *et al.*, 2011). Upon secretion or cell damage, β -glucosidases release benzoxazinoid aglucones, cyclic hemiacetals that can act as electrophiles to react with thiols and amines, for instance (Wouters *et al.*, 2016). Benzoxazinoids provide multiple benefits to plants. They protect them against insect pests by acting as repellents and digestibility reducers (Glauser *et al.*, 2011; Maag *et al.*, 2016), they provide pathogen and aphid resistance by triggering callose deposition (Ahmad *et al.*, 2011; Glauser *et al.*, 2011; Meihls *et al.*, 2013), and they improve iron acquisition at the seedling stage (Hu *et al.*, 2018a).

Downward travel in the food web occurs (Fig. 1) when benzoxazinoids are secreted to soil. They are abundant constituents of root exudates of wheat and maize and in the rhizosphere, benzoxazinoids structure the microbiomes (Cadot *et al.*, 2021, and references cited therein). These microbial changes affect soil functioning, leading to enhanced pest resistance in the following plant generation, in some cases at the expense of growth (Hu *et al.*, 2018b). While the exuded benzoxazinoids are relatively short-lived in soil, microbial degradation products such as phenoxazinones are more stable (Macías *et al.*, 2004) and may have long-term consequences for plant and soil health. Phenoxazinones can for instance inhibit histone deacetylases (Venturelli *et al.*, 2015), and may thereby influence other organisms.

Benzoxazinoids travel up the food web (Fig. 1) when animals or humans ingest green foliage, silage, cereal products or superfoods such as sprouts (Adhikari *et al.*, 2015). For instance, adapted maize insect herbivores such as the western corn rootworm take up and accumulate benzoxazinoids. Through their iron-chelating properties, benzoxazinoid improve iron homeostasis and growth of this important agricultural pest (Hu *et al.*, 2018a). By stabilizing and converting benzoxazinoids and their breakdown products into insect-specific glucosides, which again can be de-glucosylated upon attack, the western corn rootworm gains protection against biocontrol agents such as entomopathogenic nematodes and their endosymbiotic, insect-killing bacteria (Robert *et al.*, 2017). Bacteria and nematodes again can evolve behavioural and metabolic resistance to sequestered benzoxazinoids (Zhang *et al.*, 2019; Machado *et al.*, 2020), thus increasing their efficacy and potential as biological control agents for sustainable agriculture. The impact of benzoxazinoids on farm animal and human health is less well understood. For sure, humans can be exposed to high doses of benzoxazinoids through food (Pedersen *et al.*, 2011; Pihlava & Kurtelius, 2016) that are then deglucosylated, taken up and partially reduced by phase-2 metabolism in pigs, rats and humans (Adhikari *et al.*, 2012a,b; Jensen *et al.*, 2017). Several studies indicate that benzoxazinoids may have immunoregulatory and anticancer effects and may stimulate the central nervous system (Adhikari *et al.*, 2015), but whether such effects can be triggered by dietary uptake of benzoxazinoids is unclear. Finally, benzoxazinoids are considered as promising chemical lead structures for the development of novel antibiotics that may lead to human medical applications (de Bruijn *et al.*, 2018).

Similar to glucosinolates, the effects of benzoxazinoids on other food web components exemplify that these phytochemicals present important health modulators connecting soils, plants, animals and humans.

IV. Direct and indirect microbiome-mediated health effects

Phytochemicals can cause direct or indirect health effects. Indirect health effects can occur through microbiomes, as each food web component hosts a multitude of commensal microorganisms (Fig. 1). Direct health effects were illustrated by some of the examples from above. For instance, glucosinolates have regulatory function on plant growth and development (Erb & Kliebenstein,

2020), promote thyroid hormones secretion to change rumen physiology (Barnett *et al.*, 2012) or have direct anti-inflammatory and antioxidant functions on human cells (Narbad & Rossiter, 2018). Similarly benzoxazinoids have direct health functions such as in plant immune signalling (Ahmad *et al.*, 2011), driving insect behaviour (Robert *et al.*, 2012; Zhang *et al.*, 2019) or possibly immunoregulatory and anticancer effects on humans (Adhikari *et al.*, 2015). Simply, the antimicrobial activities of such phytochemicals (Romeo *et al.*, 2018; Poveda *et al.*, 2020) can be seen as a direct health effect on a food web component, as direct action on pathogens precludes disease emergence.

Indirect effects occur when phytochemicals change the composition and functioning of the microbiome and thereby affect health of an organism. Such microbiome-mediated indirect health effects by the phytochemicals become more and more apparent, also in a food web context. One example is the benzoxazinoid-driven and rhizosphere microbiome-mediated defence and growth legacy effects found in consecutive maize cultivation (Hu *et al.*, 2018b). This example provides a rationale for studying microbiota modulating effects in other systems such as for instance the guts of animals and humans and testing to which extent consumption of glucosinolates or benzoxazinoids would indirectly affect host health through eventual microbiome changes. This is an important research avenue, as phytochemicals with gut microbiota-reconfiguring capacities would open novel medical intervention possibilities, e.g. for common microbiome-linked health conditions like obesity and type-2 diabetes (Fan & Pedersen, 2021).

Phytochemicals present important connections between soil, plant, animal and human health, and we particularly highlight to incorporate each component's microbiome into such holistic food web thinking.

V. Conclusion: phytochemicals modulate food web health

Based on their bioactivity and because of their journey through the food web, phytochemicals are systemically relevant for food web health. Glucosinolates and benzoxazinoids present just two examples for bioactive and health modulating phytochemicals. However, there are many more compounds, including flavonoids, cardenolides, terpenes and alkaloids, and many of them have beneficial properties for one or another food web component. It appears plausible that the deliberate management of travel routes and specific bioactivities of phytochemicals can be used to optimize food web health and productivity. Biofumigation is an example of successful bioprospecting of the glucosinolate travel route, but we anticipate that more applications are possible, where quantities and qualities of travelling bioactive phytochemicals are specifically engineered. For instance, breeding enhanced crops with dual functions of improving soil health when cultivated *and* as superfood having health promoting properties for the consumers. Alternatively, plant cultivars may enhance ecosystem services, for instance during agricultural production. Or, crops with augmented root exudation may enhance soil carbon inputs that mitigate global warming, or they improve soil health and nutrient cycling to reduce agrochemicals. From applying integrative systems thinking to the

food web framework it emerges that the vast diversity of plant-derived molecules remains an underexplored reservoir to optimize and promote food web health and productivity.


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Author contributions


All authors have contributed to the writing of the manuscript.

ORCID

Matthias Erb  <https://orcid.org/0000-0002-4446-9834>

Josef J. Gross  <https://orcid.org/0000-0002-2578-6076>

Siegfried Hapfelmeier  <https://orcid.org/0000-0002-6913-7932>

Klaus Schlaeppi  <https://orcid.org/0000-0003-3620-0875>

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