JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

Article

pubs.acs.org/JAFC

Antidiabetic II Drug Metformin in Plants: Uptake and Translocation to Edible Parts of Cereals, Oily Seeds, Beans, Tomato, Squash, Carrots, and Potatoes

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ABSTRACT: Residues of pharmaceuticals present in wastewater and sewage sludge are of concern due to their transfer to aquatic and terrestrial food chains and possible adverse effects on nontargeted organisms. In the present work, uptake and translocation of metformin, an antidiabetic II medicine, by edible plant species cultivated in agricultural soil have been investigated in greenhouse experiment. Metformin demonstrated a high uptake and translocation to oily seeds of rape (*Brassica napus* cv. Sheik and *Brassica rapa* cv. Valo); expressed as an average bioconcentration factor (BCF, plant concentration over initial concentration in soil, both in dry weight), BCF values as high as 21.72 were measured. In comparison, BCFs for grains of the cereals wheat, barley, and oat were in the range of 0.29−1.35. Uptake and translocation to fruits and vegetables of tomato (BCFs 0.02−0.06), squash (BCFs 0.12−0.18), and bean (BCF 0.88) were also low compared to rape. BCFs for carrot, potato, and leaf forage *B. napus* cv. Sola were similar (BCF 1−4). Guanylurea, a known degradation product of metformin by microorganisms in activated sludge, was found in barley grains, bean pods, potato peel, and small potatoes. The mechanisms for transport of metformin and guanidine in plants are still unknown, whereas organic cation transporters (OCTs) in mammals are known to actively transport such compounds and may guide the way for further understanding of mechanisms also in plants.

KEYWORDS: *bioconcentration factor (BCF), Brassica, metformin, OCTs, pharmaceuticals, seeds*

INTRODUCTION

Pharmaceuticals became recognized as emerging environmental contaminants at the end of the 1990s.[1−3] Pathways for the entrance of pharmaceuticals to the environment, and subsequently to the human food web, are application of manure (veterinary pharmaceuticals),[4,5] use of sewage sludge as soil fertilizer and conditioner,[6−8] and irrigation of fields with wastewater containing pharmaceutical residues.[8,9] The concerns about residues of pharmaceuticals in the environment are related to these compounds' high biological activity and unknown effects on nontargeted organisms and healthy individuals.

Many high production volume medicines are poorly investigated with regard to their environmental distribution and transport. The antidiabetic II medicine metformin is among the most prescribed pharmaceuticals,[10,11] and is excreted nonmetabolized in the urine.[12] Thus, not surprisingly, metformin has been detected in surface water, in concentrations up to 1.7 μg L^{-1},[13,14] in wastewater treatment plant influent and effluent in the ranges of 101−129 and 2.2−21 μg L^{-1}, respectively,[14] and in sewage sludge in the range of 500−1600 μg kg^{-1} dw.[15] The environmental fate of metformin is not clear, but, apparently, metformin is degraded by bacteria in activated sludge to the dead-end product guanylurea under aerobic conditions.[16] Guanylurea has also been suggested as a degradation product of metformin during wastewater treatment.[14]

Recently, we demonstrated that metformin is taken up in agricultural plants and translocated to seeds.[17] Although the fate of metformin in plants is not known, it is possible that the plant attempts to accumulate and, if feasible, metabolize metformin as related nitrogen-containing natural compounds, for example, galegine and arginine (Figure 1). French lilac or goat's rue (*Galega officinalis*) has been used as an herbal remedy against several illnesses, including diabetes symptoms, since medieval times. *G. officinalis* is rich in guanidine and galegine (isoamylene guanidine or dimethylallylguanidine), both of which were studied and used as antidiabetic agents in the beginning of the previous century.[18] Several biguanides were later tested for their effects in humans or other mammals, and metformin arose as a suitable compound without side effects during the 1970s.[18]

Today, generic knowledge on pharmaceutical compounds in the environment, their chemical and physical properties, and uptake and translocation in plants is insufficient. Due to the high environmental loading of pharmaceuticals and general lack of information on the environmental fate of this group of bioactive compounds, increased knowledge is necessary to allow regulative environmental and food authorities to take action, for example, introduce recommendations or restrictions concerning the growth of certain crops in fields with elevated concentrations of such contaminants.

The goals of the present study were to (i) determine the uptake and translocation of metformin into different edible plant compartments used as forage or human food and (ii)

Received: March 26, 2012
Revised: June 17, 2012
Accepted: June 19, 2012
Published: June 19, 2012

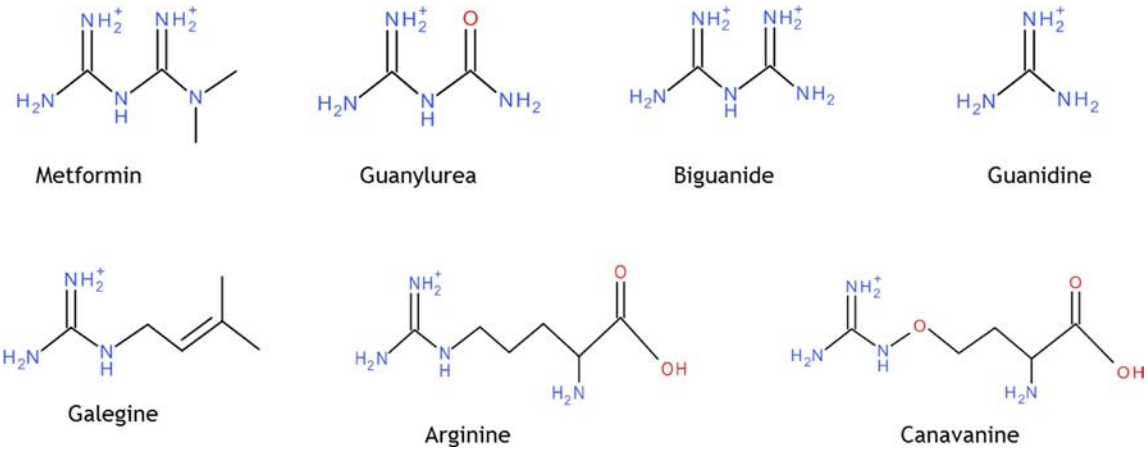

Figure 1. Structures of metformin, guanylurea, and related natural plant compounds.

Table 1. Chemical Properties of Metformin (CAS Registry No. 657-24-9)

MW	pK_a	log P or log D at pH 6[a]	log K_{oc}	water solubility (g/L)
129.17	12.25 and 3.11 (est)[b]	log D −3.3 (est);[b] log P −1.83 to −0.5 (est);[c] log D −4.9 (est)[d]	−0.67 to 1.43 (est)[d]	freely water-soluble as salt[e] 1.38 (est)[c]

[a]Log P, octanol−water distribution coefficient for only neutral compound; log D, octanol−water distribution coefficient that combines log P and pK_a and gives an apparent partition coefficient for any pH value. [b]ACD/pK_a v8.02. [c]Drugbank, http://www.drugbank.ca/drugs/DB00331. [d]ChemIDplus Advanced. [e]Information from producers, e.g., Glucophage (metformin HCl) from Sanofi (www.products.sanofi.ca/en/glucophage.pdf).

investigate if metformin shows a similarly high translocation to seeds of *Brassica napus* as observed for *Brassica rapa*.

MATERIALS AND METHODS

Growth Experiment. The plant uptake study was performed as a greenhouse pot experiment at Bioforsk Vest Særheim. Sowing was done at the end of April, and harvesting was done during June−August 2010. Soils from agricultural fields in western Norway were used in the experiments; loamy sand soil with low organic content, 7.3 g of total organic carbon (OC) kg^{-1}, pH 5.4, and cation exchange capacity (CEC) = 46.6 $mmol_c$ kg^{-1}; and sandy loam soil with high organic content, 31 g of OC kg^{-1}, pH 5.02, and CEC = 158 $mmol_c$ kg^{-1}. Soil with low OC was used in a previous uptake experiment with metformin.[17,19] Because reduced growth for carrots was recognized, but not for any other crop species tested, when exposed to metformin, an extra set of pots in which carrots were cultivated in soil with higher OC to overcome the phytotoxic effects was included. Both soils were mixed with a controlled slow-release fertilizer (3 g kg^{-1} soil), Multicote 4 (N:K:P, 15−7−15 (2+) TE, Haifa Chemicals Ltd.). For each pot, the soil was weighed, spiked with 50 mL of a solution of metformin (Chiron, Trondheim, Norway, purity = 96%; for properties see Table 1), mixed thoroughly by hand, and added into the pot. Pot sizes from 4 to 15 L were used, and different spiking solution concentrations were added to a nominal initial soil concentration of 10 mg kg^{-1}. The purpose of the experiment was to investigate uptake and translocation, and a certain soil concentration was needed to measure metformin in plant materials. The chosen nominal soil concentration was therefore higher than expected if, for instance, sewage sludge with 1.6 mg kg^{-1} [15] was used as fertilizer in agricultural soil.

Stock solution was made by dissolving metformin in a small amount of acetone and then diluted with distilled water to a final concentration of 40 mg mL^{-1}. The actual initial metformin concentrations in the soils were also analyzed.

Important crops and forages of contrasting growth forms and edible plant parts were selected (grasses, cereals, root vegetables, oilseeds). Species included in the experiments were barley (*Hordeum vulgare* cv. Edel), wheat (*Triticum aestivum* cv. Bjarne), oat (*Avena sativa* cv. Berlinda), carrot (*Daucus carota* cvs. Napoli and Amagar), potato (*Solanum tuberosum* cv. Astrix), tomato (*Solanum lycopersicum* cv. Suzanne), zucchini (*Cucurbita pepo* cv. Black Beauty), bean (*Vicia faba* cv. Red Epicure), and rape (*Brassica rapa* cv. Valo, *Brassica napus* cv. Sheik, and *Brassica napus* cv. Sola). An overview of plant species and analyzed plant tissues is presented in Table 2. Except for one set of carrot plants, which was cultivated in soil with high organic matter (3.1% OC), all other crop species were cultivated in soil with low organic content (0.7% OC). Seeds were sown in pots, covered by a transparent plastic film, and kept at 14 °C until germination, before pots were transferred to a greenhouse with 16 h of light/8 h of darkness at 20/14 °C. The pots, triplicate exposure, were placed on

Table 2. Overview of Crop Species Cultivated and Plant Compartments Analyzed in the Experiment[a]

English name	Latin name, cultivar	analyzed compartment
tomato	*Solanum lycopersicum* cv. Suzanne	fruit from first and fourth trusses
squash	*Cucurbita pepo* cv. Black Beauty	first and fourth fruits
wheat	*Triticum aestivum* cv. Bjarne	seeds
barley	*Hordeum vulgare* cv. Edel	seeds
oat	*Avena sativa* cv. Berlinda	seeds
rape	*Brassica rapa* cv. Valo	seeds
rape	*Brassica napus* cv. Sheik	seeds
forage rape	*Brassica napus* cv. Sola	leaves
bean	*Vicia faba* cv. Red Epicure	fruit
carrot	*Daucus carota* cv. Napoli[b]	root (peel and core separate;[c] small whole)
carrot	*Daucus carota* cv. Amagar	root (peel and core together; small whole)
potato	*Solanum tuberosum* cv. Astrix	root (peel and core separate; small whole)

[a]All selected cultivars are commonly grown in Norway. [b]Carrot cv. Napoli, grown in both 0.7 and 3.7% OC soils. All other crops were grown only in 0.7% OC. [c]Only for carrot grown in 3.7% OC.

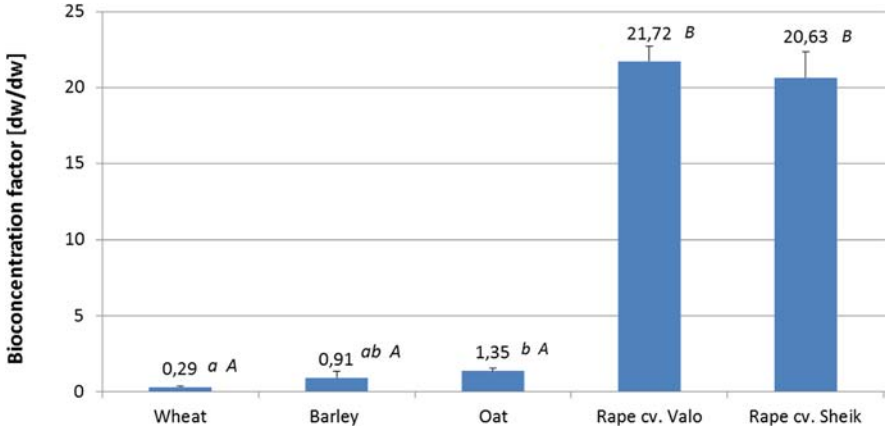

Figure 2. Metformin bioconcentration factors for cereal grains and oily seeds. Data are the mean of three samples, and standard deviations are given. Significant differences between cereals are given in lower case letters and between all cereals and oily seeds in capital letters.

individual trays and irrigated with fertilized water (pH 7.4, EC = 1.5 mS cm^{-1}). Control pots with plants without test compounds and control pots with test compounds without plants (two pots for each soil) were also included in the experiment.

Plant materials were harvested when mature and depending on plant species during a period of 2−3.5 months. Roots were carefully washed in tap water. Plant material was dried for 3 days (1 day at 50 °C, 2 days at 40 °C), ground by a metallic grinder, and frozen at −18 °C until analyzed. Control and exposed plant material was dried in separate drying ovens to prevent cross-contamination. Soil was sampled at start immediately after spiking and at the end of the experiment and stored at 4 °C until analyzed.

Analytical Methods. Methods for metformin determination in plants and soil have been published elsewhere,[17,19] but a short description follows. Metformin HCl (97%) was purchased from Aldrich (Steinheim, Germany) and guanylurea phosphate from Sigma-Aldrich (Norway). Lyophilized plant material (0.1 g) or soil (1 g) was homogenized (20 s with an Ultra-Turrax S 25N − 10G dispersing tool) with an extraction solution of ammonium acetate/formic acid and chloroform and centrifuged. The supernatant was transferred to a solid phase extraction column, eluted, filtered (0.2 μm), and injected into the LC-MS/MS with a series 200 micropump and autosampler (Perkin-Elmer, Norwalk, CT, USA) and an API 2000 MS/MS system (Applied Biosystems, Ontario, Canada) equipped with a Turbo-Ion Spray ion source. A Propyl column (150 mm × 4.6 mm i.d., 5 μm particle size, Restek, Bellafonte, PA, USA) was used for separation utilizing a mobile phase step gradient made from 0.1% formic acid in water and 0.1% formic acid in methanol. For metformin determination, the precursor ion 130.2 giving product ions 71.1 and 60.1 was used for quantification and confirmation. Blank control matrices were spiked and applied for preparation of standard curves.[17,19] Limits of detection (LoD) and quantification (LoQ) were found to be 15 and 30 ng g^{-1}, respectively. For guanylurea determination, the precursor ion 103.4 giving product ions 60.1 and 86.4 was used for quantification and confirmation, and the LoD was 50 ng g^{-1}.

Statistical Analysis. Differences in concentrations of the compounds between the plant species were tested using the multiple-comparison method called the Ryan−Einot−Gabriel−Welsch range test (calculated by the procedure GLM, General Linear Models, in SAS 9.0). For all of the test results, the significance level was set at $p < 0.05$.

RESULTS AND DISCUSSION

All soil and plant concentrations are reported on the basis of dry weight (dw). Measured initial soil concentrations were lower than the nominal concentration of 10 mg kg^{-1}, that is, 5.5 ± 0.6 mg kg^{-1} for low organic matter soil and 6.4 ± 0.2 mg kg^{-1} for high organic matter soil (n = 6, triplicates from two separate control pots).

Metformin showed high uptake and translocation in oily seeds of rape *B. rapa* cv. Valo and *B. napus* cv. Sheik (Figure 2). Expressed as a bioaccumulation factors (BCF) (mg kg^{-1} dw plant over mg kg^{-1} dw measured initial soil concentration), BCFs as high as 21.72 were measured. The BCFs for the cereals were 15−70 times lower, 0.29, 0.91, and 1.35 for wheat, barley and oat, respectively. High allocation of nitrogen from vegetative tissues to pods and seeds of *B. napus* has been demonstrated previously;[20−23] nearly 48% was recovered in mature pods.[21] At harvest, the seeds contained 80% of the total nitrogen in shoots, whereas the stem and pod walls each contained about 10%.[23] Metformin is a small molecule with structural similarity to natural plant compounds such as guanidine, galegine, and arginine (Figure 1). Possibly a mimicking effect of metformin with natural nitrogen compounds may induce transporters to carry metformin across membranes, and this could provide an explanation for the unexpected high allocation to oily seeds of rape *B. napus* and *B. rapa*.

Compared to a previous study on the uptake of metformin,[17] the BCFs for seeds of cereals and rapes in the present investigation were 11−24 times higher (Table 3). Irrigation has been demonstrated to increase nitrogen accumulation in *B. napus* (winter oilseed rape).[23] The present growth experiment was performed during the summer period (late April to mid-August), and a higher transpiration would be expected compared to the previous experiment performed during winter to early spring. Plants transpire more rapidly at higher

Table 3. Comparison of Metformin Bioconcentration Factors in Seeds of Wheat, Barley, and Rape Grown during the Summer Period (Present Experiment) and during the Winter Period (Eggen et al.[17])[a]

plant species	present study[b]	previous data[c]
wheat	0.29 ± 0.09	0.03 ± 0.00
barley	0.91 ± 0.44	0.04 ± 0.02
rape cv. Valo	21.72 ± 1.0	1.55 ± 0.59
rape cv. Sheik	20.63 ± 1.7	

[a]The crops were of similar cultivars and grown in the same soil (0.7% TOC). Data are the mean of three samples, and standard deviations are given. [b]Growth period: April−harvesting during July and August. [c]Growth period: late December−harvesting during March and April (Eggen et al.).[17]

dx.doi.org/10.1021/jf301267c | J. Agric. Food Chem. 2012, 60, 6929−6935

Table 4. Bioconcentration Factors of Metformin in Peel, Core, Whole (Peel + Core) and Small Whole Carrot and Potato[a]

plant species	peel	core	whole[b]	whole small
carrot cv. Napoli[c]	3.52 ± 1.11	1.32 ± 0.32	1.61 ± 0.38	
carrot cv. Napoli[d]				2.87 ± 0.64
carrot cv. Amagar[d]				1.50 ± 0.89
potato[d]	2.75 ± 1.39	1.51 ± 0.42	1.64 ± 0.51	2.41 ± 0.23

[a]Potato and carrot cv. Amagar were grown in soil with 0.7% OC and carrot cv. Napoli in both 0.7 and 3.1% OC soils. Data are the mean of three samples, and standard deviations are given. [b]peel+core. [c]3.1% OC. [d]0.7% OC.

temperatures, which also implies increased uptake and allocation of minerals and other solutes from the soil to the plants. Average BCFs for carrot cv. Napoli and cv. Amagar in a previous study[17] were 1.95 and 9.03, respectively, but due to high standard deviations (40−53%) there was no significant difference between these data and BCFs for cv. Napoli and cv. Amagar in the present experiment (BCF 2.87 and 1.50, respectively, 22−59% std) (Table 4). In addition, the phytotoxic effects observed on carrots cultivated in soil with low OC in both growth experiments might cover possible differences between the two studies. Only carrot cultivars showed a negative effect on growth and development.[17]

The metformin accumulation factors in fruits of tomato and squash were significantly lower than in barley and oat grains and oily seeds (Table 5). To measure for possible translocation

Table 5. Bioconcentration Factors (BCFs) of Metformin for Fruits of Tomato, Squash, and Bean and Rape Leaf Forage[a]

plant species	BCF (av ± SD)
tomato, first truss of ripe fruit	0.024 ± 0.005
tomato, fourth truss of ripe fruit	0.058 ± 0.014
squash, first fruit/vegetable	0.122 ± 0.013
squash, fourth fruit/vegetable	0.182 ± 0.088
bean, capsule and seed	0.880 ± 0.811
forage rape cv. Sola, leaf	3.237 ± 0.501

[a]For squash, the first and fourth ripe fruits and for tomato the first and fourth ripe trusses were analyzed. For beans, the value represents the average of all ripe fruits (capsule and seeds). Data are the mean of three samples, and standard deviations are given.

rates of metformin to fruits with different distances from the root, the first and fourth trusses of tomatoes and fruits of squash were analyzed separately. The BCF for the first truss of mature fruits (0.024) of tomato was significantly lower than that of the fourth truss (0.058). A corresponding, but not significant, trend for BCF for the first (0.122) and fourth (0.182) fruits of squash was found. The BCF for fruits of bean was 0.88 (Table 5), but demonstrated a higher standard deviation than other plant species. Seeds and capsules were homogenized and analyzed together. Allocation of metformin to seed and capsule might differ, just like allocation of amino acids to different compartments, and thus separation of the two compartments might have shown significant differences. Leaves from rape (*B. napus* cv. Sola) are used as forage, and only the leaves were analyzed in the present experiment. BCF of rape leaves was 3.2 (Table 5), which is lower than for seeds of *B. napus* cv. Sheik or *B. rapa* cv. Valo but clearly higher than the previously reported metformin BCFs of leaves of meadow fescue (*Festuca pratense*), carrot cv. Napoli (BCF < 0.22), and barley (BCF 1.4).[17]

The BCFs for peels (2.8−3.5) were higher than for cores (1.3−1.5) for both carrot cv. Napoli and potato vegetables (Table 4); however, significant differences between peel and core were obtained only for carrot cv. Napoli. For carrots (cv. Napoli and Amagar) and potatoes too small for peeling, BCFs within the same range (1.0−3.6) were obtained (Table 4). The present BCFs were generally high compared to published data for PAHs, PCBs, and persistent organic pesticides in cultivars of carrot and potato[24] and for pharmaceuticals in carrot.[25] The BCFs presented by Zohair et al. (given as core + peel concentration/soil concentration) were all below 1, except for naphthalene (BCF 1.2).[24] In an uptake experiment with pharmaceuticals, only 4 (diazinon, enrofloxacin, florfenicol, and trimethoprim) of 10 compounds were detected and BCFs ranged from 0.01 to 0.64.[25]

Guanylurea, a detected metabolite of metformin in activated sludge under aerobic conditions,[16] was analyzed for but detected only in barley grains, bean pods, potato peel, and small potatoes in the range of 2.6−5.7 mg kg^{-1} (Table 6).

Table 6. Gyanylurea and Metformin Concentrations[a]

plant species	guanylurea (mg kg^{-1} dw)	metformin (mg kg^{-1} dw)
barley	2.65 ± 3.26	5.00 ± 2.42
bean	4.25 ± 1.90	4.85 ± 4.47
potato peel	5.66 ± 3.36	15.83 ± 7.63
potato, small	2.60 ± 1.55	13.27 ± 1.25

[a]Soil and all plant parts were analyzed for both metformin and gunaylurea; only data where guanylurea > LQD are presented. Data are the mean of three samples, and SD is given.

There was no relationship between high plant metformin concentration and detection of guanylurea. Barley grains and bean pods showed similar concentration levels of guanylurea and metformin, and small potatoes and potato peels showed 3−5 times higher metformin than guanylurea concentration (Table 6). The results indicate plant species variation for in-planta metabolism of metformin. Guanylurea was not detected in soil samples, thus supporting an in-planta degradation process rather than root uptake of guanylurea from the soil. Degradation of metformin in plants or animals has not been investigated, but dealkylation and oxidative deamination has been suggested to be the mechanism for degradation of metformin in activated sludge by microorganisms.[16] Whether such mechanisms exist in plants and are part of the explanation is unknown.

Even though the focus in this study was uptake and translocation into edible plant compartments and potential transport to the terrestrial food chain, it is worth mentioning the reduced growth and biomass production of carrot grown in low OC (metformin soil concentration = 5 mg kg^{-1}) (no data present). In a previous study, metformin, ciprofloxacin (antibiotic), and narasin (coccidiostatic) all showed negative impacts on carrot growth, whereas no effect on barley was observed (soil concentration range = 6−11 mg kg^{-1}).[17] In the

same experiment, metformin showed no negative effect on wheat, meadow fescue, and rape.

Among the metformin-similar plant nitrogen storage compounds in seeds, arginine is important (Figure 1). During germination the first step to mobilize the nitrogen in arginine is to break down the amino acid by arginase to give ornithine and urea, compounds that can be further metabolized into various amino acids for transport and anabolism.[26,27] Some legumes have a special nonprotein amino acid, canavanine, in large concentrations that is also degraded by arginase. Galegine is a compound with structural similarities to arginine and canavanine and, accordingly, is likely to serve as a storage compound for nitrogen and possibly be degraded by arginase for mobilization of nitrogen. However, to our knowledge the function of galegine in plants has so far not been studied. In contrast to arginine and canavanine (and probably galegine) metformin would not be degraded by arginase and, hence, not efficiently used as a nitrogen source during germination.

The mechanisms for metformin uptake into plant cells are not known. However, from comparison with other eukaryotes, organic cation transporters (OCTs) can be considered as putative candidates for being important in the uptake and accumulation of metformin. Substrates for mammalian OCTs have been investigated and were found to include organic cationic amines such as choline, guanidine, metformin, and the zwitterionic amine carnitine.[28,29] Except to confirm the ability to transfer carnitine,[30] substrates for the plant OCTs have so far not been studied. *Arabidopsis* OCTs are expressed in roots, xylem, leaves, flowers, and young siliques,[31] and cellular localization studies showed that OCTs were present in the plasmalemma as well as tonoplast.[30,31] Hence, expression studies as well as comparison with other eukaryotes point to the possibility that OCTs are important for metformin accumulation in plants; however, the importance of other transporter proteins should certainly not yet be excluded. Increased understanding of uptake and allocation of foreign compounds in plants, particularly high volume produced crops, is needed.

Species from the *Brassica* family have already demonstrated translocation of pharmaceuticals within the plants.[32−34] In cabbage (*B. rapa* var. *pekinensis*), the root concentrations of sulfamethoxazole, carbamazepine, salbutamol, and trimethoprim (BCFs = 7−10) were higher than in leaves (BCFs = 0.04−0.08).[32] Due to low biomass the roots and leaves of Wisconsin Fast Plants (*B. rapa*) were analyzed together, and BCFs for the four pharmaceuticals ranged from 0.03 to 1.5.[32] In seeds and seedpods, only carbamazepine and sulbutamol were detected, with BCFs based on wet weight (ww) of 0.08 and 0.05, respectively.[32] Because seeds and seedpods of rape have high dry content (in the present study, 96−98% of fresh weigh) BCF-ww based and BCF-dw based are very similar.

Metformin has high water solubility (freely soluble as salt) and low sorption (log K_{oc} = −0.67 to 1.43) (Table 1). However, because excess irrigated water was poured back to the soil in our experiment, leaching was not expected to influence the amount of available metformin in the pots. Estimated metformin half-lives in spiked control pots without plants were 14.3 and 19.7 weeks in low (0.7% OC) and high (3.1% OC) organic soils, respectively. Taking into account degradation of metformin in the soil during the growth period, approximately 1.5 times higher BCF values would be estimated.

Previously, uptake and translocation of both polar and nonpolar organic xenobiotics were suggested to be passive diffusion through lipophilic plasma membranes.[35,36] A compound's lipophilicity, normally expressed as the octanol−water coefficient (log K_{ow}), has been one of the most influential factors in plant uptake models.[37−40] However, highly water-soluble and charged compounds have low potential for diffusion through the lipophilic biomembrane and through suberin, which acts as a water barrier. Thus, such compounds are not expected to enter roots at a high rate. However, the present surprisingly high uptake and translocation of metformin, a freely water-soluble and dicationic compound, to oily rape seeds indicate that some active processes might be involved. It is assumed that xenobiotics transported from soil to aboveground compartments follow the water and solute transport via xylem fluid, driven by the water potential gradient created by plant transpiration.[41] For many years, compounds with log K_{ow} in the range of 1−2.5 had maximum xylem mobility,[38,39] but more recently it has been shown that also even more water-soluble compounds (log K_{ow} = −1) are highly mobile in xylem.[42] Translocation of xenobiotics via the phloem vascular system has been studied and modeled related to foliar application of pesticides.[43,44] Although weak bases are not particularly phloem-mobile, many strongly basic alkaloids with pK_a > 8 or salts of quaternized nitrogen heterocycles have shown high phloem mobility in *Lupinus*.[45−47] As thoroughly discussed by Rentsch et al.,[48] the understanding of the mechanisms for long-distance transport of organic N to sink organs, such as seeds, which represent a major sink during reproductive growth, is incomplete. The demonstrated high allocation of metformin to seeds of *B. napus* and *B. rapa* and the high variation between plant species clearly call for further research to better understand root uptake mechanisms and translocation processes in the vascular system.

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Funding

This research was supported by the Norwegian Research Council, the Food Program (1848339/I10 to T.E.).

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank colleagues Isak Drozdik, Mette Hjermann, Henk Maessen, and Dr. Hans Martin Hanslin for their valuable contribution during planning and throughout the growth experiment. We also thank Dr. Rune Slimestad, Plantchem AS, for valuable discussions and contribution during data interpretation and Victor Hormazabal and Dr. Tone Normann Asp, Norwegian School of Veterianary Research, for metformin and gunaylurea analysis.

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