Iodine biofortification of crops: agronomic biofortification, metabolic engineering and iodine bioavailability

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Iodine deficiency is a widespread micronutrient malnutrition problem, and the addition of iodine to table salt represents the most common prophylaxis tool. The biofortification of crops with iodine is a recent strategy to further enrich the human diet with a potentially cost-effective, well accepted and bioavailable iodine source. Understanding how iodine functions in higher plants is key to establishing suitable biofortification approaches. This review describes the current knowledge regarding iodine physiology in higher plants, and provides updates on recent agronomic and metabolic engineering strategies of biofortification. Whereas the direct administration of iodine is effective to increase the iodine content in many plant species, a more sophisticated genetic engineering approach seems to be necessary for the iodine biofortification of some important staple crops.

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Introduction

Iodine is an essential element for the human body as it is involved in the synthesis of thyroid hormones [1]. The intake of iodine is through the diet, and a daily amount in the range of 90–250 μg is recommended [2] (Figure 1a).

The geochemical cycle of iodine concentrates this element in the oceans thereby reducing its levels in mainland soils and groundwater [3**,4**]. Therefore, whereas seafood (fish, shellfish, edible seaweeds) is generally rich of iodine, vegetables and fruits from plants grown on inland soils are low and the content in most food sources is thus low as well [3**,5].

Inadequate iodine intake is one of the main micronutrient deficiencies worldwide (Figure 1b), leading to a spectrum of clinical and social issues called 'Iodine deficiency disorders' (IDDs). These are the result of an insufficient secretion of thyroid hormones, whose classic sign is goiter, the enlargement of the thyroid gland [1]. IDDs can affect all age groups leading to increased pregnancy loss, infant mortality, growth impairment and cognitive and neuro-psychological deficits [1], with effects on the quality of life and the economic productivity of a community. A significant reduction in the number of countries suffering iodine deficiency has been registered in the last two decades (Figure 1c) [2]; nevertheless, it is still a public health problem for almost one-third of the human population [3**].

Dietary iodine supplementation is widely practised and 'universal salt iodization', which is the most common iodine deficiency prophylaxis, has been successfully implemented in several countries [1,2]. However, the use of iodized salt in food processing is still extensively inadequate [2] and the volatilization of iodine during food storage, transport or cooking is high [6]. Furthermore, the policies adopted by many countries are aimed at reducing salt intake in order to prevent hypertension and cardiovascular diseases [2,7].

Complementary approaches are thus necessary. The diversification of the diet with increasing seafood consumption can be effective, but not always possible, especially in inland regions [3**,8] or in poor countries. On the other hand, the production of iodine-enriched plants through 'biofortification' [9] could represent an effective way to control iodine deficiency.

Iodine in plants

Although essential for animals and strongly accumulated in marine algae [1,3**,4**], iodine is not considered a micronutrient for higher plants, but an increasing number of studies shows that it is involved in plant physiological and biochemical processes.

Plants can take up iodine from the soil [10–22,23•], but the iodine behaviour in a soil–plant system is very complex due to the high number of factors involved [3**,4**]. Iodine in soil can be present in inorganic [iodide (I^-) and iodate (IO_3^-) ions] and organic forms. The soil composition, texture, pH and redox conditions [4**] control iodine

Figure 1
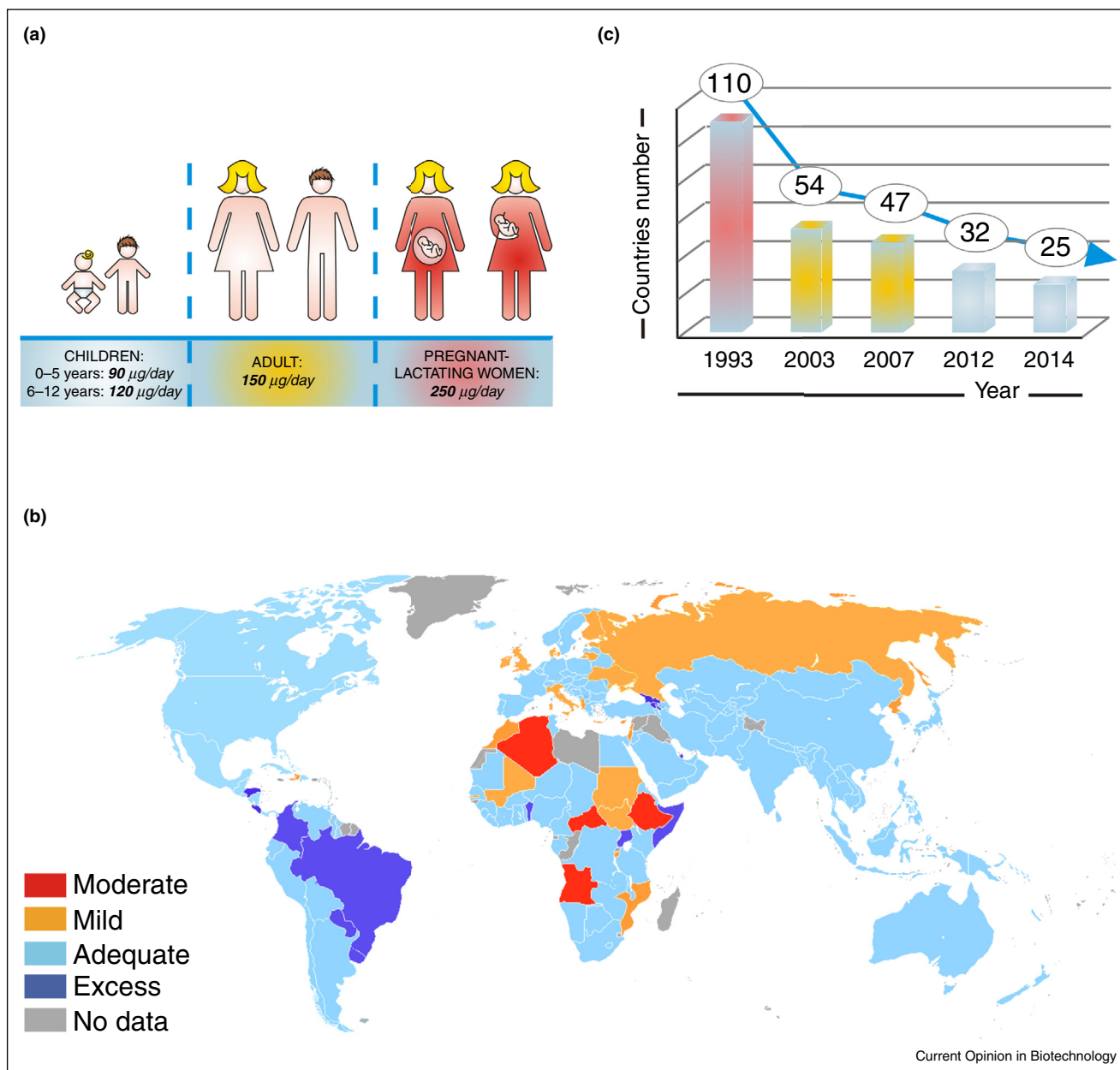
Iodine human requirements, geographical deficiency and progress. **(a)** Recommended iodine daily dietary intakes by population groups [1]. **(b)** Global iodine scorecard map updated at 2015 (adapted from: Global Map of Iodine Nutrition 2014–2015, The Iodine Global Network; URL: http://www.ign.org/scorecard.htm). The iodine status is based on median urinary iodine concentrations (UIC) of school-age children. Reference values in the figure legend: moderate iodine deficiency (UIC 20–49 μg/L); mild iodine deficiency (UIC 50–99 μg/L); adequate iodine nutrition (UIC 100–299 μg/L); excess iodine intake (UIC > 300 μg/L) [1]. **(c)** Global Iodine deficiency restraint during the past two decades. The total number of countries interested by iodine deficiency from 1993 to 2014 is reported (adapted from: Global Iodine Scorecard 2014: Number of iodine-deficient countries more than halved in the past decade, IDD Newsletter 1/2015, The Iodine Global Network; URL: http://www.ign.org/scorecard.htm).

speciation and mobility in the soil, thus affecting the uptake by roots.

Very low amounts of iodine can be beneficial for plant growth: positive effects have been described in barley, ryegrass, tomato [24], cabbage [14], and strawberry [25]. On the other hand, high concentrations may inhibit its absorption by roots [14] and over a certain threshold it becomes toxic [14,18,19,22,26–28]: actually iodine is registered as a herbicide for agricultural use [27].
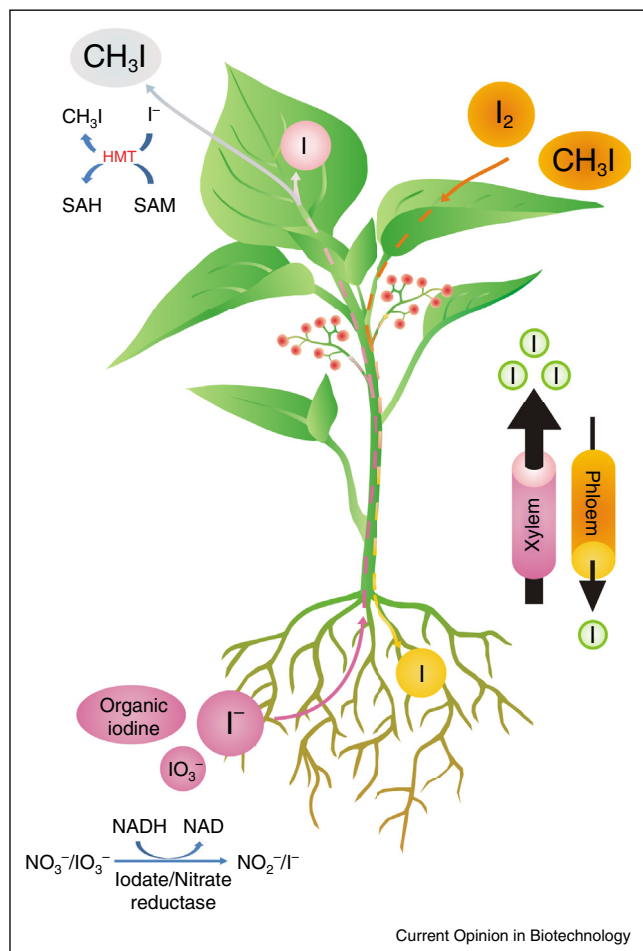
Iodine in higher plants. The iodine uptake, mobilization and emission are summarized. Major iodine species are: (i) organic-iodine, iodate (IO_3^-) and iodide (I^-) ions in the soil, (ii) gaseous iodine molecules, including molecular iodine (I_2) and methyl iodide (CH_3I), in the atmosphere [4••]. Plants can absorb iodine from the soil by root uptake and from the atmosphere through the leaves [4••,10–22,23•,33]. Iodate can be reduced to iodide by specific reductases identified in the roots [29] or, possibly, by other plant reductases which use IO_3^- as an alternative substrate (such as nitrate reductases) [4••]. Once inside the plant, iodine moves mainly by the xylematic route — the phloematic route is less efficient [4••,20,23•,27,28,30,32,34]. Iodine volatilization and emission to the atmosphere as methyl iodide occurs through an S-adenosylmethionine-dependent halide methyltransferase (HMT) enzyme [4••,37–40].

The processes of iodine uptake and accumulation have received little attention at a physiological and molecular level. Figure 2 summarizes the current knowledge. Iodate reduction activity, converting IO_3^- in I^-, was recently demonstrated in the roots of rice, soybean and barley [29], which would explain the common lower toxicity of IO_3^- compared to I^- [22,30–32]. Iodate could also be an alternative electron acceptor for plant nitrate reductases [4••]. Iodine could enter root cells via aspecific carriers or channels (reviewed in [4••,9]), although the presence of specific transporters cannot be ruled out [15,29]. Inorganic and organic iodine gaseous species are present in the atmosphere [4••,33], but the extent of the iodine uptake from leaves seems to be marginal [33].

Once inside the plant, iodine levels decrease from root to leaf, stem and fruit [8,16,25], being iodine transport mainly xylematic [4••,20,23•,27,30,32]. However the existence of a phloematic route has been demonstrated in tomato and in lettuce [20,28,34].

Few data are available on the iodine forms present in plants. In water spinach (*Ipomoea aquatica* Forsk), total iodine resulted to be equally divided in insoluble and soluble forms, with iodide species being predominant, followed by iodate and organic forms, including protein-bound iodine [26].

At low levels, iodine is able to increase the antioxidant response in plants, with protective effects against abiotic stresses, such as salinity [35] or heavy-metals [36]. These findings pave the way for exploiting multiple positive effects of iodine applications [4••], especially in difficult areas.

Finally, higher plants can emit volatile methyl iodide, whose production occurs through a reaction catalysed by a S-adenosyl-L-methionine (SAM)-dependent halide methyltransferase (HMT) or SAM-dependent halide/thiol methyltransferase (HTMT) using iodide as a substrate [4••,37–40]. These enzymatic activities have been identified in *Arabidopsis thaliana* [38,39] and in many other species [37–41]. Their exact role is not known but they contribute to the emission of central reactants in many tropospheric chemical processes. The homology with other plant methyltransferases involved in salt tolerance or in the metabolization of glucosinolates suggests a possible function in plant defense.

Iodine biofortification as an agronomic approach

The administration of iodine as an agrochemical represents the easiest approach, because it tackles the major cause of iodine deficiency in the soil (and therefore in the human diet), which means not enough iodine is available for root uptake [10]. Indeed, even if the distribution of iodine in soils can vary widely, the average iodine content is only 5.1 ppm [3••]. Most recent studies have thus consisted in optimizing the protocols of iodine application to the soil, through irrigation water, as a foliar spray or in hydroponic solutions. Different forms of iodine, organic and inorganic, different doses and systems of application, types of soils, combinations and interactions with other nutrients have been tested using various crops (Table 1). In many cases, iodine transfer from the source supplied to the edible plant tissue increases according to the amount

Table 1

Recent studies on the iodine agronomic biofortification of crops

Species	Iodine form	Iodine dose	Application	Plant organ	Iodine content (edible part)	Ref.
Hydroponic system experiments						
Rice*	KI or KIO_3	KI: 1-10 μM KIO_3:1-100 μM	Nutrient solution	Root, stem, leaf, panicle and seed	I^- treat.: ~1.3-9* IO_3^- treat.: ~1.3-8* *mg/kg DW	[30]
Spinach	I^- or IO_3^-	1-100 μM	Nutrient solution	Leaf and root	I^- treat.: ~25-1800* IO_3^- treat.: ~45-398* *mg/kg DW	[31]
Lettuce	KI or KIO_3	10-240 μM	Nutrient solution	Leaf and root	I^- treat.: ~600-1200* IO_3^- treat.: ~500-700* mg/kg DW	[32]
Water spinach	NaI, $NaIO_3$, $CH_2ICOONa$	0.05-5 mg/l	Nutrient solution	Shoot and root	I^- treat.: ~57-100* IO_3^- treat.: ~23-48* CH_2ICOO^- treat.: ~62-105* *mg/kg FW	[26]
Chinese cabbage	NaI or $NaIO_3$	0.05-5 mg/l	Nutrient solution	Edible part	I^- treat.: ~5-100* IO_3^- treat.: ~5-50* mg/kg FW	[15]
Lettuce	I^- or IO_3^-	13-129 μg/l	Nutrient solution	Leaf and root	I^- treat.: ~0.9-8.1* IO_3^- treat.: ~0.7-30.3* *mg/kg DW	[42]
Tomato (MicroTom)	KI	5-20 mM	Nutrient solution	Fruit	10-30 mg/kg FW	[28]
Tomato	KI	1-5 mM	Nutrient solution	Fruit	454-2423 μg/100 g FW	[20]
Lettuce	KIO_3	Nutrient solution: 1 mg I/dm³ Foliar treatment: 3.94 mM	Nutrient solution and/or leaf spray	Leaf and root	~60-800 mg/kg DW	[34]
Strawberry	KI or KIO_3	0.25-5 mg/l	Nutrient solution	Leaf, root, stem, and fruit	I^- treat.: ~6-41* IO_3^- treat.: ~6-33* *mg/kg DW	[25]
Pot experiments						
Pakchoi, spinach, onion, water spinach, celery, carrot	KIO_3	1-5 mg/kg	Soil	Edible part	Pakchoi: ~0-10* Spinach: ~ 0.1-50* Onion: ~0.01-1* W. spinach: ~0.02-8* Celery: ~0.02-3* Carrot: 0.1-0.9* * mg/kg FW	[12]
Spinach	KI or KIO_3	0.5-2 mg/kg	Mixed with basal fertilizers	Leaf and root	I^- treat.: 0.06-0.41* IO_3^- treat.:0.06-8.24* *mg/kg FW	[13]

Table 1 (*Continued***)**

Cucumber, aubergine, radish	Granular kelp and diatomite iodine fertilizer	I: 10-150 mg/kg	Soil	Leaf, fruit or rhizome	Cucumber: ~1-9* Aubergine: ~1-15* Radish: ~1-13* * mg/kg FW	[14]
Chinese cabbage	KI or seaweed composite (sea)	I: 10-150 mg/kg	Soil	Edible part	I^- treat.: ~10-170* Sea treat.: ~10-130* *mg/kg FW	[15]
Chinese cabbage, lettuce, tomato, carrot	KI or seaweed composite iodine fertilizer (sea)	I: 10-150 mg/kg	Soil	Edible part	Cabbage: I^- treat.: ~0-130* Sea treat.: ~0-120* Lettuce: I^- treat.: ~0-70* Sea treat.: ~0-50* Tomato: I^- treat.: ~0-10* Sea treat.: ~0-5* Carrot: I^- treat.: ~0-50* Sea treat.: ~0-40* * mg/kg FW	[16]
Pakchoi, celery, pepper, radish	KI or seaweed composite iodine fertilizer (sea)	I: 10-150 mg/kg	Soil	Edible part	Pakchoi: I^- treat.: ~5-170* Sea treat.: ~5-140* Celery: I^- treat.: ~5-160* Sea treat.: ~5-110* Pepper: I^- treat.: ~1-5* Sea treat.: ~5-10* Radish: I^- treat.: ~1-10* Sea treat.: ~1-10* * mg/kg FW	[18]
Wheat*, maize*, barley*, potato*, tomato	KI or KIO_3	0.05-0.5% KIO_3* 0.05-0.1% KI * * (w/v)	Irrigation water	Edible part	Potato I^- treat.: 272-6,245* IO_3^- treat.: 1,875-3,420* Tomato: I^- treat.: 3,900-5,375* IO_3^- treat.: 527-5,295* *µg/100g FW n.d. in cereal grains	[19]
Spinach	KI or KIO_3	I: 1-1.1 mg/dm^3	Pre-sowing fertilization (p.s.) or fertigation (fert.)	Leaf	I^- treat.: ~10 (p.s.)-15* (fert.) IO_3^- treat.: ~15 (p.s.)-65* (fert.) *mg/kg DW	[21]
Tomato	KI or KIO_3	KI: 12.8-64* KIO_3: 6.4-25.6* mg I/dm^3	Soil	Fruit	I^- treat.: ~2-10* IO_3^- treat.:~0.3-1.3* mg/kg FW	[22]
			Field experiments			
Alfalfa	KI	I: 1-2 kg/ha	Soil or leaf spray	Plant	0.15-2.01* (soil) 3.34-6.49* (leaf) * mg/kg DW	[11]
Wheat*,	KIO_3	5% solution	Fertigation	Edible	Wheat: ~7-18*	[10]

Table 1 (*Continued***)**

cabbage, corn*, bean*, potato*, sunflower		(40–80 µg/L irrigation water)	(dripped into an irrigation canal)	part and wheat straw	Wheat straw: ~8-24* Corn: ~8-26* Cabbage: ~5-22* Potato:~2.5-23* Bean: ~10-17* Sunflower: ~5-14* * µg/100g FW	
Fruit trees (plum and nectarine), potato* and tomato	KI	Trees: I: 125-312.5 g/ha Potato and tomato: I: 125-5000 g/ha	Soil and/or leaf spray	Trees: leaves, branches and fruits; Potato: leaves, stems and tubers Tomato: fruits	Plum: 5.6-9.5* Nectarine: 4-14.3* Potato: 2.0-89.4* Tomato: 0.6-144* * µg/100g FW	[20]
Spinach, cabbage, coriander, potherb mustard, chinese cabbage, tomato, cucumber, long cowpea, eggplant, hot pepper	Algal organic iodized fertilizer	I: 12-150 mg/m^2	Soil	Leaf, root, stalk or fruit	Spinach: ~5-22* Cabbage: ~10-32* Coriander:~20-80* P. mustard: ~2-52* C. cabbage: ~1-60* Tomato: ~0.5-1.5* Cucumber: ~0.3-1.2* L. cowpea: ~0.4-1.9* Eggplant: ~0.3-1.2* Hot pepper: ~0.2-1.6* * mg/kg FW	[8]
Lettuce, kohlrabi, radish	KI or KIO$_3$	I: 0.5-2 kg/ha (leaf) I: 1-15 kg/ha (soil)	Soil or leaf spray	Leaf or tuber	Kohlrabi: I$^-$ treat.: ~3-30* (soil); I$^-$ treat.: ~2-18* (leaf) IO$_3^-$ treat.:~2-130* (soil); IO$_3^-$ treat.: ~18-21* (leaf) Lettuce: I$^-$ treat.: ~10-100* (soil); I$^-$ treat.: ~80-480* (leaf) IO$_3^-$ treat.:~10-420* (soil); IO$_3^-$ treat.: ~45-300* (leaf) Radish: I$^-$ treat.: ~1-8* (soil); IO$_3^-$ treat.:~1-15* (soil) * µg/100 g FM	[23]

For each study, plant species, growth system, iodine form and dose applied, application method as well as iodine content in specific plant organs are reported. For reasons of space, the list is not exhaustive and the authors apologize to those colleagues whose research is not mentioned. Plant species labeled with a red asterisk are commonly considered as staple crops. Abbreviations: I: iodine; n.d.: not determined; treat.: treatment.

of iodine administered and iodine 'fertilization' results in its accumulation in plants at levels that can be fine-tuned for biofortification [12–14,20,22,32] (Box 1).

The soil-to-edible part transfer factor (TF) represents the ratio between the element concentration in the edible part of the plant and its concentration in the soil [12]. TF is used to estimate the intake of elements through the food chain. Foliar spray studies have shown that the xylematic transport of iodine is much more efficient than the phloematic one, suggesting that its accumulation in fruits, tubers or seeds would not be high [4**,20,23*,27,30,32] and that leafy vegetables would be therefore ideal candidates for biofortification. In fact, a very high accumulation capacity has been shown by leafy vegetables such as spinach [12], Chinese cabbage, lettuce [16,32,42], pakchoi and celery [18]. Nevertheless, some fruit and tuber vegetables, such as tomato [22], strawberry [25] or potato [20], can store amounts of iodine in their edible parts which are still significant

for biofortification, despite the low TFs of these organs. Physiological constraints seem to prevent this agronomic approach in cereals, as the amount of iodine reaching the grains is too low for human dietary requirements [30,43•]. This is a fundamental point to consider since cereals include important staple crops, such as rice, which would represent one of the most important targets for iodine biofortification in developing countries.

The influence of organic matter and the presence of other minerals in the soil have been investigated: they can interact with iodine reducing its mobility or competing for root absorption [21,22,44,45]. Iodine species can persist in the soil once applied, but with an inevitable gradual loss and reduction in bioavailability [10,12,18]. The development of fertilizers that release iodine slowly, such as those containing algae, make iodine more stable preventing its volatilization [8,12,15].

Hydroponic systems are generally more efficient than soil applications [28,45], and both are more efficient than foliar treatments. However, the use of surfactants could significantly increase the foliar 'fertilization' technique [23•]. Finally, protocols regarding multiple crop biofortification with iodine and other essential nutrients, such as selenium and zinc [34,43•], have been tested and the synergistic effects reported [34].

Breeding and metabolic engineering

The genetic improvement of crops for biofortification can be obtained by breeding and genetic engineering, which are more complex and labour intensive than agronomic studies, but can also be long-term cost-effective strategies. The ability of the crop to be biofortified is retained by its seeds and may be independent of outer inputs, such

as the iodine administration, thus making this approach particularly suitable for developing countries.

The plant genetic traits which might be of interest are those that control the uptake, mobilization, storage and volatilization of iodine. To the best of our knowledge, there have been few investigations regarding the extent of genetic variability of these characters. The mechanisms of plant iodine uptake, from the soil or the atmosphere, are largely unknown. Some hypotheses have been drawn regarding the iodine root absorption and the subsequent xylem loading based on the chemical affinities with other halogens, particularly chlorine, or other nutrients [9] (Figure 3). However, no iodine transporters have been identified in plants to date and neither the iodine forms moving within the plant nor those stored within the tissues are known precisely.

The process of iodine volatilization as methyl iodide from plant leaves and roots has been much better characterized. In this case the presence of the related HMT/HTMT enzymatic activity has been identified in some species [37–41]. Again, a systematic study on the process and the attempt to correlate it with the iodine accumulation capacity has not been carried out. Interestingly, from the few data available [37,40], species identified as good candidates for agronomic biofortification (lettuce, for example) do not appear to be able to volatilize iodine, whereas others characterized by low levels of iodine in the edible organs (rice, for example) have high HMT/HTMT activities. However, the low number of species analysed makes it impossible to draw any conclusions.

Landini *et al.* [46] used a molecular approach to analyse the different physiological mechanisms affecting iodine accumulation in the model species *A. thaliana*. In this plant, the iodine content was increased by both enhancing the iodine uptake through the expression of the human sodium-symporter (NIS) of the thyroid gland and/or by reducing its release into the atmosphere by knocking down the *HOL-1* gene encoding for an HMT enzyme. It was found that the final iodine content was controlled by the balance between the intake and release. In addition, by comparing the two processes, volatilization appeared to primarily affect iodine retention in Arabidopsis plants, particularly its mobilization towards inflorescences and thus, probably, the seeds [46].

These results clearly indicate that a correct evaluation of iodine volatilization in crops is particularly important to understand how to increase their biofortification efficiency, especially when fruits, grains or seeds represent the edible organs. The genetic variability in this trait should therefore be explored and, if not adequately found, gene silencing techniques should be undertaken to switch off HMT/HTMT encoding genes in selected crops.

Figure 3
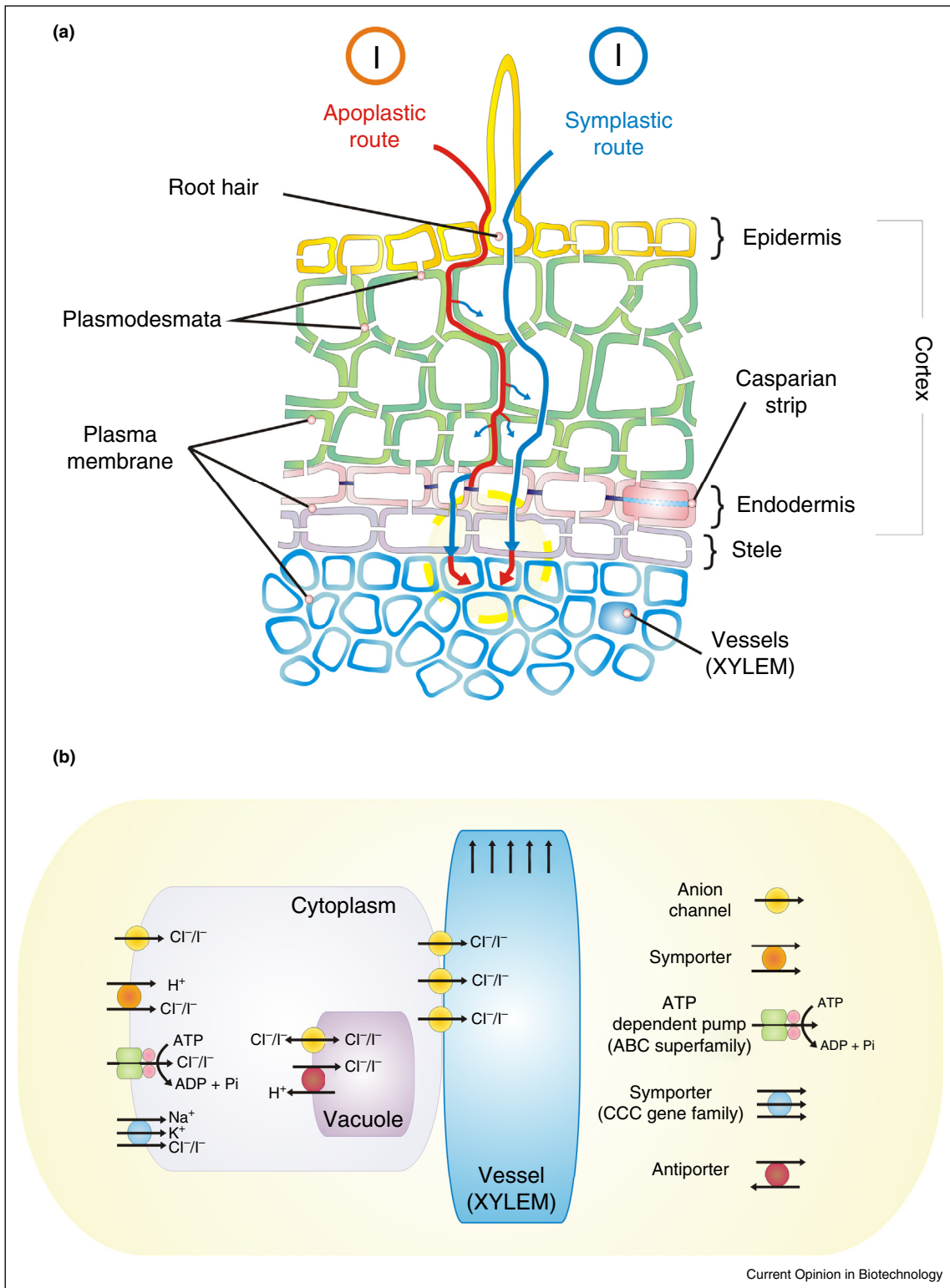
Uptake and mobilization of iodine in plants. **(a)** Apoplastic and symplastic routes are hypothesized for iodine uptake from the soil solution and its mobilization inside the root from the epidermis to the xylem vessels (adapted from URL: https://mail.sssup.it/Redirect/57FD6DAD/www.78stepshealth. us/plasma-membrane/water-and-ions-pass-to-the-xylem-by-way-of-the-apoplast-and-symplast.html). **(b)** Magnification of the contiguous stele/xylem area included in the yellow circle in (a). Iodide (I⁻) loading inside plant cells may occur through transporters and channels (reviewed in [4••,9]), whose specific identity has not been precisely established yet. Chloride (Cl⁻) channels, Na⁺:K⁺/Cl⁻ co-transporters, H⁺/Cl⁻ symporters or antiporters, and Cl⁻ transporters energized by ATP-dependent proton pumps, may be involved in iodine transport due to the high similarity of chloride with iodide ions [9].

The insufficient translocation of iodine through the phloem could be approached by genetic engineering, for example by expressing heterologous iodine transporters or carriers [47]. Finally, amylose, by complexing iodine as polyiodide chains, could be exploited as an *in planta* sink, thus making starchy staple crops ideal iodine vehicles in the human diet [48]. Varieties with high-amylose levels have already been selected in some starchy crops which could be used without genetic engineering. However, issues that need to be resolved include enabling iodine to reach the starch granule (often stored within grains or seeds), as well as proving that the iodine sequestered in the amylose complex is bioavailable once ingested [48].

Iodine bioavailability and stability in plant food

Knowledge of the quantity of iodine in a biofortified food is not enough to predict how it can meet human dietary requirements: the nutritional impact is determined by how much of it is bioavailable [49]. The bioavailability of iodine in food is generally considered high, even 99% [8,17]. However, many factors can affect micronutrient availability and the correct way to test it should be by feeding trials in deficient populations with micronutrient-enriched plant food [49]. Owing to the inherent difficulty of such an approach, model systems and animal models are more commonly used.

With regard to fortified vegetables, a study on 50 healthy volunteers fed a diet of iodine enriched potatoes, carrots, cherry tomatoes, and green salad, demonstrated a mild but significant increase in the urinary iodine concentration, that is, the recommended indicator for measuring the prevalence of IDDs [50]. This result was confirmed by more comprehensive studies carried out in animal models. A significantly higher iodine level was found in urine, faeces and selected tissues of rats fed a diet containing biofortified carrots [51••] or lettuce [52•]. The genes involved in iodine metabolism and thyroid hormone levels increased [51••], clearly indicating how the consumption of these vegetables could really improve iodine nutrition.

Food preparation and storage may strongly affect the residual amount of iodine for human intake. Results obtained in studies aimed at understanding the stability of iodine in fortified vegetables during moderate cooking procedures [19,22,53,54•] indicate that iodine persists well. For example, domestic processes of boiling or baking and heating procedures mimicking industrial pasteurization were found to be suitable for preserving iodine in biofortified potatoes, carrots and tomatoes [53].

Conclusions

Iodine agronomic biofortification of many horticultural vegetables is already a feasible strategy. For most species, the success seems to largely depend on the correct choice of the system of distribution, doses and timing of application, and on an evaluation of the cost/benefit ratio. No general protocols are effective for all species. A preliminary study is always necessary to understand the behaviour of each individual plant in the environment where the cultivation is carried out.

Commercial iodine-biofortified vegetables, whose nutritional impact tested positively [50], have been patented and marketed [53,54•]. The fortification of the diet with iodine-enriched plant food, together with the habitual use of iodized salt, may thus successfully contribute to improving the iodine nutritional status of a population. However, as for other functional foods, the knowledge and the acceptance of the biofortified vegetables by the potential beneficiaries is decisive in determining their final adoption and thus the success of the strategy [55,56], and nutritional education campaigns do have a fundamental role in this sense.

Unfortunately, a major drawback is the current lack of reliable protocols for the iodine biofortification of important staple crops, such as rice and other cereals. Such protocols would benefit many poor iodine-deficient countries. Since insufficient phloem loading and high volatilization rates seem to limit iodine accumulation in these species, further studies are necessary to understand if and how these obstacles can be circumvented. The identification of the genetic traits regulating iodine uptake, mobilization and retention in the plant and their suitable manipulation are therefore necessary for undertaking breeding programs or genetic engineering approaches, the only that seem to be adoptable for these crops.

The inclusion of iodine in the *HarvestPlus* Program would greatly benefit research in this field, as it is also advantageous for alleviating other major vitamin and nutrient deficiencies, which often occur simultaneously in the same areas, thus negatively combining their adverse effects on human health [57].

Acknowledgements

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