Bioavailability of iodine species from various commercially consumed seaweed species

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Preface

Seaweed is gaining popularity and economic importance as an ingredient in (novel) foods and is now commonly consumed across all population strata in the Netherlands. Moreover, seaweed may also provide a sustainable source of plant-based protein for human and animal provisioning.

Food safety of seaweed is an important condition for bringing seaweed-containing food products on the market. However, previous studies have shown that seaweeds can accumulate high concentrations of iodine and heavy metals, although there is high variation among seaweed species, geographic location, harvesting season, seaweed metabolic activity, and cultivation method.

The focus of this literature study, which is part of the Possibile Reduction Of Contaminants in Edible Seaweed Species (PROCESS) project, is on the bioavailability of iodine, and the possible difference in bioaccessibility and bioavailability between organic and inorganic iodine.

The results of this relatively small study can be used to assess the maximum allowable iodine intake, and what consequences this has for the consumption of specific seaweed species.

Summary

Macro algae contain both nutrients and contaminants, which are studied extensively, since it can contribute to the transition of animal to plant based proteins. Iodine, largely present in some marco algae species, is a crucial nutrient for the human body, as it plays an essential role in the synthesis of the thyroid hormones thyroxine and triiodothyronine. The relationship between iodine intake and thyroid dysfunctionalities is 'U-shaped', therefore, both iodine deficiency and excessive intake could induce thyroid dysfunctions. The Laminariales family, which includes *Saccharina latissima*, is the strongest iodine accumulator since this seaweed family is able to accumulate iodine within their tissues up to 30.000 times with respect to the surrounding iodine levels. This means that the tolerable upper intake level of 600 µg/day, as advised by the European Food Safety Authority (EFSA), could be exceeded from consumption as low as 92 mg dry weight sugar kelp per day, while the average daily consumption was estimated at 3.3 g/day. Due to the high iodine concentrations in seaweed and the risks associated with excessive iodine intake, it is important to identify the iodine fraction that will enter the systemic circulation. Within seaweed, iodine exists in multiple forms, which can generally be classified into inorganic iodine (e.g., iodide and iodate) and organic iodine (e.g., monoiodotyrosine (MIT), diiodotyrosine (DIT)).

Considering these high concentrations, it is important to evaluate the bioaccessibility and bioavailability of the different iodine species from the seaweed matrix. The bioaccessibility can be defined as the amount of iodine that is available for absorption in the gut after digestion of a specific seaweed species, whereas the bioavailability can be defined as the amount of iodine that will actually enter the systemic circulation. In general, the bioaccessibility and bioavailability can be assessed through in vitro studies (e.g., solubility assays, dialyzability assays, cell-line assays) and in vivo studies (e.g., animal studies, human intervention studies). This report aimed to provide insights into the human bioaccessibility and bioavailability of inorganic and organic iodine species from various commercially available seaweed species.

The reported in vitro bioaccessibility seemed to be rather comparable among the seaweed species and ranged from 45 - 81%, which translated into a bioaccessible concentration of 3 mg/kg iodine for *Undaria pinnatifida* to 305 mg/kg iodine for *Saccharina japonica*. Furthermore, the reported in vitro dialyzability seemed to vary among the different seaweed types and species and ranged from 2-28%, which translated into a dialyzable concentration of 0.35 mg/kg iodine for *Undaria pinnatifida* to 1226 mg/kg iodine for a mixture of *Laminaria ochroleuca* and *Laminaria saccharina*. Moreover, the reported in vitro cell transfer ranged from 3 - 10%, which was converted into a bioavailable concentration of 0.1 mg/kg iodine for *Undaria pinnatifida* to 21.3 mg/kg iodine for *Saccharina japonica*. Furthermore, it seemed that different pre-treatments (soaking, boiling, steaming) reduced the total iodine content in *Sargassum fusiforme* and (slightly) altered the bioaccessible iodine fraction, the inorganic and organic iodine composition of the bioaccessible iodine concentration and the bioavailable concentration in *Sargassum fusiforme*.

The reported iodine bioavailability through human intervention studies ranged from 28-101%. The highest bioavailable iodine concentration was reported for *Gracilaria verrucosa* (4250-7070 mg/kg iodine), while the lowest bioavailable iodine concentration was reported for *Chondrus crispus* (24 mg/kg iodine). The large variation could be attributed to differences in the daily administered dose, duration of the trial and/or age, gender, and ethnicity of the test population. Nevertheless, in this report preliminary estimations were made on the safely consumable amount based on these human intervention studies. The preliminary estimations allude to a safely consumable amount of 0.1 g/day of *Gracilaria verrucosa* to 26 g/day of *Chondrus crispus*. The preliminary estimations could mean that the average daily consumption of 3.3 g/day dry weight could lead to excessive iodine intake for some seaweed species. However, since these findings are only based on a limited number of studies, it is very important to conduct additional human intervention trials to confirm or dismiss the above stated findings.

1 Introduction

Iodine is a crucial nutrient for the human body, as it plays an essential role in the synthesis of the thyroid hormones thyroxine (T4) and triiodothyronine (T3) (Farebrother et al., 2019; Domínguez-González et al., 2017). T3 enhances the metabolic rate and protein synthesis in most of the tissues and organs in the human body and is regarded as the active form of the thyroid hormones. T4 is the precursor of T3 and is regarded as the inactive form of the thyroid hormones (Mansourian, 2010). Accordingly, an inadequate iodine intake could result in thyroid disorders. The relationship between iodine intake and thyroid dysfunctionalities is 'U-shaped', therefore, both iodine deficiency and excessive intake could induce thyroid dysfunctions (Katagiri et al., 2017).

The existence of iodine in seaweed has been known for over 200 years, ever since Bernard Courtois discovered the element by accident in 1811, as he was searching for explosive materials in the ashes of kelp during the Napoleonic Wars (Courtois, 1813). The Laminariales family, which includes *Saccharina latissima* (*S. latissima*), is the strongest iodine accumulator, since this seaweed family can accumulate iodine within their tissues up to 30.000 times with respect to the surrounding iodine levels (Gall et al., 2004, Truesdale et al., 1995). For example, within European *S. latissima*, iodine contents as high as 6500 mg/kg DW have been reported (Stévant et al., 2017). This means that the tolerable upper intake level of 600 µg/day, as advised by the European Food Safety Authority (EFSA, 2018), could be exceeded by consumption as low as 92 mg DW of sugar kelp per day, while the average daily consumption was estimated at 3.3 g/day (Banach et al., 2020). Therefore, human consumption of these seaweed species could result in excessive iodine intake. Thyroid dysfunctionalities that have been associated with excessive iodine intake include thyroid enlargement (Goiter), hypothyroidism, thyroid autoimmunity, postpartum thyroiditis, hyperthyroidism (Jod-Basedow effect), Graves' disease and thyroid cancer (Farebrother et al., 2019).

Due to the high iodine concentrations in seaweed and the risks associated with excessive iodine intake, it is important to identify the iodine fraction that will enter the systemic circulation. Within seaweed, iodine exists in multiple forms, which can generally be classified into inorganic iodine (e.g., iodide and iodate) and organic iodine (e.g., monoiodotyrosine (MIT), diiodotyrosine (DIT)) (Aquaron et al., 2002). To identify the iodine fraction that will enter the systemic circulation, it is important to evaluate the bioaccessibility and bioavailability of the different iodine species from the seaweed matrix. For the purpose of this report, the bioaccessibility can be defined as the amount of iodine that is available for absorption in the gut after digestion of a specific seaweed species, whereas the bioavailability can be defined as the amount of iodine that will actually enter the systemic circulation (Rodrigues et al., 2022). In general, the bioaccessibility and bioavailability can be assessed through in vitro studies (e.g., solubility assays, dialyzability assays, cell-line assays) and in vivo studies (e.g., animal studies, human intervention studies) (Mathias et al., 2015).

The available literature on this topic is limited, therefore, the report will not solely focus on *Ulva lactuca* and *S. latissima*, but will include all relevant studies conducted on commercially consumed seaweed species. The report therefore includes the brown seaweeds *Alaria esculenta, Ascophyllum nodosum, Fucus spiralis, Himanthalia elongata, Laminaria hyperborean, Laminaria ochroleuca, Laminaria saccharina, Saccorhiza polyschides, Sargassum fulvellum, Sargassum fusiforme, Saccharina japonica* and *Undaria pinnatifida*, the red seaweeds *Chrondrus crispus, Gracilaria verrucosa, Palmaria palmata, Porphyra lineariss* and *Porphyra umbilicalis,* and the green seaweed *Ulva rigida*. The report will focus on conducted in vitro and human intervention studies, as no relevant literature on studies with animals were available at the time of the review. Overall, the report aims to provide insights into the human bioaccessibility and bioavailability of inorganic and organic iodine species from various commercially available seaweed species and will include the following parts:

1. In vitro bioaccessibility and bioavailability of inorganic and organic iodine from commercially available seaweed species
2. Human intervention studies on the bioavailability of inorganic and organic iodine from commercially available seaweed species
3. Preliminary estimation on the amount of iodine that will enter the circulatory system of the human body and the safely consumable portion of commercially available seaweed species

2 Methodology

2.1 Search strategy

2.1.1 Keywords

The used keywords to gather the relevant literature include:

- Compounds: *Iodine, iodide, iodate, hypoiodous acid, mono-iodotyrosine, MIT, di-iodotyrosine, DIT*
- Parameters of interest: *Bioavailability, bioaccessibility, dialyzability, uptake, accumulation, toxicity, toxic, accumulate, biosorption, cultured, exposure, response, absorption*
- Type of studies: *In vitro, in vivo, human feeding study*
- Matrix: *Seaweed, macroalgae, algae, brown seaweed, red seaweed, green seaweed*

2.1.2 Databases

The databases used for this review include:

- Scopus: 43 hits
- Web of Science: 43 hits
- Pubmed: 18 hits
- Total hits: 104 hits
- Removed duplicates: 63 hits
- Relevant after screening: 7 hits
- Manually added literature: 25 hits
  - Added through snowball method and two literature theses'[1][2]

2.1.3 Inclusion and exclusion criteria

Inclusion criteria:

- In vitro studies on the dialyzability and bioavailability of pure inorganic and organic iodine species
- In vivo studies on the bioavailability of pure inorganic and organic iodine species
- Human feeding studies on bioavailability of pure inorganic and organic iodine species
- In vitro studies on the bioaccessibility, dialyzability and bioavailability of inorganic and organic iodine species from frequently consumed seaweed species
- In vivo studies on the bioavailability of inorganic and organic iodine species from frequently consumed seaweed species
- Human feeding studies on the bioavailability of inorganic and organic iodine species from frequently consumed seaweed species

Exclusion criteria:

- Abstract only, papers as preceding papers, conference papers, editorial papers and books
- Articles with no full text availability
- Case reports or series

[1] Amber A.A. Beerman (2021) Saccharina Latissima: Potential Solution for Future Global Protein Shortage?

[2] Pauline Loman (2022) Evidence Supporting the UL for Iodine and the Relation between this UL and the Iodine Content in Four Selected Brown Seaweeds.

2.2 Calculations retrieved data

2.2.1 Calculation bioaccessible, dialyzable, and bioavailable concentration (in vitro)

Within literature, the bioaccessibility and dialyzability were only reported as relative numbers. To obtain a better understanding of the reported data, the bioaccessible and dialyzable fractions were converted into concentrations (mg/kg). In Equation 1 and 2, examples are given on the conversions of the bioaccessible and dialyzable fractions (BAC_f / DAC_f) into the bioaccessible and dialyzable concentrations (BAC_c / DAC_c) in mg/kg using the total iodine concentration (TI_c) in mg/kg of the used seaweed species. Within the reviewed in vitro studies, bioavailability experiments consisted of two steps: (1) solubility experiments to determine the bioaccessible iodine fraction; (2) cellular transport experiments to determine transferable iodine fraction across the cells. The combination of these results provides an estimation on the bioavailable iodine fraction, see Equation 3. Equation 3 consists of two variables: bioaccessible concentration (BAC_c) in mg/kg and cellular transport fraction (CT_f).

$Equation\ 1$ $$Bioaccessible\ concentration\ (BAC_c) = TI_c * BAC_f$$

$Equation\ 2$ $$Dialyzable\ concentration\ (DAC_c) = TI_c * DAC_f$$

$Equation\ 3$ $$Bioavailable\ concentration\ (BAV_c) = BAC_c * CT_f$$

2.2.2 Calculation bioavailable concentration (human intervention studies)

Within the human intervention studies, the bioavailable fraction is determined in one step, as it is not possible to differentiate between the bioaccessibility and cellular transport during these types of studies. Equation 4 provides an example on the conversion of the bioavailable fraction (BAV_f) into the bioavailable concentration (BAV_c) in mg/kg using the total iodine concentration (TI_c) in mg/kg of the ingested seaweed species.

$Equation\ 4$ $$Biovailable\ concentration\ (BAV_c) = TI_c * BAV_f$$

2.2.3 Calculation safely consumable seaweed portion

The equation used for the preliminary estimation of the safely consumable seaweed portion in g/day is given in Equation 5. The equation includes the following variables: tolerable upper intake level of 0.6 mg/day, the bioavailable concentration (BAV_c) in mg/kg and a correction factor of 1000 to convert the safely consumable seaweed fraction from kg/day into g/day.

$Equation\ 5$ $$Safely\ consumable\ amount = \frac{0.6}{BAV_c}$$

3 Results and discussion

3.1 Bioavailability estimation in vitro

In general, the in vitro bioaccessibility and bioavailability can be estimated based on solubility, dialyzability and cell model assays (Etcheverry et al., 2012). In a solubility assay, the seaweed is exposed to gastric and intestinal solutions to mimic the gastrointestinal digestion in the gastrointestinal tract. The iodine that transfers to the supernatant can be regarded as an estimation of the in vitro bioaccessible iodine fraction (Etcheverry et al., 2012). Therefore, the iodine solubility assays can be regarded as an estimation of the in vitro bioaccessibility. Dialyzability assays were originally developed to estimate the bioaccessibility of iron from food matrices, but overtime has been expanded to study the bioaccessibility of other micronutrients such as iodine (Miller et al., 1981). In a dialyzability assay, the seaweed is exposed to semipermeable membranes after gastric digestion to simulate diffusion in the small intestine (Etcheverry et al., 2012, Dominguez-Gonzalez et al., 2011). The dialyzable iodine can therefore be regarded as an estimation of the in vitro bioavailability.

Cell model assays can also be used to perform cell transport and uptake assays (Etcheverry et al. 2012). The literature included in the report all made use of Caco-2 cells or a co-culture of Caco-2 and HT29-MTX cells. Caco-2 cells are human epithelial cells that were originally derived from a colon carcinoma and represent the most commonly used cell line of the human intestinal mucosa to estimate the in vitro absorption (Darling et al., 2020, Lea, 2015). HT29-MTX cells are derived from a human colon adenocarcinoma cell line and are frequently used in a co-coculture with Caco-2 cells to mimic the human intestinal epithelium and estimate in vitro permeability (Lozoya-Agullo et al., 2017, Martínez-Maqueda et al., 2015). In general, the cell lines are exposed to the bioaccessible iodine fraction. The iodine fraction that is then able to transfer across the cells can be regarded as an estimation of the in vitro cellular transport. The combination of these two steps then provides an estimation of the in vitro bioavailability. This section will discuss the in vitro bioaccessibility and bioavailability of pure iodine species and iodine containing seaweed. Furthermore, this section will also discuss potential effects of the different pre-treatments on the bioavailability and bioaccessibility of iodine. Due to the limited number of studies that focused on this topic, it is important to state that the following conclusions in this paragraph are only preliminary and based on the limited amount of data that currently exists.

3.1.1 Bioavailability of pure iodine species in vitro

In Table 1 an overview is given of reported values regarding the in vitro dialyzability and bioavailability of pure iodine species. The results presented in Table 1 allude to differences between the different iodine species with respect to the in vitro dialyzability. These results suggest that the in vitro dialyzability of iodide and MIT are relatively similar, while the dialyzability of DIT is much lower (Dominguez-Gonzalez et al., 2017). Dominguez-Gonzalez et al. suggested that this was caused by a potential interaction between DIT and the digestion components (biliary extract, pancreatin and pepsin) and stated that the interaction between DIT and proteins had been described before (Dominguez-Gonzalez et al., 2017).

Table 1 *Dialyzability and bioavailability of iodine species in vitro.*

Iodine species	TI conc. µg/mL	TDi fraction %	TBAv fraction %	Lit.
Iodide	30	47-49	NA	[1]
	3	NA	62-68	[2]
Iodate	3	NA	52-58	[2]
MIT	0.4	44-62	NA	[1]
DIT	6	25-27	NA	[1]
	3	NA	43-48	[2]

TI – Total Iodine; TDi – Total dialyzability; TBAv – Total bioavailability. NA – Not applicable. [1] – Dominguez-Gonzalez et al., 2017 [2] – Sun et al., 2021.

The inorganic components iodide and iodate seemed to be the most bioavailable iodine species, while the organic component DIT was somewhat less bioavailable (Sun et al., 2021). Furthermore, differences between the transferable iodine fraction were observed between the in vitro dialyzability and cell line assays. These differences can be attributed to several factors. The first factor includes the differences with respect to the used assays, as a dialyzability assay makes use of dialysis tubing, while a bioavailability assay makes use of cell lines (Etcheverry et al., 2012). Another important difference between the two studies includes the incubation time, as the in vitro dialyzability assay included an incubation time of 2 hours (Dominguez-Gonzalez et al., 2017), while the in vitro bioavailability assay included 24 hours incubation time (Sun et al., 2021). Therefore, the difference in incubation time could also provide an explanation for the somewhat higher values that were observed with regards to the bioavailability.

3.1.2 Bioavailability of iodine species from seaweed in vitro

In Table 2 an overview is given of reported values regarding the in vitro bioaccessibility, dialyzability and cellular transport of iodine from various seaweed species. Overall, the total iodine content seemed to greatly vary among the different seaweed types and species (7 – 6452 mg/kg). The highest iodine content was reported for the brown seaweeds, except for the boiled seaweed species and the unprocessed *Fucus spiralis*, as a fresh seaweed sample is much less concentrated than a dried seaweed sample (Dominguez-Gonzalez et al., 2017; Romaris-Hortas et al., 2011; Francisco et al., 2018). The reported total iodine content in red and green seaweed seems to be quite comparable and overall lower than the reported total iodine content in brown seaweed. The in vitro bioaccessibility was only reported for brown seaweed species and ranged from 45-81%, see Table 2. The relative bioaccessibility among the different brown seaweed species seemed to be rather comparable. The relative bioaccessibility translates into a bioaccessible iodine concentration that ranges from 3 mg/kg for *Undaria pinnatifida* to 305 mg/kg for *Saccharina japonica*, see Equation 1 and Table 2. The large range of 3-305 mg/kg is related to the different total iodine concentrations, which varied greatly, see Table 2.

The reported in vitro dialyzability seemed to vary among the different seaweed species and ranged from 2-28%. The results suggest that *Saccharina japonica* contained the highest relative dialyzable iodine fraction (20-28%), while *Undaria pinnatifida* and *Ulva rigida* contained the lowest relative dialyzable iodine fraction (2%) (Dominguez-Gonzalez et al., 2017; Romaris-Hortas et al., 2011). It is difficult to relate these results to the in vitro dialyzability of pure iodine species, as *Saccharina japonica* has been reported to contain high amounts of DIT (Romarís-Hortas et al., 2012). Dominguez-Gonzalez stated that these differences could be attributed to the interaction of the iodine species with other components in the seaweed matrix, thereby forming soluble complexes with a higher molecular weight, which could differ per seaweed species (Dominguez-Gonzalez et al., 2017, Shah et al., 2005). The in vitro dialyzable concentration was also calculated and ranged from 0.4 mg/kg for *Undaria pinnatifida* to 1226 mg/kg for a mixture of *Laminaria ochroleuca* and *Laminaria saccharina,* see Equation 2 and Table 2. Similarly to the in vitro bioaccessibility, the large range can be attributed to the large variation in the total iodine concentration of the different seaweed species, see Table 2.

The cellular transport was only reported for three brown seaweed species and ranged from 2-10%. The obtained data were converted into a bioavailable iodine concentration that ranged from 0.1 mg/kg for *Undaria pinnatifida* to 23 mg/kg for *Saccharina japonica*, see Equation 3 and Table 2. Similar as for the bioaccessibility and the dialyzability, the large range can primarily be explained by the large variation in the total iodine content of the various seaweed species, see Table 2. The cellular transport was only reported for seaweed species that underwent the pre-treatment boiling. Therefore, it is difficult to assess whether these bioavailable concentrations would also be representative for seaweed species that underwent different pre-treatments or no pre-treatment(s) at all. The effect of the pre-treatment on the bioaccessibility and bioavailability will be discussed in the following section.

Table 2 *Overview in vitro bioaccessibility, dialyzability and bioavailability of iodine from various seaweed species.*

Commercial name	Type	Genus	Species	TI conc. mg/kg	TBAc fraction %	TBAc conc. mg/kg	TDi fraction %	TDi conc. mg/kg	CT fraction %	TBAv conc. mg/kg	Sample type	Pre-treatment	Lit.
Hijiki	Brown	*Sargassum*	*fusiforme*	57-125	55-59	31-74	6-12	3-15	2-4	1-4	FW	Boiled in Milli-Q-water	[1]
Kombu	Brown	*Saccharina*	*japonica*	172-376	57-81	98-305	20-28	34-105	4-7	3-23	FW	Boiled in Milli-Q-water	[1]
Kombu	Brown	*Laminaria*	*ochroleuca*	5824-6452	NA	NA	15-19	874-1226	NA	NA	DW	Dried, ground	[2]
		Laminaria	*saccharina*	NA[1]	NA	NA	NA[1]	NA[1]	NA	NA	DW	Dried, ground	[2]
NIES-09	Brown	*Sargassum*	*fulvellum*	466-584	NA	NA	3-5	14-29	NA	NA	DW	Freeze-dried, ground, sieved, blended	[2]
Sea Spaghetti	Brown	*Himanthalia*	*elongata*	94-140	NA	NA	3-5	3-7	NA	NA	DW	Dried, ground	[2]
Sea Spaghetti & Furbelows	Brown	*Himanthalia*	*elongata*	36-38	NA	NA	ND	ND	NA	NA	DW	Boiled, canned in brine, freeze dried	[2]
		Saccorhiza	*polyschides*	NA[1]	NA	NA	NA[1]	NA[1]	NA	NA	DW	Boiled, canned in brine, freeze dried	[2]
Spiral wrack	Brown	*Fucus*	*spiralis*	34-37	47-49	16-18	NA	NA	NA	NA	FW	NA	[3]
				133-137	53-57	70-78	NA	NA	NA	NA	DW	Freeze-dried	[3]
Wakame	Brown	*Undaria*	*pinnatifida*	7-26	45-57	3-15	5-9	0.4-2.3	3-10	0.1-1.6	FW	Boiled in Milli-Q-water	[1]
Wakame	Brown	*Undaria*	*pinnatifida*	263-348	NA	NA	2	5	NA	NA	DW	Dried, ground	[2]
Dulse	Red	*Palmaria*	*palmata*	69-86	NA	NA	8-12	6-10	NA	NA	DW	Dried, ground	[2]
Nori	Red	*Porphyra*	*umbilicalis*	40-47	NA	NA	5	2	NA	NA	DW	Dried, ground	[2]
		Porphyra	*lineariss*	NA[1]	NA	NA	NA[1]	NA[1]	NA	NA	DW	Dried, ground	[2]
Sea Lettuce	Green	*Ulva*	*rigida*	64-68	NA	NA	2	1	NA	NA	DW	Dried, ground	[2]

TI – Total Iodine; TBAc – Total bioaccessibility; TDi – Total dialyzability; CT – Cell transfer; NA – Not applicable; ND – Not detected; NA[1] – Not applicable as these seaweed species were analysed as part of a mixture: *Laminaria ochroleuca* & *Laminaria saccharina; Himanthalia elongata* & *Saccorhiza polyschides; Porphyra umbalicalis* & *Porphyra lineariss*. [1] – Dominguez-Gonzalez et al., 2017 [2] – Romaris-Hortas et al., 2011 [3] Francisco et al., 2018.

3.1.3 Effect of processing on the bioavailability of iodine species from seaweed in vitro

The processing of seaweed (e.g., soaking, boiling) could be an effective method to remove iodine from the seaweed matrix (Nielsen et al., 2020, Stevant et al., 2017). Furthermore, it is also important to review the effects that these processing methods have on the bioaccessibility and bioavailability of iodine from seaweed. In 2021, Sun et al. published a research article in which the effects of the pre-treatments on the in vitro bioaccessibility and bioavailability of iodine from *Sargassum fusiforme* was studied. An overview of the reported data is given in Table 3. Unfortunately, at this moment only one study focussed on this matter, therefore, the following conclusions in this section are only preliminary.

The reported total iodine content indicated that every pre-treatment reduced the total iodine content. Boiling seemed to be the most effective method to reduce iodine (55%). For soaking and steaming, iodine reductions of 41 and 8% were reported respectively. The relative ratio between inorganic and organic iodine was also reported by Sun et al. (2021), see Table 3. Dried *Sargassum fusiforme* reportedly primarily contained organic iodine (80%) and a smaller fraction consisted of inorganic iodine (20%). The reported ratios did not seem to be affected by the pre-treatments boiling and soaking. However, the relative ratio did seem to be affected by the pre-treatment steaming. Sun et al. (2021) reported that the inorganic iodine concentration was higher in the steamed seaweed opposed to the seaweed that was only dried. It was suggested that the steaming procedure caused a small conversion of organic iodine into inorganic iodine.

The reported bioaccessibility seemed to be relatively similar between the dried seaweed (73-75%) and the soaked seaweed (71-74%), and between the boiled (82-84%) and the steamed seaweed (81-83%), see Table 3. It is possible that the heating in these two pre-treatments altered the seaweed matrix, which could have resulted in a higher bioaccessibility. Furthermore, the two heating treatments also seemed to alter the inorganic/organic iodine (I^-/OI) ratio quite differently, as the I^-/OI ratio after boiling was considerably different from the I^-/OI ratio after the other pre-treatments. Therefore, it is likely that this pre-treatment alters the seaweed matrix. Based on this, two theories could explain these observations. These alterations could either result in a lower bioaccessibility of inorganic iodine or result in higher bioaccessibility of organic iodine, with the latter being the more feasible option. Similarly to the bioaccessibility, the highest relative bioavailability was reported for the pre-treatments boiling and steaming. The highest bioavailable concentration was reported for the steamed seaweed (146 mg/kg) and the lowest one for the pre-treatment soaking (79 mg/kg). Based on this, the pre-treatment soaking would be the most effective processing method, as it resulted in a 28% reduction of the total bioavailable iodine.

Table 3 *Effect of pre-treatments on the iodine concentration, bioaccessibility and transfer in vitro of iodine species from Sargassum fusiforme (Sun et al., 2021).*

Pre-treatment	TI conc. mg/kg	TI ratio I^-/OI	TBAc fraction %	BAc ratio I^-/OI	CT fraction %	TBAv I mg/kg
Dried	622	20/80	73-75	80/20	22-26	100-121
Dried, soaked	364	20/80	71-74	70/30	27-33	70-89
Dried, boiled	280	20/80	82-84	55/45	32-38	73-89
Dried, steamed	574	30/70	81-83	85/15	29-33	135-157

TI – Total Iodine; TBAc – Total bioaccessibility; I^- – Iodide; OI – Organic Iodine; CT – Cell transfer; TBAv – Total bioavailability.

3.2 Bioavailability estimation through human intervention studies

The most relevant approach to estimate the human bioavailability is through human intervention studies. These types of studies provide the highest level of evidence with regards to the human bioavailability of iodine from seaweed. The most important aspects within an intervention study include the identification of the target population (e.g., gender, age), sample size, metabolic pathway and dietary intervention. Overall, human intervention studies are designed as trials in which (a part of) the target population will receive the dietary intervention. In some cases the other part of the target population will receive a placebo. The estimated human bioavailability is then based on the recovered iodine within the sampled urine of the target population (Olmedilla-Alonso, 2019, Welch et al., 2011). This section will discuss the estimation of the bioavailability of pure iodine species and iodine containing seaweed through human intervention trials. Similarly to in vitro studies, only a limited number of studies were available that focused on this topic. Therefore, it is important to state that the following conclusions in this paragraph are only preliminary due to the limited amount of data that currently exists.

3.2.1 Bioavailability of pure iodine species

In Table 4 an overview is given of reported data on the bioavailability of pure iodine species within the human body. With regards to pure iodide the reported bioavailability ranged from 46-96% and seemed to differ among the two studies. This could be attributed to several factors, like the administered dose, the number of participants, gender and country which all differed from one another in the two studies. Furthermore, within the same participant, the reported bioavailability of the organic iodine component MIT (80%) seemed to be lower than that of the inorganic component iodide (96%).

Table 4 *Overview bioavailability of pure iodine species within the human body.*

Iodine species	Administered dose iodine (µg/day)	TBAv fraction %	Sample size (n)	Male / female (%)	Age range (years)	Duration (days)	Country	Health	Lit.
Iodide	712	46-74	22	0/100	18-48	1	UK	NFT	[1]
Iodide	2500	96	1	100/0	NA	1	France	NFT	[2]
MIT	1685	80	1	100/0	NA	1	France	NFT	[2]

TBAv – Total bioavailability; NFT – Normal functioning thyroid. [1] – Combet et al., 2014 [2] – Aquaron et al., 2002.

3.2.2 Bioavailability of iodine from seaweed

In Table 5 an overview is given of the reported bioavailable total iodine fraction from seaweed through human intervention studies. Overall, the reported relative iodine bioavailability ranged from 28-101%. The highest relative iodine bioavailability was reported for the red species *Gracilaria verrucosam* (85-101%), while the lowest relative iodine bioavailability was reported for the brown species *Ascophyllum nodosum* (28-46%), see Table 5 (Aquaron, 2002; Combet et al., 2014). The calculated bioavailable iodine concentration ranged from 24 mg/kg for *Chondus crispus* to 7070 mg/kg for *Gracilaria verrucosa*, see Table 5 and Equation 4 (Andersen et al., 2019; Aquaron, 2002). Moreover, the difference in bioavailability seemed to be unrelated to the different seaweed types and seaweed species, see Table 5.

Table 5 *Overview bioavailability of iodine from commercially available seaweed species within the human body.*

Commercial name	Type	Genus	Species	TI conc. mg/kg	Administered dose iodine (mg/day)	Inorganic fraction %	Organic fraction %	TBAv fraction %	TBav conc. mg/kg	Sample size (n)	Male / female (%)	Age range (years)	Duration (days)	Country	Health	Lit.
Winged kelp	Brown	*Alaria*	*esculenta*	95	0.475	NA	NA	60	57	25	0/100	NA*	42	USA	NTF	[1]
Rockweed	Brown	*Ascophyllum*	*nodosum*	712	0.356	NA	NA	28-46	199-328	42	0/100	18-48	1	UK	NTF	[2]
Rockweed	Brown	*Ascophyllum*	*nodosum*	102	4590	NA	NA	42	43	4	NA	18-50	14	Greenland	NA	[3]
Tangle	Brown	*Laminaria*	*hyperborean*	5000-7000	2	80	20	62-90	3075-6300	9	100/0	50-69	1	Belgium, France	NTF	[4]
Kombu	Brown	*Saccharina*	*japonica*	2333	35, 70	NA	NA	57-71	1330-1656	13	60/40	NA	1	Japan	NTF	[5]
Irish moss	Red	*Chondrus*	*crispus*	47	2120	NA	NA	50	24	4	NA	15-39	7-10	Greenland	NA	[3]
Ogonori	Red	*Gracilaria*	*verrucosa*	5000-7000	2	20	80	85-101	4250-7070	9	100/0	50-69	1	Belgium, France	NTF	[4]

TBAv – Total bioavailability; NFT – Normal functioning thyroid; NA – Not applicable; NA* - Post-menopausal age. [1] – Teas et al., 2007 [2] – Combet et al., 2014 [3] – Andersen et al., 2019 [4] – Aquaron, 2002 [5] – Miyai et al, 2008.

Furthermore Aquaron (2002) also specified the inorganic and organic fraction of the seaweed species used in the human intervention trial. Before the human intervention trial, they also conducted a human intervention study on pure iodine species, which are depicted in Table 4. These results suggested that inorganic iodine (96%) was more bioavailable than organic iodine (80%). Contrary to these results, the iodine from *Gracilaria verrucosa*, which primarily contained organic iodine (80%), was more bioavailable than the iodine from *Laminaria hyperborean*, which contained 80% inorganic iodine. Based on these results, it is possible that the bioavailability is not only dependent on the composition of the iodine species, but potentially also on the composition of the seaweed matrix. However, since these statements are only based on one reference, the conclusions are preliminary, and more studies are needed to confirm this. Moreover, it is difficult to compare the studies, as each study was different with respect to the administered dose, sample size, gender, age range, duration of the trial and country. However, it is interesting to note that the reported bioavailability seemed to be higher when conducting the trial on an all-male subject group, see Table 5. The all-male intervention studies reported bioavailable fractions that ranged from 62-101%, while for all-female intervention studies this ranged from 28-60% (Teas et al., 2007; Combet et al., 2014; Aquaron, 2002).

3.3 Estimation safely consumable seaweed portion

For the purpose of this report, a preliminary estimation on the safely consumable seaweed portion was made based on the gathered data. The estimation was based on the tolerable upper iodine intake level of 600 µg/day, as advised by the EFSA and on the assumption that seaweed would be the only dietary intake of iodine (EFSA, 2018). The equation used for the calculation is described in the methodology chapter (Equation 5). As stated in the equation, the safely consumable amount is dependent on the tolerable upper iodine intake level and the bioavailable concentration of iodine from seaweed. An overview of the estimated safely consumable amount is given in Table 6.

Based solely on the in vitro studies, the estimated safely consumable amount would range from 4 g/day of *Sargassum fusiforme* till 4286 g/day of *Undaria pinnatifida* (Sun et al., 2021; Dominguez-Gonzalez et al., 2017), whereas the estimated safely consumable amount based on human intervention studies would range from 0.1 g/day of *Gracilaria verrucosa* till 26 g/day of *Chondrus crispus* (Aquaron, 2002; Andersen et al., 2019). The large range with respect to the safely consumable amount is primarily related to the large variation in the total iodine content within the respective seaweed species. Furthermore, the estimated amounts based on the in vitro studies and the human intervention studies seem to differ from one another. It has been reported before that in vitro studies are not always representative for the human body, which could explain the differences between the reported results of the in vitro studies and the human intervention studies (Gonzalez et al., 2011). Therefore, only the reported results from the human intervention study will be used for the concluding statements.

As stated in the previous paragraph, the results imply a difference in the iodine bioavailability between males and females. Based on these preliminary estimations, the safely consumable portion for females would range from 2 g/day of *Ascophyllum nodosum* to 11 g/day of *Alaria esculenta* (Combet et al., 2014; Teas et al., 2017), while for males this would range from 0.1 g/day of *Gracilaria verrucosa* to 0.2 g/day of *Laminaria hyperborean* (Aquaron, 2002). However, these estimations are not solely dependent on the variation in bioavailability, but are mainly related to the large variation with respect to the initial iodine concentration of the different seaweed species. Furthermore, the differences could also be caused by variations with regards to the age of the test population, duration of the trial and the country in which the trial was conducted, as these parameters all differed from one another in the different studies.

In the introduction it was stated that the average daily consumption of seaweed was estimated at 3.3 g/day (Banach et al., 2020). Therefore, the preliminary estimations could mean that the average daily consumption of 3.3 g/day could lead to excessive iodine intake for some seaweed species, including *Ascophyllum nodosum, Laminaria hyperborean, Saccharina japonica, Gracilaria verrucosa* (Combet et al., 2014; Aquaron, 2002; Miyai et al., 2008). However, these findings are only based on a limited number of studies, therefore, it is of great importance to conduct additional human intervention trials to obtain more knowledge on this topic.

Table 6 *Estimation safely consumable seaweed fraction based on in vitro and in vivo bioavailability of iodine from seaweed.*

Commercial name	Type	Genus	Species	TI content mg/kg	TBAv fraction in vitro %	TBAv fraction in vivo %	TBAv content mg/kg	Safely consumable fraction (g/day)	Pre-treatment	Lit.
Winged kelp	Brown	*Alaria*	*esculenta*	95	NA	60	57	11	Sun-dried, ground	[1]
Rockweed	Brown	*Ascophyllum*	*nodosum*	712	NA	28-46	199-328	2-3	Dried, milled	[2]
				102	NA	42	43	14	Grated, thawed	[3]
Tangle	Brown	*Laminaria*	*hyperborean*	5000-7000	NA	62-90	3075-6300	0.1-0.2	Dried, ground	[4]
Hijiki	Brown	*Sargassum*	*fusiforme*	622	16-19	NA	100-118	5-6	Dried	[5]
				364	19-24	NA	69-87	7-9	Dried, soaked	[5]
				280	26-32	NA	73-90	7-8	Dried, boiled	[5]
				574	24-27	NA	138-155	4	Dried, steamed	[5]
				57-125	1-3	NA	1-4	160-1053	Boiled in Milli-Q-water	[6]
Kombu	Brown	*Saccharina*	*japonica*	172-376	2-6	NA	3-23	27-174	Boiled in Milli-Q-water	[6]
				2333	NA	57-71	1330-1656	0.4-0.5	Dried	[7]
Wakame	Brown	*Undaria*	*pinnatifida*	7-26	2-6	NA	0.1-1.6	385-4286	Boiled in Milli-Q-water	[6]
Irish moss	Red	*Chondrus*	*crispus*	47	NA	50	24	26	Grated, thawed	[3]
Ogonori	Red	*Gracilaria*	*verrucosa*	5000-7000	NA	85-101	4250-7070	0.1	Dried, ground	[4]

TI – Total iodine content; TBAv – Total bioavailability; NA – Not applicable. [1] Teas et al., 2007 [2] Combet et al., 2014 [3] Anderson et al., 2019 [4] Aquaron, 2002 [5] Sun et al., 2021 [6] Dominguez-Gonzalez et al., 2017 [7] Miyai et al., 2008.

4 Conclusions and recommendations

Conclusions

This report aimed to provide insights into the human bioaccessibility and bioavailability of inorganic and organic iodine species from various commercially available seaweed species. For this purpose, both in vitro and human intervention studies were reviewed on this topic. Data on the in vitro bioaccessibility of iodine from seaweed was unfortunately limited to only brown seaweed species. The relative in vitro bioaccessibility seemed to be rather comparable and ranged from 45 - 81%, which translates into a bioaccessible iodine concentration that ranges from 3 mg/kg for *Undaria pinnatifida* to 305 mg/kg for *Saccharina japonica*. The in vitro dialyzability seemed to vary among the different seaweed types and species and ranged from 2-28%, which translates into a dialyzable iodine concentration of 0.35 mg/kg for *Undaria pinnatifida* to 1226 mg/kg for a mixture of *Laminaria ochroleuca* and *Laminaria saccharina*. Based on the reported data, *Saccharina japonica* contained the highest bioaccessible (57-81%) and dialyzable (20-28%) iodine fraction. The lowest dialyzable fraction was reported for the seaweed species *Undaria pinnatifida* and *Ulva rigida* (2%).

Similarly to the bioaccessibility, the data on the in vitro bioavailability were limited to brown seaweed species. The reported in vitro cell transport ranged from 3 - 10%, which was converted into a bioavailable iodine concentration of 0.1 mg/kg for *Undaria pinnatifida* to 21.3 mg/kg for *Saccharina japonica*. Due to the differences with regards to the in vitro dialyzability and bioavailability of pure iodine species and iodine from seaweed, it is hypothesized that the differences could be attributed to the interaction of the different iodine species with other components within the seaweed matrix, which could alter the dialyzability and bioavailability of the individual iodine species. Furthermore, it is important to note that the in vitro bioavailability estimation was based on seaweed species that underwent the pre-treatment boiling. It is likely that these levels are not representative for seaweed species that underwent different pre-treatments. This is reinforced by a study that revealed that the pre-treatments boiling, soaking, and steaming all reduced the total iodine content, (slightly) altered the bioaccessible iodine fraction, inorganic/organic iodine composition of this fraction and altered the bioavailable fraction of *Sargassum fusiforme*. The highest total iodine reduction was reported for the pre-treatment boiling (55%). The lowest bioavailable iodine concentration was reported for the pre-treatment soaking.

The reported iodine bioavailability through human intervention studies ranged from 28-101%. The highest bioavailable iodine concentration was reported for *Gracilaria verrucosa* (4250-7070 mg/kg), while the lowest bioavailable iodine concentration was reported for *Chondrus crispus* (24 mg/kg). Nevertheless, this was primarily related to the extremely high administered dose. The comparison of the different studies provided a great challenge as each study was different with respect to the administered dose, sample size, gender, age range, duration of the trial and country. Nevertheless, the difference in bioavailability seemed to be random with regards to the different seaweed types and species. Furthermore, a preliminary estimation on the safely consumable seaweed portion was made based on the gathered data. Based solely on the in vitro studies, the safely consumable amount would range from 4 g/day of *Sargassum fusiforme* till 4286 g/day of *Undaria pinnatifida*, whereas the estimated safely consumable amount based on human intervention studies would range from 0.1 g/day of *Gracilaria verrucosa* till 26 g/day of *Chondrus crispus*. The large range with respect to the safely consumable amount is primarily related to the large variation in the total iodine content within the respective seaweed species. It has been reported before that in vitro studies are not always representative for humans, which could also explain part of the differences.

Based on the preliminary estimations, the safely consumable fraction for females would range from 2 g/day of *Ascophyllum nodosum* to 11 g/day of *Alaria esculenta*, while for males this would range from 0.1 g/day of *Gracilaria verrucosa* to 0.2 g/day of *Laminaria hyperborean*. It is hypothesized that these differences could be related to the higher prevalence of females to thyroid dysfunctionalities. The preliminary estimations could mean that the average daily consumption of 3.3 g/day could lead to excessive iodine intake for some seaweed species. However, since these findings are only based on a limited number of studies, it is very important to conduct additional human intervention trials to confirm or dismiss the above stated findings.

Recommendations

The hypothesis that the human iodine bioavailability would be related to gender could be of great interest and is therefore important to study more in depth. Therefore, it is advised to conduct additional human intervention trials, which include regularly consumed seaweed species. Furthermore, it is advised to conduct these human intervention trials on both males and females to assess whether structural differences are observed. It is also advised to determine the inorganic and organic iodine composition beforehand, to assess if the iodine composition contributes to the iodine bioavailability.

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