

Review

Implications and Practical Applications of the Chemical Speciation of Iodine in the Biological Context

Astrid N. Espino-Vázquez , Flor C. Rojas-Castro and Liria Mitzuko Fajardo-Yamamoto * 

Research Department, Sanoviv Medical Institute, Tijuana-Ensenada FWY, 39th KM, Unnumbered, Int. 6 Rancho Santini, Rosarito 22710, Mexico

* Correspondence: mitzuko.fajardo@sanoviv.com; Tel.: +52-(661)-6144-9200

Abstract: Iodine is a highly reactive element with a single natural and stable isotopic form (^{127}I). In the biosphere, it is one of the 30 essential elements for life, and its chemical speciation defines its availability and biological activities. The most relevant chemical species are iodate (IO_3^-) and iodide (I^-) as the major sources of iodine, with molecular iodine (I_2) and hypoiodous acid (HIO) as the most reactive species, and thyroid hormones (THs) as the representative organic compounds. In human biology, THs are master regulators of metabolism, while inorganic species serve for the iodination of organic molecules and contribute to the innate immune system and the antioxidant cellular defense. Additionally, I^- , I_2 , δ -lactone (6-IL), and α -iodohexadecanal (α -IHDA) have shown therapeutic potential in counteracting oxidative stress, cancer, and inflammation. Both inorganic and organic species have applications in the health science industry, from the manufacturing of disinfection and wound care products to supplements, medicines, and contrast media for radiography. Even after nuclear disasters, intake of high doses of iodine prevents the accumulation of radioactive iodine in the body. Conversely, the controlled production of iodine radioisotopes such as ^{123}I , ^{124}I , ^{125}I , and ^{131}I is exploited in nuclear medicine for radiotherapy and diagnostics.

Keywords: iodine species; iodide; molecular iodine; thyroid hormones; antimicrobial activity; antioxidant effect; anticarcinogenic; immune response; iodine status; iodine deficiency disorders



Citation: Espino-Vázquez, A.N.; Rojas-Castro, F.C.; Fajardo-Yamamoto, L.M. Implications and Practical Applications of the Chemical Speciation of Iodine in the Biological Context. *Future Pharmacol.* **2022**, *2*, 377–414. <https://doi.org/10.3390/futurepharmacol2040026>

Academic Editor: Fabrizio Schifano

Received: 19 July 2022

Accepted: 29 August 2022

Published: 3 October 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Life originated in the oceans, where iodine is available in high amounts, and it is believed that, since then, it has had an ancient role in the biology of emergent organisms [1]. This element is essential in the metabolism of countless living beings from the three major domains of life [1]. Yet, depending on the chemical species and their amount, iodine acts as a nutrient showing protective roles or as a cellular stressor. For instance, catalytic inorganic iodine species inhibit microorganisms, attacking structural components such as nucleic acids, proteins, and lipids in a dose-dependent manner [2]. Contrary, in appropriate amounts, eukaryotic cells have taken advantage of the reactivity of some inorganic species to synthesize new compounds, counteract cellular oxidative stress, and modulate cell signaling pathways [3].

Despite the vast information around iodine, we consider that most recent studies have not entirely regarded critical aspects of its chemistry and stability when discussing the novel roles of this element in biological systems. This review compiles the multidisciplinary evidence of iodine, considering the characteristics of its biologically active forms to better understand the functions, modes of action, and applications. For that, we first describe the basic features of the element, such as the history, physicochemical properties, and geological distribution. Then, we list the most relevant inorganic and organic iodine species and state the fundamentals of the chemical speciation, especially under biological conditions. With those bases, we further expose and discuss the known roles and activities of the main iodine species, considering evolutive aspects. Lastly, we connect the presented information

with practical applications in the industry and health sciences, taking into account the radioisotopes of iodine.

2. History and Chemical Characteristics

In 1811, the French chemist Bernard Courtois discovered iodine when he tried to obtain saltpeter from seaweed and accidentally added too much sulfuric acid to the mixture, producing a purple vapor. Two years later, iodine was recognized as a new element receiving its name from the Ancient Greek term “οειδής” or “ioeides” which means violet [4].

The periodic table represents iodine by the I letter, which has an atomic number of 53, an atomic mass of 126.9045 Da, and belongs to group 17 of halogens [5]. There are 37 known isotopes of the element with masses from 108 to 144 (^{108}I – ^{144}I). Most are artificially produced and lose energy via radiation (radiation decay) in days, hours, or less; except for ^{127}I , the natural and only 100% stable isotope, and ^{129}I , with a half-life of 15.7 million years, which is naturally produced in traces by spontaneous fission and cosmic-ray reactions (see applications of radioisotopes in Section 7.4) [6,7].

Iodine lacks an electron to fulfill the valence shell; hence, it cannot exist in nature as a free element (neutral atom) because of its high reactivity and electronegativity (2.66 on the Pauling scale). Instead, the diatomic form of I_2 , formed by a nonpolar covalent bond between two iodine atoms, is recognized as the stable state of the element [5,8]. Likewise, iodine can combine with most elements (except noble gases and most synthetic elements), yielding broad inorganic and organic chemical forms (iodine species) with oxidation states of -1 , 0 , $+1$, $+3$, $+5$, and $+7$, distributed along the lithosphere, hydrosphere, and atmosphere.

3. Distribution of Iodine

In the Earth's crust, the richest inorganic source of iodine is oceanic sediments (68.2%) and continental sedimentary rocks (27.7%), followed by igneous and metamorphic rocks (2.7%), seawater (0.81%), and mafic oceanic crust (0.68%) [9]. In the atmosphere, sea spray aerosolization, volcanic gases, and human activities contribute to iodine emissions, but the highest discharge is given by biological conversion to volatile methyl forms, such as methyl iodide (CH_3I).

Cycling of iodine involves biotic and abiotic processes through the lithosphere, hydrosphere, and atmosphere. Into seawater, iodine species are cycled during subduction of the oceanic crust (descending of a tectonic plate below another) and via decomposition of marine organisms; whereas the flux from the atmosphere to the lithosphere occurs during rainfall, wet deposition, leaching, and runoff [9–11]. Furthermore, an important amount of iodine is accumulated and used by many living organisms, including algae, plants, corals, sponges, anemones, lobworms, shellfishes, arthropods, and bacteria, that cycle organic and inorganic iodine species in the biosphere (Figure 1) [11].

Quantities and cycling of natural iodine are determined by ^{127}I , and ratios between radioisotopes and ^{127}I serve to measure the anthropogenic impact [9]. After nuclear fission accidents, from all discharged contaminants, ^{131}I is one of the most released radioisotopes to the environment during the first days, along with significant amounts of ^{132}I and ^{133}I . In the long term, ^{129}I serves as a marker of nuclear contamination because of its long radiation decay, and it has the longest half-life of all fission products [7,12]. Quantification of ^{129}I also serves for the age dating of groundwater and meteorites [13,14].

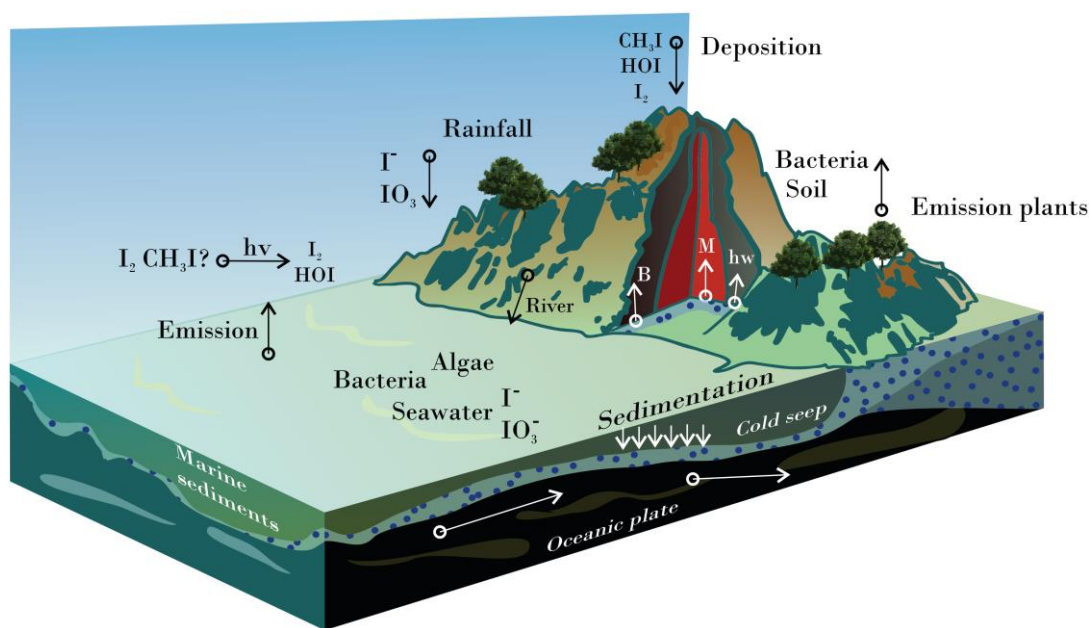


Figure 1. Iodine cycling in the environment. Adapted from [10], Royal Society of Chemistry, 2011. Abbreviations: B, brine; M, magma; *hw*, hydrothermal water; *hν*, energy of a photon (where *h* is Planck's constant = $6.62607015 \times 10^{-34}$ J·s, and *v* is the frequency of light = $c \cdot \lambda^{-1}$).

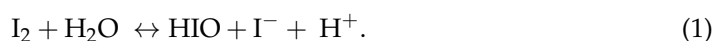
4. Relevant Iodine Species

4.1. Main Inorganic Forms

Dominant iodine species in the solid state are potassium iodate (KIO_3) and potassium iodide (KI), whereas IO_3^- and I^- ions lead to aqueous systems [15]. I_2 and CH_3I are the most abundant species in the atmosphere, produced by biotic and abiotic processes [16]. Atmospheric photochemistry promotes the speciation of gaseous iodine species (e.g., HI , IO^- , HIO , IONO_2 , INO_2 , and IO_2) [17,18]. Some of them (mainly I_2 and HIO), together with other halogen compounds, are responsible for ozone (O_3) depletion in the lower troposphere when interacting with hydrogen–oxygen species and nitrogen oxides [19].

Iodide salts are produced by electrostatic attraction between iodine and metals, held together by ionic bonds. Except for lead, silver, and mercuric iodides (PbI_2 , AgI , and HgI_2), all iodide salts have good solubility in water, where they dissociate into charged particles (ions) [4,15]. Conversely, I_2 has a much lower solubility than salts like KI (I_2 = 0.03 g/100 g H_2O at 20 °C; KI = 148 g/100 g H_2O at 25 °C), but it is easily dissolved in ethanol (I_2 = 271.7 g/kg EtOH at 25 °C) and many organic solvents such as benzene (I_2 = 164.0 g/kg Bz at 25 °C), hexane (I_2 = 13.2 g/kg Hx at 25 °C), or chloroform (I_2 = 49.7 g/kg CHCl_3 at 25 °C) [20]. The water solubility of I_2 increases when iodides are added; for example, at 20 °C in 10 g/100 mL of sodium iodide (NaI), its solubility increases 32.7-fold (from 0.03 g/100 g H_2O to 0.96 g/100 g H_2O) [8,21].

Up to 10 different iodine species can be formed when I_2 and I^- combine in water systems (Reactions (1)–(9)), where the chemical speciation is highly influenced by iodide amount ($c(\text{I}^-)$), pH, and redox potential (E_h) (Figure 2) [22–24]. An excellent example is Lugol's solution (typically made of 5% I_2 and 10% KI) used as a disinfectant and for other commercial purposes (see Sections 6, 7.1 and 7.2). Under those conditions, I_2 , I^- , triiodide (I_3^-), penta iodide (I_5^-), and hexaiodide (I_6^{2-}) coexist. I_2 is the most reactive of those, showing several biological activities (see Sections 5.1 and 5.4–5.6). I_3^- is responsible for staining, and $\text{I}_5^-/\text{I}_6^{2-}$ barely represents ~8% of the oxidizing potential [24]. However, only I^- , I_2 , and I_3^- are formed and available in significant amounts under physiological conditions [24,25].



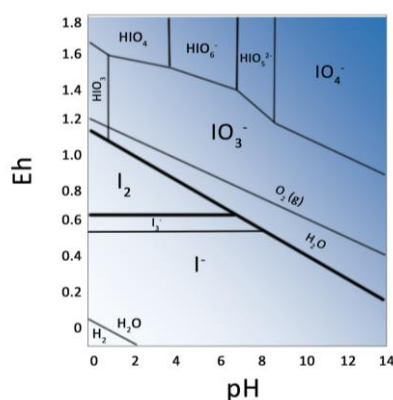


Figure 2. Iodine speciation in aqueous systems. Pourbaix diagram of iodine depicting species stability by pH and Eh [26]. Abbreviations: pH, potential of hydrogen; Eh, redox potential (measured in volts).

Iodine in iodides I_3^- and I_5^- have oxidation states of -1, in contrast to an oxidation state of 0 in I_2 . Higher values exist when iodine combines with oxygen, such as in HIO, iodite (IO_2^-), iodate (IO_3^-), and periodate (IO_4^- or IO_6^{5-}) having oxidation states of +1, +3, +5, and +7, respectively [10]. The oxidation state refers to the electronic configuration of an atom in a chemical species and represents the number of electrons gained (-) or lost (+) [10].

Hypoiodous acid and its derivatives (OI^- , HI_2O^- , I_2O^{2-} , and H_2OI^+) are very reactive species [27,28]; however, despite their potential biological activity, their amount and stability are limited in the physiological pH range (5–8) [24]. For instance, HIO dominates only in basic pH ranges (8–9) under high I^- dilution (Reactions (1), (2), (4), and (9)), and iodine cation (H_2OI^+) is only produced at $\text{pH} < 1$ (Reactions (4) and (8)) [24,29,30].

Iodate is the most thermodynamically stable of all iodine species and has no oxidative action in the basic and neutral pH range; it only achieves some reactivity at very low pH, such as HIO_3 ($\text{pK}_a = 0.77$) [24]. The main sources are calcium iodate ($\text{Ca}(\text{IO}_3)_2$), potassium iodate (KIO_3), and potassium biiodate ($\text{KH}(\text{IO}_3)_2$), some of them with better water solubility than iodides (e.g., $\text{HIO}_3 = 308 \text{ g}/100 \text{ g H}_2\text{O}$ at 25°C vs. $\text{KI} = 148 \text{ g}/100 \text{ g H}_2\text{O}$ at 25°C) [31]. IO_3^- represents a major source of iodine for living beings and is well absorbed in several organisms. Hence, it needs to be transformed into a different species to exhibit an active biological role, as described in sections below [24].

4.2. Representative Organic Species

Hundreds of iodinated organic compounds are found in nature; nevertheless, for most living organisms, the main iodine sources come from two simple inorganic species, I^- and IO_3^- [10]. Intracellularly, marine organisms reduce IO_3^- into I^- or I_2 and store it or use it to produce organic compounds [32]. Some of the iodinated organic molecules found in algae and seaweed are carbonyl diiodide (COI_2), 3-iodopropan-1-ol ($\text{C}_3\text{H}_7\text{IO}$), 1-bromo-3-iodopropan-2-ol ($\text{C}_3\text{H}_6\text{BrIO}$), 1-bromo-1,1-dichloro-2-iodoethane ($\text{C}_2\text{H}_2\text{BrCl}_2\text{I}$), 2-bromo-2-

iodoacetic acid ($C_2H_2BrIO_2$), and 2-iodoacetamide (C_2H_4INO) [32,33]. Furthermore, algae, phytoplankton, rice paddies, fungi, and bacteria produce and emit large amounts of volatile metabolites containing carbon–iodine bonds such as CH_3I (the most abundant iodine species in the atmosphere), diiodomethane (CH_2I_2), chloro(iodo)methane (CH_2ClI), 1-iodocyclopenta-1,3-diene (C_5H_5I), iodoethane (C_2H_5I), or 1-iodopropane (C_3H_7I) [9–11,32].

Land plants can absorb and accumulate iodine in different tissues and organs (mainly roots, leaves, fruits, and seeds) [34,35]. Although, their content is significantly lower (0.18–0.24 mg/kg) than in algae and sea plants (~75–6750 mg/kg) [32]. Some examples of organic species of iodine in crops are salicylic acid (iodosalicylates) and benzoic acid derivatives (iodobenzoates), and proteins (iodoproteins) [36,37].

Tyrosine residues (Tyr) containing iodine atoms covalent-bonded (iodotyrosines) are the protagonists of organic iodine species because of their hormonal role in vertebrate animals (see Section 5.3). A human adult has, on average, 0.02 mg/kg of iodine in the body, and most of it is retained by the thyroid gland (70–80%) to produce THs (organification). The remainder is distributed in other organs (salivary glands, lactating breast tissue, kidney, intestine, placenta, ovary, fallopian tubes, testicles, etc.) with different purposes [38,39]. THs comprise (i) 3-iodotyrosine or monoiodotyrosine (MIT or T1) and 3,5-diiodotyrosine (DIT or T2) as precursors, (ii) 3',5,3-triiodothyronine (T3) and thyroxine (T4), typically considered as the active hormones, and (iii) 3',5',3-triiodothyronine or reverse T3 (rT3), 3',5'-diiodotyrosine (3',5'-DIT or 3',5'-T2), and 3'-monoiodotyrosine (3'-MIT or 3'-T1), the T4 derivatives [40]. Other TH derivatives such as thyronamines (TAMs) and thyroacetic acids (e.g., 3,3',5-triiodothyroacetic acid (Triac) and 3,3',5,5'-tetraiodothyroacetic acid (Tetrac)) can be produced by decarboxylation, deamination (removal of the carboxyl group and amine group, respectively), and/or deiodination [41].

Thyroid peroxidase (TPO) is the enzyme responsible for synthesizing THs using thyroglobulin (TG) as a substrate. In fact, TG is the main iodinated compound in the thyroid gland [42–44]. TPO is also responsible for the iodination of lipids (iodolipids) as α -IHDA and 6-IL. Noticeably, 6-IL was recently related to antioxidant, anti-inflammatory, and anticarcinogenic activities (see Sections 5.4–5.6) [45,46]. Other peroxidase enzymes such as lactoperoxidase (LPO) are responsible for the synthesis of iodolactones (e.g., δ -lactone of 6-iodo-4-hydroxy-eicosa-8,11,14-trienoic acid, and ϵ -lactone of 5-iodo-4-hydroxy-7-docosapentaenoic acid) using docosahexaenoic acid (DHA) as a substrate [32]. TPO and LPO belong to the peroxidase/cyclooxygenase superfamily, a class of oxidoreductase enzymes broadly distributed in the tree of life. Plants, fungi, bacteria, and animals use them to maintain oxidative status and synthesize new compounds or even as part of the innate host defense [47].

Some organisms unable to produce their own iodinated organic compounds depend on symbiotic relationships to supply them. Sea urchins, for example, need THs to metamorphose from larva to adult rudiment but obtain them from algae feeding [48]. Symbiosis also impacts the iodinated compounds profile of microorganisms. The enteric bacterium *Escherichia coli* cannot use I^- , I_2 , MIT, or DIT, but takes T4 and T3 to iodinate proteins [49,50]. Even viruses influence the production of iodinated organic compounds of their hosts. Recently, it was observed that a cyanophage (cyanobacteria virus) encodes for a halogenase (an enzyme that replaces hydrogen atoms with halogen atoms in a molecule) with the potential of iodinating organic molecules of its host [51]. Moreover, the presence of viruses in *Emiliania huxleyi* algae changes its metabolic profile. After viral infections, algal blooms (excessive growth of marine photosynthetic organisms) discharge a large amount of organic matter containing chloro and iodinated metabolites [52]. More examples of iodinated organic compounds can be consulted in [32].

5. Biological Roles of Iodine

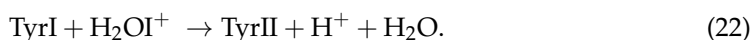
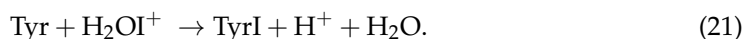
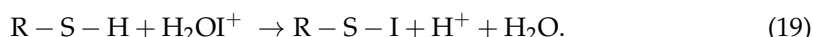
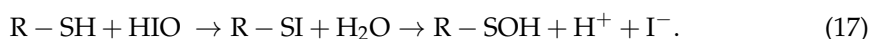
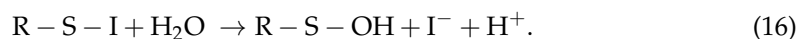
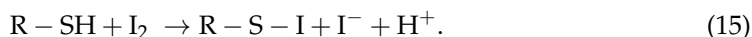
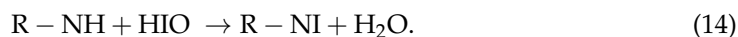
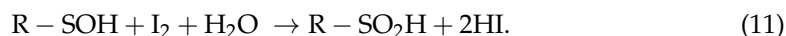
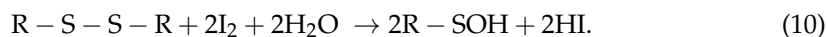
5.1. Antimicrobial Action

Iodine shows a broad antibacterial spectrum against several microorganisms, including resistant forms (e.g., spores, cysts, and biofilms) [53–55]. Of all inorganic iodine species

with antimicrobial activity, I_2 is the most abundant and the leading antimicrobial agent in iodine-based disinfectants [24]. Other iodine species recognized as antimicrobials are HIO and H_2OI^+ ; however, as mentioned, they are restricted to extreme pH ranges and by the amount of I^- [27,28]. Within solvents like alcohol, the solvated forms $I_2 \cdot H_2O$ or $I_2 \cdot ROH$ are proposed as the antimicrobial species [2].

Contrary to antibiotics or antifungals, microorganisms do not develop antimicrobial resistance to iodine, probably because of its several simultaneous mechanisms of action. In bacteria, iodine inhibits glycolysis, respiration, glucose transport, and DNA and RNA synthesis, and it compromises the integrity of the plasma membrane and cell wall. Antimicrobial iodine species are also responsible for protein (and potentially DNA) denaturalization in bacteria and viruses and damage viral envelopes [27,56,57].

The molecular modes of action described for I_2 and HIO are oxidation of nucleotides (adenine, cytosine, and guanine) and aromatic rings of amino acids (mainly Tyr) [57], interfering with the synthesis and folding of proteins via iodination of amino ($-NH$) (Reaction (13) and (14)) and sulfhydryl ($-SH$) groups (Reactions (15)–(17)) [28,30,57], or disrupting disulfide bonds ($R-S-S-R$) between cysteines (Reactions (10)–(12)) [58]. They also have a great affinity to unsaturated fatty acids, attacking the carbon–carbon double bonds (Reaction (18)) [30,59]. Cation H_2OI^+ is also responsible for attacking the $-SH$ groups of some amino acids (Reactions (19) and (20)) and iodination of tyrosine and histidine residues (Reactions (21)–(23)) [56,57]. The following reactions have been proposed for antimicrobial iodine species (most of them as chemical skeletal equations):



Eukaryotes take advantage of the reactivity of some iodine species to counteract infections, among other biological activities (see Sections 5.4–5.6). In mammals, antimicrobial iodine species can be produced as byproducts of peroxidases. Depending on the pH and I^- amounts, LPO can produce HIO and I_2 by reducing hydrogen peroxide (H_2O_2) to H_2O , using I^- as the electron donor (Reaction (24)) [60,61]. LPO is secreted in mucosal surfaces or exocrine secretions such as saliva, milk, or tears and is essential for the innate immune defense system [28,47]. The sole action of LPO is bacteriostatic; however, in conjunction with I^- , it becomes bactericidal and antiviral [62–64].

5.2. Nutrition and Human Health

Together with vitamin A, iron, zinc, folate, and vitamin B-12, iodine is considered an essential micronutrient for humans and an important marker of nutritional public health status [65]. An optimal iodine status (sufficiency) can be maintained with an appropriate diet and supplements (see Section 7.2); however, inadequate iodine ingestion drives severe health consequences in the long term, known as iodine deficiency disorders (IDD). The most common are hypothyroidism, endemic goiter (enlargement of the thyroid), and thyroid nodules. Pregnant women and fetuses are the most susceptible to IDD, inducing abortions, perinatal mortality, and congenital anomalies [66–68]. Other expected health consequences are cretinism and delayed physical development in infants and children. Cognitive impairment and increased susceptibility to nuclear radiation are seen at all ages under iodine deficiency [67,69].

Thyroid disorders in the population and exposure to iodine are correlated in a U-shaped curve, as depicted in Figure 3A, where the higher risk comes with the chronic suboptimal intake of iodine (iodine deficiency) [67,70]. Excess exposure to iodine is less common but can be dangerous, especially in iodine-deficient populations. Excessive intake is frequently associated with high consumption of iodized salt and diet [71,72], but other sources came from medications such as amiodarone (200–400 mg/day) [73], radiologic procedures (one dose of >350 mg) [74], and povidone/iodine (PVP/I)-based antiseptics (<30 mg/day) [75]. Excess iodine increases the risk of developing transient or permanent thyroid dysfunction (iodine-induced hyperthyroidism or hypothyroidism), thyroid autoimmune diseases, metabolic disorders, metabolic syndrome, hypertension, prediabetes, diabetes mellitus, impaired glucose tolerance, central obesity, and dyslipidemia (Figure 3B–F) [70,76–78]. Vulnerable groups such as the elderly, fetuses, neonates, and people already having an IDD are more susceptible to iodine-induced hyperthyroidism or hypothyroidism. In the best scenario, hypothyroidism only lasts 2–10 days (escape from acute Wolff–Chaikoff effect), but might be lethal in fetuses or neonates. Iodine-induced hyperthyroidism or Jod–Basedow syndrome has greater incidence in adults and can be related to cardiac complications [39,78].

People with normal thyroid functioning (euthyroid) tolerate excessive iodine well. In the Japanese population, the regular consumption of iodine-rich foods correlates with a higher life span, as well as fewer infant deaths, cardiac diseases, and breast and prostate cancer incidences, than in the US, whose iodine intake is typically much lower. On average, people consume 1–3 mg/day of iodine in Japan, where one of the primary sources is seaweed-based meals such as nori (*Porphyra*), wakame (*Undaria*), and kombu (*Laminaria*) [80]. Interestingly, these health markers are not attributable to genetics; Japanese emigrants increased their risk of mammary cancer from 21.1 to 49.4 per 100,000 population and from 8.4 to 32.2 of prostate cancer per 100,000 just by changing diet [81,82]. Currently, the incidence of both types of cancer in Japan is increasing, probably because of the occidentalization of diet. Prostate cancer had the highest frequency in 2020 (close to 96,000), and breast cancer new cases were over 50,000 in 2018, compared to 2003 [83]. Nevertheless, thyroid cancer represents the rarest cause of death from cancer for Japanese (600 deaths for men in 2018 and 1200 for women in 2019) [83].

Iodine sufficiency areas have a lower risk of developing IDD; however, they are not exempt from Graves' disease (with ~80% incidence in iodine-sufficient populations), nodular thyroid disease, and thyroiditis [84]. Respecting thyroid cancer (the most common endocrine cancer), some authors conclude that more than the recommended iodine ingestion could increase papillary and thyroid cancer [38,72], but others observed a lower incidence [85]. A more robust meta-analysis of humans and animals found iodine deficiency as a promotor risk factor for follicular, and possibly anaplastic, thyroid cancers [86].

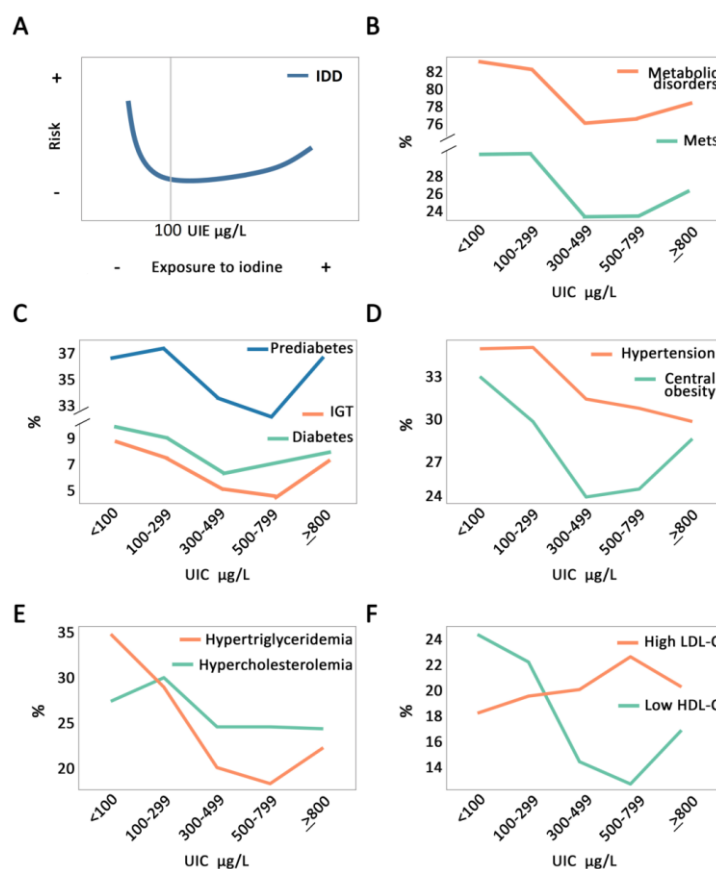


Figure 3. Association of diseases and iodine intake. (A) Exposure to iodine and the risk of developing IDD ([67] data from [79], Academic Press, 2009). Relationship between UIC (µg/L) and the prevalence (%) of (B) metabolic disorders and MetS, (C) prediabetes, diabetes, and IGT, (D) hypertension and central obesity, (E) hypertriglyceridemia and hypercholesterolemia, and (F) HDL-C and LDL-C (data from [70], Mary Ann Liebert, Inc., publishers). Abbreviations: HDL-C, high-density lipoprotein cholesterol; IGT, impaired glucose tolerance; IDD, iodine deficiency disorders; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; UIE, urinary iodine excretion; UIC, urinary iodine concentration.

5.3. Thyroid Hormones

5.3.1. TH Synthesis and Metabolism

From the anthropocentric point of view, the leading role of iodine is TH production in the thyroid gland, also known as organification. THs are iodotyrosines that can be produced by peroxidase enzymes (such as LPO and TPO) or via nonenzymatic reactions of iodine oxidative species (such as I_2) with Tyr residues (Reaction (25)) [47,87]. This section focuses on the TH synthesis carried out in vertebrate animals. The occurrence of THs in different organisms and their functions is discussed next.

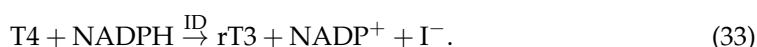
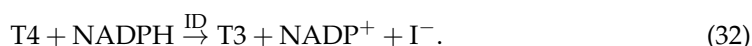
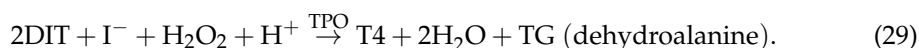
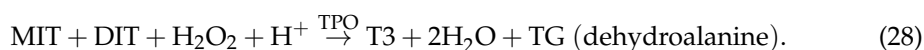
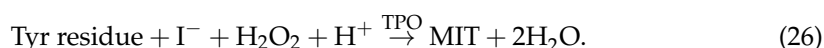
The regulation of the thyroid function is a circuit known as the thyroid axis, where, in normal conditions, TH synthesis and secretion increase in response to the thyroid-stimulating hormone (TSH) produced by the anterior pituitary gland [88]. TSH is stimulated in turn by the thyrotropin-releasing hormone (TRH), released by the hypothalamus [89]. Excess circulating T4 or T3 inhibits the hypothalamus from secreting more TRH, resulting in a decrement in TSH and, hence, in TH production [90].

As an initial step in TH synthesis, iodine must be absorbed into the body. Iodide is not diffused but is actively imported by transmembrane transporters into the bloodstream [91]. Most intake of iodine (>90%) is absorbed in the digestive tract, mainly in the small intestine by the Na^+/I^- symporter (NIS) [92]. Depending on the iodine status (sufficiency, deficiency,

or excess), the thyroid imports <10% up to 80% of the circulating iodine. Unused I^- is mainly excreted in the urine (~90%), depending on the glomerular filtration rate, with a lesser proportion in feces [39,65].

TH synthesis occurs in the thyroid follicles, composed of a colloid (follicular lumen) enclosed by follicular cells and surrounded in the interfollicular space by blood vessels and parafollicular cells [93]. In the basement membrane of follicular cells, I^- is imported by the Na^+ / I^- symporter (NIS) and moves at the apical membrane into the follicular lumen through different transporters such as the anion exchanger Pendrin, the calcium-dependent Cl^- channel Anoctamin 1 (ANO1), and possibly others such as cystic fibrosis transmembrane conductance regulator (CFTR), Cl^- / H^+ antiporter (CIC5), Cl^- / H^+ exchanger (CIC-3), and the sodium-dependent multivitamin transporter (SMVT) [94–97]. Once in the lumen, I^- needs to be oxidized into a more reactive form by the TPO. The specific iodine species formed in this step has not been determined, but the likely candidates are I_2 , iodinium (I^+), iodine free radical ($I^\bullet$), and hypoiodite (IO^-) [98].

TPO, coupled to the apical membrane of the follicles, is responsible for iodination and coupling of Tyr residues using I^- , H_2O_2 , and thyroglobulin (TG) as the substrate (a large glycoprotein of ~330 kDa) [42]. H_2O_2 is produced by a complex formed by the dual oxidase 2 (DUOX2, formerly THOX2) and dual oxidase maturation factor 2 (DUOXA2), also coupled to the apical membrane [99]. The sequence followed in TH production is incorporating one iodine atom into Tyr residues at position 3 of the ring to produce MIT (Reaction (26)) and then at position 5 to form DIT (Reaction (27)). Subsequently, T3 is constructed by an oxidative coupling reaction between one DIT and one MIT (Reaction (28)), still incorporated into the TG. At the same time, T4 is formed by coupling two adjacent DITs (Reaction (29)). At the end of the process, only 37 of the ~70 Tyr residues in the TG are known iodination targets [42,43]. To release THs, iodinated TG is transported back into follicular cells by endocytosis and hydrolyzed by proteolysis [42,90]. Most MITs and DITs produced are kept in the follicles and are eventually degraded by iodotyrosine deiodinase (IYD) enzymes into MIT and Tyr, respectively (Reactions (30) and (31)), releasing I^- which is reused and recycled [100]. However, T3 and T4 are transported into the bloodstream, mostly bound to plasma proteins. The most common are thyroxine-binding globulin (carrying up to 80% of bound T3 and ~65% of bound T4), transthyretin (transporting ~9% of T3 and ~15% of T4), and albumin (with ~11% of T3 and ~20% of T4). A lower percentage of THs circulate as free hormones (approximately 0.2% of T3 and 0.05% of T4) [40].



In the blood, T4 has the highest concentration (54–174 $\mu\text{g/dL}$) and most prolonged half-life (~7 days), but T3 (half-life < 12 h) has a higher proportion in organs, especially the kidney, liver, small and large intestine, and central nervous system [40]. Just a fraction of T3 (21.8%) is synthesized and released in the same fashion as T4; most of it is generated by the deiodination of T4 out of the thyroid by iodothyronine deiodinases (ID) [90,101]. Iodine

removal serves to activate or inactivate THs. D1 and D2 are the two kinds of ID enzymes considered as activators by converting T4 into T3 (Reaction (32)) [90,100]. D3 transforms T4 into rT3 (Reaction (33)), an inactive TH produced to maintain hormone homeostasis [102].

Deiodination is considered the most important process in the peripheral metabolism of THs, followed by conjugation, formation of analogs (via deamination and decarboxylation), and oxidation [103]. Conjugation of THs with sulfate or glucuronic acid (via microsomal glucuronyl or cytoplasmic phenol transferases) inactivates and increases the solubility of hormones, accelerating their deiodination and clearance by biliary excretion [104].

The gut microbiota also significantly contributes to TH metabolism, favoring the cycling of I^- and THs [101,102]. On the one hand, enteric bacteria are proposed as TH storage because of their ability to absorb and retain T3 and T4 [49,105]; on the other hand, the gut microbiota releases sulfatase and glucuronidase enzymes favoring the enterohepatic circulation (secretion of conjugated THs in the bile to the small intestine and back to the liver after deconjugation) [106]. Moreover, gut bacteria influence the absorption of nutrients that support the normal thyroid metabolism, such as iron, selenium, and zinc [107]. The importance of the gut microbiome in thyroid function is more evident in autoimmune thyroid diseases, where an altered microbiota composition (dysbiosis) is linked to predisposition to Hashimoto's thyroiditis and Graves' disease. Furthermore, a reduction in or lack of Lactobacillaceae and Bifidobacteriaceae families in the gut has been related to autoimmune metaplastic atrophic gastritis [107,108].

5.3.2. Actions of THs

THs are needed in all stages of life, participating in numerous biological functions in vertebrates such as regulation of the brain function, hair growth, functioning of gonads (especially in females), thermogenesis (heat produced in the body), and response to the environment and stimuli. At the molecular level, THs regulate essential cellular processes such as development, differentiation, growth, maturation, and metabolism via different mechanisms, as described below [3,40].

Excluding activation/inactivation by deiodination or conjugation, the biological activities of THs are determined by the hormonal levels inside the cells (controlled by TH transporters), thyroid hormone receptors (TRs), and other elements such as corepressors and coactivators [109]. More than 20 TH transporters have been characterized, but those with the highest affinity are the monocarboxylate transporters MCT8 (transporting T4, T3, rT3, and 3,3'-T2) and MCT10 (transporting only T3 and T4), as well as the organic anion-transporting polypeptides, such as OATP1C1 (with affinity to T4, rT3, and T4 sulfate) and OATP-F (with affinity to T4 and rT3) [110,111].

Once inside, THs activate TRs in the nucleus and mitochondria. The complex of THs/TRs binds directly to DNA regions acting as transcription factors regulating the expression of several genes [112]. In humans, two genes encode for TRs (α and β), yielding, via alternative splicing, several TR α and TR β isoforms depending on the tissues and developmental stage. For example, TR α 1 is mainly expressed in the bones, heart, intestine, skeletal muscle, and central nervous system, while TR β 1 is better expressed in the liver, kidney, and inner ear [109,113,114]. Truncated TR forms are also produced by alternative translations of start codons (AUG) or internal promoters in introns. Their cellular location is linked to post-translational modifications such as palmitoylation, phosphorylation, acetylation, ubiquitination, and sumoylation [109].

Concerning the mode of action, THs typically follow two pathways: genomic (carried out in the nucleus) and nongenomic (faster and initiated in the cytoplasm, plasma membrane, mitochondria, and possibly others) [113]. A more recent classification proposes four types of mechanisms: (1) direct interaction of THs/TRs on the DNA (as the classic genomic mechanism), (2) indirect interaction of THs/TRs on the DNA, (3) TH/TR signaling without DNA binding, and (4) TH signaling independent of TRs [115]. The classical genomic mechanism involves the activation of TRs through a complex with T3 and other proteins in the nucleus. After that, the complex binds to regulatory DNA regions known as

thyroid hormone response elements (TREs) to regulate their expression [40]. The indirect DNA binding mechanism (also considered a genomic pathway) implicates the interaction of TH and TRs with chromatin-associated proteins leading to chromatin accessibility and upregulation of gene expression [109].

Nongenomic mechanisms comprise alternative cellular compartments, novel interactors, and potentially less recognized THs. A type 2 mechanism (of the new classification) comprises the interaction of TRs with THs and kinases in the cytoplasm to activate cell signaling responses such as the phosphatidylinositol 3-OH kinase pathway (PI3K) (implicated in growth, proliferation, differentiation, etc.). Another nongenomic pathway (or type 3 mechanism in the new classification) starts with the activation of a structural protein in the plasma membrane, the integrin $\alpha v \beta 3$ receptor (with binding domains for T4 and T3), which triggers PI3K and the extracellular signal-regulated kinase 1/2 (ERK1/2) pathways, also a crucial regulator of the cell cycle, growth, and proliferation [113]. Similarly, a truncated TR $\alpha 1$ variant (p30) is found in the lipid rafts of the plasma membrane and activates the nitric oxide–cyclic guanosine monophosphate pathway (NO–cGMP) in response to T3 [109].

The mitochondrion is one of the main TH accumulators in the cell. Here, the oxidative phosphorylation system is highly influenced by different mechanisms involving truncated TR $\alpha 1$ variants (p28 in the inner membrane and p43 in the matrix). In the best-described pathway, T3 interacts with p43 on responsive elements of the mitochondrial DNA, regulating the transcription of respiratory genes (such as classic genomic mechanisms) [113,116]. The pathway that p28 follows is still unknown but shows a higher affinity to T3, and its expression affects mitochondrial physiology [117].

Previously, T3 was considered the biologically active hormone due to its higher affinity to most TRs [40]. However, the activities of T4 and other THs has been proven in different ways. For example, T4 but not T3 has the faculty to remodel the actin cytoskeleton of astrocytes and glial cells in the brain via nongenomic mechanisms [118]. Triac (antagonist to $\alpha v \beta 3$) is better than T3 for increasing thermogenesis in brown adipocytes [119], and both Triac and Tetrac are preferable treatments for TH-resistant patients [120]. T1AM, the most potent antagonist of the trace amine-associated receptor 1 (TAAR1), can decrease heart output and body temperature [120,121]. T2 may prevent body weight gain, hepatic fat accumulation, and insulin resistance [120,122]. Moreover, T1AM and T2 modulate the mitochondrial oxidative phosphorylation system [116].

5.3.3. THs out of Vertebrates

Evolutionary, when marine organisms move to environments with less availability of iodine, they have to develop strategies to compensate for iodine deficiency. It has been postulated that our marine ancestors developed iodine-storage organs (endostyle and thyroid) when they moved from oceans to fresh waters and lands [1,3]. Lampreys, the most ancient vertebrates, have all the components of the thyroid system. These organisms transform from filter-feeder larvae (ammocoete stage) to juvenile and adult jawless fishes (many of them are fish parasites) by producing high levels of T3 and T4. The TH levels drastically fall during metamorphosis until the complete conversion into fish parasites, when lampreys move from freshwater to seawater [123]. Animals such as amphioxuses (a basal group of chordates) lack the thyroid but have the endostyle, a filter-feeding organ where iodine accumulation and TH synthesis occur (Figure 4). Instead of T3 or T4, Triac is the active hormone in this model, binding with higher affinity to TRs and regulating the metamorphosis [124,125].

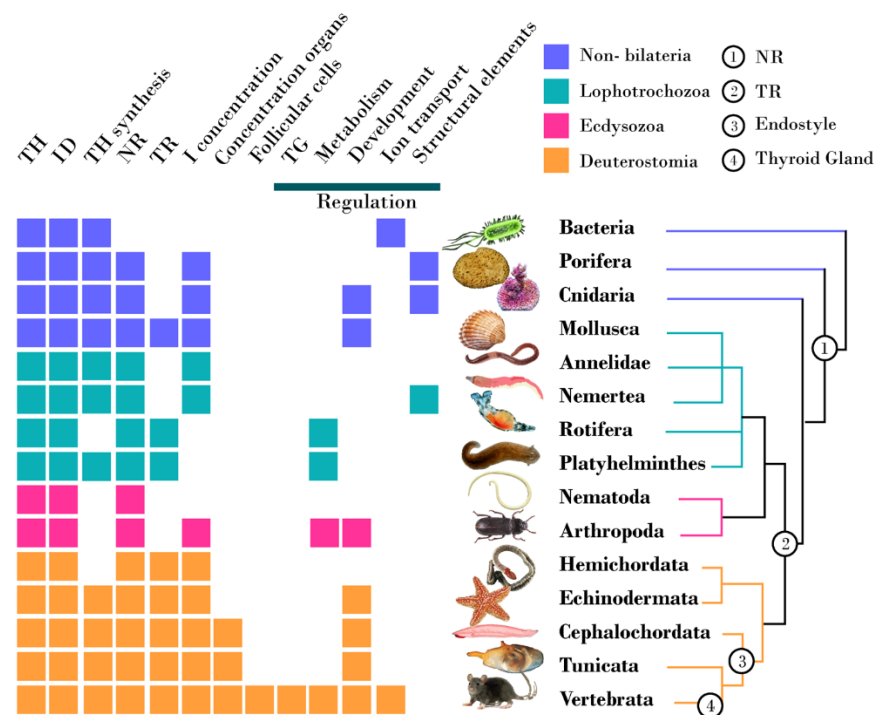


Figure 4. Components of the thyroid system in prokaryotes and eukaryotes Reprinted from Molecular and Cellular Endocrinology, 459, Taylor and Heyland, Evolution of thyroid hormone signaling in animals: Non-genomic and genomic modes of action, Pages 14-20, Copyright (2022), with permission from Elsevier. The presence of a component in a clade does not denote the occurrence in all its species. Abbreviations: I, iodine; ID, iodothyronine deiodinase; NR, nuclear receptors; TG, thyroglobulin; TH, thyroid hormones; TR, thyroid hormone receptors.

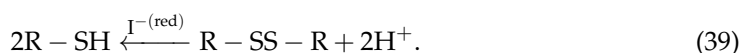
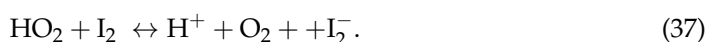
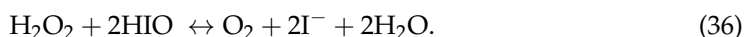
Interestingly, many organisms along the three of life produce one or more components of the thyroid system (Figure 4). Nuclear receptors (NRs) are found in all animals and can bind to several hormones (including THs); hence, they are considered ancestors of TRs [126]. TRs can be found in vertebrates and lineages of nonvertebrate deuterostomes [127]. Numerous nonbilaterians can accumulate iodine into specific cells and tissues [125]. However, only chordates have specialized iodine-concentrating organs, the endostyle in cephalochordates and the thyroid gland in vertebrates [126]. Insects, plants, protozoa, and bacteria produce THs (including analogs or derivatives) and deiodinase enzymes [125], even though the incidence of THs might have no hormonal implications outside of chordates. For instance, moon jellyfish *Aurelia aurita* synthesizes MIT, DIT, and T4 in significant amounts. Nevertheless, the transition from polyp into jellyfish (strobilation) can be induced by temperature and the addition of I^- , but is not dependent on THs [128]. Moreover, in land plants, it is suggested that THs, more than hormones, could act as protective agents by altering the metabolisms of herbivores or plagues [129].

Due to iodotyrosines being produced via enzymatic and nonenzymatic reactions, it is no coincidence that THs emerged earlier than other components of the thyroid system. Peroxidases with the potential to iodinate proteins are vastly distributed in prokaryotes and eukaryotes [47], and I_2 may react with organic matter in the environment. Regarding the hormonal role of THs, as organic compounds become more reactive when iodine is incorporated, it is believed that basal chordates developed the endostyle (afterward thyroid) to store iodine in the first place, and animals later took advantage of the reactivity of iodotyrosines produced and incorporated them into their cellular machinery as cell signaling molecules [3,130].

5.4. Antioxidant Capacity

Photosynthesis in chloroplasts and the respiratory chain in mitochondria yield multiple reactive oxygen species (ROS), including peroxides (H_2O_2 is the most common), superoxides (O_2^-), hydroxyl radicals ($\text{OH}^\bullet$), and O_3 . In appropriate amounts, ROS are involved in host defense, protection from cellular stress, cell signaling, and homeostasis [131,132]. However, some endogen and exogenous stimuli imbalance the amount of ROS, causing irreversible damage to the cells. Under oxidative stress, cellular components and essential molecules (e.g., DNA, RNA, enzymes, and fatty acids) are degraded [131,133]. Thus, cells must produce protective elements such as enzymes and antioxidant molecules (e.g., carotenes and glutathione) to prevent oxidative damage [134–136]. Electron donors such as I^- can also be considered antioxidants by serving as cofactors for peroxidase enzymes and reducing free radicals [28,137]. In addition, catalytic iodine species can react directly with free radicals by scavenging ROS.

Iodine species having antioxidant capabilities are I^- , HIO, and I_2 , with I^- being the least reactive and needed for enzymatic assistance to serve as an antioxidant (Reactions (34) and (35)). IO_3^- has no biological activity in the physiological pH range (5–8). Either way, once ingested, it is converted to I^- to be absorbed in the body [24,25]. While most studies focus on the biological activities of I^- and I_2 , HIO and its derivatives could also be relevant in studying antioxidant molecules. In water systems, I_2 is converted to HIO via hydrolysis (Reaction (1)) in a fast equilibrium reaction and, in basic pH, becomes the dominant species [24]. Both HIO and I_2 are involved in enzymatic redox reactions as byproducts (Reactions (34) and (35)) [28,90]. Additionally, as oxidizing molecules, they have the potential to reduce peroxides and free radicals by themselves (Reactions (36)–(38)) [138,139], as well as avoid the oxidation of $-\text{SH}$ groups in enzymes and proteins (Reaction (39)) [28,61].



To date, photosynthetic marine organisms are the best iodine accumulators, where the primary function of iodine is to control oxidative stress produced by ROS [140]. *Laminaria digitata* (brown algae) is a hyperaccumulator of iodine that serves for studying iodine metabolism. In this model, the protective role of iodine was demonstrated not only as an antioxidant [141] but also as an element involved in the immune response [142] and maintenance of osmotic balance [143]. *L. digitata* transports I^- in a hydrogen peroxide-dependent diffusion manner, quite different from the active transportation in thyroid follicular cells [144]. In the cell wall of brown algae, a vanadium iodoperoxidase (V-IPO) reduces H_2O_2 to produce HIO (Reaction (34)). Successively HIO can be concentrated in the cytoplasm, be transformed into I_2 , or participate in protecting lipid iodinated compounds (Figure 5) [141,143]. Many other algae are excellent iodine accumulators, from unicellular organisms such as *Cyanobacteria*, the first photosynthetic organism known, to *Macrocystis pyrifera*, a giant kelp. In these marine organisms, it is hypothesized that iodine protects against ROS produced in photosynthesis [1,140].

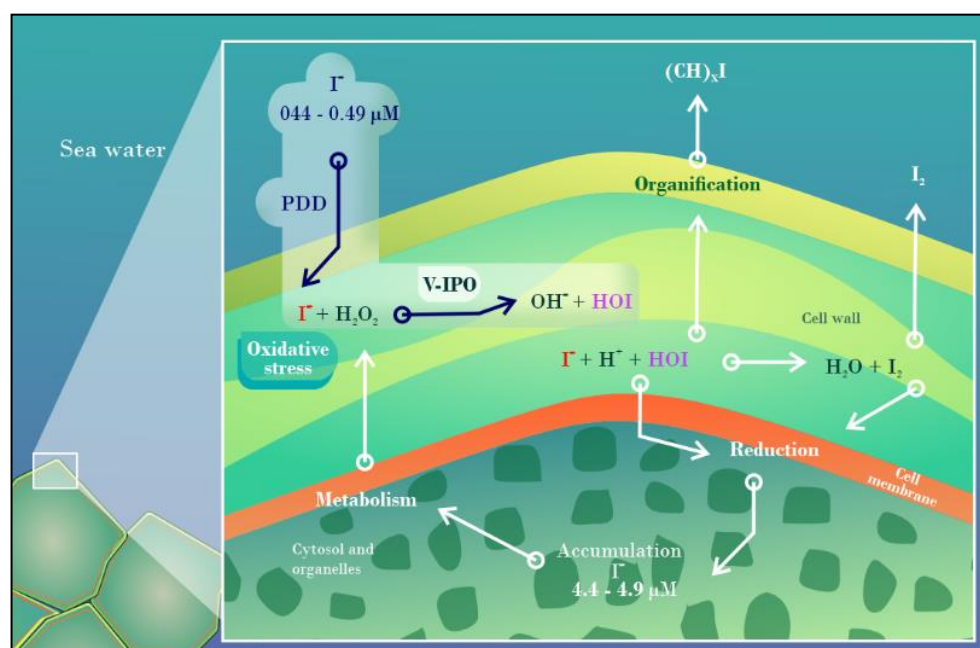


Figure 5. Iodine metabolism in brown algae. In the seawater *Laminaria digitata*, iodine uptake comprises the active transportation of I^- through H_2O_2 reduction in the cell wall by a V-IPO enzyme (adapted from [145], Frontiers Media, 2016). Intracellularly, I^- can be transformed into different inorganic species (such as HIO and I_2) and organic forms (mostly methylated forms). Abbreviations: HIO, hypiodous acid; I^- , iodide ion; I_2 , molecular iodine; PDD, hydrogen peroxide-dependent diffusion; V-IPO, vanadium iodoperoxidase.

In land plants, the antioxidant role of iodine is less evident; molecules such as ascorbic acid, polyphenols, carotenoids, and enzymes (e.g., catalase (CAT), guaiacol peroxidase (G-POX), ascorbate peroxidase (APX), and superoxide dismutase (SOD)) are best known for counteracting ROS [146,147]. Nonetheless, in lettuce, tomato, water spinach, and soybean crops, some of these antioxidant markers improve after fertilization with KIO_3 and KI [148–150].

Non-photosynthetic organisms, including bacteria, fungi, and invertebrates, express different oxidoreductase enzymes with the potential to scavenge H_2O_2 by using I^- as an electron donor [47]. For example, the marine bacterium *Pseudomonas iodooxidans* has an extracellular peroxidase system that reduces H_2O_2 by converting I^- into I_2 . Fungus *Caldariomyces fumago* has a chloroperoxidase (CPO) responsible for the oxidation of I^- and production of several organic compounds (including iodotyrosines) [32]. Furthermore, as mentioned in Section 5.3.3, moon jellyfish contain THs and other iodinated compounds as a strategy to reduce oxidative stress [128].

Mammals have four classes of peroxidases: TPO, LPO, myeloperoxidases (MPO), and eosinophil peroxidases (EPO), all with the capability of using I^- [47]. LPO, MPO, and EPO are involved in the immune response (see Sections 5.5 and 5.6), while TPO is expressed in the thyroid gland, the organ most subjected to oxidative stress. TH synthesis in vertebrates seems paradoxical because organification controls the oxidative stress caused by H_2O_2 , but TH production demands large amounts of H_2O_2 [40]. In large part, the activity of TPO reduces the H_2O_2 produced, but other antioxidant enzymes are needed to protect follicular cells from oxidative damage, such as glutathione reductase, thioredoxin reductase, peroxiredoxins, and CATs [151].

5.4.1. Markers of Oxidative Stress in Mammals

In eukaryotic cells, oxidative stress and other connected biological processes have characteristic biochemical signatures that can be used as molecular markers to evaluate the

oxidative status. In human and animal models, iodine changes oxidative stress markers depending on the chemical species and dosage.

Experimentally, the antioxidant capacity is typically valued as the total antioxidant capacity (TAC), determined by the moles of free radicals scavenged and excluding the activity of antioxidant enzymes [152]. Other common markers include ROS levels, reactive nitrogen species, lipid peroxidation byproducts (e.g., malondialdehyde (MDA)), protein peroxidation byproducts (e.g., advanced lipoxidation end products (ALEs)), reduced/oxidized glutathione (GSH/GSSG), antioxidant enzymes such as SOD and CAT, and other enzymes such as nitric oxide synthase (NOS) [132,153].

As programmed cell death is triggered when cells suffer from oxidative stress damage, apoptosis markers can be considered when studying antioxidants. Apoptosis is characterized by cellular shrinkage, DNA fragmentation, changes in morphology (like reduction in cellular size without losing membrane integrity), activation of caspases (a family of proteases in charge of degrading the cellular structures), etc. [154].

Both, I_2 and I^- species have demonstrated antioxidant effects *in vitro*. In an antioxidant assay (ferric reducing/antioxidant power assay), the TAC of I_2 was 30 to 60 times higher than in KI, Lugol's solution (containing I^- , I_2 , and I_3^-), and IO_3^- . In this assay, I_2 had 10 times more antioxidant power than ascorbic acid, used as a positive control [155]. In a cell-free system, concentrations of 25 μ M and 50 μ M I_2 (but not 10 μ M) significantly reduced the conversion of nitrate (NO_3^-) to nitrite (NO_2^-), a reactive nitrogen species [156]. In human sera, the TAC was enhanced by adding 15 μ M KI at a comparable level to 50 μ M ascorbic acid (vitamin C) [157]. Moreover, KI and sodium selenite (Na_2SeO_3) protected human placenta explants from DNA damage (using 8-hydroxy-2'-deoxyguanosine as a marker) and apoptosis (via Caspase-3 activity) under oxidative stress with menadione (vitamin K3) and antimycin A (an inhibitor of cellular respiration) [158].

Excess I^- can be an antioxidant or stressor in animals, depending on the model. In bulls, higher doses of KI in the diet (50% and 100%) improve the TAC, hormonal status (testosterone and T4), and semen quality [159]. A similar observation was registered in boar feed with organic iodine (Prost fodder additive), which increased 43.8% of the blood iodine content and showed better antioxidant, hormonal, and fertility parameters [160]. However, an excess of 100% and 500% in rats (KI 0.7/100 g body weight and 3.5/100 g body weight, respectively) increased oxidative stress markers (lipid peroxidation, SOD levels, and heme oxygenase 1 (HO-1) expression), as well as markers of inflammatory response and apoptosis, while also leading to testicular degeneration changes, reductions in sperm count and motility, and deformities [161,162].

5.4.2. Regulation of Antioxidant Pathways

The response to oxidative stress in eukaryotic cells also involves cell signaling pathways derived in the regulation of the gene expression, such as the Nrf2–ARE pathway. ARE (antioxidant responsive element) is a DNA enhancer sequence involved in the regulation of phase II detoxification enzymes (e.g., NAD(P)H:quinone oxidoreductase-1, glutathione S-transferase, and glutamate–cysteine ligase) [163] and related proteins such as SOD and CAT [164]. The transcriptional factor Nrf2 (nuclear factor erythroid 2-related factor 2) binds to ARE to regulate several target genes. In normal conditions, Keap1 (Kelch-like ECH-associated protein 1) sequesters Nrf2 in the cytoplasm by forming a complex (Nrf2/Keap1). However, under oxidative stress, the complex disassociates, and Nrf2 is translocated to the nucleus, where it binds to ARE (possibly with the transcription factor Maf), upregulating several antioxidant genes [163].

The activity of iodine directly impacts the Nrf2–ARE pathway and, as a result, indirectly influences the cellular response to oxidative stress. In human skin cells, it was demonstrated that I_2 (250 μ M) and KI (750 μ M) activate the Nrf2–ARE pathway, inducing the expression of CAT and SOD enzymes [165]. It is hypothesized that iodine favors the release of Nrf2 by targeting the cysteine residues of Keap1 and changing its 3D conformation (Figure 6) [166]. In rats, supplementation with high doses of KI (3.5–5 mg per 100 g

body weight) raised the oxidative status in the testis and diminished sperm quality. In affected tissues, a higher expression of oxidative response genes (Nrf2 and HO-1) and related elements (NF- κ B and follistatin) was registered, together with apoptotic markers (p53, Bcl-2 proteins, Survivin, cytochrome C, PPAR, Caspase-3, and Caspase-9) [161].

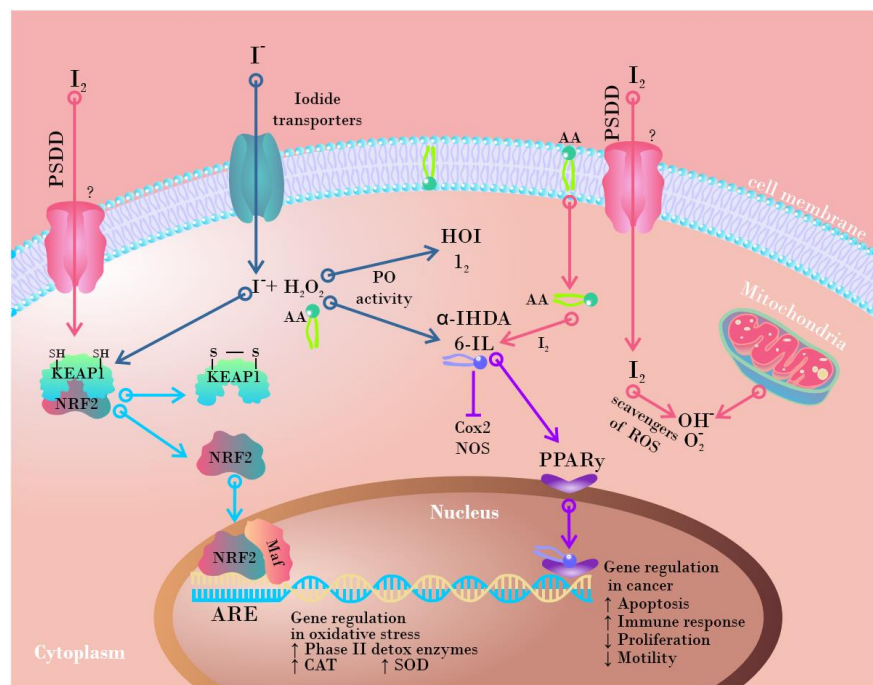


Figure 6. Molecular events influenced by iodine in mammal cells. To face the oxidative stress caused by ROS, some of the proposed molecular mechanisms of iodine are as follows: (1) using I^- as a cofactor in PO reactions (yielding I_2 , HIO, α -IHDA, or 6-IL); (2) as a direct scavenger of ROS produced by mitochondria ($OH^\bullet$ radical and O_2^-) by I_2 (yielding HIO and HI); (3) activation of the Nrf2–ARE pathway; (4) inhibition of pro-oxidant and proinflammatory enzymes NOS and Cox2 by 6-IL (adapted from [166], MDPI, 2016). Abbreviations: I^- , iodide; I_2 , molecular iodine; 6-IL, δ -lactone; AA, arachidonic acid; ARE, antioxidant response element; CAT, catalase; Cox2, cyclooxygenase type 2; Keap1, Kelch-like ECH-associated protein 1; NOS, nitric oxide synthase; Nrf2, nuclear factor erythroid 2-related factor 2; O_2^- , superoxides; $OH^\bullet$, hydroxyl radical; PO, peroxidases; PPAR γ , peroxisome proliferator-activated receptor type gamma; PSDD, protein synthesis-dependent diffusion; SOD, superoxide dismutase.

The activity of I_2 also results in the synthesis of iodolactones such as α -IHDA and 6-IL from arachidonic acid (AA) [46]. AA is a nonessential fatty acid in the plasma membrane involved in cell signaling pathways. The activation of the AA cascades begins with its release from the plasma membrane via nonenzymatic action of O_2 or via the enzymatic activity of cyclooxygenase (COX), lipoxygenase (LOX), or cytochrome P450 [167]. TPO and LPO can also react with AA and I^- to form iodolactones with antioxidant and other significant biological activities, as seen in next two sections [45,168].

5.5. Immunomodulation

The immune response can be influenced indirectly by iodine through the regulation of oxidative stress, which could be a consequence of infections and inflammation processes, or via direct participation, such as its role in the LPO system, part of the innate immune response [62]. The enzymatic activity of LPO yields HIO and other ions such as I_3^- and I_2 in the presence of I^- [28,64,169]. LPO is secreted in mucosal surfaces or exocrine secretions such as saliva, milk, or tears and is essential for the innate immune defense system [28,47].

Similarly, the leukocyte and eosinophil peroxidase enzymes (MPO and EPO) from white blood cells have the potential to react with I^- and produce HIO or I_2 to kill pathogens [170].

Human leukocytes also express components of the thyroid system such as NIS and Pendrin transporters, TG, TPO, and IDs with the potential of modulating TH metabolism [171,172]. The addition of NaI (1 mM) to white blood cells significantly impacted the gene expression and synthesis of immunomodulating agents like immunoglobulin G (IgG), without altering the viability [173]. Upregulated genes include proliferation elements (IL-2, IL-24, and CSF2), inflammatory proteins (IFN- γ , IL-6, IL-1 β , and IL-13), and especially chemokines (CCL7, CXCL5, and CXCL6). Likewise, Lugol's solution (I^- , I_2 , and I_3^-) decreases interferon-gamma (IFN- γ) levels and is involved in both early innate and adaptive immune responses. The treatment with Lugol also increases the release of IL-6, IL-10, and CXCL8 by the immune cells [171].

In the skin, inorganic iodine species revealed an anti-inflammatory potential. As mentioned in the Section 5.4.2, I^- and I_2 activate the Nrf2–ARE pathway in human skin cells. Moreover, in *ex vivo* experiments in human skin explants with induced inflammation (using lipopolysaccharides), only the KI treatment reduced proinflammatory cytokines IL-6 and IL-8. In the same study, skin explants were exposed to 24 h UVB irradiation (300 mJ/cm²), and both I_2 and KI showed a significant protective effect reflected in the higher cell viability and fewer apoptotic events [165].

Iodolipids produced by inorganic iodine species also showed immunomodulatory effects. *Ex vivo* culturing of follicular cells revealed that 40 times lower doses of 6-IL (0.05 and 0.5 μ M) were needed to induce apoptosis in thyroid cells in a similar way to KI (2–20 μ M) [174]. The proliferation of thyroid cell lines seems to be regulated by I^- and 6-IL by inhibition of the epidermal growth factor (EGF) and inositol 1,4,5-triphosphate (IP3) production (in a dose-dependent manner) but does not impact transforming growth factor beta 1 (TGF beta 1) [175–177]. α -IHDA could also be implicit in thyroid function by inhibiting adenyl cyclase, NADPH-oxidase, and TPO in thyroid cells, activating the cyclic adenosine-3',5'-monophosphate (cAMP) pathway [178], a master regulator of the adoptive and innate immune cell function [179].

As discussed in the next section, organic and inorganic species' immunomodulatory effects have great pharmacological potential in diseases. For example, in hypothyroid chinchilla with pancreatitis and insulinitis (induced by methimazole), supplementation with 0.2 mg/kg I_2 prevents lipoxidation in the serum and pancreas and increases the anti-inflammatory response via upregulation of PPAR γ receptors. However, a higher dose (2 mg/kg) exacerbates pancreatic damage and induces fibrosis and abnormal amyloid deposits [180].

PPARs are nuclear receptors activated by lipid metabolites (e.g., linolenic acids and prostaglandins) that control the expression of numerous genes involved in inflammation and metabolism. PPAR α activates fatty acid oxidation pathways, and PPAR γ regulates adipogenesis, lipid metabolism, insulin sensitivity, glucose and lipid homeostasis, and anticarcinogenic pathways [181,182]. Furthermore, 6-IL (produced either with I^- or I_2) can induce apoptosis and inhibit cell migration of cancer cells in a dependent PPAR γ activation mechanism (see Figure 6) [182].

5.6. Anticarcinogenic Effect

First observations of iodine as a protective agent were noticed in the Japanese population, whose iodine intake is typically higher and whose lifespan and health status are better than in other countries with lower iodine ingest [65]. The antioxidant capacity of iodine and its impact on several cell signaling pathways could explain these benefits. In this section, the protective role of iodine is addressed in mammal models in the context of cancer and other diseases (excluding the direct intervention of THs).

Higher oxidative status is related to aging and numerous diseases, including thyroid disorders and all types of cancer [98,132]. In these conditions, biological processes such as apoptosis, proliferation, or inflammation are connected, each with characteristic physi-

ological phenotypes and specific molecular markers. In normal conditions, apoptosis is promoted when cells suffer irreparable damage. However, cancer cells are characterized by the accumulation of DNA mutations, uncontrolled proliferation, and disruption in caspase activation pathways (e.g., p53 and Bcl-2 pathways), among other hallmarks [154]. These patterns can be modified with iodine supplementation depending on the target (organ, tissue, and specific type of cell), doses, and chemical species used.

5.6.1. Effects on Cells and Tissues

In the literature, three iodine species are best explored as potential anticarcinogenic agents in mammals: I^- , I_2 , and 6-IL. Experiments *in vitro* showed that excessive I^- did not affect non-thyroid normal and cancer cell lines (human dermal fibroblasts (PG1), osteosarcoma cells (SaOS), and endometrial carcinoma cells (HeLa)). Contrarily, on immortalized thyroid cells, I^- induced apoptosis (seen by morphological changes, DNA fragmentation, and protein crosslinking) and increased oxidative stress (higher ROS and MDA levels). In this study, the programmed cell death process was not dependent on protein synthesis, activation of p53, or proteins from the Bcl-2 family [183]. Proteins from the Bcl-2 family include both antiapoptotic (BCL-2, BCL-XL, BCL-w, MCL-1, and BFL-1/A1) and proapoptotic members (BAX, BAK, BIM, BID, BAD, BMF, and PUMA), and their expression can be linked to promotion or prevention of mitochondrial permeabilization [154].

Molecular iodine, in contrast, exhibits differential activity against breast cells and tissues. Breast cancer cell lines with low and elevated invasive potential (MCF-7 and MDA-MB231, respectively) significantly reduced their viability at 100 to 400 μM I_2 concentrations, but normal epithelial breast cells were not inhibited at the same doses [184]. In a different study, I_2 induced apoptosis in four of five breast cancer cell lines in a time- and dose-dependent manner. In those treatments, mitochondrial membrane potential was dissipated, and expression of Bcl-2 proteins was modified (Bax was upregulated, and Bcl-2 was downregulated) [185]. As caspase activation can be stimulated via two main mechanisms, the extrinsic via activation of death receptors (e.g., TNF or TRAIL) and the intrinsic starting through mitochondrial membrane permeabilization and release of cytochrome C [186], these results suggest that I_2 activates the intrinsic apoptosis pathway mediated by Bcl-2 proteins.

As mentioned, inorganic iodine species can react with AA to generate 6-IL with or without the intervention of peroxidases (Figure 6) [187]. In breast cancer cells, low doses of 6-IL (5 μM and 10 μM) and higher doses of I_2 (100 μM and 500 μM), but not I^- , reduce the proliferation rate [176,187]. In the breast cancer cell line MCF-7, the incorporation of iodine from I_2 , but not from I^- , to produce 6-IL was demonstrated by autoradiography [187]. Moreover, 6-IL formation (with I_2) was related to lower expression of the proliferating cell nuclear antigen (PCNA), vascular endothelial growth factor (VEGF), and urokinase-type plasminogen activator (uPA), while it regulated PPAR type alpha and gamma (PPAR α and PPAR γ) [188]. Additionally, a higher expression of PPAR γ in cervix cancer cells HeLa and SiHa was observed with I_2 (200 μM), together with a lower proliferation and aggregation of the cell lines, as well as a lower expression of stemness genes (CD49f, CK17, OCT-4, NANOG, SOX2, and KLF4), related to self-renewal, generation, and pluripotency [189].

5.6.2. Animal Models and Humans

The effect of iodine species in cancer progression has also been studied in animals after tumor induction with drugs or implantation of exogenous abnormal cells (xenografts). In Sprague-Dawley rats with breast-induced tumors (with *N*-methyl-*N*-nitrosourea), the absorption of radioisotopic $^{125}I^-$ and $^{125}I_2$ was comparable. However, the incidence in tumors was different when the drinking water was supplemented with I^- , I_2 , and T4. In the long term (16 weeks), continuous supplementation with I_2 exposed lower MDA levels and lower incidence of cancer (30%) than KI (93.7%), T4 (81.8%), or controls (72.7%). Serum T3 or NIS, LPO, and the p53 gene expression were not affected in I_2 treatments [190].

On immunodeficient animals (athymic nude mice) with implanted human breast cancer cells, the incidence and size of tumors were significantly lower under I₂ supplementation (25–50% and 0.4–0.5 cm³, respectively) compared with nonsupplemented controls (91.6% and 1.4–2.4 cm³, respectively). In this study, animals who drank water with I₂ maintained normal body weight gain, expressed higher levels of PPAR γ , and had decreased expression in the proliferating cell nuclear antigen (PCNA) [184], a marker of proliferation in breast cancer diagnosis [191].

Furthermore, I₂ has demonstrated adjuvant properties when supplemented with chemotherapy. Mice with neuroblastoma-induced cancer (using the cell line SK-N-BE(2)) had a preventive effect on bladder damage and a similar reduction in tumor size with I₂ (8 mg/kg/day) and chemotherapy (cyclophosphamide 20 mg/kg/day). At the molecular level, all the treatments with I₂ downregulated the expression of proto-oncogenes (MYCN and TrkB) and upregulated genes associated with neuronal differentiation (p53, PPAR γ , TrkA, and Bax) [192]. Furthermore, doxorubicin chemotherapy in combination with I₂ (3–6 mg/day) had the best anticarcinogenic effect and heart protection in female rats with induced mammary cancer (using methyl nitrosourea). Treated rats showed a significantly developed tumor size and lower proliferation rate, together with reduced MDA levels in the heart. Noticeably, I₂ suppresses tumor chemoresistance in the long-term by downregulating Bcl2 and survivin genes and upregulating Bax and PPAR γ expression [155].

Induced benign prostate tumors in rats had a comparative antioxidant and antiproliferative improvement after supplementation with I₂ (2.5 mg/day/rat) and celecoxib (1.25 mg/day/rat), an anti-inflammatory drug [156]. I₂ supplementation and celecoxib prevented lipoxidation and production of reactive nitrogen species (NO₂[−]). Likewise, I₂ repressed the expression of the PCNA gene and inhibited pro-oxidant NOS and proinflammatory Cox2 enzymes. Cox2 generates prostaglandin H₂ from AA, especially during inflammatory processes [193]. Overexpression of Cox2 is related to carcinogenesis in the prostate and other organs [194]; hence, its inhibitors potentially improve cancer progression. The anti-inflammatory and antiproliferative mechanisms of iodine related to COX expression could be complex to address, but they can be initiated by simply reducing available AA and preventing prostaglandin production by producing 6-IL.

In humans, there was one randomized pilot study in women diagnosed with early and advanced breast cancer (stages II and III, respectively) treated with I₂ (5 mg/day) and I₂ combined with a chemotherapeutic cocktail (5-fluorouracil/epirubicin/cyclophosphamide or taxotere/epirubicin). In all treatments containing I₂, the chemoresistance and side-effects improved in the patients. Most important, the 5 year survival rate was significantly higher in chemotherapy combined with I₂ than alone (82% and 46%, respectively). Transcriptional responses under I₂ and I₂ chemotherapy included upregulation in pathways related to inflammation, immune response, and survival, while antiapoptotic and chemoresistance pathways were downregulated [195]. Further transcriptomic analysis of the treated tumors revealed a higher antitumor response in I₂ supplementation alone or with chemotherapy by activating the Th1 differentiation pathway (involved in eliminating pathogens and cancerous cells). The immune cells profile in the I₂ treatments showed cytotoxic activity of natural killer and CD8⁺ cells and higher infiltration of nonactivated macrophages and B lymphocytes [196].

5.6.3. Additional Considerations

A key feature in the biological activity of iodine is the expression of transporters on the surface of target cells. The main transporters of I[−] are NIS and Pendrin, but there are others such as ANO1, CFTR, and SMVT [94,95]. To date, it is known that I₂ is not transported by NIS, Pendrin, or TPO activity but in a protein synthesis-dependent diffusion manner [187,197]. So far, no recent evidence supports the passive diffusion of I₂ or any iodine species.

In normal conditions, the thyroid, kidney, salivary glands, lactating mammary glands, and placenta express higher levels of I[−] transporters [97,166]. Contrarily, in cancer, the

profile change, and the breast, colon, pancreas, liver, ovary, and skin tumors overexpress I^- transporters. In the prostate, normal cells better express Pendrin, but NIS and CFTR dominate in the tumoral tissues [97]. The differential expression of iodine transporters could have a practical application in diagnostics. In ovary and nasopharynx cancers, the increment in CFTR expression is correlated to cancer progression and is proposed as a prognostic marker [198,199]. Moreover, higher expression of NIS and Pendrin is seen in women with a history of recurrent abortions (≥ 2) and could be a marker to predict adverse pregnancy outcomes in women with a subclinical IDD [200].

An important implication of aberrant expression of ion transporters is changing tissular pH balance. Normal cells have an intracellular pH value of ~ 7.2 and ~ 7.4 extracellularly. In cancer, these parameters are altered, resulting in a pH gradient from a more acidic pH in the outer space (~ 6.7 – 7.1) to an alkaline environment inside the cells (> 7.4) [201]. Altered pH is probably the less described hallmark in cancer research and one of the most influential variables in the chemical speciation of iodine and, consequently, a relevant feature when studying its anticarcinogenic activity.

Recent studies have shown promising results with high doses of I_2 (such as 5 mg/day) in the treatment of cancer (especially in the breast) [195]; however, this biological activity must imply the presence of I^- and possibly HIO. This is because, firstly, I_2 has poor solubility in water without additional iodide (0.293 g/L) [21] and, secondly, its chemical speciation in water systems renders I^- and, depending on pH, also HIO (Reaction (1)) [24]. As HIO is formed from I_2 in a swift reaction at $pH \geq 7$ [24], the contribution of HIO and probably some of its derivatives (such as OI^-) inside the tumoral cells could be implicit and must be taken into account [24].

Furthermore, similar anticarcinogenic effects have been observed with 6-IL and I_2 ; thus, it is necessary to consider the formation of organic iodine species (iodoproteins and iodolipids) produced by its catalytic potential. For example, in breast tumors, the composition of the cell membrane is different than in normal cells. In particular, there is a higher content of AA and PPAR α [202]. Thus, a feasible explanation of the antitumoral action of I_2 might also be given by its conversion to 6-IL. Similarly, the protective effects of I^- in the thyroid and other tissues expressing peroxidases could be partly mediated by its incorporation into lipids.

6. Iodine in the Industry

Molecular iodine is one of the most exploited chemicals in the industry, mainly as a catalyst for organic synthesis (including many heterocyclic compounds used in pharmacy), because of its low cost, efficiency, and high selectivity [203]. I^- is considered a mild reducing agent, and it is a much less reactive species than I_2 . IO_3^- is less reactive and has low toxicology; together with I^- , it can also be used as a chemical reagent or serve as an ingredient for various products (e.g., supplements and iodophors) [8,204]. Hydrogen iodide (HI), iodine pentoxide (I_2O_5), iodic acid (HIO_3), and sodium periodate ($NaIO_4$) are other frequent chemicals used in the pharmaceutical industry for organic synthesis [205,206]. In this review, the chemical synthesis is not addressed, but it is recommended to consult Küpper et al. (2011) and Wang et al. (2021).

Historically, Lugol's solution has been one of the most used iodine-based products in medicine and the industry. It was first used in the early 20th century by J.G.A. Lugol as a treatment for tuberculosis and is still considered an essential component of basic healthcare systems [207,208]. Lugol's solution is used as an antiseptic, disinfectant, supplement, and laboratory reagent, among the most important applications [2,29]. Currently, many iodine-based products are being developed, and the global demand for iodine has increased in the last decades. In 2017, the iodine market value was 833 million USD, and it is forecasted to be ~ 1.14 billion USD by 2024 [209].

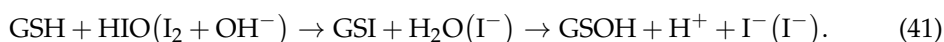
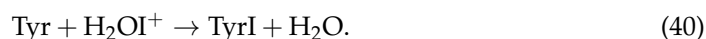
Chile and Japan lead the global production of iodine (having also the biggest reserves worldwide), followed by Turkmenistan, Azerbaijan, Indonesia, and Russia (the US has been excluded from statistics in recent years) [210,211]. In the case of radioisotopes (used

in nuclear medicine), it must be produced in nuclear reactors or cyclotrons from tellurium or xenon gases [212,213]. The major industrial applications of iodine include production of X-ray contrast media (XCM) (22%), pharmaceuticals (13%), polarization films (12%), animal feed (8%), iodophors (7%), fluorochemicals (7%), biocides (4%), nylon (4%), and human nutrition supplements (3%) [214]. The section below describes the relevant iodine applications of iodine in biomedicine and some of the representative iodine-based products.

7. Applications in the Health Sciences

7.1. Disinfection, Asepsis, and Wound Care

The first iodine-based tinctures, such as Lugol's solution, became popular as disinfectants because of their nonselective antimicrobial action against a broad range of microorganisms. However, the use of these kinds of products in drinking water disinfection is not recommended because of the risk of undesirable byproducts. More than 600 peptides are found in water [215], and reactions of chloramine (NH_2Cl), H_2OI^+ , and/or HIO with aromatic peptides (e.g., dipeptide Tyr–Gly) form highly toxic iodinated compounds of concern for people and the environment (Reaction (40)) [216]. Reactions of HIO , I_2 , OI^- species, and chloramines also affect pyridine nucleotides and glutathione (GSH), a potent and essential cellular antioxidant molecule (Reaction (41)). HIO (resulting from I_2 and OH^-) is a more selective downgrader of reduced dihydro-nicotinamide mononucleotide (NMDH) and nicotinamide adenine dinucleotide phosphate (NADH) than HOCl , and it can directly oxidize GSH or decrease its production by reducing the availability of NADPH (needed in GSH cycling) [217].



The use of iodine-based products in surgical procedures is extended. Nonetheless, classic Lugol's solution has some drawbacks, such as staining of the skin and materials, local pain, and irritation. In addition, a proportion of I_2 , the main component responsible for the antimicrobial activity, is lost by volatilization. These problems were solved in the early 1950s by the development of iodophors. The advantages of iodophoric preparations are reduced staining, increased I_2 solubility, and slow release to prolong the antimicrobial action [25,218]. Iodophors are made with solubilizing agents such as natural or synthetic polymers or surfactants, and they can be anionic, cationic, or nonionic [24,219]. Natural polymers are mostly starch and cellulose derivatives (e.g., amylose, amylopectin, Cadexomer, carboxymethyl cellulose, and methyl hydroxypropyl cellulose). Chitosan and lecithin are used in more complex iodophoric formulations (e.g., carboxymethyl chitosan and hydroxylated lecithin). Regarding synthetic polymers, PVP/I is the most used, followed by polyvinyl alcohol with iodine (PVAI). Other excellent polymeric carriers include poly(4-vinyl pyridine), poly(3-vinyl-10-methylphenothiazine), poly(2-ethyl-2-oxazoline), and poly(tetramethylene ether) glycol [219,220].

PVP/I was developed in 1956 and is suitable for wound healing because it is well tolerated on inflamed tissue, acting in a pH range of 2.5–7.0. It is also extensively applied as a disinfectant in the industry. For instance, PVP/I is routinely used as a milk and teat disinfectant and is, in fact, an important contributor to the iodine content in dairy products [221]. In the past, PVP/I was associated with bacteremia [222–224], but it was later demonstrated that contamination came from stock solutions. When working solutions were prepared according to the manufacturer's instructions, in all cases, they effectively inactivated all bacteria isolated from nosocomial infections [225,226].

Most antimicrobial effects of iodine were studied using PVP/I formulations. PVP/I has shown biocidal effects on different species of bacteria (e.g., *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Chlamydia trachomatis*), fungi (e.g., *Candida* spp. and *Trichophyton* spp.), protozoa (e.g., *Trichomonas* and *Acanthamoeba* spp.), and viruses (e.g., herpes simplex virus type I, adenovirus, influenza A viruses, rotavirus, poliovirus, and

human immunodeficiency virus) [57,225,227–233]. Enveloped viruses are susceptible to iodine, and PVP-I's efficacy (0.2–5%) was more recently proven in reducing viral loads of SARS-CoV-2 down to undetectable levels. Currently, skin, ophthalmic, nasal, and oral PVP-I-based antiseptic products are recommended to prevent transmissions during medical consultation [234–236].

Iodophors have also been exploited in novel wound healing and anti-inflammatory products because of their biocompatibility. PVAI and PVP/I-based hydrogels are good examples; they are constituted by flexible matrices that maintain asepsis and moisture. Moreover, they also absorb exudates, allow wound oxygenation, and have low toxicity and skin irritation [54,237]. Together with other components, hydrogels can serve as scaffolds for tissue regeneration, regulate medication released, or display unique properties to respond to stimuli, such as color change by temperature (thermochromism) or pH/thermal sensitivity [238,239].

7.2. Supplementation

When iodine ingestion is insufficient, there is a need to consume supplements to maintain normal thyroid function (euthyroidism). Iodine intake by groups of age is recommended as follows: 90 µg/day for infants and children 0–59 months, 120 µg/day for school children (6 to 12 years), 150 µg/day for adults, and 200 µg/day for pregnant and breastfeeding women [240]. Upper limits are much more difficult to establish because they are influenced by previous long-term iodine status [84] and even the kind of supplementation [166]. Some studies reported normal thyroid function at high doses of iodine from the diet (mainly from seaweed, 1.2 mg/day) [241], supplements (1–3 mg/day) [242], Lugol's solution, and PVP-based water disinfectants (4–8 mg/L water) [243]. However, the recommended safe iodine intake for euthyroid people by the WHO is up to 1 mg/day, except for pregnant and lactating women that have no extra benefit receiving >500 µg/day and children of <2 years that should not exceed >180 µg/day [244].

The most common and suitable indicator to evaluate the iodine status in a population is urinary iodine, given that iodine is mostly excreted in urine (~90%). In this sense, the best method is urinary iodine excretion (UIE), which is determined from the whole urine collected for 24 h. Urinary iodine concentration (UIC) from one urine sample (preferably collected in the morning) is enough and more practical to define the general status according to WHO [2013]. For most people (including lactating women), >100 µg/L UIC is considered adequate, but <100 µg/L UIC reflects insufficient intake (<20 µg/L UIC suggest severe iodine deficiency), except for pregnant women whose optimal UIC is considered 150–249 µg/L, with <100 µg/L considered insufficient [245]. Nonetheless, urinary concentrations might vary in short periods (days–hours). Thus, to determine iodine status and thyroid function of individuals, it is recommended to screen the levels of TSH and free T4 as a minimum [66,246]. Other parameters are evaluated to monitor thyroid function, such as goiter rate (%), levels of T3, rT3, TG, antibodies for TG (TgAb) or TPO (TPOAb), and thyroid-stimulating immunoglobulin (TSI) [242].

Optimal consumption of iodine can be obtained with an appropriate diet, consuming seafood (e.g., seaweed, fish, crabs, and oyster), dairy products (e.g., milk, yogurt, and cheese), tubers (e.g., turnip and saffron), beef kidney, green beans, eggs, yeast, some condiments (e.g., chili powder and mint), and iodized salt [39,247]. However, some geographical areas might have iodine-deficient water and soils; consequently, the iodine content in food is lower. For example, iodine content in plants can be up to 1 mg/kg or down to 10 µg/kg (dry weight), depending on the soil [66]. Geographic iodine-deficient areas include mountainous and inland regions of South America (e.g., the Andes and inland Brazil), Midwestern United States, Europe (e.g., Alps, Pyrenees, England, Wales, Greece, and the Netherlands), Asia (China, India, Bangladesh, Himalayan hillsides, and Indonesia), Africa (e.g., Atlas Mountains, Nigeria, Cameroon, the Central African Republic Democratic Republic of Congo, Uganda, and Ethiopia), Southern Australia, and Highlands of New Guinea [65].

The additional intake of iodine from supplements is recommended to prevent IDD in iodine-deficient areas (especially among women of reproductive age). Currently, the best strategy to face IDD in the world has been the universal iodization of table salt (with KI, NaI, or KIO₃), implemented in 1994 by the International Council for the Control of Iodine Deficiency Disorders (ICCIDD). The advantages of this product lie in the global consumption of salt, cheap cost production, long shelf-life, accessibility for remote communities, and imperceptible taste modification [248]. IDD persists even in developed countries due to the unequal consumption and distribution of iodized salt among low- and high-income households [249,250]. Moreover, it has been demonstrated that iodine can be partially or entirely lost during cooking depending on cookware materials and ingredients such as ascorbic acid, glucose, and some condiments, as well as because of impurities and storage conditions, mainly the kind of package and humidity [251,252].

In the market, there is a wide variety of supplements that can also be taken with one or more of the following components in their formulations: KI, NaI, KIO₃, I₂, iodized oil, natural products based on seaweed (from species *Laminaria* spp., *Fucus vesiculosus*, *Alaria esculenta*, *Ascophyllum nodosum*, *Ecklonia maxima*, *Eisenia bicyclis*, *Hizikia fusiforme*, *Palmaria palmata*, *Porphyra tenera*, *Postelsia palmaeformis*, and *Sargassum* sp.) or plants (e.g., *Commiphora mukul* and *Iris versicolor*) [39,253,254]. Among all supplements, natural formulations have the most variability or declare the highest iodine contents and should be avoided for pregnant women or those planning a pregnancy [254,255]. Natural or synthetic thyroid hormones are used not as supplements but under prescription to treat hypothyroidism. Currently, levothyroxine (or L-thyroxine) is the most recommended by endocrine societies (and produced worldwide) for thyroid hormone replacement therapy [256].

Probiotic consumption might improve iodine status, given that the gut microbiome participates in nutrient absorption and cycling of THs. Autoimmune thyroid dysfunctions and thyroid carcinoma are linked to dysbiosis (imbalance in the microbiota). Hypothyroidism and hyperthyroidism are correlated with the reduction in intestinal bacteria from Lactobacillaceae and Bifidobacteriaceae families [257].

Vitamin D and other nutrients such as iron, copper, selenium, and zinc are often altered in thyroid disorders. They can be considered in supplementation and the avoidance of goitrogens [65,257]. Goitrogens decrease iodine absorption, primarily by inhibiting cellular iodine transporters, interfering with TH synthesis, or reducing the conversion of T₃ from T₄ [65,258,259]. They comprise cyanide (from smoking), nitrates, fluoride, some contaminants (e.g., perchlorate and disulfides), foods rich in glucosides (e.g., cassava, lima beans, linseed, sorghum, and sweet potato), glucosinolates (e.g., broccoli, kale, cauliflower, cabbage, and turnips), and flavonoids (e.g., onions, lettuce, tomatoes, and grapes). Even nutrient deficiencies of iron, selenium, and vitamin A are considered goitrogens [259,260].

7.3. Contrast Agents

X-rays allow us to see structures of high density because the X-ray absorption coefficient (μ) is directly proportional to the atomic mass of the compound. Bones and some organs in the body can be directly distinguished by X-ray, but other less dense structures need contrast agents to visualize them [261]. X-ray contrast media (XCM) are substances that allow visualization of those biological structures, and, depending on the difference in μ , they can be classified as positive or negative. Negative XCM are gases of lower absorption coefficient (e.g., O₂ and CO₂), and positive XCM contain elements of high atomic number, such as iodine or barium, that stand out in X-ray imaging [261,262].

Positive XCM can be classified as targeted (or specific) and extracellular (or unspecific), depending on whether the contrasting reagent is metabolized in the body [15,261]. Extracellular XCM are water-soluble agents mainly used to visualize the circulatory system. The pharmacokinetics is very similar among extracellular XCM, taking 3–10 min for distribution and typically 1–2 h in elimination (via glomerular filtration). Under renal impairment, the excretion takes up to 10 h with a higher risk of nephrotoxicity [15,261].

On the contrary, targeted XCM (also biliary contrast agents) have good lipophilicity and different distribution and elimination times. The disadvantages of XCM with low hydrophilicity are less tolerability, hepatic or renal toxicity, and higher allergic reactions [261,263]. For those reasons, research on targeted XCM is now developing into noniodine compounds, although promising advances have been accomplished with liposomes and polymers as carriers [263].

The simplest contrast agent is NaI, the first iodinated XCM in the market (in 1918), with an excellent μ value but not as good tolerability at high doses. Currently, most XCM are based on molecules of one or more triiodobenzene rings. Triiodobenzene derivatives are the extracellular XCM of choice because of their stability, tolerability, low toxicity, and wide range of compounds that can be produced. The synthesis is achieved by substituting the hydrogens at positions 1, 3, and 5 of the benzene ring with I atoms. Some good examples are iohexol, iopamidol, ioversol, ioxilan, iopromide, ioxaglic acid, iotrolan, iodixanol, and diatrizoate meglumine [264]. Examples of approved targeted agents are iodipamide meglumine to visualize the bile duct and the gallbladder and lipiodol for imaging hepatocellular carcinoma [265–267].

7.4. Applications in Nuclear Medicine

All kinds of radiation can be dangerous for life, but the extent of damage depends on the decay mode and half-life of the radioactive atom. Alpha (α) and beta (β) radiation are weaker but significantly dangerous when particles are inhaled, swallowed, or absorbed in the body. Gamma (γ) and X-rays are much more powerful and penetrating, causing immediate severe cellular damage from external sources [268]. In a controlled fashion, nuclear medicine takes advantage of radioisotopes that can be detected in small amounts and represent a lesser danger for life, to diagnose and treat several diseases.

Diagnostics in nuclear medicine differ from radiology in the study of the functionality of tissues and organs, not only examining anatomic structures. For this purpose, radiopharmaceuticals are injected (most of the time), inhaled, or orally administered to follow their circulation, accumulation, or metabolism in the body [261,269]. For imaging, developed technologies are scintigraphy, single-photon emission computed tomography (SPECT), positron emission tomography (PET), or combinations with computed tomography (CT) such as SPECT/CT and PET/CT [269–271].

Radiotherapy also uses radioisotopes to target specific abnormal cells or tissues and destroy them via internal radiation (e.g., hyperthyroidism caused by Graves' disease toxic nodular goiter) [272]. The most used radioisotope for both diagnostics and therapy is technetium (^{99}Tc), followed by iodine, because of their high intensity and short half-life [269,272]. The main iodine radioisotopes of iodine exploited in medicine and for research are ^{123}I , ^{124}I , ^{125}I , and ^{131}I [273]; their physicochemical properties are described in Table 1.

The simplest agent containing an iodine radioisotope is NaI, which can be orally ingested to evaluate thyroid and parathyroid functioning (using ^{123}I or ^{124}I) or to treat thyroid disorders and thyroid cancer (with ^{131}I) [264,272]. Additionally, radioactive iodides can serve to label molecules by nucleophilic substitution (usually benzene rings derivatives), switching stable iodine (^{127}I) with the radioisotope [269]. Some pharmaceuticals having aromatic rings are meta-iodobenzylguanidine (MIBG), a norepinephrine analog (with ^{123}I , ^{124}I , or ^{131}I) for diagnosis of pheochromocytoma, neuroblastoma, and heart diseases; ioflupane ^{123}I (a cocaine analog) for detection of Parkinson's disease and dementia; iothalamate ^{125}I to evaluate glomerular filtration; ioetamine ^{123}I to detect ischemic brain diseases, and iodohippurate ^{123}I to diagnose kidney dysfunction [264,275].

Table 1. Iodine isotopes of relevance in industry and biology.

Isotope	Abundance	Atomic Mass	Half-Life	Decay Mode (%)	keV	Production	Application
^{123}I	Synthetic	122.9056	13.2232 h	β^+ (100%)	159	Cyclotron	Diagnosis (SPECT) and therapy
^{124}I	Synthetic	123.9062	4.176 d	β^+ (100%)	603	Cyclotron	Research and diagnosis (PET)
^{125}I	Synthetic	124.9046	59.392 d	ϵ (100%)	27.5	Nuclear reactor and cyclotron	Therapy and radioimmunoassay
^{127}I	Natural (1)	126.9045		Stable		Natural	Diagnosis (X-rays and CT) and therapy
^{131}I	Synthetic	130.9061	8.0249 d	β^- (100)	364.5	Nuclear reactor	Diagnosis, therapy, and RIA

CT, computed tomography; PECT, positron emission computed tomography; RIA, radioimmunoassay; SPECT, single-photon emission computed tomography. Abbreviations: d, days; ϵ , electron capture; β^- , beta– decay; β^+ , beta positive decay (includes both ϵ and positron emission e^+ ($\beta^+ = \epsilon + e^+$)) physical properties data from [274], IOP Publishing 2021.

Radiotherapy and imaging can combine (theranostic) by using a single agent for visualization and treatment of abnormal cells. For example, by taking advantage of the high accumulation of I^- in the thyroid, Na^{131}I is administrated to image and treat thyroid cancer and hyperthyroidism. Furthermore, ^{123}I and or ^{131}I combined with meta-iodobenzylguanidine (MIBG), a neurotransmitter analog, is used to treat neuroendocrine tumors [276,277]. Furthermore, theranostics might involve gene and cell-based therapy to deliver pharmaceuticals to specific cells. For example, the increment in NIS expression (by gene transfer) in non-thyroid tissues, such as in the cervix and prostate tumors, facilitates the entry of radioisotopes of iodine for inducing abnormal cell death [278,279]. Other therapeutic approaches include labeled antibodies such as ^{131}I tositumomab, approved for non-Hodgkin's lymphoma treatment, labeled nanoparticles coated with metals (e.g., gold or copper sulfide) used in SPECT/CT, or even devices such as ^{125}I seeds (within titanium capsules) used in inoperable lung tumors and nonpalpable mammary lesions, among others [272,280–282]. ^{124}I has not been used as a routine agent in diagnostics mainly because of its complex decay mode and longer half-life. However, it can be imaged by PET with more sensibility and 3D acquisition in a quantitative manner. Some interesting radiopharmaceuticals developed with it are A14-iodoinsulin ^{124}I , FIAU iodouracil ^{124}I , and AntiCEA minibodies ^{124}I , which exhibited promising results for the treatment and diagnosis of tumors [271].

7.5. Prophylaxis

Radioactive contamination after a nuclear explosion or an accident can bring severe consequences for people and the environment in the short and long term, as occurred with the atomic bombings of Hiroshima and Nagasaki in 1945 or the Chernobyl (former Soviet Union) and Fukushima (Japan) nuclear accidents in 1986 and 2011, respectively. Beyond the immediate damage of radiation, iodine radioisotopes are of particular concern because of their accumulation in the body and potential incorporation into the food chain following regular iodine cycling [283–285]. High radiation levels can induce hypothyroidism or acute thyroiditis. Lower exposure to radiation increases the risk of thyroid cancer and benign thyroid nodules in the long term, especially in infants, children, and adolescents [69].

To prevent the absorption of radioactive isotopes (prophylaxis), high doses of stable iodine (^{127}I) can be promptly distributed in the population [242]. Prophylaxis is not used to restore iodine status; instead, it takes advantage of the Wolff–Chaikoff effect, a transient inhibition of TH production induced by excess iodine. In most cases, the thyroid function is restored in 1–2 weeks but vulnerable groups (e.g., fetuses, neonates, and patients with autoimmune thyroiditis and Graves' disease or treated with antithyroid drugs) may not “escape” from this effect [286].

Prophylaxis is recommended when exposure to vulnerable groups (neonates, infants, and children) is ≥ 10 mGy (1 Gy is equal to 1 J of radiation absorbed per kg) [287]. Older adults (>40 years) have a minimal thyroid cancer risk and more side-effects with excessive iodine supplementation; therefore, prophylaxis is recommended at ≥ 100 mGy. According to WHO, a single dose of I_2 , KI, or KIO_3 is sufficient for all groups of age, as indicated in Table 2. Repetition doses are only prescribed for pregnant women from iodine-deficient areas and vulnerable people with prolonged exposure (for example, infants inhaling radioactive material) [287].

Table 2. Recommended iodine dosage as prophylaxis by age group [287].

Age Group	I_2 (mg)	KI (mg)	KIO_3 (mg)	Fraction of a Tablet (100 mg)
Adults and adolescents, including lactating women (>12 years)	100	130	170	1
Children (3–12 years)	50	65	85	1/2
Infants (1 month–3 years)	25	32	42	1/4
Neonates (birth–1 month)	12.5	16	21	1/8

Reprinted from Guidelines for iodine prophylaxis following nuclear accidents: update 1999, World Health Organization. Protection of the Human Environment, page 20, Copyright ID 390332 (2022), <https://apps.who.int/iris/handle/10665/66143>.

8. Conclusions

The chemical speciation of iodine in aqueous systems is complex and influenced by pH, redox potential, dilution, and the occurrence of chemical compounds. In this universe, four inorganic species have leading roles in biological systems: I^- , I_2 , IO_3^- , and HIO. Iodate represents a major source of iodine and is well absorbed in several organisms. However, it only achieves some reactivity at extremely low pH; hence, it needs to be transformed into a different species to exhibit a more active role. HIO and its derivatives are reactive iodine species with excellent antimicrobial and antioxidant properties; however, their amount and stability are limited or negligible under pH 7. In contrast, I_2 is also a reactive species that can be predominant in conditions compatible with life. I_2 has poor solubility in water; hence, it needs to be combined with I^- to increase its availability. Lastly, I^- has good water solubility, and it is probably the most versatile of all. I^- is not as reactive as I_2 or HIO but can be used as an electron donor in several enzymatic reactions, yielding numerous inorganic and organic species. I^- and I_2 are constantly cycled in the environment and can be linked to virtually all known biological processes involving iodine. Thus, both can be considered the main inorganic species in the biological context.

Iodine plays a fundamental role as an essential nutrient needed in all stages of life. Its deficiency has severe consequences for human health, from congenital anomalies in the prenatal and neonatal stages to severe metabolic disorders. On the contrary, iodine in higher doses can significantly improve health status by increasing the antioxidant capacity and innate immune response. Certain iodine species also show anticarcinogenic and immunomodulatory activities in some types of cancer. Moreover, after nuclear disasters, one single very high dose has the potential to protect the population from iodine radioisotopes released into the environment.

In general terms, the biological activities of iodine can be divided into (1) iodination of organic compounds (e.g., TH synthesis), (2) degradation of molecules (including neutralization of ROS and antimicrobial activities), and (3) intervention in cell signaling (from hormonal roles to cell signaling regulation). Each has a direct application in medicine, biology, biotechnology, and many other fields.

Even though hormone synthesis has the protagonist role in the performance of iodine, there is sufficient evidence to support that inorganic species are as important not only in supplementation but as active elements in the evolution of life as we know it.

Author Contributions: Conceptualization, A.N.E.-V., L.M.F.-Y. and F.C.R.-C.; investigation, A.N.E.-V.; writing—original draft preparation, A.N.E.-V.; writing—review and editing, A.N.E.-V., L.M.F.-Y. and F.C.R.-C.; visualization, A.N.E.-V. and L.M.F.-Y.; supervision, L.M.F.-Y. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: First, the authors want to thank Myron W. Wentz, founder of Sanoviv Medical Institute, for his interest in generating scientific knowledge to benefit humanity. The authors also thank the Research and Medical Departments at Sanoviv, especially the Medical Director, A. Isaac Meza Pereyra, for the support. Lastly, the authors want to recognize Alexander Ramos-Díaz's technical support in generating the graphical abstract and the artistic intervention of L. Jazmín García-Román in Figures 1 and 3–5.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

AA Arachidonic Acid, **ALE** Advanced lipoxidation end products, **ANO1** Calcium-dependent Cl[−] channel Anoctamin 1, **APX** Ascorbate peroxidase, **ARE** Antioxidant Response Element, **Bcl-2** B-cell lymphoma 2, **CAT** Catalase, **CCL** Chemokine ligand, **CFTR** Cystic Fibrosis Transmembrane Conductance Regulator, **CH₃I** Methyl iodide, **CIC5** Cl[−]/H⁺ antiporter, **CIC-3** Cl[−]/H⁺ exchanger, **COX** Cyclooxygenase, **Cox2** Cyclooxygenase type 2, **CPO** Chloroperoxidase, **CT** Computed Tomography, **CXC** Chemokine, **DHA** Docosahexaenoic acid, **DIT** 3,5-Diiodotyrosine, **EGF** Epidermal Growth factor, **Eh** Redox potential, **EPO** Eosinophil peroxidase, **ERK1/2** Extracellular signal-Regulated Kinase 1/2, **G-POX** Guaiacol peroxidase, **GSH** Reduced glutathione, **GSSG** Oxidized glutathione, **H₂O₂** Hydrogen peroxide, **H₂OI⁺** Iodine cation, **HDL-C** High-density lipoprotein cholesterol, **HI** Hydrogen iodide, **HIO** Hypoiodous acid, **HIO₃** Iodic acid, **HO-1** Heme oxygenase 1, **HOCl** Hypochlorous acid, **I** Iodine element, **I[−]** Iodide, **I₂** molecular iodine, **I₂O₅** Iodine pentoxide, **I₃[−]** Triiodide, **I₅[−]** Pentaiodide, **I₆^{2−}** Hexaiodide, **ID** Iodothyronine deiodinase, **IDD** Iodine Deficiency Disorders, **IFN-γ** Interferon-gamma, **IGT** Impaired glucose tolerance, **IL** Interleukin, **IO₃[−]** Iodate ion, **IP3** Inositol 1,4,5-triphosphate, **IYD** Iodotyrosine deiodinases, **Keap1** Kelch-like ECH-associated protein 1, **KI** Potassium iodide, **KIO₃** Potassium iodate, **LDL-C** Low-density lipoprotein cholesterol, **LOX** Lipoxygenase, **LPO** Lactoperoxidase, **MCT** Monocarboxylate transporter, **MDA** Malondialdehyde, **MetS** Metabolic syndrome, **MIBG** Meta-iodobenzylguanidine, **MIT** Monoiodotyrosine, **MPO** Myeloperoxidase, **Na₂SeO₃** Sodium selenite, **NAD** Nicotinamide adenine dinucleotide, **NADH** Nicotinamide adenine dinucleotide, **NADPH** Reduced nicotinamide adenine dinucleotide phosphate, **NaI** sodium iodide, **NaIO₄** Sodium periodate, **NF-κB** Nuclear factor kappa-light-chain-enhancer of activated B, **NH₂Cl** Chloramine, **NIS** Na⁺/I[−] symporter, **NMNH** Reduced dihydronicotinamide mononucleotide, **NO-cGMP** Nitric oxide-cyclic guanosine monophosphate pathway, **NOS** nitric oxide synthase, **NR** Nuclear Receptors, **Nrf2** Nuclear factor erythroid 2-related factor 2, **O₂[−]** Superoxides, **O₃** Ozone, **OATP** Organic Anion-Transporting Polypeptide, **OH•** Hydroxyl radical, **OI[−]** Hypoiodite ion, **PCNA** Proliferating Cell Nuclear Antigen, **PCNA** Proliferating Cell Nuclear Antigen, **PDD** Hydrogen peroxide-dependent diffusion, **PECT** Positron Emission Tomography, **PI3K** Phosphatidylinositol 3-OH Kinase pathway, **PPARα** Peroxisome Proliferator-Activated Receptor type alpha, **PPARγ** Peroxisome Proliferator-Activated Receptor type gamma, **PVAI** Polyvinyl Alcohol Iodine, **PVP-I** Povidone-Iodine, **RIA** Radioimmunoassay, **rT3** Reverse T3 or 3',5',3 triiodothyronine, **SMVT** Sodium-dependent Multivitamin Transporter, **SOD** Superoxide dismutase, **SPECT** Single-Photon Emission Computed Tomography, **T3** 3',5',3-Triiodothyronine, **T4** Thyroxine, **TAAR** Trace amine-associated receptor, **TAC** Total Antioxidant Capacity, **TAMs** Thyronamines, **Tetrac** 3,3',5,5'-Tetraiodothyroacetic acid, **TG** Thyroglobulin, **TGF** Transforming Growth Factor, **THs** Thyroid Hormones, **TPO** Thyroid Peroxidase, **TR** Thyroid hormone receptors, **TREs** Response Elements, **TRH** Thyrotropin-Releasing Hormone, **Triac** 3,3',5-triiodothyroacetic acid, **TRs** Thyroid hormone

Receptors, **TSH** Thyroid-Stimulating Hormone, **Tyr** Tyrosine, **UIC** Urinary Iodine Concentration, **VEGF** Vascular Endothelial Growth Factor, **V-IPO** Vanadium Iodoperoxidase, **XCM** X-ray Contrast Media, **6-IL** δ -lactone, **α -IHDA** α -Iodoheptadecanal, β^- Beta particle emitter, β^+ positron emitter, ϵ Electron capture.

References

- Venturi, S.; Donati, F.M.; Venturi, A.; Venturi, M. Environmental Iodine Deficiency: A Challenge to the Evolution of Terrestrial Life? *Thyroid* **2000**, *10*, 727–729. [CrossRef] [PubMed]
- Gottardi, W. Iodine as Disinfectant. In *Iodine Chemistry and Applications*; Kaiho, T., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2014; Volume 9781118466, pp. 375–410.
- Crockford, S.J. Evolutionary Roots of Iodine and Thyroid Hormones in Cellcell Signaling. *Integr. Comp. Biol.* **2009**, *49*, 155–166. [CrossRef] [PubMed]
- Küpper, F.C.; Feiters, M.C.; Olofsson, B.; Kaiho, T.; Yanagida, S.; Zimmermann, M.B.; Carpenter, L.J.; Luther, G.W.; Lu, Z.; Jonsson, M.; et al. Commemorating Two Centuries of Iodine Research: An Interdisciplinary Overview of Current Research. *Angew. Chemie Int. Ed.* **2011**, *50*, 11598–11620. [CrossRef]
- National Center for Biotechnology Information PubChem Element Summary for AtomicNumber 53, Iodine. Available online: <https://pubchem.ncbi.nlm.nih.gov/element/Iodine> (accessed on 24 April 2022).
- Meija, J.; Coplen, T.B.; Berglund, M.; Brand, W.A.; De Bièvre, P.; Gröning, M.; Holden, N.E.; Irrgeher, J.; Loss, R.D.; Walczyk, T.; et al. Isotopic Compositions of the Elements 2013 (IUPAC Technical Report). *Pure Appl. Chem.* **2016**, *88*, 293–306. [CrossRef]
- Edwards, R.R. Iodine-129: Its Occurrence in Nature and Its Utility as a Tracer. *Science* **1962**, *137*, 851–853. [CrossRef]
- Kaiho, T. Inorganic Iodides. In *Iodine Chemistry and Applications*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2014; Volume 9781118466, pp. 55–73.
- Muramatsu, Y.; Yoshida, S.; Fehn, U.; Amachi, S.; Ohmomo, Y. Studies with Natural and Anthropogenic Iodine Isotopes: Iodine Distribution and Cycling in the Global Environment. *J. Environ. Radioact.* **2004**, *74*, 221–232. [CrossRef]
- Moreda-Piñeiro, A.; Romaris-Hortas, V.; Bermejo-Barrera, P. A Review on Iodine Speciation for Environmental, Biological and Nutrition Fields. *J. Anal. At. Spectrom.* **2011**, *26*, 2107. [CrossRef]
- Amachi, S. Microbial Contribution to Global Iodine Cycling: Volatilization, Accumulation, Reduction, Oxidation, and Sorption of Iodine. *Microbes Environ.* **2008**, *23*, 269–276. [CrossRef]
- Kocher, D.C. A Dynamic Model of the Global Iodine Cycle and Estimation of Dose to the World Population from Releases of Iodine-129 to the Environment. *Environ. Int.* **1981**, *5*, 15–31. [CrossRef]
- Elmore, D.; Gove, H.E.; Ferraro, R.; Kilius, L.R.; Lee, H.W.; Chang, K.H.; Beukens, R.P.; Litherland, A.E.; Russo, C.J.; Purser, K.H.; et al. Determination of 129I Using Tandem Accelerator Mass Spectrometry. *Nature* **1980**, *286*, 138–140. [CrossRef]
- Brown, C.F.; Geiszler, K.N.; Lindberg, M.J. Analysis of 129I in Groundwater Samples: Direct and Quantitative Results below the Drinking Water Standard. *Appl. Geochemistry* **2007**, *22*, 648–655. [CrossRef]
- Crivello, J.V. Diaryliodonium Salt Photoacid Generators. In *Iodine Chemistry and Applications*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2014; pp. 457–478.
- Carpenter, L.J. Atmospheric Chemistry of Iodine. In *Iodine Chemistry and Applications*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2014; pp. 591–601.
- Cox, R.A.; Bloss, W.J.; Jones, R.L.; Rowley, D.M. OIO and the Atmospheric Cycle of Iodine. *Geophys. Res. Lett.* **1999**, *26*, 1857–1860. [CrossRef]
- Chameides, W.L.; Davis, D.D. Iodine: Its Possible Role in Tropospheric Photochemistry. *J. Geophys. Res. Ocean.* **1980**, *85*, 7383–7398. [CrossRef]
- Raso, A.R.W.; Custard, K.D.; May, N.W.; Tanner, D.; Newburn, M.K.; Walker, L.; Moore, R.J.; Huey, L.G.; Alexander, L.; Shepson, P.B.; et al. Active Molecular Iodine Photochemistry in the Arctic. *Proc. Natl. Acad. Sci. USA* **2017**, *114*, 10053–10058. [CrossRef]
- Seidell, A. Solubilities of Inorganic and Organic Compounds. A Compilation of Quantitative Solubility Data from the Periodical Literature. *J. Am. Med. Assoc.* **1928**, *91*, 1131.
- Lewis, R.A. *Hawley's Condensed Chemical Dictionary*, 15th ed.; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2007.
- Yuita, K. Dynamics of Iodine, Bromine, and Chlorine in Soil: II. Chemical Forms of Iodine in Soil Solutions. *Soil Sci. Plant Nutr.* **1992**, *38*, 281–287. [CrossRef]
- Li, J.; Wang, Y.; Guo, W.; Xie, X.; Zhang, L. Factors Controlling Spatial Variation of Iodine Species in Groundwater of the Datong Basin, Northern China. *Procedia Earth Planet. Sci.* **2013**, *7*, 483–486. [CrossRef]
- Gottardi, W. Iodine and Disinfection: Theoretical Study on Mode of Action, Efficiency, Stability, and Analytical Aspects in the Aqueous System. *Arch. Pharm.* **1999**, *332*, 151–157. [CrossRef]
- Gottardi, W. Potentiometrische Bestimmung Der Gleichgewichtskonzentrationen an Freiem Und Komplex Gebundenem Iod in W~iffligen Liisungen von Polyvinylpyrrolidon-Iod (PVP-Iod) Polyvinylpyrrolidon-Iod (PVP-Iod). *Fresenius' Zeitschrift für Anal. Chemie* **1983**, *314*, 582–585. [CrossRef]
- Bowen, H.J.M. *Environmental Chemistry of the Elements*; Academic Press: London, UK, 1979.
- Rackur, H. New Aspects of Mechanism of Action of Povidone-Iodine. *J. Hosp. Infect.* **1985**, *6*, 13–23. [CrossRef]

28. Bafort, F.; Parisi, O.; Perraudin, J.-P.; Jijakli, M.H. Mode of Action of Lactoperoxidase as Related to Its Antimicrobial Activity: A Review. *Enzyme Res.* **2014**, *2014*, 517164. [CrossRef]
29. Cooper, R.A. Iodine Revisited. *Int. Wound J.* **2007**, *4*, 124–137. [CrossRef]
30. Punyani, S.; Narayana, P.; Singh, H.; Vasudevan, P. Iodine Based Water Disinfection: A Review. *J. Sci. Ind. Res.* **2006**, *65*, 116–120.
31. Information National Center for Biotechnology PubChem Compound Summary for CID 23665710, Potassium Iodate. Available online: <https://pubchem.ncbi.nlm.nih.gov/compound/Potassium-iodate> (accessed on 24 April 2022).
32. Dembitsky, V.M. Biogenic Iodine and Iodine-Containing Metabolites. *Nat. Prod. Commun.* **2006**, *1*, 1934578X0600100. [CrossRef]
33. Edmonds, J.S.; Morita, M. The Determination of Iodine Species in Environmental and Biological Samples (Technical Report). *Pure Appl. Chem.* **1998**, *70*, 1567–1584. [CrossRef]
34. Cakmak, I.; Prom-u-thai, C.; Guilherme, L.R.G.; Rashid, A.; Hora, K.H.; Yazici, A.; Savasli, E.; Kalayci, M.; Tutus, Y.; Phuphong, P.; et al. Iodine Biofortification of Wheat, Rice and Maize through Fertilizer Strategy. *Plant Soil* **2017**, *418*, 319–335. [CrossRef]
35. Kiferle, C.; Gonzali, S.; Holwerda, H.T.; Ibaceta, R.R.; Perata, P. Tomato Fruits: A Good Target for Iodine Biofortification. *Front. Plant Sci.* **2013**, *4*, 205. [CrossRef]
36. Smoleń, S.; Kowalska, I.; Halka, M.; Ledwożyw-Smoleń, I.; Grzanka, M.; Skoczylas, Ł.; Czernicka, M.; Pitala, J. Selected Aspects of Iodate and Iodosalicylate Metabolism in Lettuce Including the Activity of Vanadium Dependent Haloperoxidases as Affected by Exogenous Vanadium. *Agronomy* **2019**, *10*, 1. [CrossRef]
37. Kiferle, C.; Martinelli, M.; Salzano, A.M.; Gonzali, S.; Beltrami, S.; Salvadori, P.A.; Hora, K.; Holwerda, H.T.; Scaloni, A.; Perata, P. Evidences for a Nutritional Role of Iodine in Plants. *Front. Plant Sci.* **2021**, *12*, 1–18. [CrossRef] [PubMed]
38. Koukkou, E.G.; Roupas, N.D.; Markou, K.B. Effect of Excess Iodine Intake on Thyroid on Human Health. *Minerva Med.* **2017**, *108*, 136–146. [CrossRef] [PubMed]
39. Zicker, S.; Schoenherr, B. Focus on Nutrition: The Role of Iodine in Nutrition and Metabolism. *Compend. Contin. Educ. Vet.* **2012**, *34*, E1–4. [PubMed]
40. Hulbert, A.J. Thyroid Hormones and Their Effects: A New Perspective. *Biol. Rev.* **2000**, *75*, 519–631. [CrossRef] [PubMed]
41. Köhrle, J. Thyroid Hormones and Derivatives: Endogenous Thyroid Hormones and Their Targets. In *Thyroid Hormone Nuclear Receptor*; Springer: Berlin, Germany, 2018; Volume 1897, pp. 85–104.
42. Citterio, C.E.; Targovnik, H.M.; Arvan, P. The Role of Thyroglobulin in Thyroid Hormonogenesis. *Nat. Rev. Endocrinol.* **2019**, *15*, 323–338. [CrossRef]
43. Dedieu, A.; Gaillard, J.-C.; Pourcher, T.; Darrouzet, E.; Armengaud, J. Revisiting Iodination Sites in Thyroglobulin with an Organ-Oriented Shotgun Strategy. *J. Biol. Chem.* **2011**, *286*, 259–269. [CrossRef]
44. Fong, P. Thyroid Iodide Efflux: A Team Effort? *J. Physiol.* **2011**, *589*, 5929–5939. [CrossRef]
45. Pereira, A.; Braekman, J.C.; Dumont, J.E.; Boeynaems, J.M. Identification of a Major Iodolipid from the Horse Thyroid Gland as 2-Iodoheptadecanal. *J. Biol. Chem.* **1990**, *265*, 17018–17025. [CrossRef]
46. Aceves, C.; Anguiano, B.; Delgado, G. Is Iodine a Gatekeeper of the Integrity of the Mammary Gland? *J. Mammary Gland Biol. Neoplasia* **2005**, *10*, 189–196. [CrossRef] [PubMed]
47. Zamocky, M.; Jakopitsch, C.; Furtmüller, P.G.; Dunand, C.; Obinger, C. The Peroxidase-Cyclooxygenase Superfamily: Reconstructed Evolution of Critical Enzymes of the Innate Immune System. *Proteins Struct. Funct. Bioinforma.* **2008**, *72*, 589–605. [CrossRef]
48. Chino, Y.; Saito, M.; Yamasu, K.; Suyemitsu, T.; Ishihara, K. Formation of the Adult Rudiment of Sea Urchins Is Influenced by Thyroid Hormones. *Dev. Biol.* **1994**, *161*, 1–11. [CrossRef]
49. Salvatore, G.; Covelli, I.; Roche, J. La Fixation Des Hormones Thyroïdiennes Par Escherichia Coli et Son Mécanisme. *Gen. Comp. Endocrinol.* **1963**, *3*, 15–25. [CrossRef]
50. Gräsbeck, R.; Lamberg, B.-A.; Björkstén, F. The Formation of Thyroxine Metabolites by Escherichia Coli. *Acta Endocrinol.* **1960**, XXXIV, 113–120. [CrossRef] [PubMed]
51. Gkotsi, D.S.; Ludewig, H.; Sharma, S.V.; Connolly, J.A.; Dhaliwal, J.; Wang, Y.; Unsworth, W.P.; Taylor, R.J.K.; McLachlan, M.M.W.; Shanahan, S.; et al. A Marine Viral Halogenase That Iodates Diverse Substrates. *Nat. Chem.* **2019**, *11*, 1091–1097. [CrossRef] [PubMed]
52. Kuhlisch, C.; Schleyer, G.; Shahaf, N.; Vincent, F.; Schatz, D.; Vardi, A. Viral Infection of Algal Blooms Leaves a Unique Metabolic Footprint on the Dissolved Organic Matter in the Ocean. *Sci. Adv.* **2021**, *7*, 1–14. [CrossRef]
53. Capriotti, K.; Pelletier, K.; Barone, S.; Capriotti, J. Efficacy of Dilute Povidone-Iodine against Multi- Drug Resistant Bacterial Biofilms, Fungal Biofilms and Fungal Spores. *J. Clin. Res. Dermatology* **2018**, *5*, 1–5.
54. Hoekstra, M.J.; Westgate, S.J.; Mueller, S. Povidone-Iodine Ointment Demonstrates in Vitro Efficacy against Biofilm Formation. *Int. Wound J.* **2017**, *14*, 172–179. [CrossRef]
55. Chang, S.L. The Use of Active Iodine as a Water Disinfectant. *J. Am. Pharm. Assoc.* **1958**, *47*, 417–423. [CrossRef]
56. HSU, Y.-C.; NOMURA, S.; KRUSÉ, C.W. Some Bactericidal and Virucidal Properties of Iodine Not Affecting Infectious RNA and DNA. *Am. J. Epidemiol.* **1965**, *82*, 317–328. [CrossRef]
57. Schreier, H.; Erdos, G.; Reimer, K.; König, B.; König, W.; Fleischer, W. Molecular Effects of Povidone-Iodine on Relevant Microorganisms: An Electron-Microscopic and Biochemical Study. *Dermatology* **1997**, *195*, 111–116. [CrossRef] [PubMed]
58. Simonsen, D.G. The Oxidation of Cysteine with Iodine: Formation of a Sulfinic Acid. *J. Biol. Chem.* **1933**, *101*, 35–42. [CrossRef]
59. Apostolov, K. The Effects of Iodine on the Biological Activities of Myxoviruses. *J. Hyg.* **1980**, *84*, 381–388. [CrossRef]

60. Kohler, H.; Jenzer, H. Interaction of Lactoperoxidase with Hydrogen Peroxide. Formation of Enzyme Intermediates and Generation of Free Radicals. *Free Radic. Biol. Med.* **1989**, *6*, 323–339. [\[CrossRef\]](#)
61. Winkler, R. Iodine—A Potential Antioxidant and the Role of Iodine/Iodide in Health and Disease. *Nat. Sci.* **2015**, *07*, 548–557. [\[CrossRef\]](#)
62. Thomas, E.L.; Aune, T.M. Lactoperoxidase, Peroxide, Thiocyanate Antimicrobial System: Correlation of Sulfhydryl Oxidation with Antimicrobial Action. *Infect. Immun.* **1978**, *20*, 456–463. [\[CrossRef\]](#) [\[PubMed\]](#)
63. Thomas, E.L.; Aune, T.M. Cofactor Role of Iodide in Peroxidase Antimicrobial Action against Escherichia Coli. *Antimicrob. Agents Chemother.* **1978**, *13*, 1000–1005. [\[CrossRef\]](#)
64. Fischer, A.J.; Lennemann, N.J.; Krishnamurthy, S.; Pócza, P.; Durairaj, L.; Launspach, J.L.; Rhein, B.A.; Wohlford-Lenane, C.; Lorentzen, D.; Bánfi, B.; et al. Enhancement of Respiratory Mucosal Antiviral Defenses by the Oxidation of Iodide. *Am. J. Respir. Cell Mol. Biol.* **2011**, *45*, 874–881. [\[CrossRef\]](#) [\[PubMed\]](#)
65. Rohner, F.; Zimmermann, M.; Jooste, P.; Pandav, C.; Caldwell, K.; Raghavan, R.; Raiten, D.J. Biomarkers of Nutrition for Development—Iodine Review. *J. Nutr.* **2014**, *144*, 1322S–1342S. [\[CrossRef\]](#)
66. Zimmermann, M.B.; Jooste, P.L.; Pandav, C.S. Iodine-Deficiency Disorders. *Lancet* **2008**, *372*, 1251–1262. [\[CrossRef\]](#)
67. Laurberg, P.; Pedersen, I.; Carlé, A.; Andersen, S.; Knudsen, N.; Ovesen, L. The U-Shaped Curve of Iodine Intake and Thyroid Disorders. In *Comprehensive Handbook on Iodine: Nutritional, Endocrine and Pathological Aspects*; Preedy, V.R., Burrow, G.N., Ross Watson, R., Eds.; Elsevier: Amsterdam, The Netherlands, 2009; pp. 449–555.
68. McCarrison, R. Observations on Endemic Cretinism In The Chitral And Gilgit Valleys.1. *Lancet* **1908**, *172*, 1275–1280. [\[CrossRef\]](#)
69. Dreger, S.; Pfänder, M.; Christianson, L.; Lhachimi, S.K.; Zeeb, H. The Effects of Iodine Blocking Following Nuclear Accidents on Thyroid Cancer, Hypothyroidism, and Benign Thyroid Nodules: Design of a Systematic Review. *Syst. Rev.* **2015**, *4*, 126. [\[CrossRef\]](#)
70. Jin, M.; Zhang, Z.; Li, Y.; Teng, D.; Shi, X.; Ba, J.; Chen, B.; Du, J.; He, L.; Lai, X.; et al. U-Shaped Associations Between Urinary Iodine Concentration and the Prevalence of Metabolic Disorders: A Cross-Sectional Study. *Thyroid* **2020**, *30*, 1053–1065. [\[CrossRef\]](#)
71. Pretell, E.A.; Delange, F.; Hostalek, U.; Corigliano, S.; Barreda, L.; Higa, A.M.; Altschuler, N.; Barragán, D.; Cevallos, J.L.; Gonzales, O.; et al. Iodine Nutrition Improves in Latin America. *Thyroid* **2004**, *14*, 590–599. [\[CrossRef\]](#) [\[PubMed\]](#)
72. Michikawa, T.; Inoue, M.; Shimazu, T.; Sawada, N.; Iwasaki, M.; Sasazuki, S.; Yamaji, T.; Tsugane, S. Seaweed Consumption and the Risk of Thyroid Cancer in Women: The Japan Public Health Center-Based Prospective Study. *Eur. J. Cancer Prev.* **2012**, *21*, 254–260. [\[CrossRef\]](#)
73. Bogazzi, F.; Tomisti, L.; Bartalena, L.; Aghini-Lombardi, F.; Martino, E. Amiodarone and the Thyroid: A 2012 Update. *J. Endocrinol. Investig.* **2012**, *35*, 340–348.
74. Rhee, C.M. Association Between Iodinated Contrast Media Exposure and Incident Hyperthyroidism and Hypothyroidism. *Arch. Intern. Med.* **2012**, *172*, 153. [\[CrossRef\]](#) [\[PubMed\]](#)
75. Nobukuni, K.; Hayakawa, N.; Namba, R.; Ihara, Y.; Sato, K.; Takada, H.; Hayabara, T.; Kawahara, S. The Influence of Long-Term Treatment with Povidone-Iodine on Thyroid Function. *Dermatology* **1997**, *195*, 69–72. [\[CrossRef\]](#)
76. Fiore, E.; Latrofa, F.; Vitti, P. Iodine, Thyroid Autoimmunity and Cancer. *Eur. Thyroid J.* **2015**, *4*, 26. [\[CrossRef\]](#)
77. Teti, C.; Panciroli, M.; Nazzari, E.; Pesce, G.; Mariotti, S.; Olivieri, A.; Bagnasco, M. Iodophylaxis and Thyroid Autoimmunity: An Update. *Immunol. Res.* **2021**, *69*, 129–138. [\[CrossRef\]](#)
78. Leung, A.M.; Braverman, L.E. Consequences of Excess Iodine. *Nat. Rev. Endocrinol.* **2014**, *10*, 136–142. [\[CrossRef\]](#)
79. Laurberg, P.; Andersen, S.; Pedersen, I.B.; Carlé, A. How Do We Optimize Iodine Intake to Minimize the Occurrence of Thyroid Disorders in Europe? *Hot Thyroidol.* **2007**.
80. Zava, T.T.; Zava, D.T. Assessment of Japanese Iodine Intake Based on Seaweed Consumption in Japan: A Literature-Based Analysis. *Thyroid Res.* **2011**, *4*, 1–7. [\[CrossRef\]](#)
81. Buell, P. Changing Incidence of Breast Cancer in Japanese-American Women. *JNCI J. Natl. Cancer Inst.* **1973**, *51*, 1479–1483. [\[CrossRef\]](#)
82. Shimizu, H.; Ross, R.; Bernstein, L.; Yatani, R.; Henderson, B.; Mack, T. Cancers of the Prostate and Breast among Japanese and White Immigrants in Los Angeles County. *Br. J. Cancer* **1991**, *63*, 963–966. [\[CrossRef\]](#) [\[PubMed\]](#)
83. Statista Research Department Statistics in State of Health. Available online: <https://www.statista.com> (accessed on 15 April 2022).
84. Sharma, A.; Stan, M.N. Thyrotoxicosis: Diagnosis and Management. *Mayo Clin. Proc.* **2019**, *94*, 1048–1064. [\[CrossRef\]](#)
85. Horn-Ross, P.L.; Morris, J.S.; Lee, M.; West, D.W.; Whittemore, A.S.; McDougall, I.R.; Nowels, K.; Stewart, S.L.; Spate, V.L.; Shiao, A.C.; et al. Iodine and Thyroid Cancer Risk among Women in a Multiethnic Population: The Bay Area Thyroid Cancer Study. *Cancer Epidemiol Biomarkers Prev.* **2001**, *10*, 979–985.
86. Zimmermann, M.B.; Galetti, V. Iodine Intake as a Risk Factor for Thyroid Cancer: A Comprehensive Review of Animal and Human Studies. *Thyroid Res.* **2015**, *8*, 8. [\[CrossRef\]](#) [\[PubMed\]](#)
87. Huwiler, M.; Bürgi, U.; Kohler, H. Mechanism of Enzymatic and Non-Enzymatic Tyrosine Iodination. Inhibition by Excess Hydrogen Peroxide and/or Iodide. *Eur. J. Biochem.* **1985**, *147*, 469–476. [\[CrossRef\]](#) [\[PubMed\]](#)
88. Song, Y.; Massart, C.; Chico-Galdo, V.; Jin, L.; De Maertelaer, V.; Decoster, C.; Dumont, J.E.; Van Sande, J. Species Specific Thyroid Signal Transduction: Conserved Physiology, Divergent Mechanisms. *Mol. Cell. Endocrinol.* **2010**, *319*, 56–62. [\[CrossRef\]](#)
89. Ren, B.; Zhu, Y. A New Perspective on Thyroid Hormones: Crosstalk with Reproductive Hormones in Females. *Int. J. Mol. Sci.* **2022**, *23*, 2708. [\[CrossRef\]](#)

90. Milanesi, A.; Brent, G.A. Iodine and Thyroid Hormone Synthesis, Metabolism, and Action. In *Molecular, Genetic, and Nutritional Aspects of Major and Trace Minerals*; Elsevier: Amsterdam, The Netherlands, 2017; Volume 1896, pp. 143–150.
91. Filetti, S.; Bidart, J.; Arturi, F.; Caillou, B.; Russo, D.; Schlumberger, M. Sodium/Iodide Symporter: A Key Transport System in Thyroid Cancer Cell Metabolism. *Eur. J. Endocrinol.* **1999**, 443–457. [[CrossRef](#)]
92. Nicola, J.P.; Basquin, C.; Portulano, C.; Reyna-Neyra, A.; Paroder, M.; Carrasco, N. The Na⁺/I⁻ Symporter Mediates Active Iodide Uptake in the Intestine. *Am. J. Physiol.-Cell Physiol.* **2009**, 296, 654–662. [[CrossRef](#)] [[PubMed](#)]
93. Khan, Y.S.; Farhana, A. Histology, Thyroid Gland. *StatPearls* **2019**.
94. Darrouzet, E.; Lindenthal, S.; Marcellin, D.; Pellequer, J.L.; Pourcher, T. The Sodium/Iodide Symporter: State of the Art of Its Molecular Characterization. *Biochim. Biophys. Acta - Biomembr.* **2014**, 1838, 244–253. [[CrossRef](#)] [[PubMed](#)]
95. Silveira, J.C.; Kopp, P.A. Pendrin and Anoctamin as Mediators of Apical Iodide Efflux in Thyroid Cells. *Curr. Opin. Endocrinol. Diabetes Obes.* **2015**, 22, 374–380. [[CrossRef](#)] [[PubMed](#)]
96. Yu, M.; Wei, Y.; Wang, P.; Deng, Z.; Mao, J.; Zhu, L.; Chen, L.; Peng, S.; Wang, L. Excess Iodide-Induced Reactive Oxygen Species Elicit Iodide Efflux via β -Tubulin-Associated CIC-3 in Thyrocytes. *Biochem. J.* **2022**, 479, 629–640. [[CrossRef](#)]
97. De La Vieja, A.; Santisteban, P. Role of Iodide Metabolism in Physiology and Cancer. *Endocr. Relat. Cancer* **2018**, 25, R225–R245. [[CrossRef](#)]
98. Smyth, P.P.A. Role of Iodine in Antioxidant Defence in Thyroid and Breast Disease. *BioFactors* **2003**, 19, 121–130. [[CrossRef](#)] [[PubMed](#)]
99. Vermot, A.; Petit-Härtlein, I.; Smith, S.M.E.; Fieschi, F. NADPH Oxidases (NOX): An Overview from Discovery, Molecular Mechanisms to Physiology and Pathology. *Antioxidants* **2021**, 10, 890. [[CrossRef](#)]
100. Kopp, P.A. Reduce, Recycle, Reuse—Iodotyrosine Deiodinase in Thyroid Iodide Metabolism. *N. Engl. J. Med.* **2008**, 358, 1856–1859. [[CrossRef](#)]
101. Nicoloff, J.T.; Low, J.C.; Dussault, J.H.; Fisher, D.A. Simultaneous Measurement of Thyroxine and Triiodothyronine Peripheral Turnover Kinetics in Man. *J. Clin. Invest.* **1972**, 51, 473–483. [[CrossRef](#)] [[PubMed](#)]
102. Gomes-Lima, C.; Burman, K.D. Reverse T₃ or Perverse T₃? Still Puzzling after 40 Years. *Cleve. Clin. J. Med.* **2018**, 85, 450–455. [[CrossRef](#)]
103. Kelly, G.S. Peripheral Metabolism of Thyroid Hormones: A Review. *Altern. Med. Rev.* **2000**, 5, 306–333.
104. DISTEFANO, J.J. Excretion, Metabolism and Enterohepatic Circulation Pathways and Their Role in Overall Thyroid Hormone Regulation in the Rat. *Am. Zool.* **1988**, 28, 373–387. [[CrossRef](#)]
105. DiStefano, J.J.; De Luze, A.; Nguyen, T.T. Binding and Degradation of 3,5,3'-Triiodothyronine and Thyroxine by Rat Intestinal Bacteria. *Am. J. Physiol. -Endocrinol. Metab.* **1993**, 264, 6. [[CrossRef](#)]
106. Rutgers, M.; Heusdens, F.A.; Bonthuis, F.; de Herder, W.W.; Hazenberg, M.P.; Visser, T.J. Enterohepatic Circulation of Triiodothyronine (T₃) in Rats: Importance of the Microflora for the Liberation and Reabsorption of T₃ from Biliary T₃ Conjugates. *Endocrinology* **1989**, 125, 2822–2830. [[CrossRef](#)]
107. Fröhlich, E.; Wahl, R. Microbiota and Thyroid Interaction in Health and Disease. *Trends Endocrinol. Metab.* **2019**, 30, 479–490. [[CrossRef](#)] [[PubMed](#)]
108. Bargiel, P.; Szczuko, M.; Stachowska, L.; Prowans, P.; Czapla, N.; Markowska, M.; Petriczko, J.; Kledzik, J.; Jędrzejczyk-Kledzik, A.; Palma, J.; et al. Microbiome Metabolites and Thyroid Dysfunction. *J. Clin. Med.* **2021**, 10, 3609. [[CrossRef](#)] [[PubMed](#)]
109. Anyetel-Anum, C.S.; Roggero, V.R.; Allison, L.A. Thyroid Hormone Receptor Localization in Target Tissues. *J. Endocrinol.* **2018**, 237, R19–R34. [[CrossRef](#)]
110. Visser, W.E.; Friesema, E.C.H.; Visser, T.J. Minireview: Thyroid Hormone Transporters: The Knowns and the Unknowns. *Mol. Endocrinol.* **2011**, 25, 1–14. [[CrossRef](#)] [[PubMed](#)]
111. Pizzagalli, F.; Hagenbuch, B.; Stieger, B.; Klenk, U.; Folkers, G.; Meier, P.J. Identification of a Novel Human Organic Anion Transporting Polypeptide as a High Affinity Thyroxine Transporter. *Mol. Endocrinol.* **2002**, 16, 2283–2296. [[CrossRef](#)]
112. Bakker, O. Thyroid Hormone Receptors. In *Encyclopedia of Endocrine Diseases*; Elsevier: Amsterdam, The Netherlands, 2004; pp. 490–495.
113. Cheng, S.-Y.; Leonard, J.L.; Davis, P.J. Molecular Aspects of Thyroid Hormone Actions. *Endocr. Rev.* **2010**, 31, 139–170. [[CrossRef](#)]
114. De Vito, P.; Incerpi, S.; Pedersen, J.Z.; Luly, P.; Davis, F.B.; Davis, P.J. Thyroid Hormones as Modulators of Immune Activities at the Cellular Level. *Thyroid* **2011**, 21, 879–890. [[CrossRef](#)] [[PubMed](#)]
115. Flamant, F.; Cheng, S.-Y.; Hollenberg, A.N.; Moeller, L.C.; Samarut, J.; Wondisford, F.E.; Yen, P.M.; Refetoff, S. Thyroid Hormone Signaling Pathways: Time for a More Precise Nomenclature. *Endocrinology* **2017**, 158, 2052–2057. [[CrossRef](#)]
116. Cioffi, F.; Giacco, A.; Goglia, F.; Silvestri, E. Bioenergetic Aspects of Mitochondrial Actions of Thyroid Hormones. *Cells* **2022**, 11, 997. [[CrossRef](#)] [[PubMed](#)]
117. Pessemesse, L.; Lepourry, L.; Bouton, K.; Levin, J.; Cabello, G.; Wrutniak-Cabello, C.; Casas, F. P28, a Truncated Form of TR α 1 Regulates Mitochondrial Physiology. *FEBS Lett.* **2014**, 588, 4037–4043. [[CrossRef](#)]
118. Leonard, J.L.; Farwell, A.P. Thyroid Hormone-Regulated Actin Polymerization in Brain. *Thyroid* **2009**, 7, 147–151. [[CrossRef](#)] [[PubMed](#)]
119. Medina-Gomez, G.; Hernández, A.; Calvo, R.M.; Martin, E.; Obregón, M.J. Potent Thermogenic Action of Triiodothyroacetic Acid in Brown Adipocytes. *Cell. Mol. Life Sci. C* **2003**, 60, 1957–1967. [[CrossRef](#)] [[PubMed](#)]

120. Senese, R.; Cioffi, F.; de Lange, P.; Goglia, F.; Lanni, A. Thyroid: Biological Actions of ‘Nonclassical’ Thyroid Hormones. *J. Endocrinol.* **2014**, *221*, R1–R12. [[CrossRef](#)] [[PubMed](#)]
121. Chiellini, G.; Frascarelli, S.; Ghelardoni, S.; Carnicelli, V.; Tobias, S.C.; DeBarber, A.; Brogioni, S.; Ronca-Testoni, S.; Cerbai, E.; Grandy, D.K.; et al. Cardiac Effects of 3-Iodothyronamine: A New Aminergic System Modulating Cardiac Function. *FASEB J.* **2007**, *21*, 1597–1608. [[CrossRef](#)] [[PubMed](#)]
122. Giammanco, M.; Di Liegro, C.M.; Schiera, G.; Di Liegro, I. Genomic and Non-Genomic Mechanisms of Action of Thyroid Hormones and Their Catabolite 3,5-Diiodo-L-Thyronine in Mammals. *Int. J. Mol. Sci.* **2020**, *21*, 4140. [[CrossRef](#)] [[PubMed](#)]
123. Manzon, R.G.; Manzon, L.A. Lamprey Metamorphosis: Thyroid Hormone Signaling in a Basal Vertebrate. *Mol. Cell. Endocrinol.* **2017**, *459*, 28–42. [[CrossRef](#)]
124. Klootwijk, W.; Friesema, E.C.H.; Visser, T.J. A Nonselenoprotein from *Amphioxus* Deiodinates Triac But Not T3: Is Triac the Primordial Bioactive Thyroid Hormone? *Endocrinology* **2011**, *152*, 3259–3267. [[CrossRef](#)] [[PubMed](#)]
125. Taylor, E.; Heyland, A. Evolution of Thyroid Hormone Signaling in Animals: Non-Genomic and Genomic Modes of Action. *Mol. Cell. Endocrinol.* **2017**, *459*, 14–20. [[CrossRef](#)]
126. Bertrand, S.; Brunet, F.G.; Escriva, H.; Parmentier, G.; Laudet, V.; Robinson-Rechavi, M. Evolutionary Genomics of Nuclear Receptors: From Twenty-Five Ancestral Genes to Derived Endocrine Systems. *Mol. Biol. Evol.* **2004**, *21*, 1923–1937. [[CrossRef](#)] [[PubMed](#)]
127. Wu, W.; Niles, E.G.; LoVerde, P.T. Thyroid Hormone Receptor Orthologues from Invertebrate Species with Emphasis on *Schistosoma mansoni*. *BMC Evol. Biol.* **2007**, *7*, 1–16. [[CrossRef](#)] [[PubMed](#)]
128. Berking, S.; Czech, N.; Gerharz, M.; Herrmann, K.; Hoffmann, U.; Raifer, H.; Sekul, G.; Siefker, B.; Sommerei, A.; Vedder, F. A Newly Discovered Oxidant Defence System and Its Involvement in the Development of *Aurelia aurita* (Scyphozoa, Cnidaria): Reactive Oxygen Species and Elemental Iodine Control Medusa Formation. *Int. J. Dev. Biol.* **2005**, *49*, 969–976. [[CrossRef](#)]
129. Eales, J.G. Iodine Metabolism and Thyroid-Related Functions in Organisms Lacking Thyroid Follicles: Are Thyroid Hormones Also Vitamins? *Exp. Biol. Med.* **1997**, *214*, 302–317. [[CrossRef](#)]
130. Mourouzis, I.; Lavecchia, A.M.; Xinaris, C. Thyroid Hormone Signalling: From the Dawn of Life to the Bedside. *J. Mol. Evol.* **2020**, *88*, 88–103. [[CrossRef](#)]
131. Schieber, M.; Chandel, N.S. ROS Function in Redox Signaling and Oxidative Stress. *Curr. Biol.* **2014**, *24*, R453–R462. [[CrossRef](#)] [[PubMed](#)]
132. Kochman, J.; Jakubczyk, K.; Bargiel, P.; Janda-Milczarek, K. The Influence of Oxidative Stress on Thyroid Diseases. *Antioxidants* **2021**, *10*, 1442. [[CrossRef](#)]
133. Lushchak, V.I. Free Radicals, Reactive Oxygen Species, Oxidative Stress and Its Classification. *Chem. Biol. Interact.* **2014**, *224*, 164–175. [[CrossRef](#)] [[PubMed](#)]
134. Nagababu, E.; Mohanty, J.G.; Friedman, J.S.; Rifkind, J.M. Role of Peroxiredoxin-2 in Protecting RBCs from Hydrogen Peroxide-Induced Oxidative Stress. *Free Radic. Res.* **2013**, *47*, 164–171. [[CrossRef](#)]
135. Jung, C.; Rong, Y.; Doctrow, S.; Baudry, M.; Malfroy, B.; Xu, Z. Synthetic Superoxide Dismutase/Catalase Mimetics Reduce Oxidative Stress and Prolong Survival in a Mouse Amyotrophic Lateral Sclerosis Model. *Neurosci. Lett.* **2001**, *304*, 157–160. [[CrossRef](#)]
136. Polefka, T.G.; Meyer, T.A.; Agin, P.P.; Bianchini, R.J. Cutaneous Oxidative Stress. *J. Cosmet. Dermatol.* **2012**, *11*, 55–64. [[CrossRef](#)] [[PubMed](#)]
137. Küpper, F.C.; Schweigert, N.; Gall, E.A.; Legendre, J.; Vilter, H.; Kloareg, B. Iodine Uptake in Laminariales Involves Extracellular, Haloperoxidase-Mediated Oxidation of Iodide. *Planta* **1998**, *207*, 163–171. [[CrossRef](#)]
138. Mohammad, A.; Liebhaufsky, H.A. The Kinetics of the Reduction of Hydrogen Peroxide by the Halides. *J. Am. Chem. Soc.* **1934**, *56*, 1680–1685. [[CrossRef](#)]
139. Stanbury, D.M. Reduction Potentials Involving Inorganic Free Radicals in Aqueous Solution. In *Advances in Inorganic Chemistry*; Elsevier: Amsterdam, The Netherlands, 1989; Volume 33, pp. 69–138.
140. Küpper, F.C.; Carrano, C.J. Key Aspects of the Iodine Metabolism in Brown Algae: A Brief Critical Review. *Metallomics* **2019**, *11*, 756–764. [[CrossRef](#)]
141. Küpper, F.C.; Carpenter, L.J.; Leblanc, C.; Toyama, C.; Uchida, Y.; Maskrey, B.H.; Robinson, J.; Verhaeghe, E.F.; Malin, G.; Luther, G.W.; et al. In Vivo Speciation Studies and Antioxidant Properties of Bromine in *Laminaria digitata* Reinforce the Significance of Iodine Accumulation for Kelps. *J. Exp. Bot.* **2013**, *64*, 2653–2664. [[CrossRef](#)] [[PubMed](#)]
142. Cosse, A.; Potin, P.; Leblanc, C. Patterns of Gene Expression Induced by Oligoguluronates Reveal Conserved and Environment-specific Molecular Defense Responses in the Brown Alga *Laminaria digitata*. *New Phytol.* **2009**, *182*, 239–250. [[CrossRef](#)]
143. Nitschke, U.; Stengel, D.B. Iodine Contributes to Osmotic Acclimatisation in the Kelp *Laminaria digitata* (Phaeophyceae). *Planta* **2014**, *239*, 521–530. [[CrossRef](#)]
144. Miller, A.E.M.M.; Heyland, A. Iodine Accumulation in Sea Urchin Larvae Is Dependent on Peroxide. *J. Exp. Biol.* **2012**, *216*, 915–926. [[CrossRef](#)] [[PubMed](#)]
145. Medrano-Macías, J.; Leija-Martínez, P.; González-Morales, S.; Juárez-Maldonado, A.; Benavides-Mendoza, A. Use of Iodine to Biofortify and Promote Growth and Stress Tolerance in Crops. *Front. Plant Sci.* **2016**, *7*, 1146. [[CrossRef](#)]
146. Blokhina, O.; Virolainen, E.; Fagerstedt, K. V Antioxidants, Oxidative Damage and Oxygen Deprivation Stress: A Review. *Ann. Bot.* **2003**, *91 Spec No*, 179–194. [[CrossRef](#)]

147. Khanna-Chopra, R.; Semwal, V.K. Superoxide Dismutase and Ascorbate Peroxidase Are Constitutively More Thermotolerant than Other Antioxidant Enzymes in *Chenopodium Album*. *Physiol. Mol. Biol. Plants* **2011**, *17*, 339–346. [\[CrossRef\]](#)
148. Gupta, N.; Shukla Bajpai, M.; Singh Majumdar, R.; Mishra, P.K. Response of Iodine on Antioxidant Levels of Glycine Max L. Grown under Cd Stress 2+. *Adv. Biol. Res. (Rennes)*. **2015**, *9*, 40–48.
149. Halka, M.; Smoleń, S.; Ledwożyw-Smoleń, I.; Sady, W. Comparison of Effects of Potassium Iodide and Iodosalicylates on the Antioxidant Potential and Iodine Accumulation in Young Tomato Plants. *J. Plant Growth Regul.* **2020**, *39*, 282–295. [\[CrossRef\]](#)
150. Weng, H.-X.; Yan, A.-L.; Hong, C.-L.; Xie, L.-L.; Qin, Y.-C.; Cheng, C.Q. Uptake of Different Species of Iodine by Water Spinach and Its Effect to Growth. *Biol. Trace Elem. Res.* **2008**, *124*, 184–194. [\[CrossRef\]](#) [\[PubMed\]](#)
151. Ameziane El Hassani, R.; Buffet, C.; Leboulleux, S.; Dupuy, C. Oxidative Stress in Thyroid Carcinomas: Biological and Clinical Significance. *Endocr. Relat. Cancer* **2019**, *26*, R131–R143. [\[CrossRef\]](#)
152. Bartosz, G. Total Antioxidant Capacity. *Adv. Clin. Chem.* **2003**, *37*, 219–292. [\[PubMed\]](#)
153. Weidinger, A.; Kozlov, A.V. Biological Activities of Reactive Oxygen and Nitrogen Species: Oxidative Stress versus Signal Transduction. *Biomolecules* **2015**, *5*, 472–484. [\[CrossRef\]](#)
154. Letai, A. Apoptosis and Cancer. *Annu. Rev. Cancer Biol.* **2017**, *1*, 275–294. [\[CrossRef\]](#)
155. Alfaro, Y.; Delgado, G.; Cárbaz, A.; Anguiano, B.; Aceves, C. Iodine and Doxorubicin, a Good Combination for Mammary Cancer Treatment: Antineoplastic Adjuvancy, Chemoresistance Inhibition, and Cardioprotection. *Mol. Cancer* **2013**, *12*, 45. [\[CrossRef\]](#)
156. Quintero-García, M.; Delgado-González, E.; Sánchez-Tusie, A.; Vázquez, M.; Aceves, C.; Anguiano, B. Iodine Prevents the Increase of Testosterone-Induced Oxidative Stress in a Model of Rat Prostatic Hyperplasia. *Free Radic. Biol. Med.* **2018**, *115*, 298–308. [\[CrossRef\]](#) [\[PubMed\]](#)
157. Winkler, R.; Griebenow, S.; Wonisch, W. Effect of Iodide on Total Antioxidant Status of Human Serum. *Cell Biochem. Funct.* **2000**, *18*, 143–146. [\[CrossRef\]](#)
158. Habibi, N.; Labrinidis, A.; Leemaqz, S.Y.L.; Jankovic-Karasoulos, T.; McCullough, D.; Grieger, J.A.; Gilbert, S.; Ricciardelli, C.; Zhou, S.J.; Perkins, A.V.; et al. Effect of Selenium and Iodine on Oxidative Stress in the First Trimester Human Placenta Explants. *Nutrients* **2021**, *13*, 800. [\[CrossRef\]](#) [\[PubMed\]](#)
159. Srivastava, R.; Tiwari, S.; Banakar, P.S.; Bhakat, M.; Mani, V.; Mohanty, T.K.; Mondal, G. Iodine Supplementation Improved Antioxidant Status, Hormonal Status, Sexual Behavior, and Semen Production Performance of Bos Indicus Bulls Under Tropical Climatic Condition. *Biol. Trace Elem. Res.* **2022**, 1–14. [\[CrossRef\]](#) [\[PubMed\]](#)
160. Fomichev, Y.P.; Nikanova, L.A. Increasing of the Reproductive Properties of Boar Semen While Using Organic Iodine in Feeding. *Russ. Agric. Sci.* **2017**, *43*, 419–422. [\[CrossRef\]](#)
161. Chakraborty, A.; Singh, V.; Singh, K.; Rajender, S. Excess Iodine Impairs Spermatogenesis by Inducing Oxidative Stress and Perturbing the Blood Testis Barrier. *Reprod. Toxicol.* **2020**, *96*, 128–140. [\[CrossRef\]](#)
162. Chakraborty, A.; Mandal, J.; Mondal, C.; Sinha, S.; Chandra, A.K. Effect of Excess Iodine on Oxidative Stress Markers, Steroidogenic-Enzyme Activities, Testicular Morphology, and Functions in Adult Male Rats. *Biol. Trace Elem. Res.* **2016**, *172*, 380–394. [\[CrossRef\]](#)
163. Lee, J.-M.; Johnson, J.A. An Important Role of Nrf2-ARE Pathway in the Cellular Defense Mechanism. *BMB Rep.* **2004**, *37*, 139–143. [\[CrossRef\]](#)
164. Kim, H.J.; Vaziri, N.D. Contribution of Impaired Nrf2-Keap1 Pathway to Oxidative Stress and Inflammation in Chronic Renal Failure. *Am. J. Physiol.-Ren. Physiol.* **2010**, *298*, 662–671. [\[CrossRef\]](#)
165. Ben-Yehuda Greenwald, M.; Frušić-Zlotkin, M.; Soroka, Y.; Ben-Sasson, S.; Bianco-Peled, H.; Kohen, R. A Novel Role of Topical Iodine in Skin: Activation of the Nrf2 Pathway. *Free Radic. Biol. Med.* **2017**, *104*, 238–248. [\[CrossRef\]](#) [\[PubMed\]](#)
166. Aceves, C.; Mendieta, I.; Anguiano, B.; Delgado-González, E. Molecular Iodine Has Extrathyroidal Effects as an Antioxidant, Differentiator, and Immunomodulator. *Int. J. Mol. Sci.* **2021**, *22*, 1228. [\[CrossRef\]](#) [\[PubMed\]](#)
167. Brash, A.R. Arachidonic Acid as a Bioactive Molecule. *J. Clin. Invest.* **2001**, *107*, 1339–1345. [\[CrossRef\]](#) [\[PubMed\]](#)
168. Dugrillon, A.; Uedelhoven, W.; Pisarev, M.; Bechtner, G.; Gärtner, R. Identification of δ -Iodolactone in Iodide Treated Human Goiter and Its Inhibitory Effect on Proliferation of Human Thyroid Follicles. *Horm. Metab. Res.* **1994**, *26*, 465–469. [\[CrossRef\]](#)
169. Schlorke, D.; Flemmig, J.; Birkemeyer, C.; Arnhold, J. Formation of Cyanogen Iodide by Lactoperoxidase. *J. Inorg. Biochem.* **2016**, *154*, 35–41. [\[CrossRef\]](#)
170. Williams, R. Killing Controversy. *J. Exp. Med.* **2006**, *203*, 2404. [\[CrossRef\]](#)
171. Bilal, M.Y.; Dambaeva, S.; Kwak-Kim, J.; Gilman-Sachs, A.; Beaman, K.D. A Role for Iodide and Thyroglobulin in Modulating the Function of Human Immune Cells. *Front. Immunol.* **2017**, *8*, 1573. [\[CrossRef\]](#) [\[PubMed\]](#)
172. Stevenson, T.J.; Onishi, K.G.; Bradley, S.P.; Prendergast, B.J. Cell-Autonomous Iodothyronine Deiodinase Expression Mediates Seasonal Plasticity in Immune Function. *Brain. Behav. Immun.* **2014**, *36*, 61–70. [\[CrossRef\]](#)
173. Weetman, A.P.; McGregor, A.M.; Campbell, H.; Lazarus, J.H.; Ibbertson, H.K.; Hall, R. Iodide Enhances IgG Synthesis by Human Peripheral Blood Lymphocytes in Vitro. *Eur. J. Endocrinol.* **1983**, *103*, 210–215. [\[CrossRef\]](#)
174. Langer, R.; Burzler, C.; Bechtner, G.; Gärtner, R. Influence of Iodide and Iodolactones on Thyroid Apoptosis. Evidence That Apoptosis Induced by Iodide Is Mediated by Iodolactones in Intact Porcine Thyroid Follicles. *Exp. Clin. Endocrinol. Diabetes* **2003**, *111*, 325–329. [\[CrossRef\]](#)
175. Gärtner, R.; Dugrillon, A.; Bechtner, G. Evidence That Iodolactones Are the Mediators of Growth Inhibition by Iodine on the Thyroid. *Acta Med. Austriaca* **1996**, *23*, 47–51.

176. Gärtner, R.; Rank, P.; Ander, B. The Role of Iodine and δ -Iodolactone in Growth and Apoptosis of Malignant Thyroid Epithelial Cells and Breast Cancer Cells. *Hormones* **2010**, *9*, 60–66. [[CrossRef](#)] [[PubMed](#)]
177. Gärtner, R.; Schopohl, D.; Schaefer, S.; Dugrillon, A.; Erdmann, A.; Toda, S.; Bechtner, G. Regulation of Transforming Growth Factor Beta 1 Messenger Ribonucleic Acid Expression in Porcine Thyroid Follicles in Vitro by Growth Factors, Iodine, or Delta-Iodolactone. *Thyroid* **1997**, *7*, 633–640. [[CrossRef](#)]
178. Dugrillon, A. Iodolactones and Iodoaldehydes—Mediators of Iodine in Thyroid Autoregulation. *Exp. Clin. Endocrinol. Diabetes* **2009**, *104*, 41–45. [[CrossRef](#)] [[PubMed](#)]
179. Sassone-Corsi, P. The Cyclic AMP Pathway. *Cold Spring Harb. Perspect. Biol.* **2012**, *4*, a011148. [[CrossRef](#)]
180. Rodríguez-Castelán, J.; Delgado-González, E.; Rodríguez-Benítez, E.; Castelán, F.; Cuevas-Romero, E.; Aceves, C. SAT-561 Protective Effect of Moderated Dose of Iodine in Pancreatic Alterations during Hypothyroidism. *J. Endocr. Soc.* **2019**, *3*, SAT-561. [[CrossRef](#)]
181. Ahmadian, M.; Suh, J.M.; Hah, N.; Liddle, C.; Atkins, A.R.; Downes, M.; Evans, R.M. PPAR γ Signaling and Metabolism: The Good, the Bad and the Future. *Nat. Med.* **2013**, *19*, 557–566. [[CrossRef](#)]
182. Nava-Villalba, M.; Nuñez-Anita, R.E.; Bontempo, A.; Aceves, C. Activation of Peroxisome Proliferator-Activated Receptor Gamma Is Crucial for Antitumoral Effects of 6-Iodolactone. *Mol. Cancer* **2015**, *14*, 1–11. [[CrossRef](#)]
183. Vitale, M.; Di Matola, T.; D'Ascoli, F.; Salzano, S.; Bogazzi, F.; Fenzi, G.; Martino, E.; Rossi, G. Iodide Excess Induces Apoptosis in Thyroid Cells through a P53-Independent Mechanism Involving Oxidative Stress1. *Endocrinology* **2000**, *141*, 598–605. [[CrossRef](#)] [[PubMed](#)]
184. Mendieta, I.; Nuñez-Anita, R.E.; Nava-Villalba, M.; Zambrano-Estrada, X.; Delgado-González, E.; Anguiano, B.; Aceves, C. Molecular Iodine Exerts Antineoplastic Effects by Diminishing Proliferation and Invasive Potential and Activating the Immune Response in Mammary Cancer Xenografts. *BMC Cancer* **2019**, *19*, 261. [[CrossRef](#)]
185. Shrivastava, A.; Tiwari, M.; Sinha, R.A.; Kumar, A.; Balapure, A.K.; Bajpai, V.K.; Sharma, R.; Mitra, K.; Tandon, A.; Godbole, M.M. Molecular Iodine Induces Caspase-Independent Apoptosis in Human Breast Carcinoma Cells Involving the Mitochondria-Mediated Pathway. *J. Biol. Chem.* **2006**, *281*, 19762–19771. [[CrossRef](#)] [[PubMed](#)]
186. Fulda, S.; Debatin, K.-M. Extrinsic versus Intrinsic Apoptosis Pathways in Anticancer Chemotherapy. *Oncogene* **2006**, *25*, 4798–4811. [[CrossRef](#)]
187. Arroyo-Helguera, O.; Anguiano, B.; Delgado, G.; Aceves, C. Uptake and Antiproliferative Effect of Molecular Iodine in the MCF-7 Breast Cancer Cell Line. *Endocr. Relat. Cancer* **2006**, *13*, 1147–1158. [[CrossRef](#)] [[PubMed](#)]
188. Aceves, C.; García-Solís, P.; Arroyo-Helguera, O.; Vega-Riveroll, L.; Delgado, G.; Anguiano, B. Antineoplastic Effect of Iodine in Mammary Cancer: Participation of 6-Iodolactone (6-IL) and Peroxisome Proliferator-Activated Receptors (PPAR). *Mol. Cancer* **2009**, *8*, 33. [[CrossRef](#)]
189. Bigoni-Ordóñez, G.D.; Ortiz-Sánchez, E.; Rosendo-Chalma, P.; Valencia-González, H.A.; Aceves, C.; García-Carrancá, A. Molecular Iodine Inhibits the Expression of Stemness Markers on Cancer Stem-like Cells of Established Cell Lines Derived from Cervical Cancer. *BMC Cancer* **2018**, *18*, 1–12. [[CrossRef](#)]
190. García-Solís, P.; Alfaro, Y.; Anguiano, B.; Delgado, G.; Guzman, R.C.; Nandi, S.; Díaz-Muñoz, M.; Vázquez-Martínez, O.; Aceves, C. Inhibition of N-Methyl-N-Nitrosourea-Induced Mammary Carcinogenesis by Molecular Iodine (I₂) but Not by Iodide (I[−]) Treatment. *Mol. Cell. Endocrinol.* **2005**, *236*, 49–57. [[CrossRef](#)] [[PubMed](#)]
191. Juríková, M.; Danihel, L.; Polák, Š.; Varga, I. Ki67, PCNA, and MCM Proteins: Markers of Proliferation in the Diagnosis of Breast Cancer. *Acta Histochem.* **2016**, *118*, 544–552. [[CrossRef](#)]
192. Álvarez-León, W.; Mendieta, I.; Delgado-González, E.; Anguiano, B.; Aceves, C. Molecular Iodine/Cyclophosphamide Synergism on Chemoresistant Neuroblastoma Models. *Int. J. Mol. Sci.* **2021**, *22*, 8936.
193. FitzGerald, G.A. COX-2 and beyond: Approaches to Prostaglandin Inhibition in Human Disease. *Nat. Rev. Drug Discov.* **2003**, *2*, 879–890. [[CrossRef](#)]
194. Hussain, T.; Gupta, S.; Mukhtar, H. Cyclooxygenase-2 and Prostate Carcinogenesis. *Cancer Lett.* **2003**, *191*, 125–135. [[CrossRef](#)]
195. Moreno-Vega, A.; Vega-Riveroll, L.; Ayala, T.; Peralta, G.; Torres-Martel, J.M.; Rojas, J.; Mondragón, P.; Domínguez, A.; De Obaldía, R.; Avelilla-Guerrero, C.; et al. Adjuvant Effect of Molecular Iodine in Conventional Chemotherapy for Breast Cancer. Randomized Pilot Study. *Nutrients* **2019**, *11*, 1623. [[CrossRef](#)] [[PubMed](#)]
196. Cuenca-Micó, O.; Delgado-González, E.; Anguiano, B.; Vaca-Paniagua, F.; Medina-Rivera, A.; Rodríguez-Dorantes, M.; Aceves, C. Effects of Molecular Iodine/Chemotherapy in the Immune Component of Breast Cancer Tumoral Microenvironment. *Biomolecules* **2021**, *11*, 1501. [[CrossRef](#)] [[PubMed](#)]
197. Aceves, C.; Anguiano, B.; Delgado, G. The Extrathyronine Actions of Iodine as Antioxidant, Apoptotic, and Differentiation Factor in Various Tissues. *Thyroid* **2013**, *23*, 938–946. [[CrossRef](#)]
198. Xu, J.; Yong, M.; Li, J.; Dong, X.; Yu, T.; Fu, X.; Hu, L. High Level of CFTR Expression Is Associated with Tumor Aggression and Knockdown of CFTR Suppresses Proliferation of Ovarian Cancer in Vitro and in Vivo. *Oncol. Rep.* **2015**, *33*, 2227–2234. [[CrossRef](#)]
199. Tu, Z.; Chen, Q.; Zhang, J.T.; Jiang, X.; Xia, Y.; Chan, H.C. CFTR Is a Potential Marker for Nasopharyngeal Carcinoma Prognosis and Metastasis. *Oncotarget* **2016**, *7*, 76955. [[CrossRef](#)]
200. Bilal, M.Y.; Dambueva, S.; Brownstein, D.; Kwak-Kim, J.; Gilman-Sachs, A.; Beaman, K.D. Iodide Transporters in the Endometrium: A Potential Diagnostic Marker for Women with Recurrent Pregnancy Failures. *Med. Princ. Pract.* **2020**, *29*, 412–421. [[CrossRef](#)] [[PubMed](#)]

201. Webb, B.A.; Chimenti, M.; Jacobson, M.P.; Barber, D.L. Dysregulated PH: A Perfect Storm for Cancer Progression. *Nat. Rev. Cancer* **2011**, *11*, 671–677. [CrossRef]
202. Chang, N.W.; Wu, C.T.; Chen, D.R.; Yeh, C.Y.; Lin, C. High Levels of Arachidonic Acid and Peroxisome Proliferator-Activated Receptor-Alpha in Breast Cancer Tissues Are Associated with Promoting Cancer Cell Proliferation. *J. Nutr. Biochem.* **2013**, *24*, 274–281. [CrossRef]
203. Wang, X.; Yan, F.; Wang, Q. Molecular Iodine: Catalysis in Heterocyclic Synthesis. *Synth. Commun.* **2021**, *51*, 1763–1781.
204. Bürgi, H.; Schaffner, T.; Seiler, J.P. The Toxicology of Iodate: A Review of the Literature. *Thyroid* **2001**, *11*, 449–456. [CrossRef]
205. Tekale, S.U.; Kauthale, S.S.; Dake, S.A.; Sarda, S.R.; Pawar, R.P. Molecular Iodine: An Efficient and Versatile Reagent for Organic Synthesis. *Curr. Org. Chem.* **2012**, *16*, 1485–1501. [CrossRef]
206. Dohi, T.; Kita, Y. Oxidizing Agents. In *Iodine Chemistry and Applications*; Kaiho, T., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2014; pp. 277–301.
207. World Health Organization. *WHO Model List of Essential Medicines—22nd List*; World Health Organization: Geneva, Switzerland, 2021; p. 66.
208. Lugol, J.G.A. Mémoire Sur l'Emploi de l'Iode Dans Les Maladies Scrofuleuses. *Glasgow Med. J.* **1832**, *5*, 83–92.
209. Fernández, L. Global Market Value of Iodine 2017 & 2024. Available online: <https://www.statista.com/statistics/1001959/market-value-iodine-worldwide/> (accessed on 2 March 2022).
210. Garside, M. Iodine Global Reserves by Countries 2020. Available online: <https://www.statista.com/statistics/264946/global-iodine-reserves-by-countries/> (accessed on 2 March 2022).
211. Garside, M. Major Countries in Iodine Production 2010–2020. Available online: <https://www.statista.com/statistics/264945/major-countries-in-iodine-production/> (accessed on 2 March 2022).
212. Rayyes, A.; Hamid, A. Technical Meeting of Project Counterparts on Cyclotron Production of I-123. In Proceedings of the Cyclotron production of Iodine-123, Sao Paulo, Brazil, 8–10 August 2001; International Atomic Energy Agency: Vienna, Brazil, 2002; pp. 81–89.
213. Chattopadhyay, S.; Saha Das, S. Recovery of ¹³¹I from Alkaline Solution of N-Irradiated Tellurium Target Using a Tiny Dowex-1 Column. *Appl. Radiat. Isot.* **2010**, *68*, 1967–1969. [CrossRef] [PubMed]
214. Statista Research Department Global Demand for Iodine by Application 2016. Available online: <https://www.statista.com/statistics/862097/global-iodine-demand-share-by-application/> (accessed on 2 March 2022).
215. Tang, Y.; Xu, Y.; Li, F.; Jmaiff, L.; Hrudey, S.E.; Li, X.-F. Nontargeted Identification of Peptides and Disinfection Byproducts in Water. *J. Environ. Sci.* **2016**, *42*, 259–266. [CrossRef]
216. Gao, Y.; Qiu, J.; Ji, Y.; Wawryk, N.J.P.; An, T.; Li, X.-F. Formation Mechanism of Iodinated Aromatic Disinfection Byproducts: Acid Catalysis with H₂OI⁺. *Environ. Sci. Technol.* **2022**, *56*, 1791–1800. [CrossRef]
217. Prütz, W.A.; Kissner, R.; Koppenol, W.H.; Rüegger, H. On the Irreversible Destruction of Reduced Nicotinamide Nucleotides by Hypohalous Acids. *Arch. Biochem. Biophys.* **2000**, *380*, 181–191. [CrossRef] [PubMed]
218. Reddy, J.M.; Knox, K.; Robin, M.B. Crystal Structure of HI 3 · 2C 6 H 5 CONH 2: A Model of the Starch—Iodine Complex. *J. Chem. Phys.* **1964**, *40*, 1082–1089. [CrossRef]
219. Makhayeva, D.N.; Irmukhametova, G.S.; Khutoryanskiy, V.V. Polymeric Iodophors: Preparation, Properties, and Biomedical Applications. *Rev. J. Chem.* **2020**, *10*, 40–57. [CrossRef] [PubMed]
220. Sukawa, H.; Yoda, Y.; Sugimoto, H.; Yoshida, S.; Yamamoto, T.; Kuroda, S.; Sanechika, K.; Nishinuma, M. Absorption of Iodine by Polymers and Electrochemical Response of Polymer Film in Aqueous Solution of Iodine. *Polym. J.* **1989**, *21*, 403–408. [CrossRef]
221. French, E.A.; Mukai, M.; Zurkowski, M.; Rauch, B.; Gioia, G.; Hillebrandt, J.R.; Henderson, M.; Schukken, Y.H.; Hemling, T.C. Iodide Residues in Milk Vary between Iodine-Based Teat Disinfectants. *J. Food Sci.* **2016**, *81*, T1864–T1870. [CrossRef]
222. Panlilio, A.L.; Beck-Sague, C.M.; Siegel, J.D.; Anderson, R.L.; Yetts, S.Y.; Clark, N.C.; Duer, P.N.; Thomassen, K.A.; Vess, R.W.; Hill, B.C.; et al. Infections and Pseudoinfections Due to Povidone-Iodine Solution Contaminated with *Pseudomonas Cepacia*. *Clin. Infect. Dis.* **1992**, *14*, 1078–1083. [CrossRef]
223. Berkelman, R.L.; Lewin, S.; Allen, J.R.; Anderson, R.L.; Budnick, L.D.; Shapiro, S.; Friedman, S.M.; Nicholas, P.; Holzman, R.S.; Haley, R.W. Pseudobacteremia Attributed to Contamination of Povidone-Iodine with *Pseudomonas Cepacia*. *Ann. Intern. Med.* **1981**, *95*, 32–36. [CrossRef]
224. Craven, D.E.; Moody, B.; Connolly, M.G.; Kollisch, N.R.; Stottmeier, K.D.; McCabe, W.R. Pseudobacteremia Caused by Povidone-Iodine Solution Contaminated with *Pseudomonas Cepacia*. *N. Engl. J. Med.* **2010**, *305*, 621–623. [CrossRef] [PubMed]
225. Berkelman, R.L.; Holland, B.W.; Anderson, R.L. Increased Bactericidal Activity of Dilute Preparations of Povidone-Iodine Solutions. *J. Clin. Microbiol.* **1982**, *15*, 635–639. [CrossRef]
226. Weber, D.J.; Rutala, W.A.; Sickbert-Bennett, E.E. Outbreaks Associated with Contaminated Antiseptics and Disinfectants. *Antimicrob. Agents Chemother.* **2007**, *51*, 4217–4224. [CrossRef] [PubMed]
227. Rösner, H.; Möller, W.; Groebner, S.; Torremante, P. Antiproliferative/Cytotoxic Effects of Molecular Iodine, Povidone-Iodine and Lugol's Solution in Different Human Carcinoma Cell Lines. *Oncol. Lett.* **2016**, *12*, 2159–2162. [CrossRef]
228. Piérard, G.E.; Piérard-Franchimont, C.; Arrese, J.E. Povidone-Iodine Wash Solutions in the Prevention of Superficial Fungal Infections; Predictive Evaluation Using the Corneofungimetry Bioassay. *Eur. J. Clin. Pharmacol.* **1997**, *53*, 101–104. [CrossRef] [PubMed]

229. Yu, H.; Tak-Yin, M. The Efficacy of Povidone-Iodine Pessaries in a Short, Low-Dose Treatment Regime on Candidal, Trichomonal and Non-Specific Vaginitis. *Postgrad. Med. J.* **1993**, *69* (Suppl. S3), S58–S61. [PubMed]
230. Gatti, S.; Cevini, C.; Bruno, A.; Penso, G.; Rama, P.; Scaglia, M. In Vitro Effectiveness of Povidone-Iodine on Acanthamoeba Isolates from Human Cornea. *Antimicrob. Agents Chemother.* **1998**, *42*, 2232–2234. [CrossRef] [PubMed]
231. Kawana, R.; Kitamura, T.; Nakagomi, O.; Matsumoto, I.; Arita, M.; Yoshihara, N.; Yanagi, K.; Yamada, A.; Morita, O.; Yoshida, Y.; et al. Inactivation of Human Viruses by Povidone-Iodine in Comparison with Other Antiseptics. *Dermatology* **1997**, *195*, 29–35. [CrossRef]
232. Asanaka, M. In Vitro Study on Inactivation of Various Viruses Including Human Immunodeficiency Virus (HIV) by PVP-I. Proc. First Asian/Pacific Congr. Antisepsis. 1988. Available online: <https://cir.nii.ac.jp/crid/1570009750369814784?lang=en> (accessed on 15 March 2022).
233. Sriwilaijaroen, N.; Wilairat, P.; Hiramatsu, H.; Takahashi, T.; Suzuki, T.; Ito, M.; Ito, Y.; Tashiro, M.; Suzuki, Y. Mechanisms of the Action of Povidone-Iodine against Human and Avian Influenza A Viruses: Its Effects on Hemagglutination and Sialidase Activities. *Virol. J.* **2009**, *6*, 124. [CrossRef]
234. Anderson, D.E.; Sivalingam, V.; Kang, A.E.Z.; Ananthanarayanan, A.; Arumugam, H.; Jenkins, T.M.; Hadjiat, Y.; Eggers, M. Povidone-Iodine Demonstrates Rapid In Vitro Virucidal Activity Against SARS-CoV-2, The Virus Causing COVID-19 Disease. *Infect. Dis. Ther.* **2020**, *9*, 669–675. [CrossRef] [PubMed]
235. Liang, B.; Yuan, X.; Wei, G.; Wang, W.; Zhang, M.; Peng, H.; Javer, A.; Mendenhall, M.; Julander, J.; Huang, S.; et al. In-Vivo Toxicity Studies and In-Vitro Inactivation of SARS-CoV-2 by Povidone-Iodine In-Situ Gel Forming Formulations. *bioRxiv* **2020**. bioRxiv:2020.05.18.103184.
236. Garcia-Sanchez, A.; Peña-Cardelles, J.F.; Ruiz, S.; Robles, F.; Ordonez-Fernandez, E.; Salgado-Peralvo, A.O.; Balloch, J.; Simon, J.C. Efficacy of Pre-Procedural Mouthwashes against SARS-CoV-2: A Systematic Review of Randomized Controlled Trials. *J. Clin. Med.* **2022**, *11*, 1692. [CrossRef] [PubMed]
237. Muppalaneni, S.; Omidian, H. Polyvinyl Alcohol in Medicine and Pharmacy: A Perspective. *J. Dev. Drugs* **2013**, *2*, 1–5. [CrossRef]
238. Miao, Z.; Sun, Y.; Tao, Z.; Chen, Y.; Ma, Y.; Zhu, D.; Huang, X.; Zha, Z. Thermochromic Polyvinyl Alcohol-Iodine Hydrogels with Safe Threshold Temperature for Infectious Wound Healing. *Adv. Healthc. Mater.* **2021**, *10*, 2100722. [CrossRef]
239. Montaser, A.S.; Rehan, M.; El-Naggar, M.E. PH-Thermosensitive Hydrogel Based on Polyvinyl Alcohol/Sodium Alginate/N-Isopropyl Acrylamide Composite for Treating Re-Infected Wounds. *Int. J. Biol. Macromol.* **2019**, *124*, 1016–1024. [CrossRef]
240. World Health Organization/United Nations Children’s Fund (UNICEF)/International Council for Control of Iodine Deficiency Disorders. *Review of Findings from 7-Country Study in Africa on Levels of Salt Iodization in Relation to Iodine Deficiency Disorders, Including Iodine-Induced Hyperthyroidism*; WHO, UNICEF, ICCIDD: Geneva, Switzerland, 1996.
241. Nagataki, S. The Average of Dietary Iodine Intake Due to the Ingestion of Seaweeds Is 1.2 Mg/Day in Japan. *Thyroid* **2008**, *18*, 667–668. [CrossRef]
242. Farebrother, J.; Zimmermann, M.B.; Andersson, M. Excess Iodine Intake: Sources, Assessment, and Effects on Thyroid Function. *Ann. N. Y. Acad. Sci.* **2019**, *1446*, 44–65. [CrossRef]
243. Backer, H.; Hollowell, J. Use of Iodine for Water Disinfection: Iodine Toxicity and Maximum Recommended Dose. *Environ. Health Perspect.* **2000**, *108*, 679–684. [CrossRef]
244. World Health Organization. *Vitamin and Mineral Requirements in Human Nutrition*, 2nd ed; World Health Organization: Geneva, Switzerland, 2005.
245. World Health Organization. *Urinary Iodine Concentrations for Determining Iodine Status in Populations*; World Health Organization: Geneva, Switzerland, 2013.
246. Ristic-Medic, D.; Piskackova, Z.; Hooper, L.; Ruprich, J.; Casgrain, A.; Ashton, K.; Pavlovic, M.; Glibetic, M. Methods of Assessment of Iodine Status in Humans: A Systematic Review. *Am. J. Clin. Nutr.* **2009**, *89*, 2052S–2069S. [CrossRef] [PubMed]
247. Milagres, R.C.; de Souza, E.C.G.; Peluzio, M.; Franceschini, S.; Duarte, M.S.L. Food Iodine Content Table Compiled from International Databases. *Rev. Nutr.* **2020**, *33*, 1–12. [CrossRef]
248. Venkatesh Mannar, M.G.; Dunn, J.T.; World Health Organization. *Salt Iodization for the Elimination of Iodine Deficiency*; International Council for Control of Iodine Deficiency Disorders: Brussels; Belgium, 1995.
249. World Health Organization Guideline. In *Fortification of Food-Grade Salt with Iodine for the Prevention and Control of Iodine Deficiency Disorders*; World Health Organization: Geneva, Switzerland, 2014.
250. UNICEF Worldwide, 89 per Cent of People Consume Iodized Salt. Available online: <https://data.unicef.org/topic/nutrition/iodine/> (accessed on 15 March 2022).
251. Chavasit, V.; Malaivongse, P.; Judprasong, K. Study on Stability of Iodine in Iodated Salt by Use of Different Cooking Model Conditions. *J. Food Compos. Anal.* **2002**, *15*, 265–276. [CrossRef]
252. Diosady, L.L.; Alberti, J.O.; Mannar, M.G.V.; FitzGerald, S. Stability of Iodine in Iodized Salt Used for Correction of Iodine-Deficiency Disorders. II. *Food Nutr. Bull.* **1998**, *19*, 240–250. [CrossRef]
253. Stansbury, J.; Saunders, P.; Winston, D. Promoting Healthy Thyroid Function with Iodine, Bladderwrack, Guggul and Iris. *J. Restor. Med.* **2012**, *1*, 83–90. [CrossRef]
254. Zimmermann, M.; Delange, F. Iodine Supplementation of Pregnant Women in Europe: A Review and Recommendations. *Eur. J. Clin. Nutr.* **2004**, *58*, 979–984.

255. Leung, A.M.; Pearce, E.N.; Braverman, L.E. Iodine Content of Prenatal Multivitamins in the United States. *N. Engl. J. Med.* **2009**, *360*, 939–940. [[CrossRef](#)] [[PubMed](#)]
256. Hennessey, J.V. The Emergence of Levothyroxine as a Treatment for Hypothyroidism. *Endocr.* **2016**, *55*, 6–18.
257. Knezevic, J.; Starchl, C.; Tmava Berisha, A.; Amrein, K. Thyroid-Gut-Axis: How Does the Microbiota Influence Thyroid Function? *Nutrients* **2020**, *12*, 1769.
258. Agrawal, V.; Ghaznavi, S.A.; Paschke, R. Environmental Goitrogens. In *Encyclopedia of Endocrine Diseases*; Elsevier: Amsterdam, The Netherlands, 2018; pp. 506–511.
259. López-Moreno, M.; Garcés-Rimón, M.; Miguel, M. Antinutrients: Lectins, Goitrogens, Phytates and Oxalates, Friends or Foe? *J. Funct. Foods* **2022**, *89*.
260. Gaitan, E. 9 Goitrogens. *Baillieres. Clin. Endocrinol. Metab.* **1988**, *2*, 683–702. [[CrossRef](#)]
261. Speck, U. *X-ray Contrast Media: Overview, Use and Pharmaceutical Aspects*; Springer: Berlin/Heidelberg, Germany, 2018.
262. Bourin, M.; Jolliet, P.; Ballereau, F. An Overview of the Clinical Pharmacokinetics of X-ray Contrast Media. *Clin. Pharmacokinet.* **1997**, *32*, 180–193. [[CrossRef](#)]
263. Krause, W. Iodinated X-ray Contrast Agents. In *Iodine Chemistry and Applications*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2014; Volume 9781118466, pp. 353–374.
264. Zhibin, Y. FDA Approved Radiopharmaceuticals. *Foreign Med. Sci. Sect. Radiat. Med. Nucl. Med.* **2000**, *24*, 161–163.
265. Bartolozzi, C.; Lencioni, R.; Caramella, D.; Palla, A.; Bassi, A.M.; Di Candio, G. Small Hepatocellular Carcinoma. *Acta Radiol.* **1996**, *37*, 69–74. [[CrossRef](#)] [[PubMed](#)]
266. Wallers, K.J.; McDermott, P.; James, W.B. Intravenous Cholangiography by Bolus Injection of Meglumine Iotroxamate and Meglumine Iodoxamate: A Comparative Trial of Two New Contrast Media. *Clin. Radiol.* **1981**, *32*, 457–459. [[CrossRef](#)]
267. Miszczuk, M.A.; Chapiro, J.; Geschwind, J.-F.H.; Thakur, V.; Nezami, N.; Laage-Gaupp, F.; Kulon, M.; van Breugel, J.M.M.; Fereydooni, A.; Lin, M.; et al. Lipiodol as an Imaging Biomarker of Tumor Response After Conventional Transarterial Chemoembolization: Prospective Clinical Validation in Patients with Primary and Secondary Liver Cancer. *Transl. Oncol.* **2020**, *13*, 100742. [[CrossRef](#)]
268. Karmaker, N.; Maraz, K.M.; Islam, F.; Haque, M.M.; Razzak, M.; Mollah, M.Z.I.; Faruque, M.R.I.; Ruhul, A. Khan Fundamental Characteristics and Application of Radiation. *GSC Adv. Res. Rev.* **2021**, *7*, 064–072.
269. Shirakami, Y. Radioactive Iodine. In *Iodine Chemistry and Applications*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2014; Volume 9781118466, pp. 603–624.
270. Zerdoud, S.; Giraudet, A.-L.; Leboulleux, S.; Leenhardt, L.; Bardet, S.; Clerc, J.; Toubert, M.-E.; Al Ghuzlan, A.; Lamy, P.-J.; Bournaud, C.; et al. Radioactive Iodine Therapy, Molecular Imaging and Serum Biomarkers for Differentiated Thyroid Cancer: 2017 Guidelines of the French Societies of Nuclear Medicine, Endocrinology, Pathology, Biology, Endocrine Surgery and Head and Neck Surgery. *Ann. Endocrinol.* **2017**, *78*, 162–175. [[CrossRef](#)]
271. Braghirolli, A.M.S.; Waissmann, W.; Da Silva, J.B.; Dos Santos, G.R. Production of Iodine-124 and Its Applications in Nuclear Medicine. *Appl. Radiat. Isot.* **2014**, *90*, 138–148. [[CrossRef](#)] [[PubMed](#)]
272. Piel, M.; Rösch, F. *Radiopharmaceutical Chemistry*; Springer: Berlin/Heidelberg, Germany, 2012; Volume 71.
273. Crişan, G.; Moldovean-Cioroianu, N.S.; Timaru, D.-G.; Andrieş, G.; Căinap, C.; Chiş, V. Radiopharmaceuticals for PET and SPECT Imaging: A Literature Review over the Last Decade. *Int. J. Mol. Sci.* **2022**, *23*, 5023. [[CrossRef](#)]
274. Kondev, F.G.; Wang, M.; Huang, W.J.; Naimi, S.; Audi, G. The NUBASE2020 Evaluation of Nuclear Physics Properties. *Chinese Phys. C* **2021**, *45*, 030001. [[CrossRef](#)]
275. Rasmussen, T.; de Nijs, R.; Olsen, L.K.; Kamper, A.L.; Bang, L.E.; Frimodt-Møller, M.; Kelbæk, H.; Sørensen, S.S.; Kjær, A.; Feldt-Rasmussen, B.; et al. Renal 123I-MIBG Uptake before and after Live-Donor Kidney Transplantation. *Diagnostics* **2020**, *10*, 802. [[CrossRef](#)]
276. Qaim, S.M.; Scholten, B.; Neumaier, B. New Developments in the Production of Theranostic Pairs of Radionuclides. *J. Radioanal. Nucl. Chem.* **2018**, *318*, 1493–1509. [[CrossRef](#)]
277. Barca, C.; Griessinger, C.; Faust, A.; Depke, D.; Essler, M.; Windhorst, A.; Devoogdt, N.; Brindle, K.; Schäfers, M.; Zinnhardt, B.; et al. Expanding Theranostic Radiopharmaceuticals for Tumor Diagnosis and Therapy. *Pharmaceuticals* **2021**, *15*, 13. [[CrossRef](#)]
278. Spitzweg, C.; Dietz, A.; O'Connor, M.; Bergert, E.; Tindall, D.; Young, C.; Morris, J. In Vivo Sodium Iodide Symporter Gene Therapy of Prostate Cancer. *Gene Ther.* **2001**, *8*, 1524–1531. [[CrossRef](#)] [[PubMed](#)]
279. Boland, A.; Ricard, M.; Opolon, P.; Bidart, J.M.; Yeh, P.; Filetti, S.; Schlumberger, M.; Perricaudet, M. Adenovirus-Mediated Transfer of the Thyroid Sodium/Iodide Symporter Gene into Tumors for a Targeted Radiotherapy. *Cancer Res.* **2000**, *60*, 3484–3492.
280. Chen, E.; Wang, J.; Zhang, H.; Zhang, Y.; Jia, C.; Min, X.; Liang, Y. Analysis of the Efficacy and Safety of Iodine-125 Seeds Implantation in the Treatment of Patients with Inoperable Early-Stage Non-Small Cell Lung Cancer. *J. Contemp. Brachytherapy* **2021**, *13*, 347–357. [[CrossRef](#)]
281. Pavlicek, W.; Walton, H.A.; Karstaedt, P.J.; Gray, R.J. Radiation Safety with Use of I-125 Seeds for Localization of Nonpalpable Breast Lesions. *Acad. Radiol.* **2006**, *13*, 909–915. [[CrossRef](#)] [[PubMed](#)]
282. Mansouri, M.; Shahbazi-Gahrouei, D. A Review on Theranostic Applications of Iodine Nanoparticles: Recent Findings and Perspectives. *Nanomedicine J.* **2021**, *8*, 234–240.
283. Zimmermann, M.B. Iodine Deficiency Disorders and Their Correction Using Iodized Salt and/or Iodine Supplements. In *Iodine Chemistry and Applications*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2014; Volume 9781118466, pp. 421–431.

-
284. Yoshida, S.; Ojino, M.; Ozaki, T.; Hatanaka, T.; Nomura, K.; Ishii, M.; Koriyama, K.; Akashi, M. Guidelines for Iodine Prophylaxis as a Protective Measure: Information for Physicians. *Japan Med. Assoc. J. JMAJ* **2014**, *57*, 113–123.
 285. Küpper, F.C.; Kroneck, P.M.H. Iodine Bioinorganic Chemistry. In *Iodine Chemistry and Applications*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2014; pp. 555–589.
 286. Markou, K.; Georgopoulos, N.; Kyriazopoulou, V.; Vagenakis, A.G. Iodine-Induced Hypothyroidism. *Thyroid* **2001**, *11*, 501–510. [[CrossRef](#)] [[PubMed](#)]
 287. World Health Organization. *Protection of the Human Environment. Guidelines for Iodine Prophylaxis Following Nuclear Accidents*; Update 1999; World Health Organization: Geneva, Switzerland, 1999; pp. 1–45.