Lugol's Solution Beyond the Thyroid: Historical Uses, Extrathyroidal Physiology, Clinical Evidence, and Safety - A Scoping Review

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Abstract

Background: Iodine is conventionally regarded as an essential micronutrient required primarily for thyroid hormone synthesis. However, several extrathyroidal tissues actively concentrate, secrete, or metabolize iodine, and iodine-containing preparations, particularly Lugol's solution, have been used for non-thyroid disorders for almost two centuries. Interest has re-emerged in potential antioxidant, antimicrobial, differentiating, immunomodulatory, and antiproliferative effects of iodine outside the thyroid.

Objective: To map and critically evaluate historical and contemporary evidence regarding extrathyroidal physiological and therapeutic effects of Lugol's solution and other iodine preparations, with emphasis on human evidence, iodine formulation, dose, organ-specific effects, and safety.

Methods: A scoping review was conducted using PubMed/MEDLINE, Google Scholar, historical medical archives, and citation tracking from the earliest retrievable literature through September 2026. Eligible evidence included historical therapeutic reports, human intervention studies, physiological human studies demonstrating extrathyroidal iodine handling, and mechanistic investigations directly relevant to identified human effects. Molecular iodine (I_2), iodide (I^-), potassium iodide (KI), Lugol's solution (I_2 + KI), and other iodine preparations were distinguished whenever possible. Conventional thyroid indications were excluded from the principal efficacy synthesis.

Results: Historical literature documented systemic and local iodine use for several extrathyroidal conditions, including intracystic treatment of ovarian and breast cysts. Modern therapeutic evidence was substantially more limited. The strongest clinical evidence concerned benign breast disease. Molecular iodine at approximately 0.07–0.09 mg/kg/day was associated with subjective and objective improvement in fibrocystic breast disease, while a randomized dose-ranging study demonstrated greater improvement in cyclic mastalgia with 3 and 6 mg/day than with 1.5 mg/day or placebo. Preliminary observations involving benign prostatic hyperplasia have been reported with low-milligram iodine exposure, although the corresponding primary clinical evidence remains insufficiently documented. A pilot study in women with diminished ovarian reserve reported favorable oocyte and cumulus-cell outcomes after 150 µg/day iodine, whereas Lugol supplementation in iodine-deficient children was associated with changes in cellular immune responses. Human physiological studies demonstrated active iodine handling in salivary glands, gastric mucosa, lactating breast, and other extrathyroidal tissues. Acute systemic iodine exposure increased salivary iodide and antimicrobial hypoiodous acid production. For most other organs, biological plausibility substantially exceeded therapeutic evidence.

Conclusions: Iodine has well-documented biological activity beyond the thyroid, but evidence for therapeutic supplementation is uneven. Benign breast disease currently provides the strongest human evidence for a clinically relevant extrathyroidal effect, particularly with molecular iodine in the low-milligram range. Salivary studies provide additional human evidence that systemic iodine availability can modify an extrathyroidal biochemical pathway. Whether low-milligram iodine exposure represents a purely pharmacological intervention or reveals tissue-specific iodine biology not captured by thyroid-centered nutritional requirements remains unresolved. Future trials should distinguish molecular iodine from iodide and Lugol's solution, quantify exposure in milligrams rather than drops, and systematically monitor iodine and thyroid status.

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Introduction

Iodine is an essential micronutrient traditionally recognized for its indispensable role in thyroid hormone synthesis. Consequently, most clinical and experimental research on iodine has focused on thyroid physiology, iodine-deficiency disorders,

goiter, thyroid dysfunction, pregnancy, and population-based iodine prophylaxis. Nevertheless, the biological distribution and actions of iodine extend considerably beyond the thyroid gland. Several extrathyroidal tissues are capable of concentrating or metabolizing iodine, suggesting that this element may exert physiological effects that are at least partly independent of its incorporation into thyroid hormones [1–6].

The sodium/iodide symporter (NIS), although most extensively characterized in thyroid follicular cells, has been identified in several extrathyroidal tissues, including the mammary gland, salivary glands, gastric mucosa, lacrimal system, placenta, and other organs [4–6]. The biological significance of this distribution is heterogeneous and remains incompletely understood. In certain tissues, however, specific physiological functions are established. The lactating mammary gland actively concentrates iodine for secretion into breast milk, whereas salivary glands transport iodide into saliva, where it can participate in the lactoperoxidase-mediated antimicrobial system [7–9].

Experimental evidence further suggests that iodine, particularly molecular iodine (I_2), may exert antioxidant, anti-inflammatory, immunomodulatory, differentiating, and antiproliferative effects independently of thyroid hormone synthesis [10–13]. Proposed mechanisms include modulation of oxidative stress and inflammatory pathways and formation of iodinated lipids capable of regulating cellular differentiation, proliferation, and apoptosis [10–13].

These observations have stimulated interest in the possibility that iodine exposure sufficient for selected extrathyroidal biological or pharmacological effects may differ from that required to maintain thyroid hormone synthesis.

Historical medical practice provides an additional perspective. Shortly after iodine entered medical therapeutics in the early nineteenth century, Jean Guillaume Auguste Lugol developed an aqueous preparation containing molecular iodine and potassium iodide that subsequently became known as Lugol's solution [14]. Long before its modern endocrine applications, iodine-containing preparations were employed for diverse disorders. Historical reports describe systemic use in glandular diseases as well as intracystic iodine administration for ovarian and breast cysts [14–17].

Although these practices preceded modern clinical-trial methodology and cannot be interpreted according to contemporary standards of efficacy and safety, they demonstrate longstanding interest in iodine as a therapeutic agent outside the thyroid.

Modern clinical observations have provided more testable evidence for some of these concepts. The most substantial human therapeutic data concern benign breast disease. Ghent *et al*. evaluated several iodine preparations in women with fibrocystic breast disease and reported that molecular iodine at approximately 0.07–0.09 mg/kg/day produced subjective and objective improvement [18].

Subsequently, Kessler evaluated fixed doses of 1.5, 3, and 6 mg/day molecular iodine in euthyroid women with cyclic mastalgia and fibrocystic breast changes. The clearest clinical responses occurred with 3 and 6 mg/day [19]. These exposures are substantially greater than conventional nutritional iodine requirements and suggest that some extrathyroidal effects may occur within a low-milligram rather than microgram exposure range.

Evidence from other organs is considerably more limited. Preliminary observations have suggested potential effects of iodine in prostate disease, immune function, and ovarian physiology [10,20,21]. Human physiological studies have additionally demonstrated active iodine handling by salivary glands and gastric mucosa [5,6,9].

However, for many proposed indications, mechanistic plausibility has not been translated into controlled clinical evidence. Moreover, chemical form may be important: molecular iodine (I_2), iodide (I^-), potassium iodide (KI), and Lugol's solution, which contains both I_2 and KI, should not automatically be considered pharmacologically interchangeable [10,18].

This distinction is particularly relevant when discussing "low-dose" Lugol's solution. Nutritional iodine recommendations are expressed in micrograms, whereas even small volumes of conventional Lugol formulations provide iodine in the milligram range. Nutritional replacement, supranutritional exposure, and pharmacological iodine administration therefore represent different concepts.

Excessive iodine exposure may also precipitate thyroid dysfunction through mechanisms including the acute Wolff–Chaikoff effect, failure to escape from this effect, and iodine-induced hyperthyroidism in susceptible individuals [22–25]. Potential extrathyroidal benefits must therefore be considered together with thyroid safety.

Accordingly, the objective of this scoping review was to map and critically characterize evidence regarding the extrathyroidal use and biological effects of Lugol's solution and other iodine preparations, with particular emphasis on human therapeutic exposure. Specifically, we sought to identify historical therapeutic applications; characterize modern human intervention studies according to organ, iodine formulation, dose, duration, and outcome; summarize evidence supporting extrathyroidal iodine physiology; distinguish molecular iodine, iodide, KI, and Lugol's solution; and examine safety implications of low-milligram and higher iodine exposure.

Methods

Study Design

A scoping review was undertaken to map the historical, physiological, experimental, and clinical literature concerning extrathyroidal effects and therapeutic uses of iodine, with particular emphasis on Lugol's solution.

A scoping-review methodology was selected because of the marked heterogeneity of available evidence, encompassing nineteenth-century medical reports, case series, observational studies, clinical trials, physiological human studies, and experimental investigations.

The review was structured according to methodological principles for scoping reviews and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR).

Review Questions

The primary review question was: "What human evidence supports physiological or therapeutic effects of Lugol's solution or systemic iodine exposure outside conventional thyroid indications?"

Secondary questions addressed which extrathyroidal organs actively accumulate, secrete, or metabolize iodine; which chemical forms have been investigated; which doses and treatment durations have been used in humans; whether effects differ between nutritional and pharmacological exposure; and which safety signals have been reported.

Information Sources and Search Strategy

The literature was searched from the earliest retrievable publications through September 2026.

Electronic searches included PubMed/MEDLINE and complementary searches of Google Scholar and historical medical archives. Reference lists of relevant reviews and included publications were hand-searched to identify additional studies, particularly historical reports not reliably captured by contemporary electronic indexing.

Search terms included combinations of "iodine," "molecular iodine," "I2," "iodide," "potassium iodide," "Lugol," "Lugol's solution," "aqueous iodine," and "iodine supplementation" with organ- and disease-specific terms including "breast," "fibrocystic breast disease," "mastalgia," "prostate," "benign prostatic hyperplasia," "ovary," "ovarian cyst," "fertility," "uterus," "endometrium," "salivary gland," "lacrimal gland," "stomach," "gastric," "pancreas," "skin," "immune," "lung," "kidney," "testis," "reproduction," "sodium iodide symporter," and "NIS."

Historical terms including "iodine injection," "ovarian dropsy," "ovarian cysts," "mammary cyst," and "scrofula" were additionally searched.

Eligibility Criteria

Studies were eligible when they described: (1) systemic or local administration of Lugol's solution in humans for an extrathyroidal indication; (2) administration of molecular iodine, iodide, or another defined iodine preparation relevant to potential extrathyroidal effects; (3) human physiological studies demonstrating iodine uptake, concentration, secretion, or metabolism by an extrathyroidal organ; or (4) experimental investigations directly relevant to an organ or clinical effect identified in the human literature.

Studies exclusively evaluating conventional treatment of hyperthyroidism, thyroid storm, preoperative thyroid preparation, radioactive iodine therapy, or routine prevention of iodine-deficiency thyroid disease were excluded from the principal therapeutic synthesis.

Animal and *in vitro* studies were not considered evidence of clinical efficacy and were used only to support mechanistic interpretation.

Historical Evidence

Historical case reports, series, monographs, and medical reports were evaluated separately. They were eligible when the iodine preparation, indication, route, or therapeutic outcome could reasonably be established.

Historical evidence was not pooled with modern clinical evidence and was not interpreted as demonstrating efficacy according to contemporary standards.

Classification of Iodine Preparations

Iodine exposure was classified whenever possible as molecular iodine (I_2), iodide (I^-), potassium iodide (KI), Lugol's solution (I_2 + KI), protein-bound or organically bound iodine, or another iodine-containing preparation.

For Lugol's solution, concentration was recorded whenever available. Doses expressed as drops or volumes were converted to milligrams only when formulation concentration and administered volume could be reasonably established.

Dose Classification

Exposure was described quantitatively whenever possible and conceptually distinguished as nutritional replacement, supranutritional low-milligram exposure, or higher pharmacological exposure.

Because no universally accepted threshold defines "low-dose Lugol," original doses were preferentially reported rather than assigned arbitrary categories.

Where sufficient information was available, molecular iodine and iodide contributions to total iodine exposure were considered separately.

Data Extraction and Synthesis

Extracted variables included author, publication year, study design, population, sample size, organ or condition, iodine preparation, route, concentration, dose, duration, comparator, outcomes, main findings, adverse events, and thyroid-function findings.

Evidence was grouped into historical therapeutic evidence, modern human intervention or physiological evidence, and mechanistic evidence supporting extrathyroidal iodine biology.

Given substantial heterogeneity and the small number of controlled clinical studies, quantitative meta-analysis was not considered appropriate.

Particular care was taken not to infer therapeutic efficacy solely from NIS expression, tissue iodine accumulation, or experimental biological effects. When clinical claims were reported in secondary literature but the corresponding primary human study could not be independently identified, they were classified as preliminary or unverified observations.

Safety Assessment

Safety findings were extracted from relevant human studies of systemic iodine exposure. Particular attention was given to TSH and thyroid hormone changes, hypothyroidism, iodine-induced hyperthyroidism, thyroid autoimmunity, gastrointestinal intolerance, dermatological reactions, and other adverse events.

Safety was interpreted according to iodine formulation, dose, duration, baseline iodine status, and underlying thyroid susceptibility.

Results

Overview Of The Evidence

The literature revealed a heterogeneous evidence base extending from early nineteenth-century therapeutic reports to randomized clinical trials and contemporary mechanistic investigations.

Evidence could be divided into three principal domains: historical therapeutic use of iodine and Lugol's solution; modern human intervention and physiological studies; and experimental or tissue-based evidence of extrathyroidal iodine transport and biological activity.

Historical reports included glandular disease and local treatment of ovarian and breast cysts. Modern therapeutic evidence was substantially more limited and concentrated predominantly in benign breast disease, with additional observations involving immune function, ovarian physiology, and prostate disease.

Human physiological studies demonstrated active iodine uptake, concentration, or secretion in several organs, particularly the salivary glands, mammary gland, and gastric mucosa.

Importantly, the chemical form and dose of iodine varied considerably among studies.

Historical Extrathyroidal Therapeutic Use

Therapeutic use of iodine outside thyroid disease dates to the early nineteenth century. Lugol employed aqueous iodine-potassium iodide preparations in patients with conditions then classified as scrofulous or glandular diseases [14].

One of the earliest organ-specific applications involved ovarian cystic disease. Mid-nineteenth-century reports described aspiration of ovarian cysts followed by intracystic iodine administration [15,16]. These procedures represented local chemical therapy rather than systemic supplementation.

A conceptually similar approach was subsequently reported for breast cysts. Bianucci and Pastorino described concentrated Lugol's solution instilled into breast cyst cavities following aspiration [17]. A total of 308 aspirations were reported, and among 194 patients followed for two years, 11 recurrences were documented.

The principal historical applications are summarized in Table 1.

Modern Human Intervention Studies

Breast and Fibrocystic Breast Disease

The strongest therapeutic evidence was identified for benign breast disease.

Ghent *et al*. evaluated several iodine preparations in women with fibrocystic breast disease [18]. Earlier phases included sodium iodide and protein-bound iodine, followed by molecular iodine.

In the controlled investigation, molecular iodine was administered at approximately 0.07–0.09 mg/kg/day. Approximately 65% of treated women demonstrated concurrent subjective and objective improvement. Molecular iodine appeared to provide a more favorable combination of efficacy and tolerability than the iodide preparations evaluated.

These doses correspond approximately to 4.2–5.4 mg/day for a 60-kg individual, 4.9–6.3 mg/day for a 70-kg individual, and 5.6–7.2 mg/day for an 80-kg individual.

Kessler subsequently evaluated 1.5, 3, and 6 mg/day molecular iodine in a randomized, double-blind, placebo-controlled multicenter study involving 111 euthyroid women with cyclic mastalgia and fibrocystic breast changes [19].

A dose-response pattern was observed. Significant decreases in pain were evident by month 3 in the 3- and 6-mg/day groups but not in the 1.5-mg/day or placebo groups. More than half of participants receiving 6 mg/day recorded a clinically meaningful reduction in overall pain. An acceptable safety profile was reported across doses.

Thus, clinically relevant breast responses were repeatedly observed within an approximate 3–6 mg/day molecular iodine range.

Prostate

Clinical evidence concerning prostate disease was substantially weaker.

Reviews from the Aceves group describe observations in patients with grade I–II benign prostatic hyperplasia treated with low-milligram iodine exposure, with reported improvement in PSA, urinary flow, and symptoms [10,26].

However, a complete primary clinical publication providing sufficient methodological detail could not be independently verified. These findings were therefore classified as preliminary observations reported in secondary literature rather than established intervention evidence.

Ovary and Female Reproductive System

Historical reports concerned primarily intracystic iodine injection and did not provide evidence for systemic supplementation.

A recent pilot investigation evaluated 150 µg/day iodine for two months in ten women with diminished ovarian reserve [20]. Supplementation was associated with an increased number of metaphase-II oocytes, increased cumulus-cell viability, reduced apoptosis, and increased proliferating cell nuclear antigen expression.

Because of the small sample size and preliminary design, these findings require confirmation.

Reports concerning milligram-range molecular iodine in polycystic ovarian conditions remain unpublished or insufficiently documented [10].

No controlled human evidence was identified demonstrating regression of ovarian cysts following oral Lugol's solution.

Immune Function

A human study involving 607 children living in an iodine-deficient region with endemic goiter provided evidence of immune changes following Lugol supplementation [21]. Of these, 215 received two drops of Lugol's solution weekly for approximately eight months, while 392 did not receive supplementation.

Treated children demonstrated a greater delayed hypersensitivity response to tetanus toxoid and changes involving lymphocyte stimulation and monocyte chemotaxis. Because the population was iodine deficient, these findings are more appropriately interpreted as restoration of immune parameters following correction of iodine deficiency than as evidence of pharmacological immune enhancement in iodine-sufficient individuals.

Human Physiological Evidence

Salivary Glands

The salivary glands demonstrate active iodine transport and secretion.

Akiba *et al*. studied 40 individuals undergoing acute systemic iodine exposure from iodinated contrast material [9]. Salivary iodide concentrations increased substantially following exposure, accompanied by increased generation of antimicrobial hypoiodous acid.

These observations provide direct human evidence for the functional sequence:

systemic iodine exposure → salivary iodide → lactoperoxidase/H_2O_2 → hypoiodous acid.

However, the study involved an acute large iodine load rather than chronic low-dose Lugol supplementation.

Stomach

Human histological studies demonstrate substantial NIS expression in gastric mucosa and active gastric iodine handling [5, 6].

Despite this physiological evidence, no convincing controlled clinical study was identified demonstrating improvement of gastritis or another gastric disorder following systemic low-dose Lugol administration.

Conversely, concentrated topical Lugol exposure during gastrointestinal chromoendoscopy has been associated with acute gastric mucosal injury, including edema and epithelial changes [27]. These findings involved direct concentrated mucosal exposure and cannot be extrapolated to diluted systemic administration.

Lacrimal System, Pancreas, and Other Tissues

NIS expression or iodine accumulation has been reported in lacrimal and other exocrine tissues [5,6,28]. No therapeutic human study of oral Lugol supplementation targeting lacrimal function was identified.

Evidence of NIS expression in pancreatic and reproductive tissues has varied across investigations, and the physiological importance remains uncertain [5,6,29].

Placental iodine transport is well established and has a clear role in maternal-fetal iodine transfer. However, routine pregnancy supplementation was outside the therapeutic scope of this review.

For endometrium, testis, kidney, lung, skin, and other tissues, molecular or physiological observations substantially exceeded human intervention evidence.

Dose Patterns and Formulation

A marked distinction emerged between conventional nutritional exposure and doses investigated for selected extrathyroidal outcomes.

The ovarian pilot study employed 150 µg/day [20], whereas the principal breast trials used molecular iodine in an approximate 3–6 mg/day range [18,19].

The limited human therapeutic literature therefore suggests two distinct exposure concepts: microgram-range nutritional replacement and low-milligram exposure investigated for tissue-specific or pharmacological effects.

Lugol's solution additionally presents a formulation issue because it simultaneously provides molecular iodine and iodide. Conventional 2% Lugol contains approximately 20 mg/mL I_2 and 40 mg/mL KI. Because KI is approximately 76.4% iodine by mass, this corresponds to approximately 50.6 mg/mL total iodine.

Assuming a nominal drop volume of 0.05 mL, one drop provides approximately 1.0 mg I_2 plus 1.53 mg iodine as iodide, or approximately 2.53 mg total iodine. Actual drop volumes vary; therefore, doses expressed solely as numbers of drops are imprecise.

Safety Findings

The distinction between nutritional and pharmacological exposure was also apparent in human safety studies.

Tan *et al*. administered 0.5 mL Lugol's solution daily for 10 days to 38 euthyroid volunteers [23]. Free T4 declined significantly at day 10 and TSH increased significantly at days 5, 10, and 15, although values remained within reference ranges.

Namba *et al*. similarly demonstrated reversible thyroid changes during excess iodide exposure in healthy individuals [24].

These observations confirm that pharmacological iodine exposure can measurably modify thyroid physiology even in initially euthyroid individuals.

Discussion

This scoping review reveals a striking contrast between the extensive extrathyroidal biology of iodine and the comparatively limited clinical investigation of iodine therapy outside conventional thyroid indications.

Iodine transport, concentration, secretion, or metabolism has been demonstrated in multiple non-thyroid tissues, and iodine-containing preparations have been used therapeutically for almost two centuries. Nevertheless, modern controlled human evidence remains concentrated in only a few conditions, particularly benign breast disease.

Thus, the available literature supports genuine extrathyroidal iodine physiology but does not support the assumption that tissue iodine uptake necessarily translates into a clinical indication for supplementation.

From A Thyroid-Centered Nutrient To An Extrathyroidal Biological Agent

The conventional understanding of iodine requirements has been shaped primarily by its role as a substrate for thyroid hormone synthesis [1–4].

This framework has been highly successful in preventing iodine-deficiency disorders. However, it does not encompass the full biological distribution of iodine.

Active iodine transport in mammary, salivary, gastric, placental, and other tissues demonstrates that iodine homeostasis is not exclusively thyroidal [5–8,28].

The physiological significance varies among organs. In the lactating mammary gland, iodine concentration facilitates transfer into breast milk [7,8]. In salivary glands, iodide contributes to the lactoperoxidase antimicrobial system [9]. Gastric iodine uptake is substantial, although its precise physiological purpose remains incompletely characterized [5,6].

This distribution raises an important conceptual question: does an iodine intake sufficient to maintain normal thyroid hormone production necessarily provide optimal iodine availability to every extrathyroidal tissue?

Current evidence cannot answer this question.

Importantly, this should not be interpreted as evidence that current nutritional recommendations are inadequate. Rather, it identifies a different research question: whether selected tissues or pathological states respond pharmacologically to iodine exposures above conventional nutritional requirements.

The Breast As The Principal Human Proof of Concept

Among all extrathyroidal organs examined, the breast provides the strongest clinical evidence.

Ghent *et al*. are particularly informative because different iodine preparations were investigated [18]. Molecular iodine at approximately 0.07–0.09 mg/kg/day was associated with subjective and objective improvement and appeared to provide a more favorable clinical profile than the iodide preparations studied.

Kessler strengthened this observation in a randomized, double-blind, placebo-controlled trial [19]. Molecular iodine was administered at 1.5, 3, or 6 mg/day for six months, with the clearest clinical responses at 3 and 6 mg/day.

Two observations are particularly important.

First, chemical form appears to matter. Molecular iodine cannot automatically be considered biologically equivalent to iodide despite both contributing to total iodine exposure.

Second, doses associated with breast responses were substantially greater than conventional nutritional intake.

These studies do not demonstrate that humans "require" 3–6 mg iodine daily. Instead, they indicate that a pharmacological or tissue-specific effect may occur within this dose range.

This distinction between nutritional requirement and pharmacological effect is central to interpretation of the literature.

Why Molecular Iodine May Behave Differently From Iodide

Experimental evidence provides biological plausibility for differences between iodine formulations.

Iodide is transported through mechanisms including NIS and participates in enzymatic iodination reactions. Molecular iodine appears capable of exerting additional redox and signaling effects [10–13].

Experimental studies suggest that I_2 can influence oxidative stress, inflammatory signaling, mitochondrial function, cellular differentiation, proliferation, and apoptosis.

One particularly interesting mechanism involves formation of iodinated lipids. Experimental work has implicated 6-iodolactone and PPARγ-related signaling in antiproliferative and pro-differentiating effects of molecular iodine [11–13].

Such mechanisms may be relevant in tissues characterized by cyclic hormonal stimulation or active proliferation, including breast and reproductive tissues.

Nevertheless, these findings remain predominantly experimental and provide biological plausibility rather than clinical proof.

Lugol's Solution Is Pharmacologically More Complex Than "iodine supplementation"

Lugol's solution simultaneously delivers molecular iodine and iodide derived from potassium iodide. Consequently, its biological effects may represent combined exposure to chemically distinct iodine species.

For conventional 2% Lugol, approximately 20 mg/mL is present as I_2 and 40 mg/mL as KI, corresponding to approximately 50.6 mg/mL total iodine.

With a nominal 0.05-mL drop, one drop would contain approximately 1.0 mg I_2 plus 1.53 mg iodine as iodide, yielding approximately 2.53 mg total iodine.

Interestingly, one nominal drop therefore provides total iodine within the same order of magnitude as the lower doses investigated in the breast literature.

However, equivalence cannot be assumed. Three milligrams of molecular iodine is not pharmacologically identical to three milligrams total iodine delivered as an I_2/KI mixture.

Clinical studies should therefore report Lugol exposure in milligrams of molecular iodine and iodide rather than simply numbers of drops.

Salivary Glands as A Second Human Proof of Concept

The salivary literature provides a different but particularly informative type of human evidence.

Following systemic iodine exposure, salivary iodide increases substantially, accompanied by increased generation of hypoiodous acid [9].

This establishes a measurable functional sequence:

systemic iodine → increased salivary iodide → increased HOI generation.

Unlike demonstration of NIS expression alone, this represents a functional consequence of systemic iodine availability in a human extrathyroidal organ.

Nevertheless, the study involved acute iodinated contrast exposure. It therefore demonstrates physiological responsiveness but does not establish that chronic Lugol supplementation improves oral or salivary health.

The Stomach: Strong Physiology, Absent Therapeutic Evidence

The stomach provides a clear illustration of the difference between biological plausibility and therapeutic evidence.

Gastric mucosa expresses iodine-transport machinery and demonstrates substantial iodine accumulation [5,6]. Potential functions include iodine recycling, redox regulation, antimicrobial activity, and epithelial homeostasis.

Yet no convincing controlled human evidence demonstrated that systemic Lugol supplementation improves gastritis, dyspepsia, peptic disease, or another gastric disorder.

Furthermore, concentrated topical Lugol can injure gastric mucosa [27].

This apparently contradictory observation emphasizes a fundamental pharmacological principle: route and concentration matter.

The stomach therefore represents a compelling target for mechanistic research rather than an established therapeutic indication.

Prostate: Biologically Attractive But Clinically Unresolved

Experimental literature indicates that prostate tissue may respond to iodine and that molecular iodine may influence oxidative stress, proliferation, differentiation, and inflammatory pathways [10,26].

Clinical observations cited in secondary literature describe improvement in men with grade I–II benign prostatic hyperplasia receiving low-milligram iodine exposure.

The reported dose is interesting because it lies close to the range investigated in breast disease.

However, the primary clinical dataset could not be independently verified in a sufficiently detailed peer-reviewed publication. These observations should therefore be considered hypothesis-generating rather than confirmatory.

Ovary and Reproductive Tissues

The ovarian literature illustrates the transition from historical intervention to emerging biological research.

Historical iodine treatment of ovarian cysts was predominantly intracystic and functioned as local chemical therapy [15,16].

Recent pilot human data in women with diminished ovarian reserve are interesting because nutritional iodine supplementation was associated with changes in mature oocyte yield and cellular markers related to viability, proliferation, and apoptosis [20].

However, the investigation involved only ten women and used 150 µg/day rather than milligram-range iodine.

At present, there is no reliable clinical evidence supporting oral Lugol for ovarian cysts or polycystic ovary syndrome.

Immune Effects

The study of iodine-deficient children provides evidence that Lugol supplementation can influence measurable immune parameters [21].

Interpretation requires caution because restoration of physiological function after correction of nutritional deficiency differs fundamentally from pharmacological immunomodulation in iodine-replete individuals.

Contemporary experimental evidence nevertheless indicates that molecular iodine can interact with inflammatory and immune pathways [10].

Iodine therefore appears capable of influencing immune physiology, but its clinical implications remain uncertain.

Micrograms Versus Milligrams: The Central Unanswered Question

Perhaps the most provocative finding of this review is the separation between conventional nutritional iodine exposure and doses investigated for some extrathyroidal effects.

Approximately 150 µg/day corresponds to conventional adult nutritional requirements, whereas the adult tolerable upper intake level for nutritional exposure is 1,100 µg/day [22].

Yet the principal breast trials investigated approximately 3–6 mg/day molecular iodine [18,19].

This creates an approximately 20- to 40-fold difference between conventional nutritional intake and doses associated with selected extrathyroidal clinical responses.

At least three interpretations are possible.

First, higher doses may simply represent pharmacological therapy. Under this interpretation, conventional microgram intake remains nutritionally adequate, whereas several milligrams of iodine produce drug-like actions unrelated to nutritional requirements.

Second, some extrathyroidal tissues could theoretically require greater iodine availability to support particular physiological pathways, meaning that euthyroidism would not necessarily define optimal iodine status in every tissue.

Third, both concepts may coexist: physiological extrathyroidal iodine functions may operate at nutritional exposure, whereas additional antioxidant, differentiating, antiproliferative, or immunomodulatory effects emerge only at pharmacological concentrations.

Current evidence cannot distinguish conclusively among these possibilities.

This question should therefore be regarded as a research hypothesis, not as justification for redefining dietary iodine requirements.

Safety Defines The Boundary of The Hypothesis

Any discussion of supranutritional iodine requires careful consideration of thyroid safety.

Acute iodine excess can transiently inhibit thyroid hormone synthesis through the Wolff–Chaikoff effect. Escape from this effect involves adaptive mechanisms including reduction of NIS expression [25].

Adaptation, however, is not universal. Susceptible individuals may develop iodine-induced hypothyroidism, whereas autonomous thyroid tissue can produce iodine-induced hyperthyroidism.

Tan *et al.* demonstrated measurable thyroid responses even in healthy euthyroid individuals exposed to Lugol's solution for only ten days [23]. Free T4 declined and TSH increased, although values remained within reference ranges. Namba *et al.* similarly demonstrated reversible thyroid changes during excess iodide exposure [24].

The 3–6 mg/day molecular iodine doses investigated in breast disease also exceed the adult nutritional UL of 1.1 mg/day [22].

Kessler reported an acceptable safety profile during six months of treatment without a dose-related increase in adverse events [19]. Nevertheless, this does not establish indefinite safety, nor can it be generalized to Lugol's solution or individuals with nodular thyroid disease, thyroid autonomy, autoimmune thyroid disease, or previous iodine-induced dysfunction.

Therefore, evidence of potential extrathyroidal benefit should not be interpreted as support for indiscriminate iodine supplementation.

Historical Evidence: Hypothesis Generation Rather Than Efficacy

The historical component provides an unusual perspective.

Iodine was applied therapeutically to extrathyroidal disorders long before endocrine iodine physiology was understood. Ovarian cyst injection, breast cyst treatment, and glandular disease illustrate the breadth of historical experimentation [14–17].

Some effects may now have plausible mechanistic explanations; others probably reflected antiseptic, irritant, inflammatory, or sclerosing properties of concentrated iodine.

Historical therapeutic persistence is informative but cannot substitute for controlled clinical investigation. Its principal value is hypothesis generation.

Research Implications

The evidence suggests several priorities.

Benign breast disease has sufficient human evidence to justify contemporary replication using standardized formulations, validated imaging and patient-reported outcomes, urinary iodine measurements, and systematic thyroid monitoring. Direct comparison between molecular iodine and Lugol's solution would be particularly informative.

Salivary physiology represents an attractive human model because iodine-dependent biological activity can be measured directly. Dose-ranging studies could evaluate urinary iodine, plasma iodide, salivary iodide, HOI generation, microbiome changes, and clinical outcomes.

Benign prostatic hyperplasia requires a properly documented randomized trial before the repeatedly cited clinical observations can be considered credible therapeutic evidence.

Studies involving ovarian physiology should distinguish nutritional iodine correction from pharmacological milligram exposure.

Across all future investigations, iodine formulation should be reported chemically rather than simply as "iodine."

Strengths and Limitations

This review integrates nearly two centuries of literature, separates historical therapeutic observations from modern clinical evidence, distinguishes different chemical forms of iodine, and evaluates extrathyroidal physiology alongside clinical outcomes.

Importantly, it does not assume that NIS expression or iodine uptake demonstrates therapeutic efficacy.

Several limitations should be acknowledged. Historical publications frequently provided incomplete descriptions of formulation, concentration, dose, and outcome assessment. Some older literature may not have been captured by contemporary databases.

Modern clinical studies were few, generally small, and concentrated predominantly in benign breast disease. Several frequently cited clinical observations, particularly involving the prostate and polycystic ovarian conditions, could not be independently verified in complete primary publications.

Substantial heterogeneity in iodine formulation, dose, route, duration, baseline iodine status, and outcome measurement precluded meaningful quantitative synthesis.

Experimental evidence substantially exceeds human clinical evidence for most organs, increasing the risk of over-extrapolation from mechanistic findings.

Finally, absence of published therapeutic evidence should not be interpreted as evidence of absence of an extrathyroidal effect; in several tissues, the relevant clinical experiments simply have not yet been performed.

Conclusions

Iodine is biologically active beyond the thyroid, and several human tissues actively concentrate, secrete, or metabolize iodine.

The strongest clinical evidence for an extrathyroidal therapeutic effect is found in benign breast disease, where molecular iodine in the low-milligram range, particularly approximately 3–6 mg/day, has demonstrated clinically meaningful effects in controlled studies.

Human salivary studies provide additional evidence that systemic iodine availability can directly modify an extrathyroidal biochemical defense pathway.

For the prostate, ovary, stomach, lacrimal system, pancreas, and other tissues, biological plausibility currently exceeds clinical evidence. Historical experience with Lugol's solution and other iodine preparations provides valuable hypotheses but cannot establish modern therapeutic efficacy.

A central unresolved question is whether low-milligram iodine doses associated with some extrathyroidal effects represent purely pharmacological exposure or reveal tissue-specific iodine biology not captured by thyroid-centered nutritional requirements.

Current evidence is insufficient to redefine physiological iodine requirements but provides a rationale for carefully designed dose-ranging human studies.

Future trials should distinguish molecular iodine from iodide and Lugol's solution, quantify exposure in milligrams rather than drops, characterize baseline iodine and thyroid status, and incorporate systematic thyroid-safety monitoring.

Such studies may determine whether the long history of extrathyroidal iodine therapy reflects primarily historical empiricism or an incompletely explored component of human iodine physiology.

Table 1: Historical extrathyroidal therapeutic applications of iodine and Lugol's solution

Reference	Organ/condition	Preparation/route	Dose or concentration	Main findings	Interpretation
Lugol, 1831 [14]	Scrofulous/glandular disorders	Aqueous iodine + KI; systemic/local	Multiple formulations	Clinical responses described	Historical origin; predates modern diagnostic criteria
Allison, 1846 [15]	Ovarian dropsy/cyst	Iodine; intracystic after tapping	Historical formulation	Improvement reported	Local chemical/sclerosing treatment
Scuh, 1860 [16]	Ovarian cysts	Iodine; intracystic	Variable	Therapeutic responses described	Historical local therapy
Bianucci & Pastorino, 1982 [17]	Breast cysts	Concentrated Lugol; intracystic	Exact delivered dose unclear	308 aspirations; 11 recurrences among 194 followed for 2 years	Local therapy, not systemic supplementation
Marani & Venturi, 1986 [21]	Immune function in iodine-deficient children	Lugol; oral	2 drops/week	Improved delayed hypersensitivity and other immune parameters	Primarily evidence in iodine deficiency
Ghent *et al*., 1993 [18]	Fibrocystic breast disease	I_2; oral	0.07–0.09 mg/kg/day	Clinical improvement	Transition to modern controlled evidence

Table 2: Modern human studies of systemic iodine exposure with extrathyroidal outcomes

Study	Organ/condition	Design/population	Preparation	Dose	Duration	Main findings	Interpretation
Ghent *et al*. [18]	Fibrocystic breast disease	Sequential studies + controlled component	I_2	0.07–0.09 mg/kg/day	Months	~65% concurrent subjective/objective improvement	Principal clinical evidence
Kessler [19]	Cyclic mastalgia/fibrocystic breast	Randomized double-blind placebo-controlled; n=111	I_2	1.5, 3, 6 mg/day	6 months	Dose-response; clearest benefit at 3 and 6 mg/day	Strongest dose-ranging evidence
Aceves group [10,26]	BPH	Observation reported in secondary literature	Iodine/I_2-KI-type exposure	Low-mg range	Months	Reported PSA/urinary improvement	Primary clinical dataset not independently verified
Masoumi *et al*. [20]	Diminished ovarian reserve	Pilot; n=10	Iodine	150 µg/day	2 months	↑ MII oocytes, viability and PCNA; ↓ apoptosis	Preliminary
Marani & Venturi [21]	Immune function	Comparative study; n=607; 215 treated	Lugol	2 drops/week	~8 months	Improved immune parameters	Iodine-deficient population
Akiba *et al*. [9]	Salivary/oral defense	Human physiological challenge; n=40	Iodinated contrast exposure	Acute high iodine load	Acute	↑ salivary iodide and HOI	Physiological proof of concept, not Lugol therapy

Table 3: Extrathyroidal iodine physiology and clinical evidence by organ

Organ/tissue	Iodine-handling evidence	Potential/established role	Human therapeutic evidence	Interpretation
Breast	Strong	Lactational transfer; redox/differentiation pathways	Controlled trials	Strongest therapeutic signal
Salivary glands	Strong	HOI/lactoperoxidase antimicrobial defense	No chronic Lugol trial	Strong human physiological evidence
Stomach	Strong	Possible recycling/redox/mucosal functions	None convincing	Physiology exceeds therapeutic evidence
Prostate	Experimental/molecular	Redox/differentiation effects proposed	Preliminary/unverified	Research priority
Ovary	Emerging/inconsistent	Reproductive/redox effects proposed	Small pilot	Preliminary
Lacrimal system	NIS/iodine accumulation	Exocrine/antimicrobial role possible	None	Biological plausibility
Pancreas	Variable	Uncertain	None	Insufficient evidence
Placenta	Strong	Maternal-fetal transfer	Nutritional context	Established physiology
Immune system	Mechanistic + deficiency study	Redox/immunological effects	Limited	Cannot extrapolate to iodine-replete subjects
Endometrium/uterus	Limited	Uncertain	None	Research gap
Testis	Limited	Uncertain	None	Research gap
Kidney	Strong role in iodine clearance	Homeostasis/excretion	None as therapeutic target	Primarily homeostatic
Lung/airway	Mechanistic plausibility	Mucosal defense	None	Research gap

Table 4: Iodine exposure, Lugol 2% equivalence, and relationship to human studies

Exposure	Approximate iodine dose	Context
Adult RDA	0.15 mg/day	Nutritional requirement
Adult UL	1.1 mg/day	Nutritional tolerable upper intake level
Kessler low dose	1.5 mg/day I_2	Less consistent breast response
1 nominal drop Lugol 2%*	~2.53 mg total iodine	~1 mg I_2 + ~1.53 mg iodine as iodide
Kessler intermediate dose	3 mg/day I_2	Significant breast response
Ghent, 60-kg individual	4.2–5.4 mg/day I_2	0.07–0.09 mg/kg/day
Ghent, 70-kg individual	4.9–6.3 mg/day I_2	0.07–0.09 mg/kg/day
Kessler high dose	6 mg/day I_2	Strongest breast response
Ghent, 80-kg individual	5.6–7.2 mg/day I_2	0.07–0.09 mg/kg/day
Lugol 2%, 1 mL	~50.6 mg total iodine	~20 mg I_2 + ~30.6 mg iodine from KI

*Calculated using a nominal drop volume of 0.05 mL. Actual drop volume varies according to dispensing device; therefore, clinical exposure should preferably be reported in milligrams rather than drops.

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