Jurnal Kesehatan Manarang

Jurnal Kesehatan Manarang, Volume 9, Number 3, December 2023, pp. 159 – 165
ISSN 2528-5602 (Online), ISSN 2443-3861 (Print)
doi: https://doi.org/10.33490/jkm.v9i3.834

THE POTENTIAL OF IODINE AS A TREATMENT FOR BREAST CANCER: A NARRATIVE REVIEW

Raihan Syah Ibrahim[1], Aisyah Elliyanti[2] ✉

[1]Department of Medicine, Faculty of Medicine, Andalas University, Padang, West Sumatra, Indonesia.
[2]Department of Radiology and Nuclear Medicine, Faculty of Medicine, Andalas University, Padang, West Sumatra, Indonesia

ARTICLE INFO

Article history

Submitted : 2022-12-21
Revised : 2023-10-04
Accepted : 2023-10-1

Keywords:

Anticancer;
Breast Cancer;
Cytotoxic;
Iodine;
Proliferation

ABSTRACT

Breast cancer is a cancer with the highest incidence of death in women in the world. Studies state that breast cancer can capture iodine molecules, making this substance a potential alternative therapy for further research and study. Opportunities for iodine as a treatment for breast cancer are supported by the fact that iodine is a molecular element widely available in nature, such as in food, plants, and oceans, so iodine is an easy substance to obtain. This article explores the potential of iodine as a treatment for breast cancer. The method used is a literature review study, in which literature is collected through the PubMed, Science Direct, and Google Scholar databases published from 2013-2022, and full text is available. The results of the review of the 10 articles obtained are the exposure of sources and intake of iodine, the physiological effects of iodine, and the effects of iodine on breast cancer cells. Iodine has the potential as a substance with anticancer activity through antiproliferative mechanisms, apoptosis, and immune system activation when given in sufficient quantities and at appropriate doses. The mechanism of iodine affecting breast cancer cells occurs through direct and indirect effects on the biological processes of cancer cells. These mechanisms occur molecularly in cancer cells by intermediary mitochondrial organelles and specific ligands in the cell. Iodine can also be combined with breast cancer chemotherapy, such as doxorubicin, which gives a good treatment response after chemotherapy. This is important to ensure sufficient daily intake of iodine for the body, especially in patients with breast cancer.

Kata Kunci:

Antikanker;
Kanker Payudara;
Proliferasi;
Sitotoksik;
Yodium;

ABSTRAK

Kanker payudara merupakan kanker dengan insiden penyebab kematian terbanyak pada perempuan di dunia. Adanya studi yang menyatakan bahwa molekul yodium dapat ditangkap oleh kanker payudara membuat zat ini dapat dijadikan sebagai terapi alternatif yang potensial untuk diteliti dan dipelajari lebih lanjut. Peluang yodium sebagai pengobatan kanker payudara didukung dengan fakta bahwa yodium merupakan elemen molekul yang banyak tersedia di alam, seperti pada makanan, tumbuhan, dan lautan sehingga yodium merupakan zat yang mudah untuk didapat. Artikel ini bertujuan untuk mengeksplorasi potensi zat yodium sebagai pengobatan kanker payudara. Metode yang digunakan yaitu studi tinjauan pustaka, yang mana pengumpulan literatur dilakukan melalui database PubMed, Science Direct, dan Google Scholar yang terbit dari tahun 2013-2022 dan tersedia full text. Hasil tinjauan dari 10 artikel yang diperoleh adalah pemaparan tentang sumber dan intake yodium, efek fisiologis yodium, dan efek yodium pada sel kanker payudara. Yodium memiliki potensi sebagai zat dengan aktivitas antikanker melalui mekanisme antiproliferatif, apoptosis, dan pengaktifan sistem imun apabila diberikan dalam jumlah yang cukup dan dosis yang sesuai. Mekanisme yodium dalam mempengaruhi sel kanker payudara terjadi melalui efek langsung dan efek tidak langsung pada proses biologi sel kanker. Kedua mekanisme tersebut terjadi secara molekuler pada sel kanker dengan perantara organel mitokondria dan ligan tertentu di dalam sel. Yodium juga dapat dikombinasikan dengan kemoterapi kanker payudara seperti dengan obat doxorubicin yang memberikan respon pengobatan yang baik setelah kemoterapi. Hal ini penting untuk memastikan tercukupinya asupan harian yodium bagi tubuh terutama pada pasien penderita kanker payudara.

✉ ***Corresponding Author:***

Aisyah Elliyanti
Department of Radiology and Nuclear Medicine, Faculty of Medicine, Andalas University
Padang, West Sumatra, Indonesia
Telp. 0812-6636-987
Email: aelliyanti@med.unand.ac.id

INTRODUCTION

Breast cancer is a disease with relatively increasing cases and the most common cause of death in women worldwide (Sung et al., 2021). Data from the World Health Organization (WHO) suggests that as many as 2.3 million women were diagnosed with breast cancer in 2020, resulting in 685 thousand deaths (WHO, 2021). Breast cancer is difficult to treat because it has a variety of disease heterogeneity, making it difficult to treat and requiring other alternative treatments (Ghoncheh et al., 2016). Previous research has proven that breast cancer cells can capture iodine in their tissues, making iodine a potential alternative therapy to be researched and studied further. Previous research proved that breast cancer cells can capture iodine in their cells, making iodine a potential alternative therapy to be researched and studied further (Aceves et al., 2013). Breast cancer is known to have the Sodium Iodide Symporter (NIS) protein, a transport protein that facilitates the capture of iodine into cells, and its role can also support normal breast growth (Poole & McCabe, 2015).

NIS protein expression can be detected in breast cancer cells with varying degrees in the cytoplasm and cell membrane. It transports iodine into the cell, and it be suggested as a new adjuvant treatment for breast cancer (Elliyanti et al., 2016, Elliyanti et al.,2020). Improving iodine intake in cancer patients will potentially reduce the likelihood of tumor progression so that the body needs to meet daily iodine requirements (Winder et al., 2022). Thus, iodine deficiency can increase the risk of developing breast cancer, which is associated with a direct effect through increased cell sensitivity to estradiol in the case of iodine deficiency. Previous research studies have shown the role of iodine as an antioxidant agent in female breast glands (Rappaport, 2017).

METHOD

The method used in writing this article is a literature review or review article through three different sources, namely PubMed, ScienceDirect, and Google Scholar, both written in Indonesian and English. The keywords used in writing this article are iodine, breast cancer, proliferation, anticancer, and cytotoxic. The search was limited to recent articles, so the publication year was limited to the last ten years (2013-2022). Articles used were in the form of original articles and review articles. The articles selected were those available in full text. The selection of articles was based on the purpose of writing, which is to determine the effect of iodine on the biological process of breast cancer cells and its potential as an alternative treatment.

RESULT

Iodine Sources and Intake

Iodine is a substance that is easily obtained and widely available in nature such as in seaweed, sea fish, and eggs that have a good iodine intake for the body. In addition, iodine can also be obtained in breast milk, table salt, and food supplements (ODS, 2022). Foods that are high in iodine are foods that are also high in protein such as fish, shrimp, shellfish, and marine algae (Astutik, 2017). The least common source of iodine consumed by people living in rural areas is marine fish. This is because the village is located in the hills and the distance from the village to the main market is quite far, causing people's food consumption to be limited to the food available there. Most of the iodine content in food and beverages is in the low category. The iodine content in marine fish is higher because the iodine found in seawater is concentrated in marine animals and plants. In addition, iodine content in food varies and is influenced by geographical location, season, and cooking method (Mahdiya Izati & Mahmudiono, 2017).

Iodine requirements in the body are within small parameters, however this substance is needed by the body in relatively small amounts as an essential micronutrient (Riwayati, 2013). Iodine intake per day based on age and pregnancy status can be seen in Table 1.

Tabel 1. Per-Day Iodine Requirement (Riwayati, 2013)

Intake Classification	Intake
Infant (first 12 months)	50 µg
Child (2-6 years)	90 µg
School age (7-12 years)	120 µg
Adults (above 12 years old)	150 µg
Pregnant women	200 µg
Nursing mothers	200 µg

Based on Table 1, the iodine requirement for the body varies according to age and certain other conditions. Children's needs are different from adults' iodine needs per day. Certain physiological conditions of the body such as pregnant women and lactating mothers will require higher iodine intake (Muftiana & Munawaroh, 2016). Iodine compounds consumed through food will be reduced in the proximal part of the small intestine to iodide which is then absorbed into the small intestinal mucosa by NIS or by diffusion. The efficiency of iodine absorption and bioavailability is related to dietary intake and the systemic requirement for iodine. Absorbed iodine then enters the plasma and circulates in the blood vessels. Most of the iodide that enters the plasma is taken up by the thyroid gland through its own NIS. In the human body, the thyroid accumulates about 75% of the 15-20 mg of total iodine in the body. Iodine is also concentrated in other tissues including breast glands, salivary glands, and gastric mucosa which all have NIS transport proteins (The Scientific Advisory Committee, 2014).

Physiological Role of Iodine

Iodine in the human body has a broad role including in metabolic processes, growth, development during the fetal period, and after birth (Andersen et al., 2019). The essential function of iodine in the human body is as the main element in the formation of thyroid hormones that function in regulating metabolic processes and development from the fetal period to adulthood (Niwattisaiwong et al., 2017). In addition, iodine also has a direct influence on children's intelligence through the formation of the hormone thyroxine. Normal female breasts are also known to accumulate iodine in their tissues. Physiologically, breast cells are able to secrete iodine in milk products to meet the iodine needs of their infants during lactation. Thus, the baby has received a source of iodine directly from its mother to support its growth and development (Yang et al., 2017).

Iodine is also important for the baby's brain development during breastfeeding. Infants are particularly sensitive to iodine deficiency as they have a high demand but low iodine stores. The first two years of age are crucial for neurological growth and development. Even mild iodine deficiency can cause irreversible damage during this period, such as low intelligence, neonatal hypothyroidism, short stature, skeletal disorders, and other growth retardation. Iodine status in breastfed infants depends on maternal iodine intake. Thus, the iodine status of the breastfeeding mother will determine the degree of growth and development of her infant (Yang et al., 2017). During breastfeeding, the mother transfers iodine to her infant through the breast glands, which concentrate iodine in the milk. To ensure that the baby gets enough iodine, breastfeeding mothers are recommended to consume 200 µg/day of iodine (Table 1) (Riwayati, 2013).

Effects of Iodine on Breast Cancer

Iodine is known to have an effect on normal and abnormal cells in the human body, one of which is breast cancer cells. The mechanism in providing anti-tumor effects that iodine has is mediated by Arachidonic Acid (AA) derivatives such as 6-iodolactone (Aranda et al., 2013). Iodine can also provide direct and indirect antiproliferative effects. The direct effect is in the form of disruption of the mitochondrial membrane potential which then stimulates apoptosis. The indirect effect is mediated by 6-iodolactone which then activates Peroxisome Proliferator Activated Receptor gamma (PPARɣ) which this receptor plays a role for carcinogenic processes (Nava-Villalba et al.,

2015). The following results resume the effect of iodine administration based on previous research studies, can be seen in Table 2.

Table 2. Published Studies of the Effects of Iodine Administration on Breast Cancer

Title (Author)	Study	Result
Effects of Molecular Iodine/ Chemotherapy in the Immune Component of Breast Cancer Tumoral Microenvironment (Cuenca-Micó *et al*., 2021)	Studi *In-vivo*	Oral I2 supplementation in breast cancer patients induces an activated immune response. The molecular mechanism involved in this immune response is a methylation/dimethylation reaction.
Adjuvant Effect of Molecular Iodine in Conventional Chemotherapy for Breast Cancer. Randomized Pilot Study (Moreno-Vega *et al*., 2019)	Studi *In-vivo*	Oral I2 supplementation in breast cancer patients along with chemotherapy showed significant results in terms of decreased side effects and no tumor chemoresistance. Tumors showed less invasive potential, and a significant increase in apoptosis, estrogen receptor expression, and immune cell infiltration.
Molecular Iodine Exerts Antineoplastic Effects by Diminishing Proliferation and Invasive Potential and Activating the Immune Response in Mammary Cancer Xenografts (Mendieta *et al*., 2019)	Studi *In-vivo* And *In-vitro*	In-vitro, iodine (I2) decreased the invasive potential of triple-negative breast cancer cell lines, and in-vivo oral supplementation resulted in activated anti-tumor immune responses.
Molecular Iodine/Doxorubicin Neoadjuvant Treatment Impair Invasive Capacity and Attenuate Side Effect in Canine Mammary Cancer (Zambrano-Estrada *et al*., 2018)	Studi *In-vivo* in experimental animals	The combination of I2 and mDOX can improve therapeutic outcomes, reduce invasive capacity, attenuate side effects and increase disease-free survival in canine breast cancer.
The Extrathyronine Actions of Iodine as Antioxidant, Apoptotic, and Differentiation Factor in Various Tissues (Aceves *et al.*, 2013)	*Literature review*	Based on this study review, in animal and human studies, molecular iodine (I2) supplementation exerts a suppressive effect on the development and size of benign neoplasia and malignancy in extrathyroidal organs such as female breast glands.
Molecular Iodine Impairs Chemoresistance Mechanisms, Enhances Doxorubicin Retention and Induces Downregulation of the CD44/CD24+ and E Cadherin+/ Vimentin+ Subpopulations in MCF-7 Cells Resistant to Low Doses of Doxorubicin (Bontempo *et al*., 2017)	Studi *In-vitro* dan *In-vivo*	Iodine (I2) molecules in-vitro can provide anti-tumor effects on breast neoplasms because they can capture iodine in their tissues so as to provide oxidant/antioxidant properties and iodolipid formation. Iodine supplementation in-vivo 200 µM has the effect of reducing the proliferation rate by 40% in breast cancer cell lines.
Molecular Iodine Has Extrathyroidal Effects as an Antioxidant, Differentiator, and Immunomodulator (Aceves *et al*., 2021)	*Literature review*	In breast malignancies, I2 produces iodolipids with nuclear effects that include activation of apoptotic pathways and inhibition of markers associated with stem cell maintenance, chemoresistance, and breast cancer survival.
Iodine A Potential Antioxidant and the Role of Iodine/Iodide in Health and Disease (Winkler, 2015)	*Literature review*	In-vitro iodine plays a role in decreasing hyaluronic acid depolymerization and increasing antioxidant status in serum. In-vivo iodine plays a role in increasing antioxidant enzyme activity and decreasing malondialdehyde and peroxides.
Iodine and Doxorubicin, A Good Combination for Mammary Cancer Treatment: Antineoplastic Adjuvancy, Chemoresistance Inhibition, and Cardioprotection (Alfaro *et al*., 2013)	Studi *In-vivo*	The I2-DOX combination exerts antineoplastic, chemosensitivity, and cardioprotective effects and could be a promising strategy against breast cancer progression.
An Iodine Treatment Effect on Cell Proliferation Rates of Breast Cancer Cell Line; In-Vitro Study (Elliyanti *et al*., 2020)	Studi *In-vitro*	*Breast cancer cell lines respond well to iodine therapy depending on the dose given.*

DISCUSSION

Iodine's potential as a breast cancer treatment

The focus of this review study on the potential of iodine in breast cancer treatment is on iodine's mechanism in inhibiting cancer cell proliferation, apoptosis, and survival. The ability of iodine to inhibit the biological processes of cancer cells is the parameter of whether this substance has a good cytotoxic effect to be used as a cancer treatment. Substances that are proven to be able to exert cytotoxic effects on cancer cells are then compared for their inhibitory doses whether they are comparable or better than anticancer drugs that are already in use today. Therefore, it is necessary to consider whether iodine has better or worse abilities than other breast cancer treatments.

In previous studies, iodine has shown an Inhibition Concentration 50% (IC50) in the low micromolar range, marking its potential to be developed as a new anticancer drug. However, the dose should certainly be lowered again, as lower doses will help reduce the appearance of unwanted side effects (Elliyanti et al., 2020). Iodine turns out to have an important role in influencing the biological process in breast cancer, because the consumption of large amounts of iodine will help cure breast cancer gradually. Of course, the consumption of iodine itself will be better if it comes from foods such as those contained in fish and seaweed (Astutik, 2017). In addition, other evidence that supports this opinion is the fact that the Japanese people have the lowest incidence of thyroid cancer, prostate cancer, and breast cancer (Poole & McCabe, 2015; Rappaport, 2017). This, of course, can be evidence that iodine can be used as an alternative ingredient to treat breast cancer.

The mechanism by which iodine affects breast cancer cells occurs through direct effects and indirect effects on cancer cell biological processes. Both mechanisms occur molecularly in cancer cells with the intermediary of mitochondrial organelles and certain ligands in the cell (Aranda et al., 2013; Nava-Villalba et al., 2015). In addition, the administration of iodine to breast cancer patients who are undergoing the chemotherapy process will get adjuvant effects from iodine in the form of decreased chemotherapy side effects and tumor chemoresistance. Tumors also show less invasive potential, and a significant increase in apoptosis, estrogen receptor expression, and immune cell infiltration (Moreno-Vega et al., 2019). The combination of iodine with chemotherapy includes the drug doxorubicin. The combination of iodine with doxorubicin chemotherapy will provide antineoplastic, chemosensitivity, and cardioprotective effects and could be a promising strategy against the development of breast cancer (Alfaro et al., 2013; Bontempo et al., 2017; Zambrano-Estrada et al., 2018). Iodine also has a suppressive effect on tumors by reducing cell proliferation and activating the body's immune response to fight these malignant cells (Cuenca-Micó et al., 2021).

The problem of iodine deficiency is very often a hidden problem that is almost unnoticed and neglected. People in general often assume that the only easily available source of iodine is the table salt they consume daily. Some people think that consuming iodized salt is enough to fulfill their daily iodine needs. However, the fact that has recently been discovered is that some of the iodine from the salt will evaporate when the package is opened. This means that when the salt is left in a container with an open hole, most of the iodine component in it will be lost. On the other hand, the consumption of iodine obtained from salt alone is not enough to fulfill the daily requirement of iodine. The functions of iodine are enormous for the body. And a number of them can be linked to cancer. That's why previous research has provided understanding for people to realize how important it is to ensure the daily sufficiency of iodine for the body.

CONCLUSIONS AND SUGGESTIONS

Iodine has potential as a substance with anticancer activity through antiproliferative, apoptotic, and immune system activating mechanisms when administered in sufficient amounts and appropriate doses. It is important to ensure that the body must meet a good enough iodine requirement, especially in breast cancer patients per day. Iodine can also be combined with breast cancer chemotherapy such as with the drug doxorubicin which provides a good treatment response after chemotherapy. Over the past two decades, research progress on iodine can be considered valuable for the development of new alternative therapies. The data in this literature review can be used as a reference and further research needs to be done. Therefore, it is necessary to study the mechanism of iodine in affecting breast cancer more fully and in more detail.

REFFERENCES

Aceves, C., Anguiano, B., & Delgado, G. (2013). The extrathyronine actions of iodine as antioxidant, apoptotic, and differentiation factor in various tissues. *Thyroid*, *23*(8), 938–46. https://doi.org/10.1089/thy.2012.0579

Aceves, C., Mendieta, I., Anguiano, B., & Delgado-González, E. (2021). Molecular iodine has extrathyroidal effects as an antioxidant, differentiator, and immunomodulator. In *International Journal of Molecular Sciences* (Vol. 22, Issue 3, pp. 1–15). MDPI AG. https://doi.org/10.3390/ijms22031228

Alfaro, Y., Delgado, G., Carabes, A., Anguiano, B., & Aceves, carmen. (2013). Iodine and Doxorubicin, A Good Combination for Mammary Cancer Treatment: Antineoplastic Adjuvancy, Chemoresistance Inhibition, and Cardioprotection. *Molecular Cancer*, *11*. https://doi.org/10.1186/1476-4598-11-10

Andersen, S., Noahsen, P., Rex, K., Florian-Sorensen, H., & Mulvad, G. (2019). Iodine in Edible Seaweed, its Absorption, Dietary Use, and Relation to Iodine Nutrition in Arctic People. *Journal Medikal Food*, *22*, 421–425. https://doi.org/10.1089/jmf.2018.0187

Aranda, N., Sosa, S., Delgado, G., Aceves, C., & Anguiano, B. (2013). Uptake and antitumoral effects of iodine and 6-iodolactone in differentiated and undifferentiated human prostate cancer cell lines. *Prostate*, *73*(1), 31–41. https://doi.org/10.1002/pros.22536

Astutik, V. Y. (2017). Tingkat Pengetahuan, Pola Kebiasaan Lingkungan Hidup Berhubungan Dengan Motivasi Ibu Dalam Memilih Kondisi Garam. *Care : Jurnal Ilmiah Ilmu Kesehatan*, *5*(2), 220. https://doi.org/10.33366/cr.v5i2.541

Bontempo, A., Ugalde-Villanueva, B., Delgado-Gonzalez, E., Rodríguez, Á. L., & Aceves, C. (2017). Molecular iodine impairs chemoresistance mechanisms, enhances doxorubicin retention and induces downregulation of the CD44+/CD24+ and E-cadherin+/vimentin+ subpopulations in MCF-7 cells resistant to low doses of doxorubicin. *Oncology Reports*, *38*(5), 2867–2876. https://doi.org/10.3892/or.2017.5934

Cuenca-Micó, O., Delgado-González, E., Anguiano, B., Vaca-Paniagua, F., Medina-Rivera, A., Rodríguez-Dorantes, M., & Aceves, C. (2021). Effects of molecular iodine/chemotherapy in the immune component of breast cancer tumoral microenvironment. *Biomolecules*, *11*(10), 1–10. https://doi.org/10.3390/biom11101501

Elliyanti, A., Veronika, Y. S., Sri, S., & Pasupuleti, V. R. (2020). An Iodine Treatments Effect on Cell Proliferation Rates of Breast Cancer Cell Line In Vitro Study. *An Iodine Treatments Effect on Cell Proliferation Rates of Breast Cancer Cell Line In Vitro Study*, *8*(B), 1064–1070. https://doi.org/10.3889/oamjms.2020.5447

Elliyanti, A., Wikayani, T. P., Noormartany, Masjhur, J. S., & Achmad, T. H. (2016). Deteksi Natrium/Iodide Symporter (NIS) pada Galur Sel Kanker Payudara SKBR3 dengan Imunositofluoresens. *Majalah Kedokteran Bandung*, *48*(1), 15–18. https://doi.org/10.15395/mkb.v48n1.729

Ghoncheh, M., Mahdavifar, N., Darvishi, E., & Salehiniya, H. (2016). Epidemiology, Incidence and Mortality of Breast Cancer in Asia. *Asian Pacific J Cancer Prev*, *17*, 47–52. https://doi.org/10.7314/apjcp.2016.17.s3.47

Mahdiya Izati, I., & Mahmudiono, T. (2017). Pola Konsumsi Makanan Sumber Yodium dan Goitrogenik dengan GAKY pada Anak Usia Sekolah di Ponorogo Iodine and Goitrogenic Intake among School Children in Ponorogo. *Amerta Nutrition*, *1*(2), 88–97. https://doi.org/10.2473/amnt.v1i2.2017.88-97

Mendieta, I., Nuñez-Anita, R. E., Nava-Villalba, M., Zambrano-Estrada, X., Delgado-González, E., Anguiano, B., & Aceves, C. (2019). Molecular iodine exerts antineoplastic effects by diminishing proliferation and invasive potential and activating the immune response in mammary cancer xenografts. *BMC Cancer*, *19*(1). https://doi.org/10.1186/s12885-019-5437-3

Moreno-Vega, A., Vega-Riveroll, L., Ayala, T., Peralta, G., Torres-Martel, J. M., Rojas, J., Mondragón, P., Domínguez, A., De Obaldía, R., Avecilla-Guerrero, C., Anguiano, B., Delgado-Gonzélez, E., Zambrano-Estrada, X., Cuenca-Micó, O., De La Puente Flores, O., Varela-Echavarría, A., & Aceves, C. (2019). Adjuvant effect of molecular iodine in conventional chemotherapy for breast cancer. randomized pilot study. *Nutrients*, *11*(7).

https://doi.org/10.3390/nu11071623

Muftiana, E., & Munawaroh, S. (2016). Kadar Yodium Garam Rumah Tangga di Desa Krebet Kabupaten Ponorogo. *Ejournal .Umm*, *3*(2), 58–66. http://eprints.umpo.ac.id/2292/

Nava-Villalba, M., Nuñez-Anita, R., Bontempo, A., & Aceves, C. (2015). Activation of peroxisome proliferator-activated receptor gamma is crucial for antitumoral effects of 6-iodolactone. *E. Mol Cancer*, *14*(1), 1–11. https://doi.org/10.1186/s12943-015-0436-8

Niwattisaiwong, S., Burman, K. D., & Li-Ng, M. (2017). Iodine deficiency: Clinical implications. *Cleveland Clinic Journal of Medicine*, *84*(3), 236–244. https://doi.org/10.3949/ccjm.84a.15053

ODS. (2022). Iodine - Health Professional Fact Sheet. *National Institutes of Health (NIH)*. https://ods.od.nih.gov/factsheets/Iodine-HealthProfessional/

Poole, V. L., & McCabe, C. J. (2015). Iodide transport and breast cancer. In *The Journal of endocrinology* (Vol. 227, Issue 1, pp. R1–R12). https://doi.org/10.1530/JOE-15-0234

Rappaport, J. (2017). Changes in dietary iodine explains increasing incidence of breast cancer with distant involvement in young women. In *Journal of Cancer* (Vol. 8, Issue 2, pp. 174–177). Ivyspring International Publisher. https://doi.org/10.7150/jca.17835

Riwayati. (2013). Iodium Mineral Sebagai Zat Gizi. *Jurnal Keluarga Sehat Sejahtera*, *11*(22), 35–41. https://doi.org/10.24114/jkss.v11i22.3561

Sung, H., Ferlay, J., Ervik, M., Lam, F., Colombet, M., Mery, L., & Piñeros, M. (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*, *71*(3), 209–249. https://www.who.int/news-room/fact-sheets/detail/cancer

The Scientific Advisory Commitee. (2014). *Sacn Statement on Iodine and Health*. *February*, 1–44. https://www.gov.uk/government/publications/sacn-statement-on-iodine-and-health-2014

WHO. (2021). Breast Cancer. *News Room*. https://www.who.int/news-room/fact-sheets/detail/breast-cancer

Winder, M., Boral, A., & Chudek, J. (2022). *The Impact of Iodine Concentration Disorders on Health and Cancer*. 1–17. https://doi.org/10.3390/nu14112209

Winkler, R. (2015). Iodine—A Potential Antioxidant and the Role of Iodine/Iodide in Health and Disease. *Natural Science*, *07*(12), 548–557. https://doi.org/10.4236/ns.2015.712055

Yang, J., Zhu, L., Li, X., Zheng, H., Wang, Z., Hao, Z., & Liu, Y. (2017). Maternal iodine status during lactation and infant weight and length in Henan Province, China. *BMC Pregnancy and Childbirth*, *17*(1), 1–6. https://doi.org/10.1186/s12884-017-1569-0

Zambrano-Estrada, X., Landaverde-Quiroz, B., Dueñas-Bocanegra, A. A., De Paz-Campos, M. A., Hernández-Alberto, G., Solorio-Perusquia, B., Trejo-Mandujano, M., Pérez-Guerrero, L., Delgado-González, E., Anguiano, B., & Aceves, C. (2018). Molecular iodine/doxorubicin neoadjuvant treatment impair invasive capacity and attenuate side effect in canine mammary cancer. *BMC Veterinary Research*, *14*(1). https://doi.org/10.1186/s12917-018-1411-6