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The Estrogenic Contaminants in Food: the Type of Methods for Detection: A Systematic Review

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Running head: estrogenic contaminants in food

Abstract

BACKGROUND: Many compounds are known as estrogen contaminants. Estrogenic components may enter the body through food.

OBJECTIVES: The aim of this systematic review was to determine the types of estrogens contaminants and the foods that are primarily contaminated with these compounds, as well as their common detection methods.

METHODS: The research studies with the keywords estrogen, detection, and food were systematically searched in PubMed, and Scopus databases. Science Direct and google scholar were also searched.

RESULTS : A total of 221 studies were obtained regardless of publication time. The initial screening was based on exclusion and inclusion criteria of the study. Then the qualitative evaluation of the articles was done and finally 9 articles were selected. Among different foods, most estrogenic compounds of seafood were identified. This indicates that estrogenic compounds are entering the waters. The most reported compound was Bisphenol A. Cell culture are used for bioassay evaluation, and liquid chromatography methods were used for analysis method.

CONCLUSIONS: Both analytical and bioassay methods were used in the evaluation of estrogenic compounds. Most studies found that the bioassays method was also valid.

KEYWORDS: Bioassay, Detection, Estrogen, Food, Analytical methods

Introduction

Estrogens in the body act through alpha and beta receptors and have beneficial effects including protecting the cardiovascular system (Gurrala et al., 2021). It is necessary for the metabolic and natural processes of the body. This hormone plays a role in calcium absorption (Qaid & Abdoun, 2022). But, Endocrine disturbance chemicals can interfere with the release, synthesis, activity, and metabolism of endogenic hormones (Law *et al*., 2012). One of the toxins that lead to endocrine-disrupting is environmental estrogens. Environmental pollution of these components is widespread (Capriotti *et al*., 2013), so the probability of entering the food chain is very high. These toxins are also called environmental estrogens. 90% of human exposure to environmental estrogen is through contaminated food (Muhammad Adeel, Xiaoming Song, Yuanyuan Wang, Dennis Francis, & Yuesuo Yang, 2017; Law *et al*., 2012). Hormones act in small amounts in the body, so if similar compounds enter the body, they have significant side effects. These compounds have negative effects on human and plant health (Cheraghi, Zargushi, Kerishchi Khyabani, & Nasri, 2021). In fish, these compounds lead to feminism fish (Van Nuijs, Tarcomnicu, & Covaci, 2011). Fish is one of the food sources that are considered to be contaminated with estrogenic compounds (Rahmati, Morovvati, & Abdi, 2022). Environmental studies have shown that low amounts of estrogens in water have a negative effect on the reproduction of fish and amphibians (Ojoghoro, Scrimshaw, & Sumpter, 2021).

Wastes from pharmaceutical factories and plastic factories, and pesticides that have estrogenic activity enter the waters (Dey, 2022). These components affect both sexes. Increased estrogen in females leads to various cancer, including the uterus, colon, pituitary, and breast as well as blood clots and cardiovascular diseases (Muhammad Adeel *et al*., 2017; Watson, Jeng, & Guptarak, 2011). The estrogenic chemicals reduce sperm and increase prostate cancer in men (Muhammad Adeel *et al*., 2017). Estrogenic compounds are found in pesticides, PVC, food packaging materials, PET bottles, and various industrial materials (Inoue *et al*., 2002; Wagner & Oehlmann, 2009). According to previous studies, the mineral water in PET and Tetra Pak packages has more estrogenic properties than the mineral water in glass bottles (Wagner & Oehlmann, 2009). Foods of animal origin can contain significant amounts of these estrogens (Chighizola & Meroni, 2012). Sometimes synthetic hormones with these effects are used in livestock breeding (Qaid & Abdoun, 2022). In addition, soybean is used in animal feed. This feed provides the protein needed by livestock (Messina, 2022). But, one of the active components of soybean is isoflavones, which are called phytoestrogens (Qaid & Abdoun, 2022).

Analytical methods such as GC and HPLC are used to identify estrogens (Giese, 2003). Furthermore, these compounds bind to estrogen receptors or transcription factors (Watson *et al*., 2011). They can bind to estrogen receptors at very low doses, and lead to cellular changes such as the proliferation of apoptosis and metastasis (Qie *et al*., 2021). Bioassay methods are used to identify active compounds in different matrices (Amoli, Sadighara, Barin, Yazdani, & Satari, 2009). One of the bioassay methods is E-screen, which is usually used to evaluate estrogenic activity in food (Sadighara, Mahdavi, Tahmasebi, & Saatloo, 2022). In addition to threatening human health, these compounds are a critical threat to water resources, soil, and plants (M. Adeel, X. Song, Y. Wang, D. Francis, & Y. Yang, 2017). Therefore, the method of identifying them is essential. This review discusses the type of foods along with estrogenic contaminants of them and the diagnostic methods of these compounds in foods.

Materials and Methods

This systematic review was written based on the PRISMA checklist. Two authors performed all stages including evaluation of inclusion and exclusion criteria, and data extraction to prevent bias (P.S and S.M).

Search strategy

The articles in the English language were searched on 14 May 2021. There was no time limitation. The chosen databases were PubMed, and Scopus. The research team compiled the keywords based on the prepared protocol. Possible synonyms were also checked for words that did not have a specific case. The keywords for searching were set: estrogenic AND detection AND food. In order to complete the search process, in addition to selected databases with compiled keywords, Science Direct, and Google Scholar were also searched.

Inclusion and exclusion criteria

The two reviewers (P.S and S.M) searched the keywords in databases independently. Inclusion criteria for this systematic review included original articles that measured xenoestrogen levels by valid methods of measuring. At first, the title and abstract of the papers were read. Papers that were not in accordance with the aims and research questions were excluded from the study. The articles were screened by two of the authors. In case of disagreement, the opinions of the responsible author were obtained.

Data extraction and data item

The name of the first author, time of the study, type of food and estrogen, country, and method of measuring xenoestrogens were extracted. Furthermore, the types of estrogen in three classifications of natural, industrial and synthetic estrogens with relevant examples were extracted from the articles. The data were extracted by two reviews independently. If the full text of the articles was not available, the authors of the article were emailed.

Results

Study selection

221 articles were achieved by searching PubMed, Scopus, ScienceDirect, and Google scholar. 67 articles were excluded from the study due to duplicating. The abstracts of the remaining articles were carefully screened. 121 articles were excluded from the study at this stage. 5 articles were excluded due to conference abstracts, 54 animal studies articles, 25 biomonitoring articles, detection in water, feed, packages, sediments and wastewater. 37 articles were review articles and were excluded from the study.

Then the full text of 33 papers was taken. Ultimately, 9 articles were selected based on the inclusion criteria of the proposals and their quality assessments were performed. To evaluate the quality of the articles, 5 factors were considered. Papers that received a score of three or more were included in this study. This step was also performed independently by the two authors. This systematic review used the PRISMA flow diagram (Fig 1).

Classification of types of estrogenic compounds in food

Table 1 shows the estrogens identified in food. Most of the compounds mentioned in this table are due to human activities and industrial pollution. In foods of animal origin, the hormonal compounds of 17αestradiol (αE2), 17β estradiol (βE2), estrone (E1), and estriol(E3) are found that the estrogenic power of these compounds is higher than plant and fungal estrogens (Capriotti *et al.*, 2013). The Possible source of nonylphenol (NP) is due to their use in car washes (Fenlon, Johnson, Tyler, & Hill, 2010). Furthermore, a human can expose to NP of medical PVC devices *(Inoue et al.*, 2002). Some pesticides, such as Methiocarb, have estrogenic properties (Sinha, Ma, & Zhao, 2021). Furthermore, most organochlorine insecticides have estrogenic properties (Sharma et al., 2021).

Discussion

Environmental estrogens enter the body through food. Estrogen acts in very low doses, so tracking and determining the amount of them in food is required. Zearalenone (ZEN) is a known xenoestrogen among fungal metabolites that has a very high affinity for estrogen receptors (D. Braun, Ezekiel, Marko, & Warth, 2020). Zearalenone passes through the placenta and enters the fetal body, leading to estrogenic effects (Dominik Braun, Schernhammer, Marko, & Warth, 2020). ZEN leads to infertility and major changes in the reproductive system. This mycotoxin is produced by *Fusarium culmorum* and *Fusarium graminearum* (Videmann, Mazallon, Prouillac, Delaforge, & Lecoeur, 2009). Two studies were conducted on the evaluation of ZEN in breast milk. In both studies, amounts of ZEN were not measured (Dominik Braun et al., 2020). In both studies, LC-MS/MS method was used for diagnosis. This method is reliable and sensitive.

Another estrogenic compound that was identified was Bisphenol A. It is one of the monomers of polycarbonate and is used as an additive in many plastics including polystyrene resins (Ocharoen, Boonphakdee, Boonphakdee, Shinn, & Moonmangmee, 2018; Vivacqua *et al*., 2003). Bisphenol A has negative effects on the reproductive system and can lead to cancer and diabetes (Ocharoen *et al*., 2018). Bisphenol A is released from lacquer-coated cans. One of the major exposures to bisphenol A is throgh canned foods. Exposure also occurs through water stored in polycarbonate bottles (Le, Carlson, Chua, & Belcher, 2008). Bisphenol A contamination is also found in rivers and groundwater (Pignotti, Farré, Barceló, & Dinelli, 2017). In the study of Vivacqua *et al*., the level of contamination with bisphenol A and 4-Nonylphenol in fresh food was also observed (Vivacqua *et al.,* 2003). In the study of Lu *et al* (Lu, Wu, Stoffella, & Chris Wilson, 2012) estrogenic compounds were measured in plant-based foods. All samples had bisphenol A and 17-β-Estradiol. In this study, 17-α-estradiol and 17-α-Ethynylestradiol were not detected in any of the samples.17-α-ethynylestradiol is a synthetic estrogen that is used by humans.

Therefore, its presence in food seems unlikely. In this study, all compounds were measured with GC/MS. One of the most common methods of measuring bisphenol A is GC/MS (Adeyi & Babalola, 2019; Howdeshell *et al.*, 2003). This method has a higher diagnostic power and is cheaper than LC/MS/MS for the detection of bisphenol A (Martín-Pozo, Martín-Bueno, Moscoso-Ruiz, & Zafra-Gómez, 2022).

In the study of Brotons et al., LC-MS/MS and bioassay tests were used to detect bisphenol A in canned food products. The cell proliferation in MCF7 cells was used as an E-screen test. In this study, a positive correlation was observed between the amount of bisphenol A and estrogenic activity bioassay assessment (Brotons, Olea-Serrano, Villalobos, Pedraza, & Olea, 1995). Green mussel is a type of seafood. Significant amounts of bisphenol A and 17β-estradiol were found in them in the study of Ocharoen *et al.*, (Ocharoen *et al.*, 2018). In this study, HPLC chromatography was used to measure bisphenol A and 17β-estradiol. Samples were collected from near industrial centers that do not manage wastewater treatment (Ocharoen *et al.*, 2018).

PCBs are estrogenic compounds that causes sperm reduction and abnormalities in the reproductive system and malformation (Bagale, 2021). Furthermore, PCBs have other toxic effects, including immunotoxicity and neurotoxicity (Garritano *et al.*, 2006). The presence of PCBs was investigated by both GC chromatography and bioassay method in this study. A correlation wasn't found between the amount of PCBs and estrogenic activity (Garritano *et al.*, 2006).

In the study of Teh *et al*., a planar yeast estrogen screen (pYES) assay was used for cold-pressed hemp, flax, and canola seed oil (Teh & Morlock, 2015). This modified yeast has a human estrogen receptor. In this study, all three oils contained estrogenic activity, which is due to phytoestrogens that are naturally present in the composition of these oils (Teh & Morlock, 2015). In previous studies, the sensitivity of this method to identify estrogenic compounds in food packaging has been confirmed (Bergmann, Simon, Schifferli, Schönborn, & Vermeirssen, 2020). This method has also been used to identify estrogenic compounds in water. Its sensitivity and specificity have been confirmed as a screen test to identify these compounds in water (Bistan, Podgorelec, Marinšek Logar, & Tišler, 2012).

In the study of Law *et al*., receptor-mediated responses by estrogen and androgen hormones, glucocorticoid-like, progesterone-like, and dioxin-like components in food of animal and marine origin were investigated for the detection of hormonal residues (Law *et al*., 2012). The luciferase reporter assay test was used in this study. The concentration of these compounds was higher in the skin of fish and chickens. Luciferase assay is one of the bioassays that has high sensitivity in detecting estrogenic compounds in food. In a study, it was observed that this assay is capable of detecting low amounts of bisphenol A in food (Ishida et al., 2023). Furthermore this method is a cost-effective for assessing estrogenic compounds in foods for risk assessment (Law *et al*., 2012).

Table 2 shows that the LC-MS/MS reports more than other chromatographic methods. In previous studies, this method has been emphasized (Van Nuijs *et al*., 2011). Chromatographic methods are expensive methods. The GC /MS method for the detection of estrogens requires derivation (Van Nuijs et al., 2011). In this systematic review, the sensitivity of bioassay tests was identified in some studies. Therefore, these bioassay methods can be used for regular food monitoring.

One of the limitations of this study is that in some studies, both methods were not investigated together. More research studies are needed that both tests (bioassay and chromatography) are used together to evaluate these compounds.

Conclusion

In this study, the types of estrogen contaminants in food were identified. These contaminants are divided into three categories: industrial estrogens, natural estrogens, and synthetic estrogens. Measurement of bisphenol A is more prominent than other estrogenic contaminants among the selected studies. Bisphenol A is due to human and industrial activities, so we need more processes for wastewater treatment. The analytical methods are costly. Therefore, screen tests can be applied to identify these components in foods. According to the some polished manuscript, bioassay methods are valid, so they can be used to detect these toxic compounds in food. In future studies, it is recommended, that the correlation between analytical and bioassay methods and the sensitivity of these methods are measured for the detection of different estrogenic compounds in different food matrices.

Abbreviations

ZEN: Zearalenone; HPLC: High performance liquid chromatography; GC/MS: Gas chromatography-Mass spectrometry; LC-MS: liquid chromatography- Mass spectrometry; LOQ: limit of quantification.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

The data used to support the findings of this study are included within the article.

Competing interests

The authors of this article declare that they have no conflict of interests.

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Authors' contributions

P.S. designed the study and searched the databases; S.M. extracted the data; N.V., I.L.,M.S., T.Z. and P.S. drafted the paper. All authors read the final version.

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Table 1. The various type of estrogen in food

Industrial estrogen	Natural estrogen			Synthetic estrogen		
	Mycoestrogen	Phytoestrogen	mammalian estrogens,	Hormonal agent	Alkyl phenol	Pesticide
2,3,7,8-tetrachloodibenzo-p-dioxin (TCDD), PCBs	zearalenone (ZON)	Isoflavones Polyphenols Lignans	17αestradiol (αE2), 17β estradiol (βE2), estrone (E1), and estriol(E3)	diethylstilbestrol (DES) 17-α-Ethynylestradiol	bisphenol A (BPA), octylphenol (OP), nonylphenol (NP),	chlorinated insecticides

Table 2. The type of food xenoestrogen and the detection method according to the published data

Authors / Year	Country	Type of xenoestrogen	Type of food	Analysis method	Bioassay	Statements
Braun/2020(Dominik Braun et al., 2020)	Austria	Zearalenone (ZEN)	Breast milk	LC-MS/MS	-	<LOQ
Braun/2020(D. Braun et al., 2020)	Austria	Zearalenone (ZEN)	Breast milk	LC-MS/MS	-	All samples were free of ZEN and its metabolites
Brotons/1995(Brotons *et al., 1995)*	Spain	bisphenol-A	Canned food : Peas, Artichokes, Green beans, Mixed vegetables, Corn, Mushrooms, Asparagus, Palm, hearts ,Peppers	LC-MS/MS	E-screen test(Cell proliferation in MCF7 cells)	Different levels of bisphenol A were found in the range of 22.9 to ND(µg/can) The highest amount of bisphenol A was found in canned peas A direct relationship was observed between analytical and bioassay

						methods
Garritano/2006(Garritano *et al.*, 2006)	Italy	Total PCBs	Fish	GC-ECD	*vitro* yeast reporter gene assay	Among PCBs studied, PC180, PC153,PC101 and PC28 had the highest estrogenic activity
LAW/2012 (Law *et al.*, 2012)	Hong Kong	residual hormonal	Meat, fish ,chicken	-	luciferase reporter assays	Residual concentrations of hormones in fish and poultry skins are higher than elsewhere
Lu/2012 (Lu *et al.*, 2012)	USA	alkylphenols, bisphenol A, Estrone, 17-α-Estradiol, 17-β-Estradiol, 17-α-Ethynylestradiol	Lettuce, tomato, potato, citrus	GC/MS	-	Bisphenol A and 17-β-Estradiol was detected in all samples In none of the samples 17-α-Estradiol and 17-α-Ethynylestradiol was not detected

Ocharoen/2018 (Ocharoen *et al.*, 2018)	Thailand	Bisphenol-A 17β-estradiol	Green mussel	HPLC	-	Detection range for bisphenol: 15.3–109.97 ng/g and for 17β-estradiol:12.96–152.8 ng/g
Teh/2015 (Teh & Morlock, 2015)	Germany	Phytoestrogen	Cold-pressed hemp, flax and canola seed oil	-	estrogen-sensitive yeast cells S. cerevisiae (pYES assay)	These oils have estrogenic activity
Vivacqua/2003 (Vivacqua *et al.*, 2003)	Italy	Bisphenol-A 4-nonylphenol	Apple ,Cherry, Courgette Cucumber Eggplant Fennel Green bean Lettuce, Medlar, Orange , Peach , Pepper Strawberry, Tomato	GC/MS	Proliferation assay transfection assays	Detection range for bisphenol: 0.25 to 1.11mg/kg and for 4-nonylphenol :0.12 to 1.2

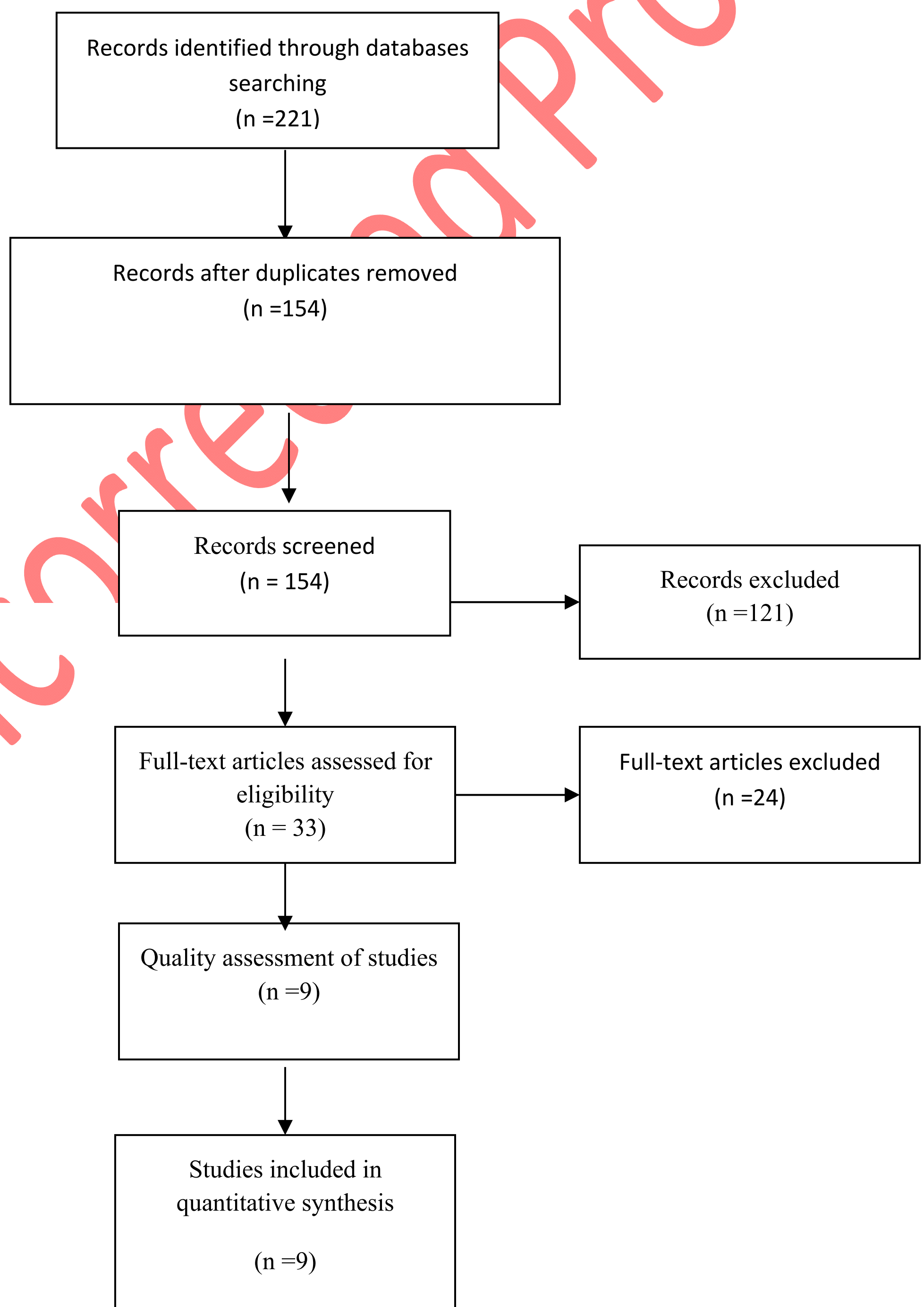
Records identified through databases searching
(n =221)
Records after duplicates removed
(n =154)
Records screened
(n = 154)
Records excluded
(n =121)
Full-text articles assessed for eligibility
(n = 33)
Full-text articles excluded
(n =24)
Quality assessment of studies
(n =9)
Studies included in quantitative synthesis
(n =9)

Fig 1: The diagram of systematic search of the study

آلاینده‌های استروژنیک در غذا: روش های شناسایی: سیستماتیک ریویو

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چکیده فارسی

زمینه مطالعه: بسیاری از ترکیبات به عنوان آلاینده‌های استروژن شناخته می شوند. اجزای استروژنی ممکن است از طریق غذا وارد بدن شوند.

هدف: هدف از این بررسی سیستماتیک تعیین انواع آلاینده‌های استروژن و غذاهایی که عمدتاً به این ترکیبات آلوده هستند و همچنین روش‌های تشخیص رایج آنها بود.

روش کار: مطالعات پژوهشی با کلیدواژه‌های استروژن، شناسایی و غذا به طور سیستماتیک در پایگاه‌های اطلاعاتی پاب‌مد و اسکوپوس جستجو شدند. علاوه بر این، science direct و Google scholar نیز مورد جستجو قرار گرفتند.

نتایج: در مجموع 221 مطالعه بدون توجه به زمان انتشار به دست آمد. در ابتدا غربالگری اولیه صورت گرفت و سپس ارزیابی کیفی مقاله انجام شد. در نهایت تنها 9 مقاله بر اساس معیارهای خروج و ورود انتخاب شدند. در بین غذاهای مختلف، بیشتر ترکیبات استروژنیک در غذاهای دریایی شناسایی شد. این موضوع موید آن است که ترکیبات استروژنی در حال ورود به آبها هستند. بیشترین ترکیب گزارش شده هم بیسفنول A بود. برای ارزیابی زیست سنجی از کشت سلولی و برای روش آنالیز از روش کروماتوگرافی مایع استفاده شد.

نتیجه گیری نهایی: در ارزیابی این ترکیبات از روش تحلیلی و زیست سنجی استفاده می شود. اکثر مطالعات نشان دادند که روش سنجش زیستی نیز معتبر است.

کلمات کلیدی: استروژن، سنجش زیستی، شناسایی، غذا، روش های دستگاهی