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Review Article

The Concentration of Lead, Cadmium, Copper, Nickel, Zinc, Manganese and Iron in Saffron: A Meta-analysis and Systematic Review

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Abstract
Background: We aimed to investigate the concentrations of metals, including lead (Pb), cadmium (Cd), copper (Cu), nickel (Ni), iron (Fe), zinc (Zn), and manganese (Mn), in various types of saffron.
Methods: All published studies until 2022 were searched from PubMed, Scopus and Web of Science databases. The published articles' references were also evaluated to investigate the prevalence of heavy metal contamination in different types of saffron. The heterogeneity and concentration were estimated using I^2 and the random effect model, respectively.
Results: Among 128 articles retrieved in the identification phase, eight articles were included in this meta-analysis. The Pb exhibited the highest concentration among metals, with an average concentration of 0.10 mg/kg and a range of 0.11-0.10 mg/kg. Cd had the lowest concentration, with an average of 0.009 mg/kg and a range of 0.008-0.010 mg/kg. The concentration of Ni, Fe, Zn, Mn, and Cu were also in accordance with the sequence of Ni>Fe>Zn>Mn>Cu. Specifically, Ni demonstrated the highest concentration among essential metals in the sample, with an average of 2.81 mg/kg and a range of 2.76-2.86 mg/kg, while Cd displayed the lowest concentration, with an average of 0.022 mg/kg and a range of 0.023-0.023 mg/kg.
Conclusion: The concentration of different metals in the examined saffron was variable, which can be attributed to several factors, including characteristics of the metals, nature of the saffron plant, composition of the irrigation water and the soil used for production of the plant, water conditions and crop cultivation.
Keywords: Metals, Systematic review, Meta-analysis, Saffron

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Introduction

Saffron is the dried powder of the three-branched stamens of the saffron flower, commonly known as Crocus sativus L. It is a perennial plant of the Iridaceae family.[1] Saffron is one of the most water-efficient crops globally, while being a low-maintenance plant in terms of nutrient requirements. Apart from Iran, saffron cultivation is widespread in countries such as Greece, Italy, Spain, India, Morocco, and Azerbaijan. This crop thrives in regions of Iran characterized by cold winters and hot summers.[2] For centuries, this plant has served both as a coloring and flavoring agent in foods and as herbal medicine. The reddish-yellow color of saffron is attributed to crocins, a family of water-soluble mono- and diglycosyl esters of the polyandicarboxylic acid crocetin. Safranal, a monoterpene aldehyde, and pyrocrocin, a safranal glycoside, are additional compounds in saffron contributing to its distinct aroma and bitter taste. This part of the plant is utilized as the most expensive spice in the world. Iran is the largest producer of saffron in the world, producing 95% of the world's saffron.[3] The saffron samples from this country exhibit the highest levels of the mentioned secondary metabolites. Saffron also possesses medicinal properties, notably serving as a sedative and exhibiting antispasmodic effects.[4] Also, some of its anti-cancer properties are being investigated in recent decades. Despite the significant role played by these compounds in the human diet, a major concern arises from the potential contamination of saffron with impurities and agricultural-related substances, including metals. Given that potentially toxic elements like heavy metals and trace elements are naturally present in the environment, human activities can alter their concentrations, posing potential harm to both human and animal health. So, it is necessary to do research on them.[5] According to previous studies, more than 90% of human contact with toxic metals is related to consuming contaminated food. Various metals are necessary for plants' growth and development, including saffron. However, their higher amounts can lower the quality and stability of saffron and affect its nutritional health. These metals find their way to environmental resources, including water and soil, through human activities. Many cases and factors have effect on the physiological characteristics and performance of plants, among which the presence of heavy metals in the soil are so important. Essential and non-essential heavy metals in high amounts can cause toxicity and damage the cell membranes, change enzyme properties, disrupt cell functions and damage DNA structure.[6] The variety of metals and their amounts can be determined by geochemical factors and the plant's ability to harvest these types of metals. Heavy metals are one of the most important environmental pollutants that are present in the soil in a non-degradable and stable form. These metals can cause super toxic effects in living organisms, including humans. So far, different types of guidelines have been set by different countries to monitor the level of toxic metals in food products, confirming their safety for human consumption.[7] Metals are classified into essential and non-essential classes. Essential metals, including copper (Cu), nickel (Ni), and zinc (Zn), are crucial for human health. These metals serve as vital coenzymes in the body, playing significant roles in growth and respiration. Conversely, metals like lead (Pb) and cadmium (Cd) are regarded as toxic and non-essential, lacking biological activity. Exposure to these metals can lead to nutritional issues and pose serious risks to human health.[8] Previous studies indicate that Pb has the potential to occupy the site of Zn in red blood cells, thereby binding to aminolaevulinic acid dehydratase and inhibiting its function in the body.[9] Cd is considered as a carcinogenic metal that can cause some diseases such as thyroid and pancreatic cancer in the body.[10] Multiple sources contribute to metal contamination that can impact the quality of saffron. The sources include soil and agricultural water pollution resulting from the presence of these metals, along with the quantity and nature of pesticides and chemical fertilizers used during planting, and contamination from water sources applied during production.[9] Also, the pollution during packaging and processing technologies can cause toxicity in this plant. Meta-analysis is an approach that involves the synthesis of data from various individual studies. This method proves highly beneficial, potentially leading to the discovery of new insights and results.[11] Given the absence of prior meta-analyses on metal concentrations in saffron and the growing global consumption of this plant, coupled with concerns regarding the adverse effects on human health resulting from metal contamination, the objective of the current study is to estimate the concentration of heavy metals (Pb, Cd, Iron [Fe], Zn, Ni, Cu, and manganese [Mn]) in saffron through a systematic review.

Materials and Methods

Literature Search and Search Strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Guidelines (PRISMA) (Figure 1)[12] Major international electronic databases including PubMed, Web of Science, Scopus, Mag Iran were investigated until 2022. Also, the list of references in the selected studies were reviewed in order to find potentially eligible studies. The following search strategies were used by each database: Scopus: ((ti/ab ("trace element") OR ((ti/ab("metals") ORti/ ab ("metal(oid)s"))) OR ti/ab ("heavy metals")AND ((ti/ab Saffron; PubMed: search ((("Metals"[Mesh]) OR (((trace element [Ti/Ab]) OR (((heavy metals [Ti/Ab]) OR metals [Ti/Ab]) OR metal(oid)s [Tit_Abs]))) AND (((((((Saffron, including [Ti/Ab]); Embase: ('metals':abt OR 'heavy metals':abt OR' metal(oid)s: abt) AND' Saffron :abt. It should be mentioned that all the keywords were selected based on MeSH.

Meta-analysis and Statistical Analysis

The quality of the studies was evaluated using the Newcastle Ottawa Statement (NOS) Manual.[13] In this guideline, we systematically evaluated studies based on predefined criteria, examining the selection of subjects, comparability, exposure, and outcome. Each study was allocated a maximum of 9 stars according to the established criteria. Studies earning seven stars or more were categorized as high-quality, while those with six stars or fewer were classified as low-quality. To assess

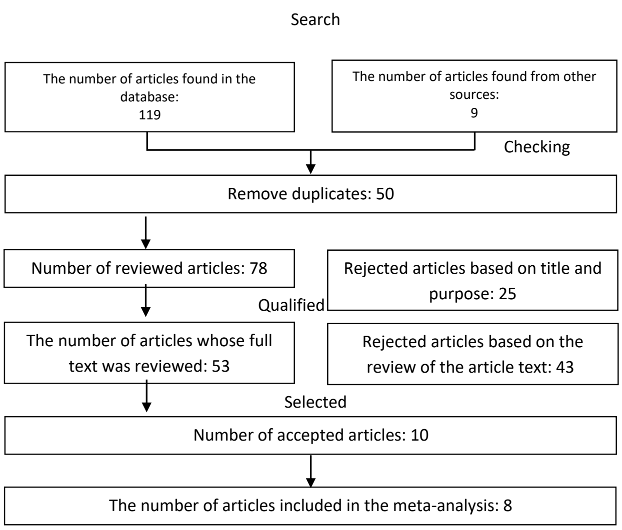

Figure 1. The Process of Article Selection in Different Phases of the Review

the potential for bias in study results, two researchers independently conducted investigations. Discrepancies between researchers were resolved through a process of negotiation. Heterogeneity of the results was investigated using the chi-square test[14] and I^2 statistic.[15] The publication bias was investigated using Begg[16] and Egger[17] statistical tests. The study encompassed the entire population of research and laboratory studies focused on investigating and measuring heavy metals in various samples associated with saffron. The primary outcome of interest was the prevalence of heavy metal contamination observed in diverse saffron samples. Identified studies were compiled, and their compatibility with the predetermined criteria for this investigation was independently assessed by two researchers. Any disagreements that arose during this evaluation process were resolved through a negotiation procedure. A comprehensive data collection form was meticulously designed and utilized for the electronic extraction of relevant information from the selected studies. In instances where essential data were lacking, direct communication with the authors of the articles was initiated to acquire the necessary details. The concentration of metals in different saffron samples was measured with a confidence level of 95%, ensuring robustness in the reported findings. The utilization of a confidence level provides a statistical measure of the reliability of the results. To conduct the data analysis, STATA 14 software was employed. A random-effect model was applied consistently across all analyses, enhancing the robustness and generalizability of the study's findings. The use of random-effect modeling accounts for potential heterogeneity within the collected data, contributing to a more comprehensive analysis.

Inclusion and Exclusion Criteria

In this study, the inclusion criteria comprised (1) full-text articles, (2) cross-sectional studies, and (3) reporting the average or a range of metal concentrations in saffron. Conversely, clinical trials, qualitative studies, case reports, review articles, and letters to editors were excluded based on the predefined exclusion criteria. Data collected from each study included the study year, country, mean, sample size, standard deviation, and concentration range of the toxic metals. For the sake of uniformity, all units representing the concentration of toxic metals, such as ng/g, ppb, µg/kg, were converted to mg/kg dry weight. This standardization ensures consistency in the reporting of metal concentrations across studies and enhances the comparability of results.

Results and Discussion

Processing the Systematic Review

The results depicting the presence of various heavy metals in different saffron samples are presented in Table 1 and Figure 1. In total, 128 articles were acquired—119 retrieved from electronic databases up to September 2022 and 9 obtained through the review of the sources listed in selected articles. Using Endnote software, 50 duplicate articles were identified and subsequently removed. Additionally, 68 articles were excluded after a thorough review of their titles and abstracts, as they did not align with the objectives of this study. Subsequently, ten articles were chosen for an in-depth examination of their full text. However, two of these articles did not meet the criteria for inclusion in this structured review and meta-analysis and were consequently excluded. The final selection comprised eight studies eligible for inclusion in the meta-analysis, all focused on environmental exposures within the field. As a result, the outcomes and discussions are exclusively confined to environmental exposures, as detailed in Table 1.

Meta-analysis of Metals in Saffron

Based on the findings presented in Tables 2 and 3, the results derived from the meta-analysis indicate a significant difference in the concentration of toxic metals across various studies ($P < 0.001$). Notably, Pb exhibited the highest average concentration (0.10 mg/kg) with the range of 0.10-0.11 mg/kg, while Cd demonstrated the lowest average concentration (0.009 mg/kg) with the range of 0.008-0.010 mg/kg. These concentrations represent the highest and lowest levels, respectively, among toxic metals found in saffron samples.

Meta-analysis of Essential Metals in Saffron

As indicated in Tables 2 and 3, the results obtained from the meta-analysis reveal a significant difference in the concentration of trace metals across various studies ($P < 0.001$). The order of concentration, from highest to lowest, is Ni > Fe > Zn > Mn > Cu. Specifically, Ni exhibited the highest average concentration range (2.86-2.76) at 2.81 mg/kg, while Cu showed the lowest average concentration range (0.023-0.021) at 0.022 mg/kg. These concentrations represent the highest and lowest levels, respectively, among essential metals found in saffron samples.

The results of our meta-analysis on the concentration of various metals in saffron are presented in Tables 1-3 and Figure 1. The analysis encompasses both toxic and essential metals in saffron. Notably, Cd and Ni exhibited the highest concentrations among toxic and essential metals, respectively, while Pb and Cu showed the lowest concentrations. These findings are summarized in the tables and visually represented in Figure 1. The toxicity of heavy metals varies based on factors such as type, intensity, frequency, duration, and routes of exposure. Different countries have established various guidelines for assessing the concentration of toxic metals in food to ensure their safety for human health.[26] Previous published studies highlight that certain metals, including Fe, Zn, and Cu, are essential for human health. In contrast, metals such as Cd, Pb, and As are deemed toxic and have the potential to induce neurological and biochemical changes in the body.[27-29] As indicated in various studies, heavy metals have the capacity to disrupt neurological and mental functions,

Table 1. Characteristics of the Studies Included in the Meta-analysis for Different Metals in the Saffron Plant

Year	Country	Number	Fe		Zn		Cu		Ni		Mn		Pb		Cd		Ref.
			Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
2022	Iran	10	15.52	1.29	71.33	5.9	-	-	-	-	-	-	-	-	-	-	18
2013	Iran	11	18.11	0.90	14.69	0.45	2.20	0.14	3.42	0.45	5.59	0.31	0.09	0. 1	0.008	0.09	19
2021	Iran	21	0.24	0.12	0.06	0.03	0.0	0.07	-	-	-	-	1.22	0.6	0.57	0.28	20
2020	Iran	13	-	-	70.8	35.4	-	-	0.95	0.34	-	-	-	-	-	-	21
2019	Iran	36	-	-	-	-	-	-	-	-	-	-	0.77	0.1	2.62	1.41	22
2018	Iraq	12	0.79	0.39	0.30	0.15	0.37	0.18	-	-	-	-	-	-	-	-	23
2012		12	43.59	15	12.44	0.31	3.51	0.12	-	-	10.68	0.18	-	-	-	-	24
2016	Italy	9	48.45	24.22	35.77	17.88	-	-	0.97	0.47	23.97	11.8	-	-	0.16	0.08	25

Table 2. Meta-analysis Results of Metal Concentration in Saffron (mg/kg)

Metals	Number of Studies	Concentration	95% CI	Weight
Mn	4	0.138	(0.135, 0.140)	0.110
Zn	7	0.080	(0.148, 0.154)	0.151
Cu	4	0.022	(0.021, 0.023)	1.390
Pb	3	0.010	(0.010, 0.011)	12.65
Ni	2	2.815	(2.762, 2.868)	0.001
Fe	6	0.443	(0.432, 0.454)	0.010
Cd	4	0.009	(0.008, 0.010)	26.40

Table 3. Meta-analysis Results of Metal Concentration in Saffron (mg/kg)

Metals	*df*	Statistics	*P* value	I^2 (%)
Mn	3	530000	0.001 >	100
Zn	6	370000	0.001 >	100
Cu	3	150000	0.001 >	100
Pb	2	3266.88	0.001 >	99.9
Ni	1	1557.84	0.001 >	99.9
Fe	5	63020.80	0.001 >	100
Cd	3	0.000	0.001 >	100

the blood circulatory system, detoxification pathways in various tissues (including the liver, colon, kidney), the endocrine system, skin, and the immune system. They may also contribute to increased allergic reactions and genetic mutations.[30,31] In line with our study, various types of research have been conducted on the concentration of different metals in the saffron plant. For example, Zheng et al in 2012 showed that the concentration of Fe, Zn, Mn and Cu metals in saffron was 43.95, 12.44, 10.68 and 3.51 mg/kg, respectively.[24] Chichiriccò et al reported that the concentration of Cd, Fe, Mn, Ni and Zn in saffron was 0.16, 48.45, 23.97, 0.97 and 35.37 mg/kg, respectively.[25] Sadegh et al[22] showed that the concentration of Cd and Fe metals was 0.77 and 2.62 mg/kg, respectively. In this regard, Feizy et al[20] also showed that the concentration of Zn, Fe, Cu, Pb and Cd metals in saffron was 0.06, 0.24, 0.01, 1.22 and 0.57 mg/kg, respectively. According to the results, the concentration of different metals in the studied saffrons was very diverse, which can be related to several factors such as the characteristics of the metals, the nature of the saffron plant, the composition of irrigation water and soil used in the production of the plant, weather conditions, and crop cultivation conditions. The changes observed can be influenced by various factors, including the types and quantities of fertilizers applied, storage conditions, and the utilization of different technologies.[32] In line with our study, as highlighted in various research findings, one crucial factor influencing these changes is the characteristics of metals. Notably, the elevated concentrations of metals such as Zn, Cu, and Ni, in contrast to other investigated elements like Pb and Cd in most samples, can be attributed to their higher absorption and transfer rates. This phenomenon leads to a more pronounced accumulation of these elements in the plant.[33] Metals like Fe and Cu exhibit high mobility, swiftly transferring from the soil to plants. In contrast, metals such as Pb display low mobility, accumulating in plant roots with a concentrated presence.[34] While certain metals may share similar bioavailability, variations in saffron contamination could be influenced by other sources. The type of metals, plant species, and environmental conditions, including soil composition and weather (geopedology), play a substantial role in these differences. Broadly, soil quality can be impacted by industrial and urban activities such as proximity to busy roads, factories, mines, and highways, as well as the use of chemicals like fertilizers or fungicides, in addition to climatic conditions and agricultural practices. These factors can contribute to regional and national disparities in observed changes.[8] As indicated by Khazaei et al[35] metal concentrations are primarily contingent on soil conditions and the application of diverse fertilizers. Essential parameters like organic matter content, soil pH, and phosphate concentration play a pivotal role in the metal stability across various cultivated plants. Notably, an elevation in pH substantially diminishes the mobility of metals—a phenomenon that may arise from soil irrigation with wastewater and the cultivation of plants with different species. Consequently, this circumstance can lead to the formation of carbonates and hydroxides, along with an increase in soil organic matter, contributing to a reduction in the levels of various metals. In another investigation conducted by Sadeghi et al[22] in 2019 it was demonstrated that the levels of Pb, Cu, and Cd in saffron plant soil are predominantly influenced by human activities. Specifically, Pb contamination is often attributed to activities such as mining, metal smelting, sewage systems, and the combustion of gasoline in car emissions, contributing to environmental exposure. The use of fertilizers and agricultural pesticides also increases Pb in the soil. Cd is introduced into the environment through various industrial activities, including the production of batteries, pigments, plastics, ceramics, glass, and electroplating materials. Additionally, a significant source of Cd in the environment, particularly from phosphorus fertilizers, is associated with chemical fertilizers.[36] The utilization of chemical fertilizers to enhance soil often leads to an increase in Fe concentration. Conversely, the presence of insoluble organic compounds in the soil forms complexes with Fe, resulting in the removal of Fe from the environment. This process ultimately diminishes the Fe content in the plant.[37] A study indicated that irrigation with wastewater, as opposed to clean water or underground water, results in a noteworthy escalation in metal content within both soil and various crops.[38] Prolonged and consistent irrigation with wastewater has evident impacts on the total organic matter content, bioavailability, and metal concentration in irrigation products. Moreover, both domestic and industrial wastewater can directly influence the transfer rate (bioavailability) and, consequently, the accumulation of metals in the resulting products.[35] Other important influencing factors that cause the difference in the concentration of metals in the saffron plant from different regions can be the method used to identify and measure these metals. In 2013, Esmaeili et al demonstrated that among three different methods—Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-OES), Neutron Activation Analysis (NAA), and Atomic Absorption Spectroscopy (AAS)—utilized for determining metal concentrations, the ICP method stands out. With its high accuracy and sensitivity, ICP is capable of simultaneously identifying multiple metals in a single run.[19] In comparison to other methods, it proves to be the most suitable for metal determination, particularly in eliminating matrix interferences.[4] This suggests a recommendation for the use of the ICP method in future risk assessment studies.

Conclusion

In this study, we conducted a meta-analysis to investigate the concentrations of both toxic and essential metals in various types of saffron plants. The results revealed distinct metal pollution patterns among saffron plants in different regions. Specifically, the concentrations of Fe, Zn, Cu, and Ni were found to be higher in the majority of saffron samples compared to other elements investigated, such as Pb and Cd. Various factors, including physicochemical properties, plant type and species, soil and water characteristics, and the processes involved in saffron plant production, play a crucial role in metal absorption by the plant. To mitigate metal concentrations in saffron, preventive measures, such as monitoring the soil and water used for cultivation, employing clean water for irrigation, and adopting appropriate cultivation methods, should be considered by both governments and farmers. This study investigated metal concentrations in diverse types of saffron plants across different regions. Future studies focusing on health risk assessments for both children and adults could provide valuable insights.

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Competing Interests

The authors declare that there are no conflicts of interest.

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