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Elemental impurity risk assessment in St. John's Wort supplements

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Sarı kantaron takviyelerinde elementel safsızlık risk değerlendirmesi

Abstract: The content of elemental impurities in herbal supplements often exceeds safety limits, particularly if they are grown or harvested in polluted areas. Therefore, numerous reports have focused on the health risk assessment of elemental impurities in herbal supplements. In this study, the levels of cadmium (Cd), lead (Pb), arsenic (As) and mercury (Hg) within herbal supplements containing St. John's Wort, and a carcinogenic and non-carcinogenic health risk assessment associated with elemental impurity exposure was conducted. Four elemental impurities in 10 herbal supplement capsules were analyzed by Inductively coupled plasma mass spectrometry (ICP-MS) using a Microwave Digestion system. Risk calculations were performed considering the recommended Daily intake (IR) dose advised for adult use on the supplement labels. The Estimated Daily Intake (EDI) was first determined for each elemental exposure. Subsequently, the calculated EDI value was used to compute the Target Hazard Quotient (THQ) and HI values for non-carcinogenic risk assessment, and the CR and TCR values for carcinogenic risk assessment. Upon evaluating both the HI values for non-carcinogenic effects and the TCR values for carcinogenic effects, it was determined that only two samples S1 and S3, among the 10 supplements studied, do not present any carcinogenic (the CR or TCR values were between 1×10^{-6} and 1×10^{-4}) or non-carcinogenic health hazards (HI < 1). The consumption of S1 and S3 at the specified dosages in adults was deemed safe. These findings emphasize the necessity for more extensive data in the quality evaluation of herbal dietary supplements and accentuate the significance of regulatory supervision and policy formulation in this domain.

Key words: Carcinogenic risk, non-carcinogenic risk, toxic element, herbal supplement

Özet: Bitkisel takviyelerdeki elementel safsızlık içeriği, özellikle kirlenmiş bölgelerde yetiştiriliyor veya hasat ediliyorsa, genellikle güvenlik sınırlarını aşmaktadır. Bu nedenle, çok sayıda rapor, bitkisel takviyelerdeki elementel safsızlıkların sağlık risk değerlendirmesine odaklanmıştır. Bu çalışmada, sarı kantaron içeren bitkisel takviyelerdeki kadmiyum (Cd), kurşun (Pb), arsenik (As) ve cıva (Hg) seviyeleri ve elementel safsızlık maruziyetiyle ilişkili kanserojen ve kanserojen olmayan sağlık risk değerlendirmesi yapılmıştır. 10 bitkisel takviye kapsülündeki dört elementel safsızlık, mikrodalga sindirim sistemi kullanılarak İndüktif Olarak Eşleştirilmiş Plazma Kütle Spektrometresi (ICP-MS) ile analiz edilmiştir. Risk hesaplamaları, takviye etiketlerinde yetişkin kullanımı için önerilen Günlük Alım (IR) dozu dikkate alınarak yapılmıştır. Her bir elementel maruziyet için Tahmini Günlük Alım (EDI) ilk olarak belirlenmiştir. Daha sonra, hesaplanan EDI değeri, kanserojen olmayan risk değerlendirmesi için Hedef Tehlike Katsayısı (THQ) ve HI değerlerini ve kanserojen risk değerlendirmesi için CR ve TCR değerlerini hesaplamak için kullanıldı. Hem kanserojen olmayan etkiler için HI değerleri hem de kanserojen etkiler için TCR değerleri değerlendirildikten sonra, incelenen 10 takviyeden sadece iki örneğin (S1 ve S3), kanserojen (CR veya TCR değerleri 1×10^{-6} ile 1×10^{-4} arasında) veya kanserojen olmayan sağlık tehlikesi (HI < 1) göstermediği belirlendi. S1 ve S3'ün belirtilen dozlarda yetişkinlerde tüketimi güvenli kabul edildi. Bu bulgular, bitkisel besin takviyelerinin kalite değerlendirmesinde daha kapsamlı verilere duyulan ihtiyacı vurgulamakta ve bu alanda düzenleyici denetim ve politika oluşturmanın önemini ortaya koymaktadır.

Anahtar Kelimeler: Kanserojenik risk, kanserojenik olmayan risk, toksik element, bitkisel takviye

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1. Introduction

Currently, 70–80% of the world's population primarily uses medicinal plants and herbal supplements containing them for alternative healthcare (Rojas et al., 2023; Muhammad et al., 2024). Herbal supplements, which contain raw materials or extracts derived from medicinal plants, fall under the category of nutritional supplements. Consequently, they are classified as a special food category and are subject to food legislation rather than pharmaceutical regulations. This classification can lead to more flexibility in the sale and control of herbal supplements compared to pharmaceuticals (Ćwieląg-Drabek et al., 2020). The herbal supplement of *Hypericum perforatum* L. (St. John's Wort), known to be effective in treating Central Nervous System (CNS) disorders globally, is widely marketed. The efficacy of St. John's Wort has been investigated in various clinical trials, and according to literature reviews, it has been found to be superior to placebo and as effective as standard antidepressants in patients with major depression (Agapouda et al., 2019). The well-established use dosage of St. John's Wort supplements recommended in the literature (Barnes et al., 2001; Nobakht et al., 2022; Farasati Far et al., 2024) and by the European Medicines Agency (EMA) for antidepressant effects is in the range of 600–1800 mg per person per day (EMA, 2021). EMA has issued an herbal monograph for *Hypericum perforatum* extracts (Agapouda et al., 2019). The main active components are considered to be hypericin and hyperforin. However, other biologically active components, such as flavonoids, phenols, tannins, and volatile oils, are also present (Barnes et al., 2001). The

European Pharmacopoeia specifies a minimum (total) hypericin content of %0,08 for *Hypericum perforatum*. However, for the dry extract, the total hypericin content is specified as %0,1-0,3 (Agapouda et al., 2019). In addition to the bioactive compounds they contain, dry herbs within herbal supplements may harbor high amounts of detrimental elements that are difficult to biodegrade, such as cadmium (Cd), lead (Pb), arsenic (As), and mercury (Hg), which can be absorbed from the soil via roots, through wet or dry atmospheric deposition, or as a result of contamination during processing. Consequently, these toxic elements can enter the human body via the food chain, posing a health risk (Derkach and Khomenko, 2018; Meng et al., 2022). The content of elemental impurities in herbal supplements often exceeds safety limits, particularly if they are grown or harvested in polluted areas. Indeed, the quality of plants is significantly influenced by their growing environment (soil, nutrients, pollution, etc.). Therefore, numerous reports have focused on the health risk assessment of elemental impurities in herbal supplements (Meng et al., 2022). Contamination of herbal medicines by elemental impurities, especially Pb and Cd, is well-documented (Rojas et al., 2023).

The primary molecular mechanism underlying the emergence of carcinogenic and non-carcinogenic health risks from toxic elements in biological systems is the generation of Reactive Oxygen Species (ROS), which causes oxidative stress. ROS can (i) damage DNA and alter the repair mechanism; (ii) lead to the misfolding, denaturation, and inactivation of enzymes, and their aggregation; and (iii) damage cell membranes and the cell itself. Furthermore, there is a corresponding impairment of the antioxidant defense system (Rojas et al., 2023). Pb and Cd induce various negative bimolecular functional effects even at low doses. As and Hg, on the other hand, can damage the lungs, nervous, renal, and respiratory systems and may cause cutaneous pathologies. Furthermore, these toxic elements can lead to disorders in the CNS, liver, lungs, heart, kidneys, and brain. They contribute to hypertension, abdominal pain, skin rashes, intestinal ulcers, and are associated with various types of cancer. Therefore, conducting a comprehensive risk assessment concerning heavy metal contamination in herbal medicines is a necessary and urgent matter (Luo et al., 2021).

The Maximum Limits (MLs) or maximum levels permitted for elemental impurities in medicinal plants can vary significantly among countries and organizations in some instances. Studies by Luo et al. (2021) and Kenny et al. (2022) have reported that the permissible ML values across different countries and organizations are 3.0–30.0 mg kg^{-1} for Pb; 0.6–5.0 mg kg^{-1} for As; 0.2–4.0 mg kg^{-1} for Cd and 0.02–1.0 mg kg^{-1} for Hg. In contrast, the ML values specified for pharmaceuticals in the the International Conference on Harmonization (ICH) Q3D (R2) guidelines are 0.5 mg kg^{-1} for Pb; 1.5 mg kg^{-1} for As; 0.5 mg kg^{-1} for Cd and 3 mg kg^{-1} for Hg (ICH, 2021). Currently, there are no universal limits for elemental impurities in medicinal herbs or their products, indicating a lack of uniformity (Jurowski et al., 2022; Kenny et al., 2022). Two possible solutions for consideration are: the readjustment of the ML limits specified for pharmaceuticals in the ICH Q3D (R2) guidelines to be applicable to phytopharmaceuticals; or, alternatively, the creation of an extended package of toxicologically significant specifications for the control of inorganic metal contaminants in plant-derived products, encompassing both ML and analytical procedures. Exceeding these limits does not automatically confirm the presence of a risk; rather, it acts as a 'trigger' requiring further investigation (Kenny et al., 2022).

The determination of levels of Cd, Pb, As and Hg elements which have a high potential for toxic effects upon exposure and are classified as Class 1 in the risk groups specified by the United States Pharmacopeia (USP) 232, EMA and ICH guidelines in herbal supplements is of great importance for assessing the carcinogenic and non-carcinogenic risks to human health (USP, 2017; ICH, 2022; Canbolat, 2023; 2024). For non-carcinogenic health risk assessment in international guidelines, the Hazard Index (HI) value caused by the elemental impurities within the supplement is taken into consideration. An HI value greater than one indicates that a potential health risk may occur (Okumuş et al., 2025; Acar et al., 2025). In carcinogenic risk assessment, the carcinogenic risk (CR) and/or total CR (TCR) values induced by the elemental impurities within the supplement are considered. A CR or TCR value exceeding 1×10^{-4} is considered to indicate a potential carcinogenic health risk. CR or TCR values between 1×10^{-6} and 1×10^{-4} are generally accepted as representing a tolerable risk level. A CR or TCR value below 1×10^{-6} is considered to suggest that no significant health risk will occur (Okumuş et al., 2025; Acar et al., 2025).

Therefore, determining the levels of elemental impurities and performing a health risk assessment following exposure in St. John's Wort supplements, which are widely consumed globally, will be effective in identifying the potential carcinogenic and non-carcinogenic health risks that may arise during the medicinal use of these supplements (De Wit et al., 2021). Consequently, in this study, the levels of Cd, Pb, As and Hg elements within herbal supplements containing St. John's Wort were determined using Inductively coupled plasma mass spectrometry (ICP-MS), and a carcinogenic and non-carcinogenic health risk assessment associated with elemental impurity exposure was conducted.

2. Materials and Method

Nitric acid (HNO_3; 60%) and hydrogen peroxide (H_2O_2; ≥30%) for the evaluation of the elemental impurities were obtained from Sigma-Aldrich (USA). For ICP-MS elemental impurity analysis, a tunnig solution (1 µg L^{-1}) and stock solution (1000 mg L^{-1}) of each element were acquired from inorganic ventures (USA).

2.2. Sample collection

Ten different St. John's Wort supplements of national and international origin were purchased from an online marketplace. The supplements were in capsule form containing %0.3 hypericin in dry herbal extracts (Table 1). The Recommended Daily Intake (IR; mg day^{-1}) indicated on the label of each purchased product was specified as two capsules per person (Table 1).

2.3. Study design and analysis

Four elemental impurities including Cd, Pb, As and Hg in 10 herbal supplement capsules were analyzed by ICP-MS using a Microwave Digestion system. Risk calculations were performed considering the IR values advised for adult use on the supplement labels (as shown in Table 1). The

Table 1. Content and recommended daily intake (IR) doses of supplements included in the study

Supplement	Formula	Content	Recommended daily intake (IR) dose (mg day^{-1})
S1	Capsule	St. John's Wort extract, Herbal capsule, hydroxypropyl methyl cellulose, agar, carrageenan, stabilizers, Hypericin (0.3%)	600
S2	Capsule	St. John's Wort extract, Vegetable agar, Hypericin (0.3%)	600
S3	Capsule	St. John's wort extract, hydroxypropyl methyl cellulose, stabilizers, Hypericin (0.3%)	600
S4	Capsule	St. John's Wort Extract, Herbal Capsule, Hypericin Perforatum (80 mg)	800
S5	Capsule	St. John's wort extract, herbal capsule, stabilizers, hypericin perforatum (80 mg)	800
S6	Capsule	St. John's wort extract, bulking agent (maltodextrin), herbal capsule, anti-caking stabilizers, hypericin (0.3%)	600
S7	Capsule	St. John's Wort extract, Herbal capsule, stabilizers, Hypericin (0.3%)	600
S8	Capsule	St. John's Wort Extract, Herbal Capsule, Hypericin (0.3%)	600
S9	Capsule	St. John's Wort extract, Herbal capsule, hydroxypropyl methyl cellulose, agar, carrageenan, stabilizers, Hypericin (0.3%)	600
S10	Capsule	St. John's Wort Extract, Herbal Capsule, Hypericin (0.3%)	600
S10	Capsule	St. John's Wort Extract, Herbal Capsule, Hypericin (0.3%)	600

fixed values used for the assessment of carcinogenic and non-carcinogenic risks associated with elemental impurities are presented in Table 2. The table includes the Oral Reference Dose (RfD; mgkg^{-1}day^{-1}), the ML (mgkg^{-1}) for elemental impurities in pharmaceuticals from ICH Q3D (R2), and the ML for the four elemental impurities found in medicinal herbs (products) by 27 countries and various international organizations, as reported in the literature by Luo et al (2021) and Kenny et al., (2023). Table 2 also contains the Cancer Slope Factor (CSF; (mg kg^{-1}day^{-1})$^{-1}$)) value for Cd, Pb and As.

2.4. Elemental impurity analysis

Considering the assessments of elemental impurities documented in the literature and our previous studies (Canbolat, 2023; 2024; Cansever and Söğüt, 2025). 8 mL of HNO_3 (Merck Suprapur, 65%) and 2 mL of H_2O_2 (Merck Suprapur, %30) were added to 0.45 g of samples. The samples were let to remain in a fume hood for about 20 minutes to enable the regulated release of gases prior to closing the tubes. The sealed tubes were then digested in a microwave digestion system (Ethos Easy, Milestone Srl., IT) for 30 minutes. Upon completion of microwave digestion, the sample solutions were diluted to a final volume of 50 mL with ultrapure water (Elga FELX4, 18.2 MΩ, TOC: 1 ppb). Subsequent to microwave digestion, materials were analyzed using the Thermo iCAP RQ ICP-MS (Thermo Fisher Scientific, USA) at the Central Research Laboratory Application and Research Center of Eskişehir Osmangazi University (ESOGU ARUM, Türkiye). ICP-MS was employed to examine the prepared sample solutions. Analyses were conducted in triplicate. The instrument settings and technique quantification parameters are detailed in Table 3.

2.5. Risk assessment

Calculations were performed by considering the criteria recommended by the U.S. Environmental Protection Agency (USEPA) for carcinogenic and non-carcinogenic risk assessment (USEPA, 2010; Okumuş et al., 2025; Acar et al., 2025). The Estimated Daily Intake (EDI) was first determined for each elemental exposure using the formula specified in Equation 1. Subsequently, the calculated EDI value was used to compute the Target Hazard Quotient (THQ) and HI values for non-carcinogenic risk assessment, and the CR and TCR values for carcinogenic risk assessment.

$$EDI = (C \times IR \times EF \times ED)/(BW \times AT) \qquad \text{Equation 1}$$

EDI represents the estimated daily intake (mg kg^{-1} day^{-1}); C is the concentration of the elemental impurity in the supplements (mg kg^{-1}); IR is the intake rate (mg day^{-1}, Table 1); EF, is the exposure frequency (90 days year^{-1}) (Meng et al., 2022; Kenny et al., 2022); ED is the exposure duration (adults = 20 years) (Luo et al., 2021; Islam et al., 2024); BW is the body weight (adults = 70 kg) (Kenny et al., 2022); AT is the average time over which a person is exposed to a contaminant; in this study, it was taken as 7300

Table 2. The fixed values used for the assessment of risks associated with elemental impurities

Element	RfD	ML(literature)	ML (ICH Q3D (R2))	CSF	Reference
Cd	0.0005	0.2–4.0	0.5	6.3*	Luo et al., 2021; Kenny et al., 2022; ICH, 2022; Miletić et al., 2023
Pb	0.0035	3.0–30.0	0.5	0.0085	Luo et al., 2021; Kenny et al., 2022
As	0.0003	0.6–5.0	1.5	1.5	Luo et al., 2021; Kenny et al., 2022; ICH, 2022 Canbolat, 2024;
Hg	0.0003	0.02–1.0	3		Luo et al., 2021; Kenny et al., 2022; ICH, 2022
Hg	0.0003	0.02–1.0	3		Luo et al., 2021; Kenny et al., 2022; ICH, 2022

RfD ; oral reference dose (mgkg^{-1}day^{-1}). ML; The Maximum Limit (mg·kg^{-1}). CSF; Cancer Slope Factor ((mg kg^{-1}day^{-1})$^{-1}$). Cd is a risk element with the highest values for exposure through ingestion. The ICH guidelines do not specify a CSF value for Cd ingestion. However, in the literature, there is a wide range of CSF values for Cd ingestion. Among all current CSF values, 0.38, 6.1, 6.3, 0.51, 3.8, and 15 (mg kg^{-1}day^{-1})$^{-1}$ are included. Among the values used in recent studies, 6.3 is reported in the literature (Miletić et al., 2023). In this study, the value 6.3 was used for the calculation (Miletić et al., 2023).

Table 3. Inductively coupled plasma-mass spectrometry (ICP-MS) Operating Condition and quantification parameters

Parameter	Value
RF Power	1550 W
RF Voltage	35.31 V
RF Current	44.48 A
S/C Temperature	2.7°C
Sample Depth	15 mm
Nebulizer Gas	0.9650 L/min
Nebulizer Pump	40 rpm/ rps
Exraction lens	-197.3 V
CCT Focus lens	-6,9 V
Focus lens	17,39 V
Detector voltage (Analog)	-1884,65 V
Detector voltage (Counting)	1587,49 V
Tune Solution	1 µg/L; Ba, Bi, Ce, Co, In, Li, U
Mass and Detector calibration solution	35 µg/L: Be; 20 µg/L: Zn; 15 µg/L: Cu, Ni; 10 µg/L: Al, Ga, Mg; 8 µg/L: Co, Li, Sc; 6µg/L: Ag, Mn; 5 µg/L: Sr; 4 µg/L: Ba, Tl; 3 µg/L: Bi, Ce, Cs, Ho, In, Rh, Ta, Tb, U, Y
Stock standard solution	1000 mgL-1
Quantification parameters	
LOD (µgkg-1)	Cd, Pb, As and Hg: 0.0273, 0.0086, 0.0720 and 0.007 respectively.
LOQ (µgkg-1)	Cd, Pb, As and Hg are 0.091, 0.029, 0.24 and 0.024, respectively.
R2	Cd, Pb, As and Hg are 0.9996, 0.9997, 0.9998 and 0.9945
Relative Standard Error (RSE) (%)	Cd, Pb, As and Hg: 2.562, 5.691, 2,916 and 26.650 respectively.

LOD; limit of detection LOQ; limit of quantification, R2 ; coefficient of determination

days (365 days year^{-1}× 20 year) for non-carcinogenic risk in adults and 25550 days (365 days year^{-1} × 70 year) for carcinogenic risk in adults (Luo et al., 2021; Magna et al., 2021; Meng et al., 2022; Kenny et al., 2022; Okumuş et al., 2025; Acar et al., 2025).

Noncarcinogenic risk assessment

According to the criteria established by the USEPA, the calculation of THQ and HI values is essential in the non-carcinogenic risk assessment caused by elemental impurities (Okumuş et al., 2025; Acar et al., 2025). The THQ represents the Target Hazard Quotient for a single element exposure (Equation 2), and when this value is greater than one, it is interpreted as indicating that the elemental exposure may pose a non-carcinogenic risk.

THQ= EDI/RfD Equation 2

THQ, represents the Target Hazard Quotient; RfD (mgkg^{-1}day^{-1}) is the oral reference dose, representing the maximum permissble daily intake of the elements (Table 2).

When multiple elemental impurities are present in a supplement, they may cause greater harm to the human body than a single detrimental element. Therefore, to assess the aggregated harm of various elemental impurities to human health, the Hazard Index (HI) is applied to specify the total magnitude (Equation 3). When this value is greater than one, it is interpreted as indicating that the combined elemental exposure may pose a non-carcinogenic risk (Canbolat, 2023; 2024, Okumuş et al., 2025; Acar et al., 2025).

HI: $THQ_{Cd} + THQ_{Pb} + THQ_{As} + THQ_{Hg}$ Equation 3

Carcinogenic risk assessment

This is used to assess the potential risk of consumers' lifetime exposure to carcinogens (Equation 4).

CR = EDI Carcinogenic Risk × CSF Equation 4

Here EDI (mgkg^{-1}day^{-1}) is the Estimated Daily Intake used for carcinogenic risk. CSF is the counterpart of the RfD and is utilized in carcinogenic risk calculations. CSF is the Cancer Slope Factor ((mg kg^{-1}day^{-1})$^{-1}$) and is provided for Cd, Pb and As in Table 2.

For the assessment of TCR, the formula given in Equation 5 was applied (Irshad et al., 2024).

TCR: $CR_{Cd} + CR_{Pb} + CR_{As}$ Equation 5

In carcinogenic risk assessment, the CR and TCR values induced by the elemental impurities within the supplement are considered. A CR or TCR value of ≤ $1×10^{-6}$ is interpreted as negligible and is considered to pose no health risk. CR or TCR values between $1×10^{-6}$ and $1×10^{-4}$ generally indicate an acceptable or tolerable risk level within limits. When the CR or TCR value is > $1×10^{-4}$, any risk is considered unacceptable and potentially carcinogenic (Liu et al., 2023; Irshad et al., 2024). Furthermore, if the CR or TCR value is <10^{-3}, the situation is considered more severe and necessitates urgent, high-priority intervention (Irshad et al., 2024; Okumuş et al., 2025; Acar et al., 2025).

2.6. Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics, Version 30. The level of statistical significance was set at $p < 0.05$ (two-tailed). Due to each supplement containing just three technical replicates and the inability to confidently assume normality, non-parametric statistical approaches were employed. Descriptive statistics were calculated for each metal and supplement, encompassing the mean, standard deviation, median, mode, and interquartile range, to encapsulate central tendency and variability. The Kruskal–Wallis test was utilized to assess variations in metal concentrations among the 10 supplement samples, as it does not need assumptions of normality or homogeneity of variances, making it appropriate for small sample numbers and ordinal or non-normally distributed data. Upon obtaining significant findings, pairwise comparisons with Bonferroni correction were used to ascertain particular group differences.

Associations among the four metals (Cd, Pb, As, and Hg) were analyzed using Spearman's rank correlation coefficients, which assess the strength and direction of monotonic relationships without supposing linearity or normal distribution. Correlation coefficients were accompanied by p-values and 95% confidence intervals. Visualizations, including bar charts (mean ± SE) and heatmaps, were used to facilitate the interpretation of inter-metal relationships and inter-sample variability.

3. Results and Discussion

3.1. Elemental impurity levels

The analyzed supplement samples (S1–S10), each measured in triplicate, demonstrated significant variability in concentrations of Cd, Pb, As, and Hg across the samples (Table 4).

The mean values for Cd varied from 0.00 to 1.83 mg kg^{-1}, with the maximum concentration recorded in S4 (M = 1.83, SD = 0.10, Median = 1.83, Mode = 1.73) and the minimum in S1 (M = 0.00, SD = 0.00). It has been reported in the literature that St. John's Wort species are known hyper-accumulators of Cd and Pb (Masarovičová et al., 2010; Özyigit et al., 2018). Studies conducted over the last 20 years concerning the Cd, Pb, As and Hg levels in St. John's Wort indicate that; Gasser et al., (2009) reported a maximum Cd level of 2.51 mg kg^{-1} in the analyzed St. John's Wort samples. Kenny (2022) found a Cd level of 0.13 mg kg^{-1} in St. John's Wort samples collected in Spain. Kandić et al. (2023) reported the Cd levels ranging from 0.35 to 2.00 mg kg^{-1} in St. John's Wort samples collected from three different locations. In the present study, the maximum Cd level in St. John's Wort supplements is 1.83 mg kg^{-1} (Table 4). The Cd level found in this study showed similarity to the Cd levels reported in the literature, suggesting that St. John's Wort may be a Cd accumulator, as noted by Masarovičová et al., in 2010 (Masarovičová et al., 2010).

Lead concentrations varied between 0.00 and 1.32 mg kg^{-1}, with S1 presenting the highest mean (M = 1.32, SD = 0.10, Median = 1.32, Mode = 1.22), while S3 displayed non-detectable levels (Table 4). Gasser et al., (2009) reported a maximum Pb level of 14.51 mg kg^{-1} in the analyzed St. John's Wort samples. Kenny (2022) determined the Pb level in St.John's Wort samples collected in Spain to be 0.19 mg kg^{-1}. Kandić et al., (2023) reported a Pb level of 5.30 mg kg^{-1} in their plant samples. In the present study, the maximum Pb level is 1.32 mg kg^{-1} (Table 4). The Pb level in this study falls within the range of Pb levels reported in the literature, but was detected at lower concentrations compared to some literature values. Suljić et al. (2023) demonstrated that St. John's Wort significantly absorbs Cd and Pb. In our study, Pb was not detected in only one sample. The Pb levels in all other samples fall within the range reported in the literatüre. These study data support the findings in the literature.

Samples S1–S3 exhibited undetectable levels of As. Samples S4–S10 exhibited concentrations ranging from 0.19 to 0.55 mg kg^{-1}, with S8 demonstrating the highest concentration (M = 0.55, SD = 0.10, Median = 0.55, Mode = 0.45) (Table 4). In the study by Popović et al. (2017), the elements Cd, Pb, and As were analyzed in St. John's Wort herbal teas, and As was not detected in any of the samples. In our study, As was not detected in three samples, whereas the remaining samples contained As in the range of 0.19 to 0.55 mg kg^{-1} (Popović et al., 2017).

Mercury concentrations were below the detection limits in all samples except S3 (M = 0.10, SD = 0.05, Median = 0.10, Mode = 0.05) (Table 4). In the study by Gasser et al. (2009), the maximum Hg level detected in St. John's Wort samples

Table 4. Elemental impurity levels (mg·kg–1) detected in supplements

Supplement	Cd (mg·kg^{-1})			Pb (mg·kg^{-1})		
	Mean ± SD	Mode	Median	Mean ± SD	Mode	Median
S1	ND	.00	.00	1.32±0.1	1.22a	1.32
S2	0.06±0.01	.05a	.06	0.05±0.01	.04a	.05
S3	0.02±0.01	.01a	.02	ND	.00	.00
S4	1.83±0.1	1.73a	1.83	0.52±0.1	.42a	.52
S5	1.32±0.1	1.22a	1.32	0.80±0.2	.70a	.80
S6	0.80±0.1	.70a	.80	0.60±0.1	.50a	.60
S7	0.63±0.46	.10a	.84	0.65±0.2	.55a	.65
S8	1.12±0.1	1.02a	1.12	1.08±0.01	1.07a	1.08
S9	0.79±0.1	.69a	.79	0.84±0.1	.74a	.84
S10	0.13±0.1	.03a	.13	0.17±0.1	.10a	.17

Supplement	As (mg·kg^{-1})			Hg (mg·kg^{-1})		
	Mean ± SD	Mode	Median	Mean ± SD	Mode	Median
S1	ND	.00	.00	ND	.00	.00
S2	ND	.00	.00	ND	.00	.00
S3	ND	.00	.00	0.10±0.01	.05a	.10
S4	0.19±0.1	.09a	.19	ND	.00	.00
S5	0.27±0.2	.17a	.27	ND	.00	.00
S6	0.52±0.1	.42a	.52	ND	.00	.00
S7	0.23±0.1	.13a	.23	ND	.00	.00
S8	0.55±0.2	.45a	.55	ND	.00	.00
S9	0.47±0. 1	.37a	.47	ND	.00	.00
S10	0.20±0.1	.15a	.20	ND	.00	.00

a. Multiple modes exist. The smallest value is shown. ND.–not detected (below limit of detection (LOD) of the ICP-MS method) was reported as 0.10 mg kg^{-1} (Gasser et al, 2009). In the study by Kenny et al., (2022), the Hg level in St. John's Wort samples collected in Spain was found to be 0.008 mg kg^{-1} (the value was converted to mg kg^{-1} to match the units used in the literature). In the study by Kandić et al. (2023), Hg levels in plant samples were reported to be below the detection limit. In the present study, Hg was detected at 0.1 mg kg^{-1} in only one of the ten supplement samples, while Hg levels in the remaining samples were below the detection limit (Table 4). Considering both the literature findings and the analytical results, Hg is present at low levels or is not detectable in St. John's Wort plant material and its supplements.

The median values aligned closely with the mean concentrations, indicating symmetric distributions within the limited sample sets. However, multiple modes were noted in several instances, highlighting variability in measurements across technical replicates. The descriptive statistics reveal variability in elemental impurity content across the supplements, especially for Cd and Pb, indicating possible inconsistencies in formulation or source materials.

Cd and Pb were not detected in only one sample each, whereas As was not detected in three samples and Hg was not detected in nine samples (Fig. 1a). Spearman's rank correlation analysis was performed to investigate the relationships among the concentrations of Cd, Pb, As, and Hg in all supplement samples (Fig. 1b). The findings demonstrated a significant positive correlation between Cd and As ($\rho = .62$, $p < .001$), indicating that supplements with increased Cd content were also likely to show higher levels of As. The pronounced correlation between Cd and As suggests the presence of shared contamination pathways for both metal(loid)s during the production of herbal supplements. Similar agricultural cultivation conditions, the use of fertilizers and pesticides, as well as environmental exposures that may occur during post-harvest processing and drying steps, could explain this concurrent accumulation (Luo et al., 2021).

Moderate positive correlations were identified between Pb and As ($\rho = 0.44$, $p = 0.015$) and between Cd and Pb ($\rho = 0.21$, $p = 0.269$), with the latter lacking statistical significance. In the literature, Çolak et al. (2020) reported a low positive correlation ($\rho = 0.14$) between Cd and Pb in St. John's Wort samples, while Kenny et al. (2023) reported a near-zero correlation between Cd and Pb. In our study, although a moderate positive correlation was observed between Cd and Pb, this relationship was not statistically significant, and the analytical results are consistent with the findings reported in the literature.

Kenny et al. (2023) also did not identify a significant positive correlation between Cd and Hg. In contrast to the other elements examined in our study, Hg exhibited negative associations with all other metals, revealing significant inverse correlations with Cd ($\rho = -0.40$, $p = 0.029$), Pb ($\rho = -0.52$, $p = 0.003$), and As ($\rho = -0.41$, $p = 0.025$). The 95% confidence intervals validated the direction and strength of these relationships (e.g., Cd–As: 0.33 to 0.81; Pb–Hg: -0.75 to -0.19). The findings suggest that Cd, Pb, and As commonly co-occur in similar samples, while Hg levels show a contrasting trend, indicating different sources of contamination or varying accumulation behaviors among the metals analyzed.

The Kruskal–Wallis test was performed to analyze the distributions of elemental impurity concentrations among the 10 dietary supplement samples (Fig. 2, 3). The results indicated statistically significant differences among samples for all metals: Cd, $H(9) = 27.50$, $p = 0.001$; Pb, $H(9) = 27.78$, $p = 0.001$; As, $H(9) = 26.51$, $p = 0.002$; and Hg, $H(9) = 28.91$, $p < 0.001$. The results demonstrate significant variation in the concentration levels of each metal among different supplement brands. Post hoc pairwise comparisons with Bonferroni adjustment showed that for Cd, the most pronounced differences were observed between S1 and S4 ($p < 0.01$) and between S1 and S5 ($p = 0.041$). Significant differences in Pb levels were observed between S3 and S8 ($p = 0.038$) and between S3 and S1 ($p = 0.008$) (Fig. 2).

In S6–S8, higher concentrations of As were significantly different from the undetectable levels observed in S1–S3 (adjusted p values < 0.15) (Fig.3). Significant pairwise differences in Hg levels were observed between S3 and all other samples ($p = 0.003$), reflecting its distinct measurable Hg content. The results indicate diverse contamination patterns across supplements, with cadmium and lead

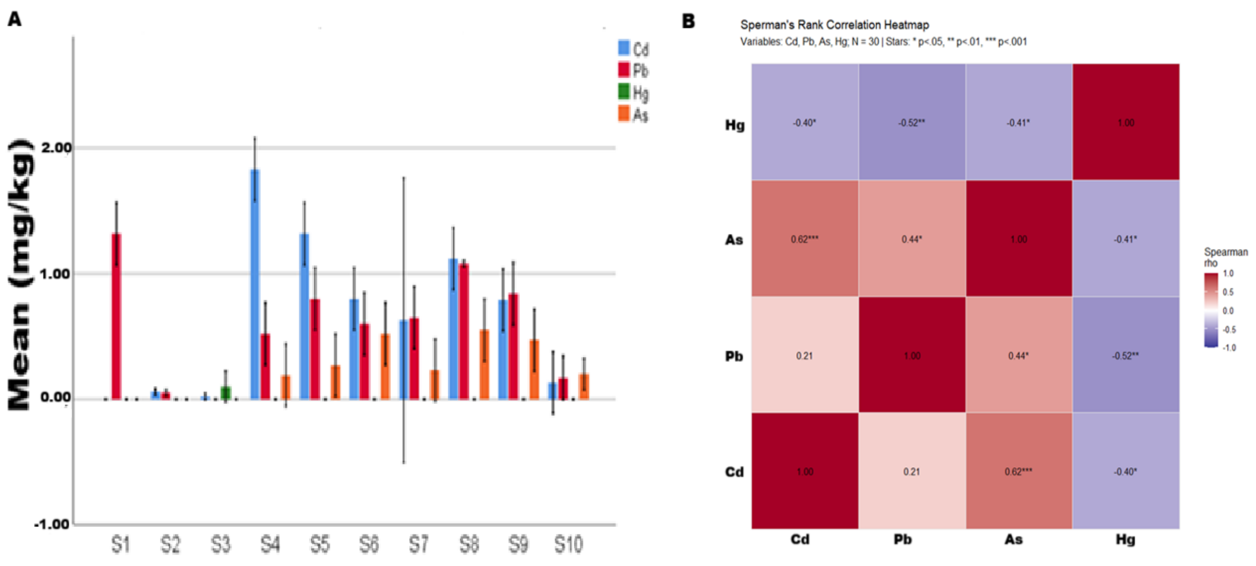

Figure 1. Elemental impurity levels in supplements and correlation graph of elemental impurities

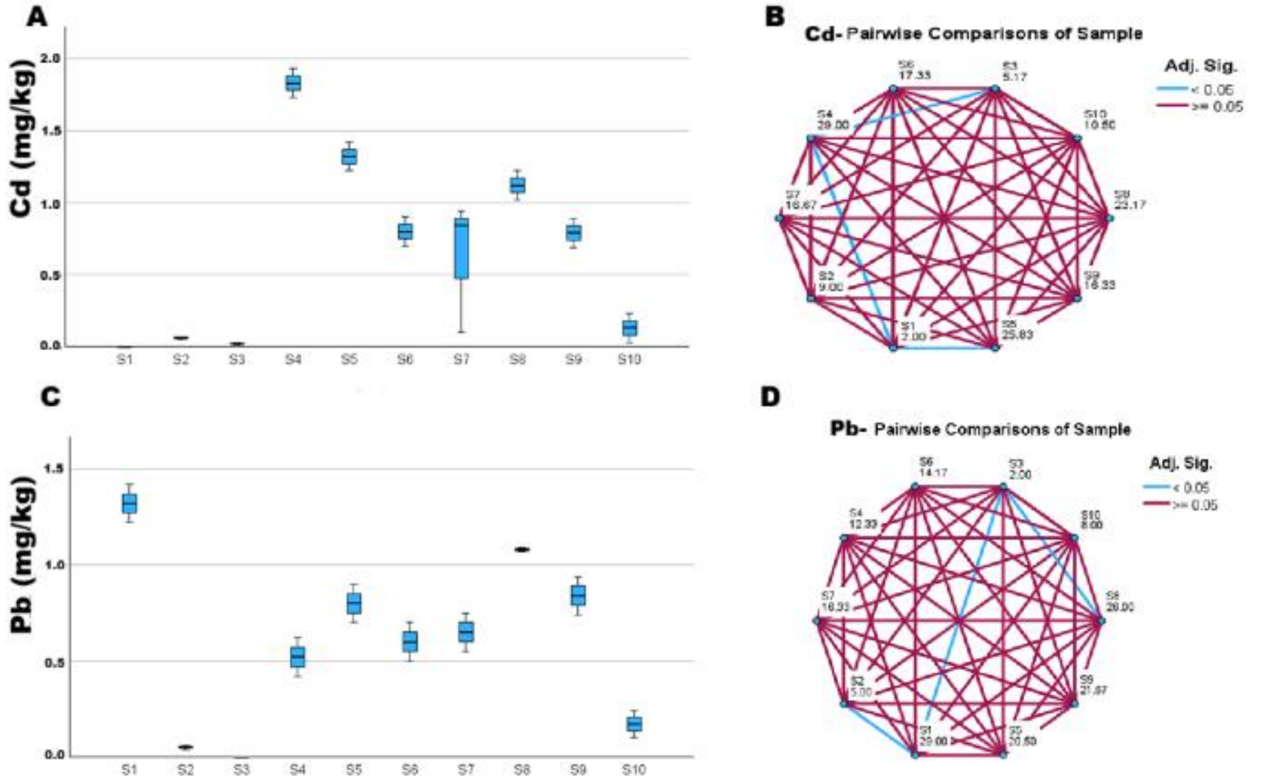

Figure 2. The distributions of Cd and Pb concentrations among the 10 dietary supplement samples

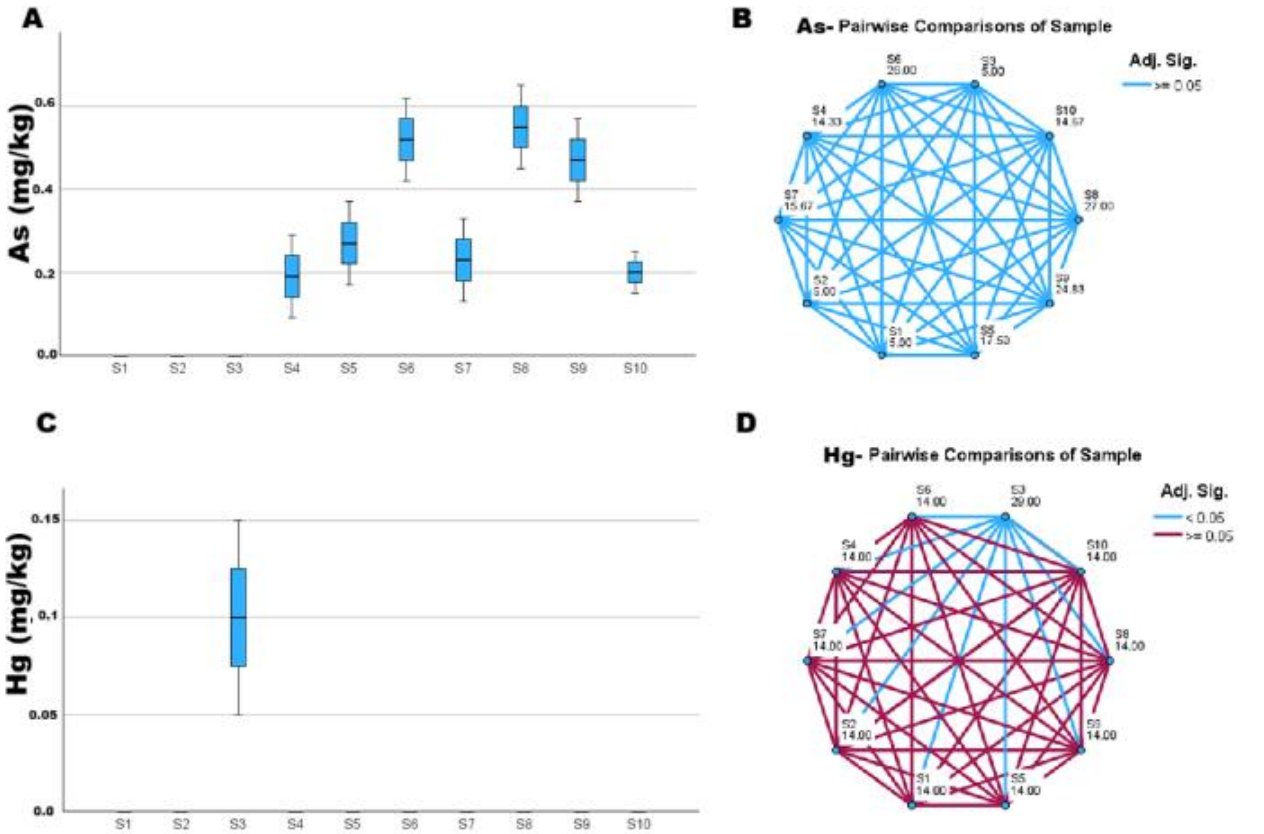

Figure 3. The distributions of As and Hg concentrations among the 10 dietary supplement samples. Statistical significance was set at $p < 0.05$

exhibiting significant inter-sample variability, while mercury levels were predominantly undetectable, except in one product (Figure 3).

Permitted MLs for elemental impurities in medicinal plants can vary substantially between countries and organizations (Table 2) (Luo et al., 2021; Kenny et al., 2022). However, the ML values established for pharmaceuticals are clearly defined in ICH Q3D (R2) (Table 2). At present, there are no universal limits for inorganic metal impurities in medicinal plants or plant-derived products, and such limits may never be fully harmonized. Considering the uncertainties associated with phytochemical products, the data obtained in this study were evaluated using the ML values specified for pharmaceuticals in ICH Q3D (R2) and the ML ranges reported in the literature by Luo et al. (2021) and Kenny et al. (2023).

Based on the Cd, Pb, As, and Hg levels detected in this study (Table 4), the Cd concentrations in samples S4, S5, S6, S7, S8, and S9 were 1.83, 1.32, 0.80, 0.63, 1.12, and 0.79 mg kg^{-1}, respectively, all of which exceed the ML defined for Cd in ICH Q3D (R2). Cd levels in the remaining samples were below the ML value specified in ICH Q3D (R2). Examination of Pb levels revealed that Pb concentrations in samples S1, S5, S6, S7, S8, and S9 were 1.32, 0.80, 0.60, 0.65, 1.08, and 0.84 mg kg^{-1}, respectively, which exceed the ICH Q3D (R2) ML for Pb. Pb concentrations in the other samples, as well as As and Hg levels in all samples, were below the MLs established for metal impurities in pharmaceuticals according to ICH Q3D (R2). When the elemental impurity levels observed in all samples are compared with the ML ranges permitted by different countries and organizations as presented in Table 2, it is evident that the concentrations fall within these broader ranges. Although the analytical data fall within the wide ML range reported by Kenny et al. (2023), the ML interval is notably broad (Kenny et al., 2023) and, importantly, Cd and Pb levels in several samples exceed the ML limits specified in ICH Q3D (R2). Therefore, both carcinogenic and non-carcinogenic health risk assessments were performed for the samples.

3.2. Risk Assessment

The results of the carcinogenic and non-carcinogenic risk assessments for the elemental impurities detected in the supplements are presented in Table 5.

Table 5. Risk assessment of elemental impurity levels detected in supplements

Supplement	Elemental Impurity	THQ	HI	CR	TCR
S1	Cd	NC		NC	6.80 × 10-6
	Pb	0.80		6.80 × 10-6	
	As	NC		NC	
	Hg	NC	0.80	NC	
S2	Cd	0.23	0.27	2.09 × 10-4	2.09 × 10-4
	Pb	0.03		2.77 × 10-7	
	As	NC		NC	
	Hg	NC		NC	
S3	Cd	0.09	0.79	8.37 × 10-5	8.37 × 10-5
	Pb	NC		0	
	As	NC		0	
	Hg	0.70		0	
S4	Cd	10.30	12.48	9.27 × 10-3	9.50 × 10-3
	Pb	0.42		3.55 × 10-6	
	As	1.76		2.26 × 10-4	
	Hg	NC		NC	
S5	Cd	7.41	10.57	6.67 × 10-3	6.99 × 10-3
	Pb	0.65		5.49 × 10-6	
	As	2.51		3.22 × 10-4	
	Hg	NC		NC	
S6	Cd	3.38	7.38	3.04 × 10-3	3.51 × 10-3
	Pb	0.36		3.10 × 10-6	
	As	3.64		4.67 × 10-4	
	Hg	NC		NC	
S7	Cd	2.66	4.67	2.39 × 10-3	2.61 × 10-3
	Pb	0.39		3.32 × 10-6	
	As	1.62		2.08 × 10-4	
	Hg	NC		NC	
S8	Cd	4.71	9.22	4.24 × 10-3	4.74 × 10-3
	Pb	0.65		5.55 × 10-6	
	As	3.85		4.95 × 10-4	
	Hg	NC		NC	
S9	Cd	3.34	7.16	3.00 × 10-3	3.43 × 10-3
	Pb	0.51		4.33 × 10-6	
	As	3.32		4.27 × 10-4	
	Hg	NC		NC	
S10	Cd	0.56	2.05	5.02 × 10-4	6.82 × 10-4
	Pb	0.10		8.47 × 10-7	
	As	1.39		1.79 × 10-4	
	Hg	NC		NC	

THQ: The target hazard quotient, HI: The hazard index, CR: Carcinogenic risk, TCR: Total carcinogenic risk, NC: Not calculated indicates that HQ and CR values could not be calculated because the corresponding elementel impurity levels were below the limit of detection (ND in Table 4). In addition, CR values for Hg were not calculated as mercury is not classified as a carcinogenic element.

In evaluating the potential health risks associated with exposure to toxic elements through consumption of dietary supplements, it is important to consider both carcinogenic and non-carcinogenic risks simultaneously. The non-carcinogenic health effects of Cd, Pb, As, and Hg included in the analysis may pose adverse outcomes for human health. Moreover, given the carcinogenic potential of Cd, Pb, and especially As, the presence of these elements in daily supplement intake may further increase the magnitude of the associated health risks.

Cadmium is classified as a known carcinogen, and its toxicity has been reported to cause a range of adverse health effects, including reproductive, renal, skeletal, and neurological damage (Ring et al., 2021). Evaluation of the non-carcinogenic effects of Cd in the supplements analyzed showed that the HQ values for samples S2, S3, and S10 were below 1 when consumed at the labeled doses (Table 5). In these samples, Cd alone does not pose a non-carcinogenic health risk. However, in the remaining samples (S4, S5, S6, S7, S8, and S9), the HQ values attributed to Cd exceeded 1. The elevated Cd concentrations in these supplements may therefore raise potential non-carcinogenic health concerns. Considering that excessive exposure to Cd can lead to both acute and chronic effects, including kidney and skeletal damage and increased human cancer risk, consumers should exercise caution (Irshad et al., 2024).

Lead is a highly toxic heavy metal classified by the IARC as a possible human carcinogen. The nervous system is the primary target of Pb toxicity; however, additional symptoms include anemia, kidney damage, and impairment of the immune and reproductive systems (Ring et al., 2021). Elevated Pb levels can lead to a wide range of health problems, including hypertension, neurological damage, cognitive impairment, behavioral abnormalities, and reduced cognitive function. Due to its ability to interfere with or mimic Ca, Pb can alter blood Ca concentrations and affect protein kinase C activity, which regulates neuronal excitability and memory, even at very low concentrations (Irshad et al., 2024). Evaluation of the non-carcinogenic effects of Pb showed that, when used at the labeled doses, the HQ values for samples S1, S2, S4, S5, S6, S7, S8, S9, and S10 were below 1 (Table 5). In these samples, Pb alone does not pose a non-carcinogenic health risk.

Another element that is toxic to humans is As. As toxicity affects the cardiovascular, dermatological, nervous, hepatobiliary, renal, gastrointestinal, respiratory, and other systems (Tchounwou et al., 2012). Chronic exposure to As can lead to cancers of the skin, lung, bladder, kidney, and liver (Rojas et al., 2023). Evaluation of the non-carcinogenic effects of As showed that, when used at the labeled doses, the HQ values for samples S4, S5, S6, S7, S8, S9, and S10 exceeded 1 (Table 5). The elevated As concentrations in these supplements may therefore raise potential non-carcinogenic health concerns.

The inorganic heavy metal element Hg can be extremely harmful to humans. Acute mercury poisoning is linked to neurological and gastrointestinal issues and can be lethal (Ring et al., 2021). Mercury was identified solely in sample S3. The assessment of the non-carcinogenic effects of Hg in S3 revealed that the HQ was below 1, signifying that Hg alone does not present a non-carcinogenic health concern in this sample (Table 5).

The evaluation of the cumulative non-carcinogenic effects of all risk items identified in each supplement revealed that the HI values for samples S1, S2, and S3 at the specified doses were below 1 (Table 5). This signifies that the intake of S1, S2, and S3 at the advised dosages does not present a non-carcinogenic health hazard from exposure to elemental impurities. For the remaining samples (S4, S5, S6, S7, S8, S9, and S10), HI values surpassed 1, indicating that the elemental impurities identified in these supplements may represent a possible non-carcinogenic health risk (Table 5). Kenny et al. (2022) demonstrated that predicted theoretical exposure levels in plant supplements from Spain posed no risk from the oral use of St. John's Wort (HQ and HI < 1), thereby categorizing these items as safe. In accordance with these findings, our investigation revealed no non-carcinogenic risk for S1, S2, and S3 at the specified levels, but non-carcinogenic risk was detected for the other supplements.

The carcinogenic risk assessment of Cd, Pb, and As, elements with potential carcinogenic health risks, in the supplements indicated that in all samples where Pb was detected, the CR values ranged from 1×10^{-4} to 1×10^{-6} or less than 1×10^{-6}, suggesting that Pb alone does not present a carcinogenic health risk (Table 5). The assessment of the carcinogenic effects of Cd indicated that, at the specified dosage, the CR value for sample S3 fell within the range of 1×10^{-4} to 1×10^{-6}, suggesting that Cd alone does not present a carcinogenic health concern in this sample (Table 5). In sample S2, the CR value for Cd above 1×10^{-4}, indicating a possible carcinogenic health risk. Upon separate evaluation of the carcinogenic effects of Cd and As in the other samples, it was noted that, at the specified doses, both Cd and As in samples S4, S5, S6, S7, S8, S9, and S10 exhibited CR values over 1×10^{-4}, signifying a potential carcinogenic health risk (Table 5).

Upon evaluating the cumulative carcinogenic effects of all risk factors identified in each supplement, the TCR values for samples S1 and S3 at the specified doses were determined to be within tolerable and acceptable limits ($<1 \times 10^{-4}$), signifying that these supplements do not present a carcinogenic health hazard (Fig. 4). Conversely, for all other samples, TCR values at the specified levels beyond the acceptable limit ($>1\times10^{-4}$), indicating possible carcinogenic health risks.

Upon evaluating both the HI values for non-carcinogenic effects and the TCR values for carcinogenic effects, it was determined that only samples S1 and S3, among the 10 supplements studied, do not present any carcinogenic or non-carcinogenic health hazards. The consumption of S1 and S3 at the specified dosages in adults was deemed safe.

4. Conclusion

As the global array of herbal-based health products expands, assessing the concentrations of risk elements in herbal dietary supplements is essential for consumer protection. This study examined the concentrations of Cd, Pb, As, and Hg in 10 St. John's Wort supplements and evaluated both carcinogenic and non-carcinogenic health concerns for adults. Upon evaluating both risk evaluations concurrently, only two supplements (S1 and S3) were deemed safe for adult use at the specified levels, with no expected health issues related to elemental impurity exposure. Nonetheless, the findings of this study suggest

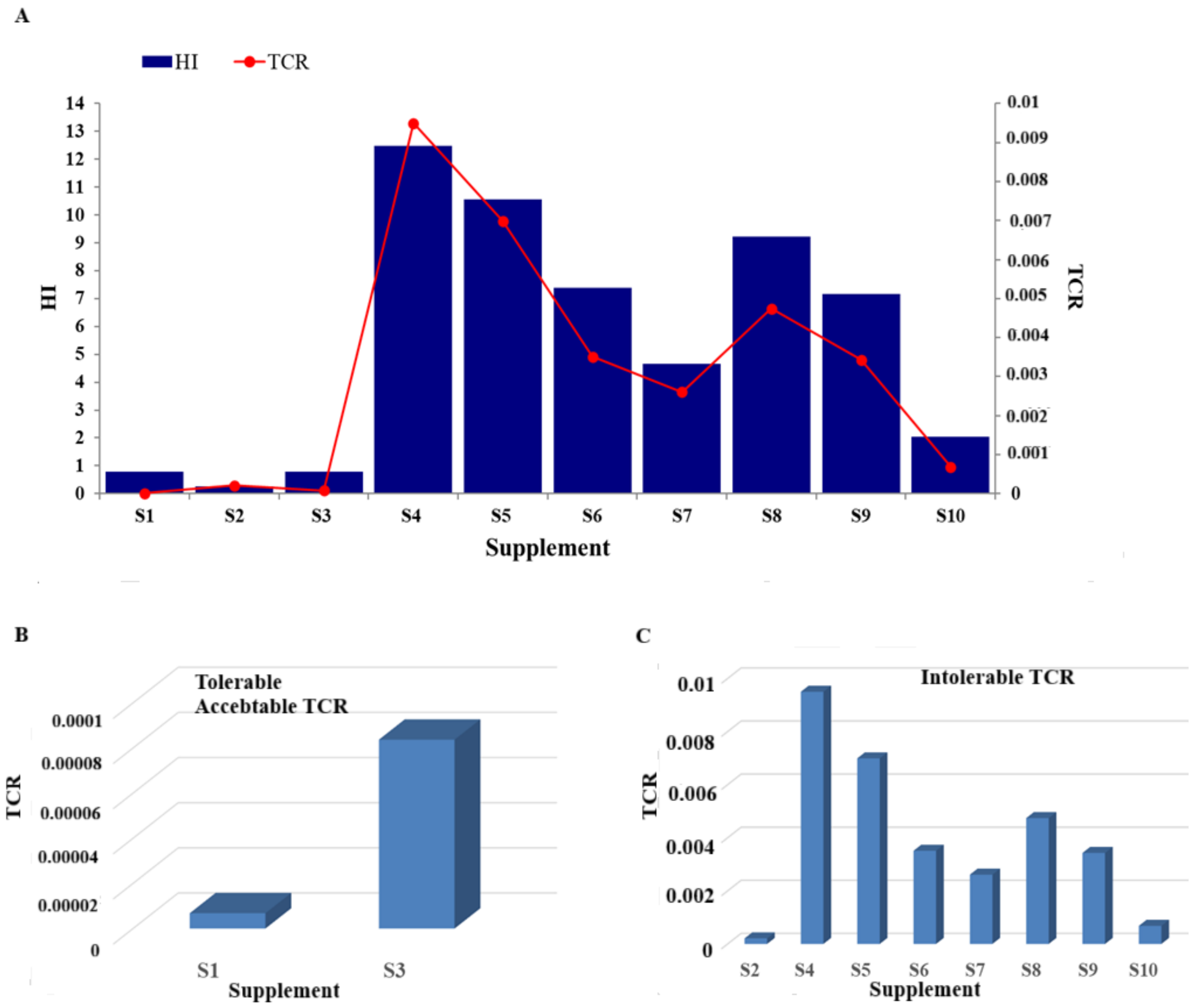

Figure 4. Assessment of carcinogenic and non-carcinogenic risks in supplements. A) Combined display of carcinogenic and non-carcinogenic risk levels, B) Tolerable, accebtable carcinogenic risk, C) Intolerable carcinogenic risk

that risk factors in herbal supplements can attain levels that may present potential health hazards. These findings emphasize the necessity for more extensive data in the quality evaluation of herbal dietary supplements and accentuate the significance of regulatory supervision and policy formulation in this domain.

This study offers a comprehensive analytical framework and novel reference profiles for assessing elemental impurities in herbals and herbal supplements, aimed at quality evaluations. This study aims to enhance the risk analysis of botanical components and establish a basis for future research in this domain.

Conflict of Interest

The author declares no conflicts of interest.

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References

Acar İ, Canbolat F, Ayata F (2025). Determination of the elemental impurity levels in different mushroom species and probabilistic risk sssessment. Environmental Toxicology 41: 5-17. https://doi.org/10.1002/tox.24556

Agapouda A, Booker A, Kiss T, Hohmann J, Heinrich M, Csupor D (2019). Quality control of *Hypericum perforatum* L. analytical challenges and recent progress. Journal of Pharmacy and Pharmacology 71(1): 15-37. https://doi.org/10.1111/jphp.12711

Barnes J, Anderson LA, Phillipson JD (2001). St John's wort (*Hypericum perforatum* L.): a review of its chemistry, pharmacology and clinical properties. Journal of pharmacy and pharmacology 53(5): 583-600. https://doi.org/10.1211/0022357011775910

Canbolat F (2023). Analysis of non-carcinogenic health risk assessment of elemental impurities in vitamin C supplements. Iranian Journal of Basic Medical Sciences 26(2): 216-227. https://dx.doi.org/10.22038/IJBMS.2022.67487.14789

Canbolat F (2024). Elemental impurity analysis in five different types of coffee: Assessment of carcinogenic and non-carcinogenic risks. Sakarya University Journal of Science 28(4): 866-875. https://doi.org/10.16984/saufenbilder.1488500

Cansever I, Söğüt O (2025). An analytical approach for determining macro-and micro-elements in two different growing periods of *Artemisia abrotanum* L. BioMetals 38(5):1535-1550. https://doi.org/10.1007/s10534-025-00718-1

Ćwieląg-Drabek M, Piekut A, Szymala I, Oleksiuk K, Razzaghi M et al. (2020). Health risks from consumption of medicinal plant dietary supplements. Food Science & Nutrition 8(7): 3535-3544. https://dx.doi.org/10.1002/fsn3.1636

Çolak S, Yazıco K, Akca SB (2020). Determination of heavy metal contents in St. John's Wort (*Hypericum* spp) in Zonguldak, Turkey. Fresenius Environmental Bulletin 29(5): 3571-3578

Derkach T, Khomenko V (2018). Elemental composition of the medicinal plants *Hypericum perforatum*, *Urtica dioica* and *Matricaria chamomilla* grown in Ukraine: a comparative study. Pharmacognosy Journal 10(3): 486-491. https://dx.doi.org/10.5530/pj.2018.3.80

De Wit L, Jeurissen S, Chen W (2021). Risk assessment of herbal preparations containing St John's wort. Netherland: National Institute for Public Health and the Environment.

EMA (2021). European Union herbal monograph on *Hypericum perforatum* L., herba (well-established and traditional use), Amsterdam: European Medicines Agency Committee on Herbal Medicinal Products (HMPC).

Farasati Far B, Gouranmohit G, Naimi-jamal MR, Neysani E, El-Nashar H A et al., (2024). The potential role of *Hypericum perforatum* in wound healing: A literature review on the phytochemicals, pharmacological approaches, and mechanistic perspectives. Phytotherapy Research 38(7): 3271-3295. https://dx.doi.org/10.1002/ptr.8204

Gasser U, Klier B, KuhnAV, Steinhoff B (2009). Current findings on the heavy metal content in herbal drugs. Pharmeuropa 1: 37-49.

ICH (2022). Guideline for elemental impurities Q3D(R2) Guidance for Industry. Rockville: U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER).

Irshad M, Ahmed M, Ramzan M, Fatima M, Aftab F et al. (2024). Appraisal of potentially toxic metals contamination in protein supplements for muscle growth: A chemometric approach and associated human health risks. Journal of Trace Elements in Medicine and Biology 85: 1-13. https://doi.org/10.1016/j.jtemb.2024.127481

Islam N, Zamir R, Faruque MO (2024). Health risk assessment of metals in antidiabetic herbal preparations: a safety screening. Evidence-Based Complementary and Alternative Medicine 2024(1): 1-12. https://doi.org/10.1155/2024/6507185

Jurowski K, Fołta M, Tatar B, Krośniak M (2022). The level of cadmium impurities in traditional herbal medicinal products with Plantago lanceolata L., folium (Ribwort plantain leaves) available in Polish pharmacies—comprehensive toxicological risk assessment including regulatory point of view and ICH Q3D Elemental Impurities Guideline. Biological Trace Element Research 200(6): 2963-2969. https://doi.org/10.1007/s12011-021-02861-5

Kandić I, Kragović M, Petrović J, Janaćković P, Gavrilović M (2023). Heavy metals content in selected medicinal plants produced and consumed in Serbia and their daily intake in herbal infusions. Toxics 11(2): 198. 1-19. https://doi.org/ 10.3390/toxics11020198

Kenny CR, Ring G, Sheehan A, Mc Auliffe MA, Lucey B et al. (2022). Novel metallomic profiling and non-carcinogenic risk assessment of botanical ingredients for use in herbal, phytopharmaceutical and dietary products using HR-ICP-SFMS. Scientific Reports 12(1): 1-24. https://doi.org/10.1038/s41598-022-16873-1

Liu H, Tang J, Chen T, Zhu P, Sun D et al. (2023). Assessment of heavy metals contamination and human health risk assessment of the commonly consumed medicinal herbs in China. Environmental Science and Pollution Research 30(3): 7345-7357. https://doi.org/10.1007/s11356-022-22647-z

Luo L, Wang B, Jiang J, Fitzgerald M, Huang Q et al. (2021). Heavy metal contaminations in herbal medicines: Determination, comprehensive risk assessments, and solutions. Frontiers in pharmacology 11: 1-14. https://dx.doi.org/10.3389/fphar.2020.595335

Magna EK, Koranteng SS, Donkor A, Gordon C (2021). Health risk assessment and levels of heavy metals in farmed Nile Tilapia (*Oreochromis niloticus*) from the Volta Basin of Ghana. Journal of Chemistry 2021(1): 1-10. https://doi.org/10.1155/2021/2273327

Masarovičová E, Kráľová K, Kummerová M (2010). Principles of classification of medicinal plants as hyperaccumulators or excluders. Acta Physiologiae Plantarum 32(5): 823-829. https://doi.org/10.1007/s11738-010-0474-1

Muhammad, MAA, Abdullahi SUR, Sulaiman M, Abba A, Olaleye A et al. (2024). Carcinogenic and noncarcinogenic health risk assessment of heavy metals on some selected traditional herbal drugs. Research Journal of Food Science and Quality Control (RJFSQC), 9(32024): 66-79. https://dx.doi.org/10.56201/rjfsqc.v10.no3.2024.pg66.79

Meng C, Wang P, Hao Z, Gao Z, Li Q et al. (2022). Ecological and health risk assessment of heavy metals in soil and Chinese herbal medicines. Environmental geochemistry and health 44(3): 817-828. https://doi.org/10.1007/s10653-021-00978-z

Miletić A, Lučić M, Onjia A (2023). Exposure factors in health risk assessment of heavy metal (loid) s in soil and sediment. Metals 13(7): 1-28. https://doi.org/10.3390/met13071266

Nobakht SZ, Akaberi M, Mohammadpour AH, Moghadam AT, Emami SA (2022). *Hypericum perforatum*: Traditional uses, clinical trials, and drug interactions. Iranian Journal of Basic Medical Sciences 25(9): 1045-1058. https//dx.doi.org/10.22038/IJBMS.2022.65112.14338

Okumuş E, Canbolat F, Acar İ (2025). Evaluation of antioxidant activity, anti-lipid peroxidation effect and elemental impurity risk of some wild *Agaricus* species mushrooms. BMC Plant Biology 25(1): 1-12. https://doi.org/10.1186/s12870-025-06520-y

Özyiğit İİ, Yalcin B, Turan S, Saracoglu IA, Karadeniz S et al. (2018). Investigation of heavy metal level and mineral nutrient status in widely used medicinal plants' leaves in Turkey: Insights into health implications. Biological trace element research 182(2): 387-406. https://dx.doi.org/10.1007/s12011-017-1070-7

Popović S, Pantelić A, Milovanović Ž, Milinkov J, Vidović M (2017). Analysis of tea for metals by flame and graphite furnace atomic absorption spectrometry with multivariate analysis. Analytical Letters 50(16): 2619-2633. https://doi.org/10.1080/00032719.2017.1307849

Ring G, Sheehan A, Lehane M, Furey A (2021). Development, validation and application of an ICP-SFMS method for the determination of metals in protein powder samples, sourced in Ireland, with risk assessment for Irish consumers. Molecules 26(14): 1-20. https://doi.org/10.3390/molecules26144347

Rojas P, Ruiz-Sánchez E, Rojas C, García-Martínez BA, López-Ramírez AM et al. (2023). Human health risk assessment of arsenic and other metals in herbal products containing St. John's Wort in the metropolitan area of Mexico City. Toxics 11(9): 801. 1-20. https:// doi.org/10.3390/toxics11090801

Suljić A, Bečić E, Husejnović MŠ, Ademović Z (2024). St John's Wort as a possible tool for remediation of the soil contaminated with heavy metals. In: Arslanagić-Kalajdžić M, Ademović N, Tufek-Memišević T (eds) Interdisciplinary Advances in Sustainable Development II. BHAAAS 2023. Lecture Notes in Networks and Systems, vol 804. Cham: Springer, Pp. 61-69. https://doi.org/10.1007/978-3-031-46692-2_6

Tchounwou PB, Yedjou CG, Patlolla AK, Sutton DJ (2012). Heavy metal toxicity and the environment. In: Luch A (edt.) Molecular, clinical and environmental toxicology. Experientia Supplementum 101. pp: 133-164 Basel: Springer. https://doi.org/10.1007/978-3-7643-8340-4_6

USP (2017). Elemental impurities – limits. In USP 40 e NF 35, First supplement. The United States Pharmacopeia Convention, https://www.usp.org/sites/default/files/usp/document/our-work/chemical-medicines/key-issues/232-40-35-1s.pdf / [accessed 03 June 2025].

USEPA (2010) Risk-based concentration table. Washington: United State Environmental Protection Agency. http://www.epa.gov/reg3hwmd/risk/human/index.htm. / [accessed 15 May 2025].