DETECTION AND QUANTIFICATION OF SILDENAFIL AND TADALAFIL IN DIETARY SUPPLEMENTS MARKETED AS NATURAL SEXUAL ENHANCERS IN BOSNIA AND HERZEGOVINA

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SUMMARY

Objectives: The primary aim of this study is to detect and quantify the presence of Sildenafil (SDF) and Tadalafil (TDF) in dietary supplements marketed as natural sexual enhancers in Bosnia and Herzegovina. Additionally, the study seeks to utilize these findings to inform relevant authorities, enabling further testing in reference laboratories and prompting the necessary actions to remove these adulterated products from the market.

Methods: Using high-performance liquid chromatography with diode array detection (HPLC-DAD), 20 samples were analysed for the PDE-5 inhibitors.

Results: The analysis revealed that seven of the samples contained either SDF or TDF, with mean concentrations ± standard deviation (SD) ranging from 2,075.57 ± 0.47 μg/g to 33,808.857 ± 99.43 μg/g, and TDF concentrations ranging from 24.16 ± 0.11 μg/g to 3,994.66 ± 6.95 μg/g.

Conclusion: These findings indicate a significant health risk posed by the adulteration of these products. The widespread presence of these active pharmaceutical ingredients (APIs) in products falsely labelled as natural underscores the urgent need for stringent regulatory oversight and enhanced quality control measures to protect consumer safety. This study adds to the growing body of evidence concerning the adulteration of dietary supplements and emphasizes the critical importance of regulatory compliance and monitoring in safeguarding public health.

Key words: Sildenafil, Tadalafil, PDE-5 inhibitors, dietary supplements, sexual enhancement, adulteration

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INTRODUCTION

In recent years, the use of dietary supplements has increased due to the public perception that herbal products are "natural" and fundamentally safe compared to synthetic drugs (1). People consume food supplements for reasons such as improving nutrition, correcting nutritional deficiencies, maintaining health, preventing chronic diseases and enhancing sexual or athletic performance (2).

Food supplements within the meaning of the Regulation on the Health Safety of Dietary Products Authorized for Sale (Official Gazette of the Federation of Bosnia and Herzegovina, No. 7/14) and the European Directive 2002/46/EC are concentrated sources of nutrients or substances with a nutritional or physiological effect that are available in dosed form such as capsules, tablets or powder (3, 4). Regulations, including Regulation (EC) No. 1169/2011, govern the correct labelling of foods and permitted health claims, which must be scientifically substantiated and approved by the European Food Safety Authority (EFSA) (4–6).

Despite these regulations, some manufacturers make unauthorized claims and illegally add synthetic compounds or illegal botanicals to meet consumer expectations and increase sales (1). In the European Union (EU), reports of non-compliance with nutritional regulations have increased, particularly in relation to unauthorized formulations of food supplements, as reported through the Rapid Alert System for Food and Feed (RASFF) (7). Although Bosnia and Herzegovina is not a member of the EU, it participates in the RASFF through competent institutions such as the Food Safety Agency (7).

The adulteration of food supplements with synthetic compounds is a growing problem. Unlike medicinal products, food supplements are neither subject to pharmacovigilance nor do they have to demonstrate consistent quality, making adulteration difficult to detect. Undisclosed adulteration poses serious risks, including serious adverse effects and interactions with prescribed medications that may not be recognized by consumers who are unaware of the hidden ingredients (1).

The demand for herbal or natural sexual enhancers, often sold anonymously online or in unregulated markets, is high due to the stigma of sexual dysfunction. However, these products are frequently adulterated with undeclared phosphodiesterase type 5 (PDE5) inhibitors like Sildenafil (SDF), Tadalafil (TDF), Vardenafil, or their analogs, posing significant health risks (4).

Sildenafil and Tadalafil are potent, selective PDE-5 inhibitors that increase cGMP levels in the penile corpus cavernosum, leading to smooth muscle relaxation and erection (8–10). Clinically, they treat erectile dysfunction and conditions like pulmonary hypertension, but their use is associated with adverse effects, especially in combination with nitrates or alpha-blockers, and they can cause serious events like myocardial infarction in at-risk patients (11–14). Common side effects include flushing, headache, and nasal congestion, while rare but severe risks include priapism (12).

The primary aim of this study is to detect and quantify SDF and TDF in dietary supplements marketed as natural sexual enhancers in Bosnia and Herzegovina. The findings will inform authorities, enabling further testing in reference laboratories and necessary regulatory actions to remove adulterated products from the market, ultimately protecting consumer safety.

MATERIALS AND METHODS

Chemicals

Pharmaceutical grade Sildenafil and Tadalafil (purity 99.8%) were purchased from Sigma-Aldrich Chemie GmbH, Germany, along with phosphoric acid and triethylamine. Acetonitrile (for HPLC-super gradient, Reag. Ph. Eur., ACS water < 30 ppm, suitable for UPLC/UHPLC instruments) was obtained from Chromasolv, USA, and methanol was sourced from Honeywell, USA.

Sample Preparation

A total of 20 samples marketed as sexual enhancers were collected in April 2024 from various sources across the Bosnian market, including pharmacies, retail stores, and gas stations. These products, all classified as dietary supplements, came in various forms such as capsules, tinctures, chocolates, honey, fruit bars, and ginseng candies. Due to national regulations and institutional policies, detailed information on product names, manufacturers, and batch numbers cannot be disclosed publicly and will only be provided to the competent local regulatory authorities upon formal request. To ensure consistency in analysis, all solid samples – except for powders and liquids – were finely ground using a mortar and pestle. Approximately 1 g of each sample was weighed and quantitatively transferred into a 50 mL volumetric flask, dissolved in 70% methanol (MeOH), and sonicated for 30 minutes. The extracts were then filtered using PTFE syringe filters (0.45 μm).

Sample Analysis

The high-performance liquid chromatography (HPLC) analysis was conducted using an Agilent Technologies HPLC 1260 Infinity II system (Agilent Technologies, Inc., Santa Clara, USA) equipped with a diode array detector (DAD) for screening and quantitative analysis. Separation was achieved using an Agilent Eclipse Plus C18 column (250 × 4.6 mm ID, 5 μm), maintained at 30 °C. The injection volume was set at 20 μL, and UV detection was carried out at 284.4 and 292.4 and retention time 5.678 and 9.876 for SDF and TDF, respectively. The wavelengths 284.4 nm and 292.4 nm were selected as they correspond to the respective absorption maxima of SDF and TDF, ensuring optimal sensitivity and specificity for their simultaneous detection. The mobile phase consisted of two components, A and B. Mobile phase A was a mixture of acetonitrile and water in an 80:20 ratio. Mobile phase B was composed of methanol and 0.3% triethylamine with a pH of 7.5, adjusted with 0.3% phosphoric acid, in a 57:43 ratio. These components were mixed in a 30:70 ratio and vacuum filtered through a nylon filter paper with a diameter of 0.45 μm. Isocratic elution was applied at a flow rate of 1.0 mL/min. For the quantitative and qualitative data analysis, OpenLAB CDS ChemStation and Microsoft Excel were utilized, facilitating thorough statistical evaluation and interpretation of the results. Viagra tablets 50 mg, Pfizer, and Tadalafil Sandoz® tablets 20 mg, Sandoz, were used as positive control. Each analytical run was performed in duplicate to ensure the reliability and reproducibility of the results.

Method Validation

Method validation was performed using HPLC by considering the following parameters: limit of detection (LOD), limit of quantification (LOQ), method detection limit (MDL), method quantification limit (MQL), linearity, and recovery according to the requirements published by the International Conference on Harmonisation in the Harmonised Tripartite Guideline (15). The limits of detection and quantification were calculated using the formulas LOD = 3.3SD/a and LOQ = 10SD/a, respectively. Here, SD represents the standard deviation of the response, and "a" is the slope of the calibration curve for the analyte. The slope (a) was determined from the calibration curve, while SD can be obtained from the standard deviation of the calibration curve, particularly within the range of the LOQ. This standard deviation was measured as the standard deviation of the y-intercept.

MDL and MQL were estimated from the LOD and LOQ values, respectively. The linearity was determined from five-point calibration curves in the concentrations of 5–100 μg/mL for SDF, and 1–20 μg/mL for TDF. The recovery was evaluated by comparing the percentage of the peak area of the standard solution with that of the spiked blank samples.

RESULTS

The validation of the analytical method was performed following the International Conference on Harmonisation (ICH) guidelines to ensure the reliability and accuracy of the high-performance liquid chromatography with diode array detection (HPLC-DAD) analysis used for detecting and quantifying SDF and TDF in dietary supplements (15). The validation results demonstrated that the HPLC-DAD method is robust and reliable for detecting and quantifying SDF and TDF in dietary supplements. The limits of detection were 2.05 μg/mL for SDF and 0.54 μg/mL for TDF, while the limits of quantification were 20.21 μg/mL for SDF and 5.39 μg/mL for TDF. The method detection limits were calculated to be 6.21 μg/g for SDF and 1.63 μg/g for TDF, and the method quantitation limits were 62.16 μg/g for SDF and 16.34 μg/g for TDF. The correlation coefficients (R^2) of the calibration curves were higher than 0.999, indicating excellent linearity for both analytes across their respective concentration ranges (Fig. 1).

The recovery rates were 99.88% for SDF and 99.50% for TDF, demonstrating high accuracy in the quantification process. Ad-

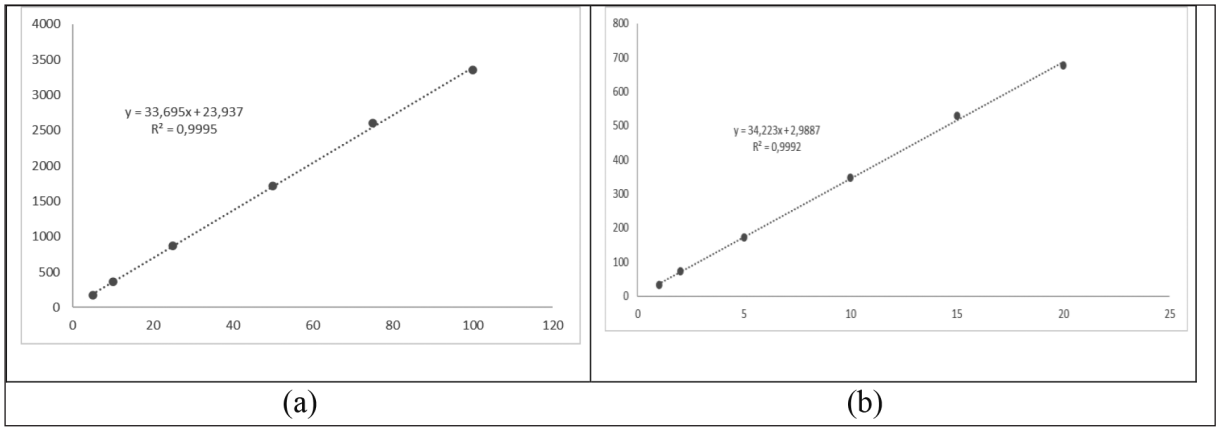

Fig. 1. *Calibration curves for SDF (a) and TDF (b).*

ditionally, the relative standard deviations (RSD) were 0.08% for SDF and 0.35% for TDF, indicating the precision of the method (Table 1). The peak purity indices for SDF and TDF peaks were calculated and found to exceed 0.995 and 0.997, respectively, confirming the peaks represented single components without co-eluting interferences. These results confirm that the method is highly sensitive, accurate, and precise, making it suitable for the reliable detection and quantification of SDF and TDF in dietary supplements. Figure 2 shows the representative chromatogram of positive sample to illustrate the consistency of detection.

Sample Analysis

The study included a total of 20 samples purchased from the Bosnian market, registered as dietary supplements. These samples were marketed as sexual enhancers and presented in various forms, including capsules, tinctures, chocolates, honey, fruit bars, and candies. The products claimed to enhance libido, improve erection, and support reproductive health. Many of these supplements were based on herbal ingredients like ginseng, maca extract, L-arginine, and various vitamins and minerals. Notably, several products were labelled for use 30 minutes before sexual activity.

Our findings revealed that 7 (35%) samples contained Sildenafil or Tadalafil at levels comparable to or exceeding therapeutic doses (Table 2). The detected mean concentrations ± SD of SDF ranged from 207.557 ± 0.47 µg/g to 33,808.857 ± 99.43 µg/g, while TDF mean concentrations ± SD ranged from 24.16 ± 0.11 µg/g to 3,994.66 ± 6.95 µg/g. These levels are alarmingly high and indicate substantial adulteration of these products with potent

Table 1. *Method validation parameters*

Compounds	LOD (µg/mL)	MDL (µg/g)	LOQ (µg/mL)	MQL (µg/g)	Recovery (%)	RSD (%)	Peak purity
Sildenafil	2.05	6.21	20.21	62.16	99.88	0.08	0.995
Tadanafil	0.54	1.63	5.39	16.34	99.50	0.35	0.997

LOD – limit of detection; MDL – method detection limit; LOQ – limit of quantification; MQL – method quantitation limit; RSD – relative standard deviation
MDL: LOD (µg/mL) × solvent quantities (mL) ÷ sample amount (g)
MQL: LOQ (µg/mL) × solvent quantities (mL) ÷ sample amount (g)

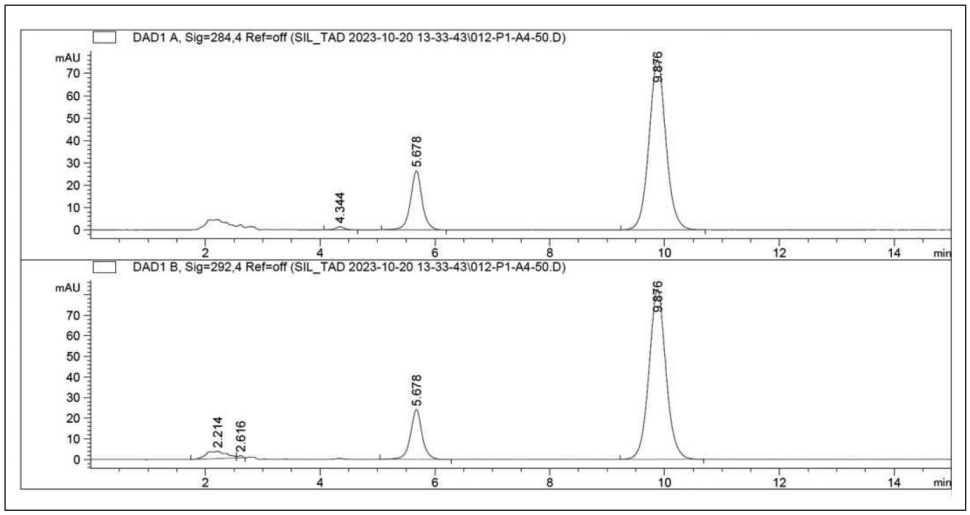

Fig. 2. *Representative HPLC chromatogram at 284.4 and 292.4 nm of a positive sample (capsules).*

Table 2. *SDF and TDF values determined in the samples*

Sample ID	Detected SDF amount (μg/g) Mean (SD)	Detected TDF amount (μg/g) Mean (SD)
DS1	2,075.57 (0.47)	24.16 (0.11)
DS2	8,333.75 (2.20)	125.34 (0.14)
DS3	2,299.93 (3.49)	50.75 (1.24)
DS4	33,808.57 (99.43)	3,994.66 (6.95)
DS5	<LOD	<MQL
DS6	8,144.30 (16.53)	29.96 (0.06)
DS7	13616.09	28.86

SDF – Sildenafil; TDF – Tadanafil; <LOD – lower than limit of detection; <MQL – lower than method quatifiaction limit

pharmaceutical ingredients. The remaining 13 samples had SDF and TDF concentrations below the method quantification limit.

DISCUSSION

The highest concentrations of SDF and TDF were observed in samples DS4 (chocolate) and DS2 (candy), respectively. Such high levels of these active pharmaceutical ingredients (APIs) pose significant health risks to consumers, especially those who might be taking these supplements without medical supervision or alongside other medications. The variability in the detected concentrations further underscores the inconsistency in product labelling and the potential for unintentional overdosing, which can lead to serious adverse effects. Our findings are consistent with previous research that has highlighted the widespread issue of adulteration in dietary supplements marketed as natural sexual enhancers. For example, a study by Gheorghiu et al. detected Sildenafil, Tadalafil, or both in 73.3% of dietary supplements labelled as natural. Their analysis using high-performance thin-layer chromatography (HPTLC) and ultra-high-performance liquid chromatography coupled with high-resolution mass spectrometry (UHPLC-HRMS-MS) revealed that the quantities of these adulterants were similar to or higher than those found in approved medicinal products. This study underscores the significant inconsistencies in product labelling and the presence of undeclared pharmaceutical ingredients in dietary supplements intended for sexual enhancement (16).

Similarly, Jairoun et al. conducted a study in the United Arab Emirates, analysing 158 sexual enhancement supplements. They found that 13.9% of these supplements contained significant levels of Sildenafil, Tadalafil, or Vardenafil. The study used reverse-phase liquid chromatography tandem mass spectrometry (RP-HPLC-MS-MS) and noted that while individual supplement levels might be low, the cumulative exposure from consuming multiple supplements daily poses a substantial health risk (17).

Further supporting these findings, Ulloa et al. reported the detection of unapproved PDE-5 inhibitor analogues, such as Amino Tadalafil, in dietary supplements marketed for erectile dysfunction in Latin America. Their study used a combination of thin-layer chromatography (TLC) and high-performance liquid chromatography (HPLC) diode-array detection, alongside other advanced spectroscopic techniques, to confirm the presence of these analogues. This research highlighted the global issue of adulteration in these products and the associated health risks due to the presence of unapproved and potentially harmful substances (18).

These consistent findings across various studies and regions highlight a pervasive problem with the adulteration of dietary supplements. The variability in the detected concentrations of SDF and TDF, as seen in our study and others, is particularly concerning. It indicates the potential for unintentional overdosing and serious adverse effects among consumers, who might be unaware of the presence of these potent substances in products marketed as natural and safe (12).

The adulteration of dietary supplements marketed as natural sexual enhancers with potent pharmaceutical ingredients such as SDF and TDF poses significant health risks to all consumers, but young men represent a particularly vulnerable population. This demographic group is often attracted to these products due to marketing claims of natural and safe enhancement, making them more susceptible to the adverse effects and potential misuse of these adulterated supplements. Young men are at increased risk due to a higher likelihood of unsupervised use, a propensity for risky behaviour such as combining supplements with other medications or recreational drugs, and psychological vulnerability stemming from the pressure to perform sexually, which can lead to dependency and mental health issues (19, 20). Given these factors, it is essential to highlight the specific risks faced by young men due to the widespread adulteration of dietary supplements. This situation demands enhanced regulatory measures and targeted consumer education to protect this vulnerable population and ensure product safety and integrity.

Furthermore, it is noteworthy that all the supplements analysed in this study, which tested positive for the presence of SDF and TAD, are labelled to be taken 30 minutes before sexual activity. This is unusual for dietary supplements, as they typically do not exhibit effects within such a short period. Dietary supplements generally require consistent and prolonged use to accumulate their intended benefits, unlike pharmaceutical drugs that can produce rapid effects. The recommendation for these supplements to be taken shortly before activity raises questions about their ingredients and mechanisms of action, suggesting the possibility of undisclosed active pharmaceutical ingredients that can act quickly, similar to prescription medications like PDE-5 inhibitors. This highlights the need for rigorous testing and validation to ensure

consumer safety and verify the authenticity of product claims. According to the Regulation on the Health Safety of Dietary Products Authorized for Sale (Official Gazette of the Federation of Bosnia and Herzegovina, No. 7/14), Article 54 states that the Commission for Dietary Supplements and Other Preparations of the Federal Ministry of Health "may request from competent and other expert institutions the verification of the identification of medicinal plant species, the composition and quantity of active ingredients in dietary supplements, as well as an opinion on their safety" (4).

The current regulatory framework for dietary supplements in Bosnia and Herzegovina mandates that dietary supplements must meet specific health safety conditions to be marketed (4). However, the framework appears insufficient to prevent the sale of adulterated products containing undeclared pharmaceutical ingredients such as SDF and TDF. Key issues include inadequate regulatory oversight, lack of mandatory pre-market testing, insufficient regulations on labelling and marketing claims, and weak market surveillance and enforcement mechanisms. These deficiencies allow harmful products to reach consumers, leading to deception and potential health risks. Furthermore, there is a significant lack of public awareness programmes about the dangers of adulterated supplements. Addressing these issues requires strengthening the regulatory framework through mandatory testing for undisclosed APIs, implementing stricter guidelines for labelling and marketing, enhancing market surveillance through annual monitoring, and increasing consumer education. The findings of this study highlight the urgent need for regulatory reform to ensure the safety and integrity of dietary supplements in Bosnia and Herzegovina. Regulatory bodies must implement and enforce stricter regulations on the marketing and labelling of dietary supplements to prevent misleading claims about natural ingredients. Additionally, robust testing and monitoring are crucial to detect and prevent the sale of adulterated products. The pervasive adulteration of dietary supplements with undeclared PDE-5 inhibitors, as demonstrated by our study and supported by other research, poses significant health risks to consumers. Urgent improvements in regulatory oversight and quality control are necessary to safeguard consumers from the dangers of unregulated and adulterated supplements.

Study Limitations

This study has several limitations. A sample size of 20 products may not fully represent the extent of counterfeits on the market, especially considering that the number of samples covered in this research is greater than the number of samples listed in the official Register of Dietary Supplements on the official website of the Food Safety Agency of Bosnia and Herzegovina (21) and the Ministry of Health and Social Welfare of the Republika Srpska (22), potentially limiting the generalization of the findings. Geographically, the research is confined to Bosnia and Herzegovina, which might not reflect the situation in other regions. Additionally, while HPLC-DAD is an effective detection method, it may not identify all potential adulterants or analogues of PDE-5 inhibitors present in the samples. Another limitation is the absence of confirmatory analysis using mass spectrometry or thin-layer chromatography. Although HPLC-DAD provides reliable quantitative results, future studies or regulatory authorities should apply complementary techniques such as MS or TLC for definitive confirmation.

Another limitation is the lack of consumer usage data, which could provide insight into how consumption patterns might influence the risk of adverse effects. Addressing these limitations in future research could provide a more comprehensive understanding of the scope and impact of adulteration in dietary supplements.

Despite these limitations, the study has several notable strengths. It provides crucial data on the presence of potent pharmaceutical ingredients in dietary supplements marketed as natural, highlighting a significant public health concern. The use of HPLC-DAD ensured precise and accurate quantification of Sildenafil and Tadalafil, adding robustness to the findings. Furthermore, the study contributes to the growing body of evidence regarding the adulteration of dietary supplements and underscores the need for stringent regulatory oversight and enhanced quality control measures. This research serves as an important foundation for future studies aiming to protect consumer health and ensure the integrity of dietary supplements.

CONCLUSION

Our research detected significant levels of SDF and TDF in 7 out of 20 dietary supplements marketed as natural sexual enhancers in Bosnia and Herzegovina. The detected concentrations of SDF and TDF approach or exceed therapeutic doses used in prescription medications. Therefore, their presence in dietary supplements poses significant health risks, including potential cardiovascular complications, priapism, or dangerous interactions with other medications, especially when consumed without medical supervision. These findings align with recent studies, which also report widespread adulteration of similar products in various markets. This consistent evidence points to a pervasive issue of mislabelling and adulteration, posing significant health risks to consumers. Therefore, there is an urgent need for enhanced regulatory measures and stringent quality control to ensure the safety and integrity of dietary supplements. Ensuring these products meet regulatory standards will help protect consumers from the potential dangers associated with unregulated and adulterated supplements.

Conflicts of Interest
None declared

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