

Investigation of Water-Soluble Preservatives in Frequently Used Energy-Stimulating Herbal Drugs in Rajshahi City, Bangladesh

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Abstract

The prevalence of erectile dysfunction is on the rise. Patients are turning to herbal drugs as an alternative to allopathic therapy or are drawn towards natural alternatives. However, there are concerns about the safety of these medications. An effort was made to determine the level of two commonly used water-soluble preservatives, sodium benzoate and potassium sorbate in 54 finished energy-stimulating herbal preparations. Maceration-assisted UV-Vis spectrometry was adopted for determining the analytes in bulk and finished formulations. Concern about harmful effects on human health has been raised after 5% of samples were found to be risky for oral ingestion of sodium benzoate. If ingested exceeding the prescribed daily dose, the high concentration of potassium sorbate in some formulations raises concerns regarding daily consumption. To assess the preservative levels in herbal medicines, more laboratory-based studies are required.

Keywords: Erectile dysfunction, Energy-stimulating herbal preparations, Sodium benzoate, Potassium sorbate, Health risk.

1. Introduction

The worldwide prevalence of erectile dysfunction makes it a common healthcare problem [1-6], affecting the quality of life of men of all ages [7-10]. The number of people suffering from distress is increasing in tandem with the surge in lifestyle diseases, with reported increases ranging from 6% to 50-70% among individuals aged 20-29 years and 40-79 years, respectively [2]. The model predicts by 2025, people suffering from erectile dysfunction will pass 300 million [11]. Indian subcontinent reports a high incidence of erectile dysfunction. Patients suffering from erectile dysfunction are often found to be associated with other problems like lack of sexual desire (libido), ejaculation complications, and premature ejaculation due to vascular abnormalities of the penile blood supply, erectile tissue and decreased testosterone levels [3, 12]. Some diseases (cardiovascular diseases, hypertension, type- 2 diabetes etc.) and some drugs (tranquilizers, appetite suppressants, antihistamines, antidepressants etc.) can also trigger

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erectile dysfunction [1, 3, 9]. When they consult physicians or specialists in sexual health care, synthetic drugs are prescribed to them. Dapoxetine was prescribed for patients suffering from erectile dysfunction and premature ejaculation. Udenafil, although prescribed, comes with an enormous cost burden. For severe cases, papaverine, chlorpromazine and alprostadil are recommended via the intra-cavernosal route [13].

However, treatment failures, exorbitant costs associated with allopathic therapy and unpleasant side effects associated with mainstream treatment (Sexual Function Health Council, 2004) have prompted patients to search for alternatives. The majority of people living below the poverty line in developing countries do not have health insurance. Therefore, when they fall ill, they have to bear out-of-pocket (OP) expenditures, adding financial burden to them. This resulted in a search for affordable herbal medicines [14-16]. This is in contrast with allopathic treatment, which requires consultation fees, pathological tests, etc. Therefore, people often search for alternatives where doctors offer free consultations, and tests are not required. Taking advantage of this opportunity, herbal drug manufacturers employ deceptive marketing strategies to attract patients towards their products. These clever marketing tactics lead patients to believe that herbal drugs are less expensive. With their iconic claims that their products are derived from natural sources, the producers of herbal drugs claim their drugs are safe to consume. However, different investigations into the safety of herbal medicines found the presence of different contaminants in objectionable amounts [17, 18]. Concerns also arise with the addition of excipients like preservatives [19, 20].

Pharmaceutical formulations require storage prior to consumption. The duration they can be stored before spoiling depends on the formulations. Factors like microbiological, enzymatic, or chemical changes affect shelf life. To extend the shelf life of the formulations, preservatives are added as excipients to delay the alteration and degradation of the product [21]. Water-soluble preservatives, sodium benzoate and potassium sorbate are frequently used as preservatives in pharmaceutical formulations [22-25]. Moreover, there is evidence of preservatives being added in high doses [26-29]. These preservatives are generally recognized as safe (GRAS). However, if the allowable limit is exceeded, then short-term or long-term complications may arise. Due to growing concerns, the scientific community and regulatory authorities are showing increasing interest in assessing the safety of these preservatives [23, 30, 31].

Among Bangladeshi adults, erectile dysfunction is a common disease [15]. With the increase of diabetes and hypertension, erectile dysfunction can also gain momentum. A person's sexual orientation is a significant component of their personality and affects their psychological, social and physical well-being. As a Muslim-majority country, it has a predominantly conservative culture, and therefore, discussion of such issues is taboo. This increases anxiety among sufferers. Recognising this, herbal manufacturers take the opportunity to provide sufferers with an alternative therapy perceived as easy, safe, and effective compared to allopathic alternatives. Consequently, the market for herbal drugs for treating this disorder thrives in this region. However, there is a lack of investigation into the quantity of preservatives present in frequently consumed plant-based drugs in this region. Therefore, there is a distrust towards the quality of the drugs. This poses a risk to drug safety and public health. To address this concern, an assessment of the safety of sodium benzoate and potassium sorbate in these formulations was conducted. The findings of the investigation would contribute information to the scientific community and help regulatory authorities to plan interventions.

2. Materials and Method

2.1. Sample collection, coding and preservation

In total, 54 energy-stimulating herbal drugs were collected from different popular herbal drug-selling locations within the Rajshahi City Corporation area. These locations included manufacturer outlets, superstores, health stores and distribution points (Figure 1). Herbal drugs sold as finished formulations and commercially available were selected for investigation. The collected samples were transported to the Advance Research Laboratory, Department of Chemistry, University of Rajshahi. Prior to preservation, information about each sample (name of the drug, batch number, manufacturer, manufacturing date, expiration date, dosage, and dosage form) was recorded and the samples were assigned individual numeric codes to avoid selection bias during assessment. The samples were preserved following the written directions on the primary packaging wall.

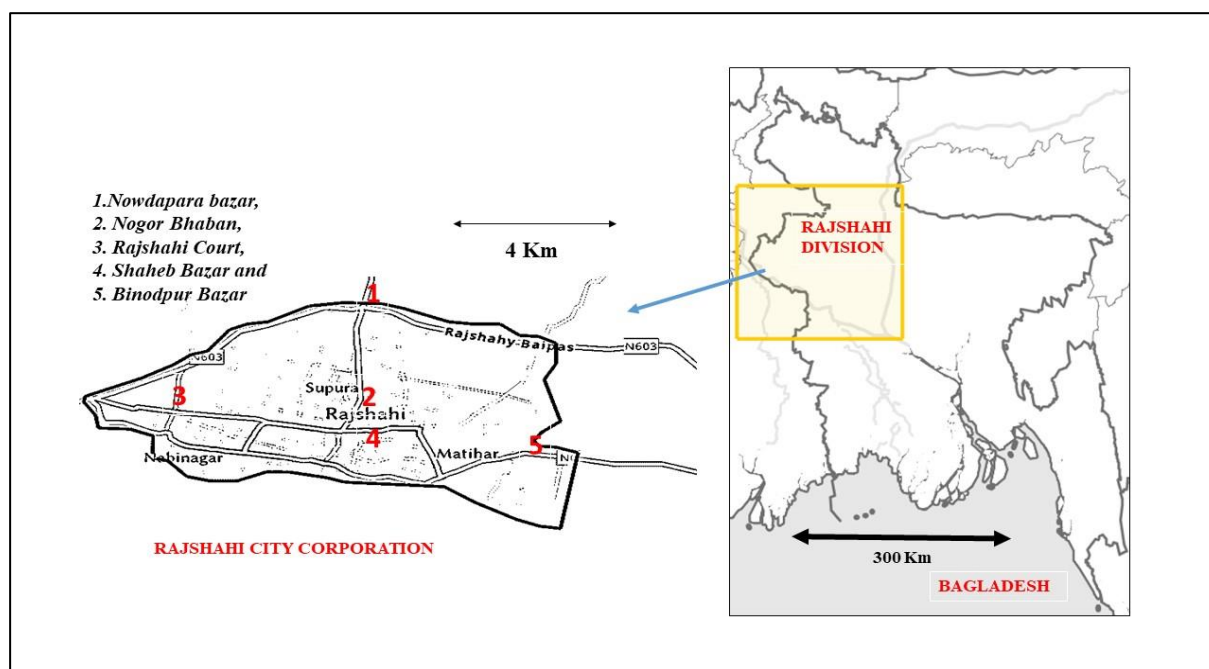


Figure 1. Sampling area.

2.2 Instrumentation

Sodium benzoate and potassium sorbates were analyzed using the Shimadzu 1900i UV-Vis spectrophotometer (Shimadzu Corporation, Kyoto, Japan). The device is equipped with two 10 mm quartz cell match pairs. Its ultra-fast scanning (29000 nm/ min) among its series, enables rapid detection of analytes. With the lowest stray light (0.5% at 198 nm) among its series, accuracy in measurement is ensured. Precise weighing of standards and samples was carried out using an electronic balance with good precision (≤ 0.10 mg) and linearity (± 0.20 mg) from the Shimadzu ATY 224 model, Philippines.

2.3 Reagents and standards

Analytical grade sodium benzoate and potassium sorbate were purchased from Scharlab S.L., Spain through a local manufacturer. The analytes were provided with certification from their manufacturer with a claimed purity of 99-100%. Distilled water was procured from a local manufacturer.

2.4 Preparation of standards

A precisely measured quantity of 100 mg sodium benzoate/ potassium sorbate was added to a 1000 mL volumetric flask and dissolved in water to acquire a 100ppm standard stock solution. Calibration standards of different concentrations (10 ppm, 20 ppm, 30 ppm, 40 ppm and 50 ppm) for sodium benzoate and potassium sorbate were made by diluting the standard stock solution.

2.5 Determination of analytical wavelength

Using computer-aided lab solution software, baseline spectra for solvent were obtained. Medium scanning of sodium benzoate and potassium sorbate at 0.5 nm data interval from 200-400 nm wavelength range was performed. Analytical wavelength or maximum wavelength (λ_{max}) for sodium benzoate and potassium sorbate were found at 224 nm and 254 nm, respectively (Figures 2 and 3). The analytical wavelength matches the literature-provided spectra [19].

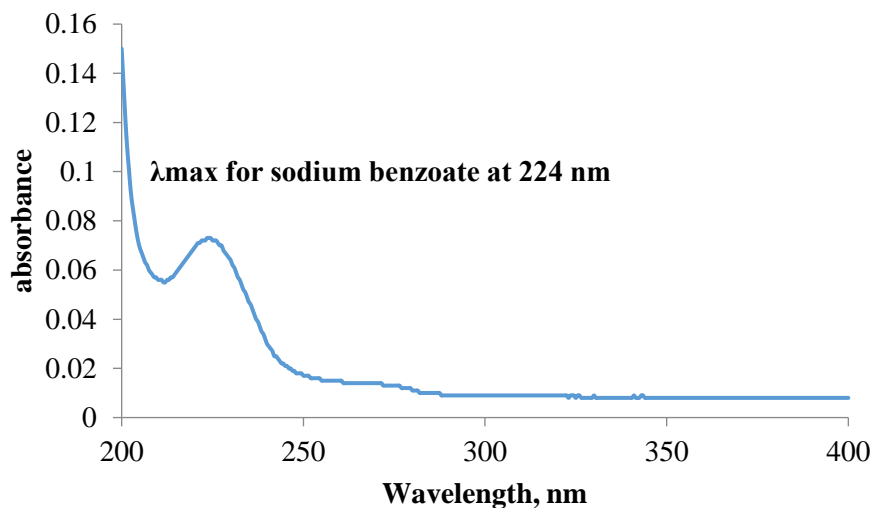


Figure 2. Spectra for sodium benzoate at varying wavelengths.

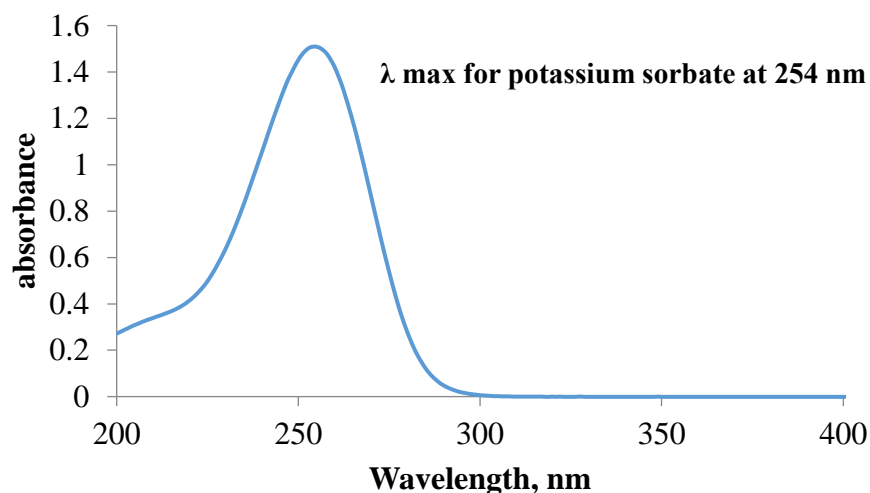


Figure 3. Spectra for potassium sorbate at varying wavelengths.

2.6 Construction of calibration curves

Prior to running calibration standards, solvent absorbance was adjusted to null. Aliquots of calibration standards (10 ppm, 20 ppm, 30 ppm, 40 ppm and 50 ppm) were taken to the quartz cell of the spectrophotometer in sequence, maintaining lower to higher concentrations. The signal of respective concentration was obtained as a result of the interaction of light with analytes. Lab solution software produces a calibration curve with its associated regression equations. Linearity of the calibration curves was observed from calibration co-efficient values 0.9949 and 0.9979 for sodium benzoate and potassium sorbate, respectively. Regression equations for sodium benzoate and potassium sorbate were $y = 0.0074x - 0.0778$ and $y = 0.0311x + 0.0032$, respectively (Figures 4 and 5).

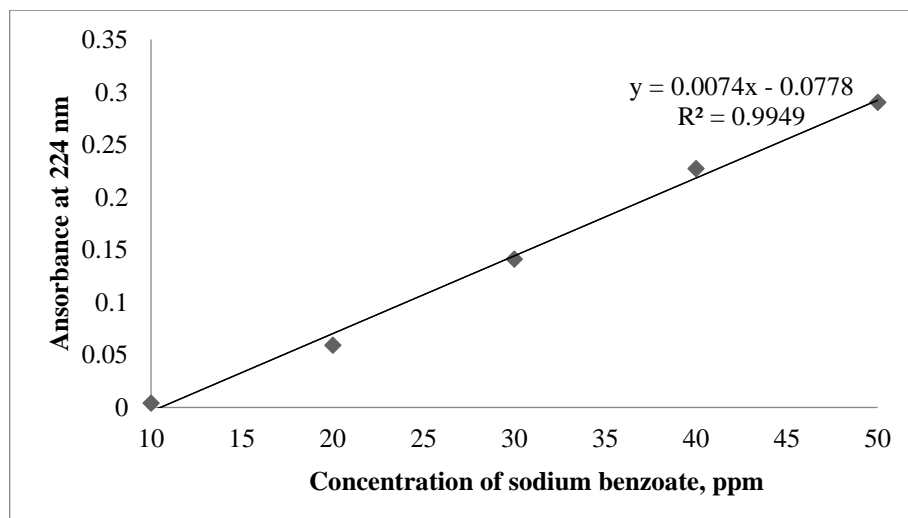


Figure 4. Calibration curve for sodium benzoate.

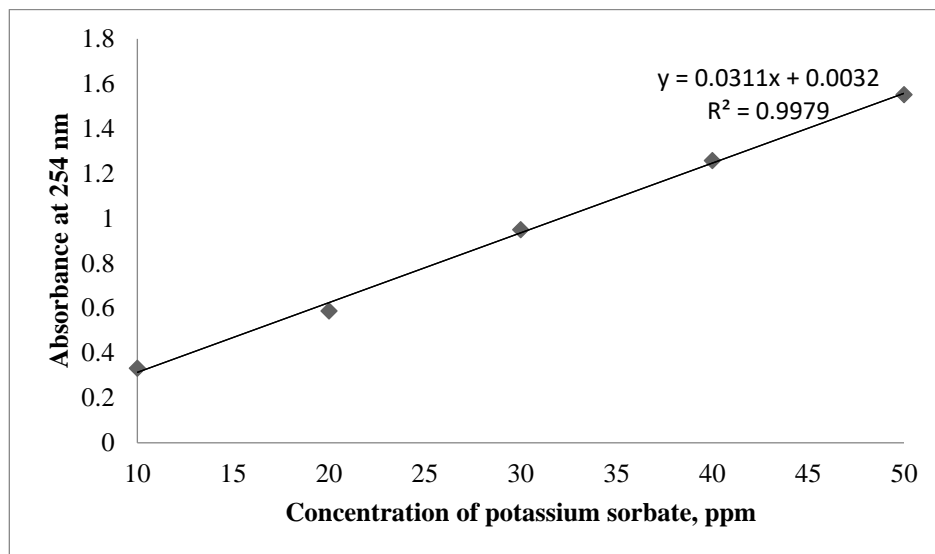


Figure 5. Calibration curve for potassium sorbate.

2.7 Preparation of formulations

Single tablet or capsule formulations were weighed and taken in conical flasks. De-ionized water (80 ml) was added and macerated for 72 hrs with occasional shaking [19, 32], resulting in a heterogeneous mass. Using a cellulose filter (Whatman filter paper 42) suspended particles were separated and filtrate was collected in a 100 mL volumetric flask. To aid extraction yield, 20 mL of deionized water was poured over filter paper and the washing was added to the volumetric flask to make the volume 100 mL, resulting in a clear solution. The solution was diluted 100 times and an aliquot was used for analysis. For the liquid sample, 1 gm sample was weighed and the aforementioned process was repeated. In both instances, the concentration of the unknown sample solution was determined from the calibration curve using the Beer-Lambert law. The concentration data were converted to actual sample concentration by multiplying them with their respective dilution factors. From the actual concentration, the daily intake value was calculated [19].

2.8 Validation study

2.8.1 Precision and Accuracy Study

The accuracy and precision of the analytical method were verified by the recovery study. The known amount of potassium sodium benzoate and potassium sorbate (10 ppm, 20 ppm and 40 ppm) were spiked in analyte-free plant-extract [19]. A similar extraction procedure was followed [19, 32]. Concentration and absorbance data of the spiked samples were taken in triplicates. Sodium benzoate and potassium sorbate were recovered in the range of 98.30- 99.63% and 99.13- 102.47%, respectively (Table 1).

Table 1. Accuracy and precision study.

Spiked amount, ppm	%Recovery of analyte, mean±SD	
	Sodium benzoate	Potassium sorbate
10	98.30±0.00	99.13±0.12
20	98.57±0.21	102.47±0.06
40	99.63±0.14	101.85±0.03

2.8.2 Method sensitivity

Method sensitivity was assessed by determining limit of detection (LOD) and limit of quantification (LOQ) values. LOD and LOQ were calculated as, $LOD = 3 \times SD$ of the response/slope of the analytical curve and $LOQ = 10 \times SD$ of the response/slope of the analytical curve, respectively. LOD and LOQ for sodium benzoate were 0.17 and 0.50 ppm, respectively. LOD and LOQ for potassium sorbate were 0.56 and 1.70 ppm, respectively.

3. Results and discussion

The consumption of energy-stimulating herbal drugs is increasing in Bangladesh due to some influencing factors. Despite the expanding herbal drug market, there is still a lack of strict quality assurance (QA) procedures targeting the remedies. Adherence to QA procedures could benefit the consumers. The Directorate General of Drug Administration (DGDA) oversees the licensing of herbal formulations like allopathic drugs. Critics of the remedies would also have been replenished with evidence-based safe consumption data if Charry Eyes had been in place from manufacturing to selling of the formulations. Reports of suspected adverse drug reactions (ADRs) are regularly received and post-marketing drug withdrawal takes place afterwards. However, causes of the ADRs are rarely examined. There are still reports on the harm of additives, and therefore, a large number of synthetic chemicals used as additives are under scrutiny. However, sodium benzoate and potassium sorbate are considered relatively safe preservatives. In line with this, the preservatives are used in different formulations in higher quantities compared to others. Sodium benzoate and potassium sorbate are salts of benzoic acid and sorbic acid, respectively. With excellent antibacterial and antifungal activities, some unique characteristics like being free from odor and taste make them popular preservatives. Consumption of these preservatives beyond safety limits can increase the risk of adverse health effects. However, the regulatory authority in Bangladesh has neither set safety limits for preservatives in finished herbal drugs nor assessed the drugs for safety according to international regulations.

In the current investigation, sodium benzoate and potassium sorbate in finished herbal formulations were estimated using UV-Vis spectrometry, followed by the maceration extraction procedure. The concentration data of analytes were converted to daily intake (DI) data and were compared with international regulatory authority safety endpoints.

Sodium benzoate was detected in all the investigated samples. Maximum and minimum sodium benzoates were in sample 51 (524.04 mg/ day) and sample 22 (0.12 mg/ day), respectively. Three samples, sample 14 (507.94 mg/ day), sample 45 (432.20 mg/ day) and sample 51 (524.04 mg/ day) exceeded the maximum allowable permissible limit for daily consumption (350 mg/ day for an adult of 70 Kg body

weight) [30] (Figure 6). In line with this investigation, Islam et al. detected lower instances of sodium benzoate exceeding the safe limit in their studied anti-diabetic herbal drug samples [19].

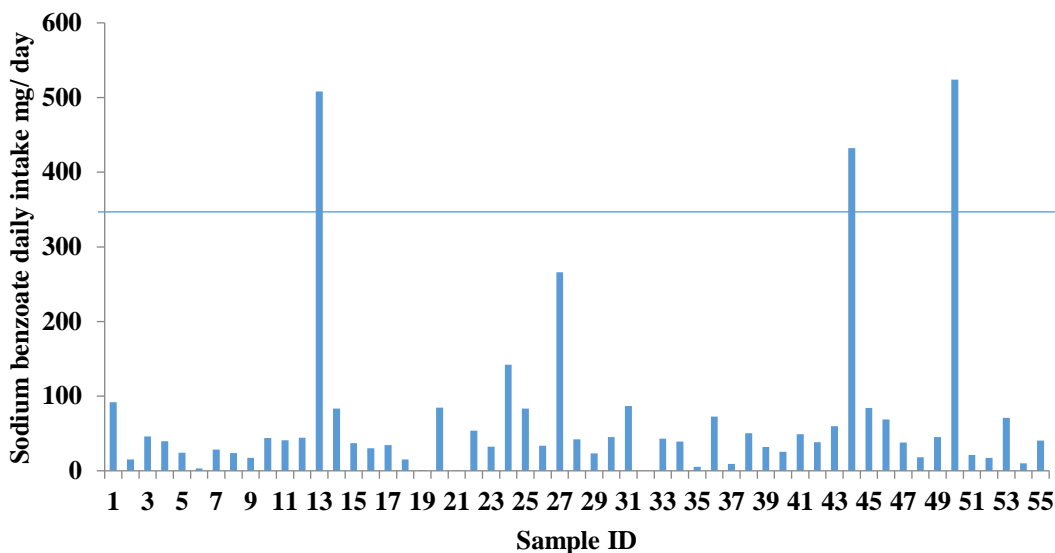


Figure 6. Daily intake of sodium benzoate through investigated samples.

Accumulation of sodium benzoate in the human body is not reported as the compound conjugates with glycerine to form hippurate in the liver and kidney. After entering the matrix, the acid radical is first converted to benzoyl-coenzyme A (CoA)(ligase), followed by conversion into glycerin *N*- acyltransferase upon reaction to glycerine. The mitochondrial matrix hosts the reaction. Excretion of the glycerin *N*-acyltransferase occurs primarily through the urinary system [30]. Sodium benzoate intake in high amounts should be approached with caution because it has the potential to cause a deficiency in glycine, which can therefore have a deleterious impact on brain neurochemistry.

Therefore, it is recommended to add the preservative in strictly defined doses. The daily permissible limit of this preservative is 350 mg for a 70 kg adult, provided the preservative is not being consumed from other sources. Prolonged exposure to excess doses can generate oxidative stress and cause mutagenic effects. In animal trials, male rats were administered with different doses of sodium benzoate for different periods of time. Some groups showed decreased levels of antioxidant enzymes, glutathione (GSH) and malondialdehyde (MDA). Another investigation saw an increase of oxidative stress in a randomized control trial which involved dose-dependent sodium benzoate administration in different groups at constant time duration [30]. Hormonal disruption and reduction of fertility have also been reported in different investigations.

Most of the samples contained potassium sorbate in varying degrees. Maximum potassium sorbate was consumed through sample 46 (1367.97 mg/ day). Potassium sorbate was not detected in three samples. None of the samples exceeded the maximum daily consumption for the analyte (the allowable limit for potassium sorbate is 1750 mg/ day for a 70 Kg healthy adult) [31] (Figure 7). Another national investigation also found herbal drugs use potassium sorbate within safe levels (below detection limit- 246.24 mg/ day) [19]. Batch-to-batch variation in samples can result in the samples falling into the unsafe consumption zone.

Herbal drugs are sometimes prescribed or consumed in doses above the mentioned limit. This could also raise the possibility of unsafe consumption.

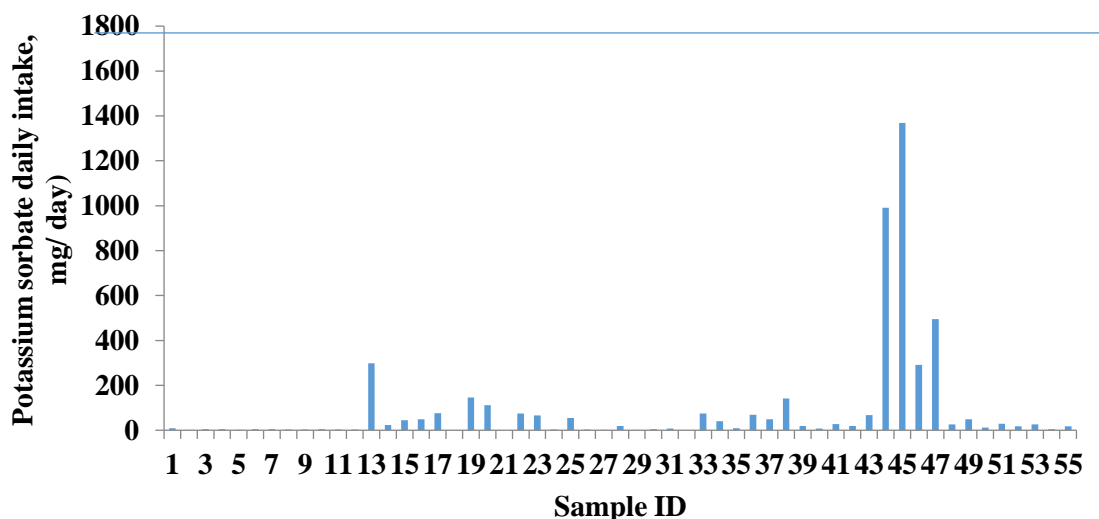


Figure7. Daily intake of potassium sorbate through investigated samples.

4. Conclusions

A person's sexual orientation is a crucial component of their identity. It has an impact on their overall well-being. Some individuals who find allopathic therapy unappealing or who are directly drawn to herbal therapy, opt for herbal formulations. However, with questionable safety, concern remains with the consumption of the drugs. The assessment of frequently used water-soluble preservatives in the formulations was aimed at ascertaining their safety. Instrumental analysis revealed that three samples containing sodium benzoate were found unsafe for consumption, raising concerns regarding adverse effects on human health. The presence of a higher amount of potassium sorbate in some formulations also raises concerns for daily consumption if consumed above the recommended daily dose. Further lab-based research into the safety assessment of other herbal preparations is necessary to gain a deeper understanding of the preservative content in herbal drugs in the country.

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Conflict of Interest

We declare no conflict regarding the publication of the study.

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