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RESEARCH ARTICLE

# Health risk assessment of Macro, Trace-elements and heavy metal in various Indian Antidiabetic Polyherbal formulations

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## Abstract

Diabetes mellitus, a global pandemic, can be holistically managed with the use of polyherbal formulations which is an accessible form of treatment in developing countries due to fewer side effects, economical and easily available. Commercial polyherbal formulation lacks systemic based scientific study, thus it is suspected to be associated with many contaminations and related toxicities, one of which is considered to be elemental health hazards. Therefore, the present study is designed to assess six selected antidiabetic polyherbal formulations from the Indian market for their element contents, quality, and health risk assessment. Concentrations of 35 essential and non-essential trace-elements were quantified by Handheld X-ray spectrophotometer and health risk assessment was calculated by estimated daily intake (EDI) and Total hazard quotient (THQ). Elements were found to be in a vast range of concentration in the tested APH. Among the 35 elements analyzed, Ca (23100±0.033ppm) and K (14800 ±0.021 ppm) in "MH" and Zn (15600±0.025 ppm) in "DB" were found to be the highest. The lowest concentrations of Rb and Nb (3±2 ppm) were observed in the formulation "MH" and "SN" respectively. THQ of all the elements was calculated to be less than unity except for Rb in the formulation "MA". Rb is rarely associated with toxicities as it is rapidly excreted in sweat and urine**.** V, Co, Ni, Cu, As, Se, Y, Ag, Sn, Sb, Ba, W, and Hg were absent in all the APH. Therefore the present study indicated the presence of essential elements some of which are important for the management of diabetes and hence can be considered safe for use.

**Keywords** Antidiabetic polyherbal formulation · Heavy metals · Trace elements · Marco elements · Health risk assessment · Handheld X-ray spectrophotometer

## Introduction

Ayurveda originated in India 2000 years ago**,** has a wide range of use in human healthcare. World health organization (WHO) recommends the use of polyherbal formulation (PHF) in the national health care system as an emerging therapy for various diseases (WHO 2010). Diabetes mellitus (DM) accounted for 5 million deaths worldwide in 2017 which stances a huge challenge in developing countries because of its inadequate resources (Cho et al. 2018). India is considered as the diabetic capital of the world and therefore to overcome the challenge, antidiabetic polyherbal formulation (APH) can be considered as a contender to resolve the present scenario as the synergistic effect of the herbs present in APH achieves efficiency in multidirectional approach. With the expanding demand, there is raising concern with the safety and efficacy of APH (Choudhury et al. 2018). Herbal formulations have shown lack of safety assessment in previously reported studies (Archibong et al. 2017; Choudhury et al. 2018). A study conducted on APH sold in the market of Ghana was found to be surpassing the safety limits (Mensah et al. 2019).

The geochemical characteristic of the soil, water, and air around the environment where the plants are grown significantly affect the quality of PHF. Plants accumulate essential and non-essential elements by absorbing them from the soil, water, and air around further deposit these in their parts. Heavy metal contamination from soil and water has been reported previously (Eriyamremu et al. 2005). Environment

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pollution being at its peak becomes a critical challenge for reducing heavy metal contamination in plants, continuous exposure of heavy metals in and around the plant growth environment results in elevated levels of heavy metals in plants used for PHF preparation. When these contaminated raw materials are used in the preparation of PHF, heavy metals enter the food chain and accumulate, leading to detrimental consequences. Special concern is given to cadmium, mercury, lead, arsenic, and nickel as they are potential toxins at low concentrations (Rao et al. 2011). The presence of potential toxins like Pb and Cd was reported in Herbal products of Iran exceeding the permissible limits (Mousavi et al. 2014).

Essential trace elements such as chromium, copper, iron, manganese, etc. are important as they are essential for the proper functioning of biological system but rise in intake of essential trace elements above permissible limits is associated with several detrimental health risks such as decreased immunological resistance, cardiac dysfunction, fetal distortion, compromised psychosocial and neurological behavior, gastrointestinal cancer, etc. (Dghaim et al. 2015). Preceding reports for essential elements such as Zn, Cu, Fe, Mn and Cr suggested the presence of these elements beyond permissible limits could be toxic for human consumption (Kohzadi et al. 2018).

Production principles laid by WHO for manufacturing of PHF include element analysis with special reference to toxic heavy metals (WHO 1978, 1989, 1991). Due to lack of data on preparation, storage, transportation, collection of raw material, and also the complexities associated with bioactive constituents in PHF, the safety of commercial formulations are unclear, thereby there is an urgent need for safety assessment. There is a systematic requirement for monitoring and surveillance studies to protect the health and also give an overview of health benefits from the concentration of elements ingested (Dhanavathy and jayakumar 2017). Analysis of Heavy metals is reported previously for herbal formulations but an elemental composition of an herbal formulation is rarely studied and hence, the current study is aimed to evaluate the concentrations of 35 essential elements, trace elements, and heavy metals present in selected six commercial APH and also to appraise the associated health risks which would assure the pre-market and post-market quality of APH available in the Indian market.

## Material and methods

### Sample Collection and Preparation

Six widely used APH were purchased from the Indian market and they were randomly coded: BG, DB, DT, MA, MH, and SN.

### Metal analysis by Handheld X-ray spectrophotometer (HH-XRF):

Hand held XRF (HHXRF) is the need of the hour to analyze metals, powders and alloys. HH-XRF was used as other XFR technique was cumbersome and difficult to handle. To test the efficiency of the HHXRF 6 powders of antidiabetic polyherbal formulation was analyzed to detect elements. The sample was powdered finely and was placed in a cubical box for irradiation by X-ray tube (Rhodium tube was used for irradiation). The spectrum was obtained in 20 seconds. The beam lines were obtained of (Beam 1 from 12 to 36 keV) and Beam 2 from 0-12 KeV) (Denni et al. 2019).

### Health risk assessments

Health risks assessment of elements in APH can be projected by the methods which are used for assessing carcinogenic or noncarcinogenic risks. Estimated daily intake (EDI) and target hazard quotient (THQ which is introduced by the US Environmental Protection Agency for noncancer risk assessment (USEPA 1989, 1992, 1993; Zhu et al. 2013).

### Estimated daily intake of the heavy metals

The estimated daily intake (EDI) of each element present in the APH was determined by the following equation which is recommended by US-EPA:

$$EDI = ED \times C \div W_{AB}$$

Where; EDI is the estimated daily intake of the elements, C is the determined macro-elements, trace-elements and heavy metals content in the APH, ED is the daily dosage of the APH (Table 1) and $W_{AB}$ is the Indian average body weight; (70 kg adults) (Mensah et al. 2019).

### Target hazard quotient (THQ)

The human health hazard posed by element exposure is assessed by target hazard quotient (THQ), which is the ratio of the average EDI to the reference dose (RfD) for an individual pathway and chemical.

$$THQ = C \times IR \times EF \times ED \div BW \times AT \times RfD$$

Where, IR: ingestion rate (dosage of the formulation/day); EF: exposure frequency (365days/year); ED: exposure duration (35 years) equivalent to vulnerable age of diabetic population subtracted from average lifespan which is considered as 70 years; BW: body weight in kilogram; and AT is the average time for non-carcinogens (365days/year ×number of exposure years, assuming 70 years). International oral reference dose values for the elements RfDo (mg kg−1 day−1). The reference values as stated by FAO/WHO or previously published literature material (Institute of medicine, food and nutrition board 1997, 2010; Mensah et al. 2019).

### Statistical analysis

Data in the present study are represented as mean ± SD.

## Result and Discussion

Six commercial APH were assessed for thirty-five elements (Mg, Al, Si, P, S, K, Ca, Ti, Mn, Fe, Zn, Rb, Sr, Zr, Nb, Mo, Cd, Th, Cr, Pb, Bi, U, V, Co, Ni, Cu, As, Se, Y, Ag, Sn, Sb, Ba, W, and Hg), representing the data in ppm (Table 2) and Fig 1A-1F represents the X-Ray spectrum of the APH by HH-XFR (Beam 1: 12 to 36KeV and Beam 2: 0-12KeV). Concentrations of metals detected in six tested formulations varied significantly, which can be due to different geochemical characteristics of soil from which the plants are grown and used for preparing the APH. Additionally types of herbs used and the different parts of plants including the tubers, leaves, seeds etc. (Table 1) might play an important role for the vast range of concentrations of elements (Rao et al. 2011). The average concentration of elements in descending order is represented (Table 3). V, Co, Ni, Cu, As, Se, Y, Ag, Sn, Sb, Ba, W, and Hg were not detected in any tested APH, hence, can be concluded that these formulations are devoid of toxicities arising from the above elements.

The highest concentrations of elements observed in all six APH were Ca> K> P. Ca at a range of (23100 ppm in MH to 4454 ppm in MA), followed by K (14800 ppm in MA to 632 ppm in MH) whereas P ranging from (2330 ppm in SN to 780 ppm in MH). Major requirements of Ca and P are associated with the structure and function of bones and teeth (Takeda et al. 2004; Heaney 2012). K is considered an important element in maintaining intracellular fluid volume and balanced electrochemical gradients, previous studies suggested that K concentrations also control glucose levels in type II diabetes (Stone et al. 2016). In the present study, Mg was observed in DT (12400 ppm), which is associated with the regulation of diverse biochemical reactions and glucose metabolism in the body. K and Mg levels in APH can turn out to be beneficial for the management of diabetes (Laires et al. 2004). A moderate level of sulfur was detected in all the formulations except for MH. Sulfur is one of the key intermediates for major amino acid methionine, lack of which can lead to a deficiency of protein impeding various biochemical reactions (Nimni et al. 2007). Our result are in accordance with the previously reported study of various herbs in Iran where the

**Table 2** Element analysis of Six APH in ppm (Note: Anything beyond 10000 ppm is represented in % and ND represents not detected)

| Elements | DT | DB | BG | MA | MH | SN |
|---|---|---|---|---|---|---|
| **Mg** | 1.24%±0.92 | ND | ND | ND | ND | ND |
| **Al** | 2900±1200 | 1300±1100 | ND | 1400±1200 | ND | 1500±1100 |
| **Si** | 5860±370 | 7889±410 | 8960±440 | 1280±250 | ND | 430±220 |
| **P** | 2150±120 | 2150±120 | 1420±110 | 2080±120 | 780±120 | 2330±130 |
| **S** | 1452±91 | 978±89 | 1128±85 | 803±84 | ND | 507±85 |
| **K** | 1.36%±0.024 | 9520±170 | 8360±140 | 1.48%±0.021 | 632±62 | 1.02%±0.016 |
| **Ca** | 7610±140 | 1.10% | 1.39%±0.019 | 4454±83 | 2.31%±0.033 | 1.25%±0.017 |
| **Ti** | 520±250 | 220±220 | 240±230 | ND | ND | ND |
| **Mn** | 141±33 | 114±29 | 94±30 | 137±32 | 28±26 | 76±28 |
| **Fe** | 5140±140 | 8740±190 | 633±46 | 954±53 | 100±25 | 659±46 |
| **Zn** | 23±5 | 1.56%±0.025 | 18±5 | 20±4 | 21±5 | 26±5 |
| **Rb** | 8±2 | 15±2 | 6±2 | 10±2 | 3±2 | 7±2 |
| **Sr** | 18±2 | 44±3 | 13±2 | 10±2 | 6±2 | 25±2 |
| **Zr** | 7±4 | 15±4 | ND | 8±3 | 4±4 | 5±3 |
| **Nb** | 4±3 | ND | 5±3 | 4±3 | 9±3 | 3±3 |
| **Mo** | 7±5 | ND | 6±5 | ND | 7±5 | ND |
| **Cd** | 30±17 | ND | 22±17 | 32±16 | ND | 31±16 |
| **Th** | 10±9 | ND | ND | ND | 22±10 | ND |
| **Cr** | ND | ND | ND | ND | 30±18 | ND |
| **Pb** | ND | 7±4 | ND | ND | ND | 7±4 |
| **Bi** | ND | 48±12 | ND | ND | ND | ND |
| **U** | ND | ND | ND | ND | 4±4 | ND |

**Table 1** Composition, Batch number of the product used for elemental analysis and dosage of Six APH

| Sample ID | Composition | Batch No | Dosage Kg/ day |
|---|---|---|---|
| BG | *Berberis aristata* DC, *Pterocarpus marsupium* Roxb, *Gymnema sylvestre* (Retz.) R.Br. ex Sm, *Rubia cordifolia* L, *Trigonella foenum-graecum* L, *Tinospora cardifolia Miers*, *Berberis Aristata* and *Tinospora cordifolia* | 989-H | 0.0025 |
| DB | *Gymnema sylvestre*, *Pterocarpus marsupium*, Yashtimadhu, *Glycyrrhiza glabra*, *Casearia esculenta*, *Syzygium cumini*, *Asparagus racemosus*, *Boerhavia diffusa*, *Sphaeranthus indicus*, *Tinospora cordifolia*, *Swertia chirata*, *Tribulus terrestris*, *Phyllanthus amarus*, *Gmelina arborea*, *Gossypium herbaceum*, *Berberis aristata*, *Vidangadi lauham*, *Momordica charantia*, *Piper nigrum*, *Ocimum sanctum*, *Abutilon indicum*, *Rumex maritimus, Curcuma longa* | 326 | 0.02 |
| DT | *Syzigium cumin*, *Plectranthus Amboinicus*, *Andropogan Muricatus*, *Cinanamum zeylanicum*, *Anacyclus Pyrethrum,Cassia fistula*, *Strychnos potatorum*, *Cocculus cordifolius, Gymnema sylvestre* | 52 | 0.002 |
| SN | *Vachellia nilotica*, *Tinospora cordifolia*, *Catharanthus roseus*, *Momordica charantia*, *Andrographis pinculata*, *Gymnema sylvestre*, *Trigonella foenum-graecum*, *Azadirachta indica*, *Ficus racemosa*, *Ocimum tenuiflorum*, *Phyllanthus niruri*, *Cinnamomum verum, Curcuma longa*, *Picrorhiza kurrooa* | 16 | 0.006 |
| MA | *Momordica charantia* , *Syzygium cuminii*, *Mangifera indica*, *Gymnema sylvestre* | AL0041 | 0.015 |
| MH | *Pterocarpus marsupium, Salacia reticulata, Curcuma longa*, *Emblica officinalis*, *Momordica charantia*, *Tinospora cordifolia* | 1801 | 0.02 |

highest concentrations of macro-elements observed were as follows Ca (20,000±26.3 mg/kg), Mg (9600± 45.4 mg/kg), N (59,955±11.55 mg/kg), P (6544±20 mg/kg), and K (56,563.2±18 mg/kg) (Mohammad et al. 2020). The presence of macro-elements in APH is advantageous for the proper biochemical and physiological function of human health (Castillo-Sanchez et al. 1998). The levels of macro-elements detected in six APH were found within the permissible limit according to developed Dietary Reference Intakes (DRIs) (Institute of Medicine, Food and Nutrition Board 2001).

Following trace elements (Al, Mn, Fe, Zn, Mo, Cr, Si, Ti, Rb, Sr, Zr, Nb, Cd, Th, Pb, Bi, and U) were analyzed in the tested formulations. Toxicity levels of the trace elements detected in the formulations were assessed by EDI (Table 4) and THQ (Table 5) to analyze the risk associated with daily intake of the elements for a prolonged period of time (USEPA 1989). Though most of the elements detected were observed within permissible range, it fails to give an overview of any health threat hence, the EDI and THQ were also analyzed. EDI value gives an account of the elements ingested, according to the body weight and exposure period based on daily dosage of APH. THQ reports the assessment of health risks associated with consumption of the calculated EDI (USEPA 1989). In the present study, THQ of all elements were lower than unity except for Rb in MA which is in accordance with the previously reported study (Mensah et al. 2019).

Aluminum was detected in MA, SN, DB, and DT at a range of 1300ppm DB to 2900ppm DT which is in contrast with earlier reports of (3064 ppm) in *Borago officinalis* and 2839 ppm in *Viola odorata* (Kohzadi et al. 2018). Al is not considered toxic, however, a prolonged period of exposure may cause health complications such as central nervous system disorders and pulmonary fibrosis (Klotz et al. 2017). Manganese was detected in all six samples, ranging from 28 ppm in MH to 141 ppm in DT which was observed to be lower than previously reported study in *Alpinia officinalis* (Raju et al. 2006; Mohammad et al. 2020). Manganese, an essential trace element is associated with carbohydrate and fat metabolism, hence an important element for diabetes-related complications (Kirmani et al. 2011). Iron is an essential element for hemoglobin, muscle metabolism, and cellular functioning (Aggett 2012). Fe was detected in all six formulations ranging from 8740 ppm in DT to 100 ppm in MH, and results were contrary to previous reports in *Bunium persicum* (987±75.27 mg/kg) (Mohammad et al. 2020; Kulhari et al. 2013). The THQ of Al, Mn, and Fe was lower than 1 for the six APH assessed, hence the presence of these elements poses no potential threat to human health.

**Table 3** Decreasing order of elements detected in six APH

| Formulations | Decreasing order of elements detected |
|---|---|
| DT | K> Mg> Ca> Si> Fe> Al> P> S> Ti> Mn> Cd> Zn> Sr> Th> Rb> Mo> Zr> Nb |
| DB | Zn> Ca> K> Fe> Si> P> Al> S> Ti> Mn> Bi> Sr> Zr> Rb> Pb |
| BG | Ca> Si> K> P> S> Fe> Ti> Mn> Cd> Zn> Sr> Mo> Rb> Nb |
| MA | K> Ca> P> Al> Si> Fe> S> Mn> Cd> Zn> Rb=Sr> Zr> Nb |
| MH | Ca> P> K> Fe> Cr> Mn> Th> Zn> Nb> Mo> Sr> Zr=U> Rb |
| SN | Ca> K> P> Al> Fe> S> Si> Mn> Cd> Zn> Sr> Pb> Rb> Zr> Nb |

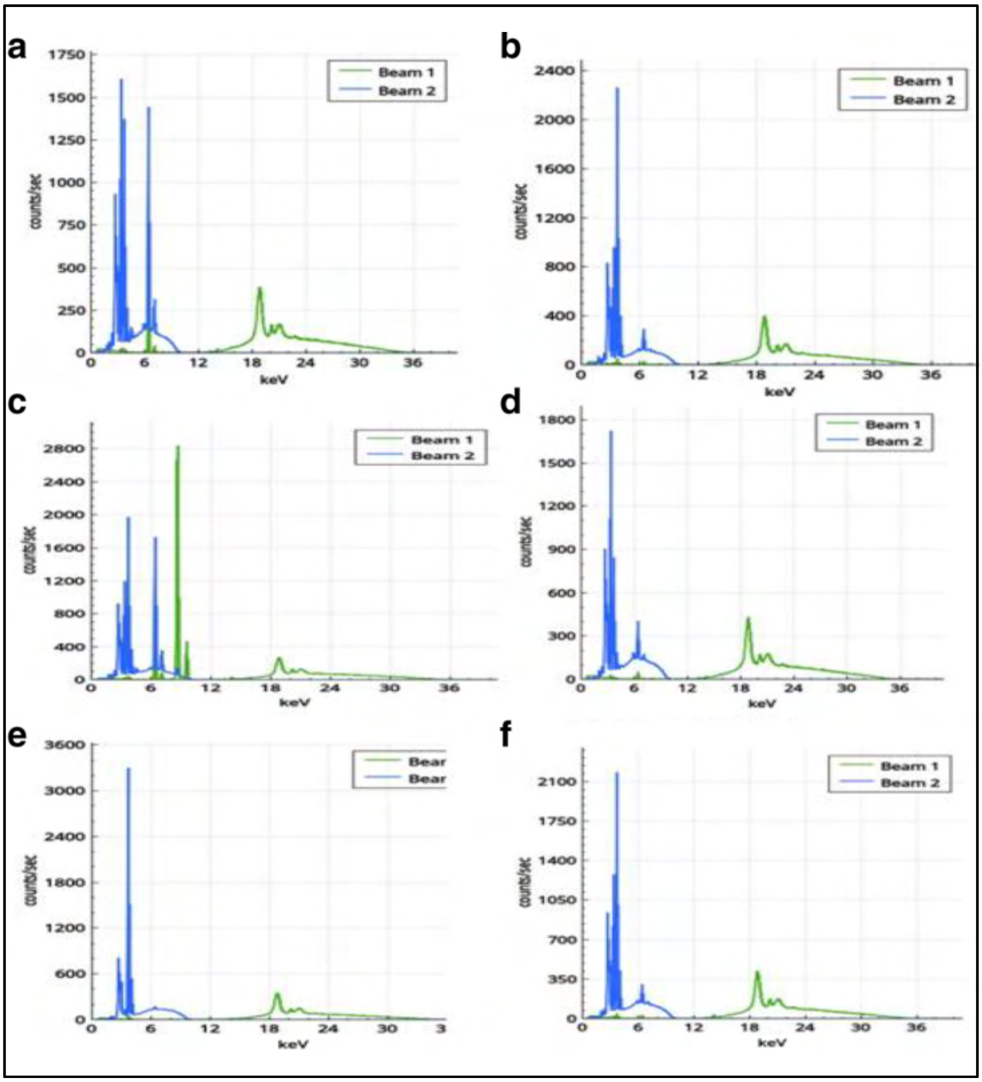


**Fig 1** a- f, X-Ray spectrum of Six Antidiabetic Polyherbal formulations by HH-XFR (Beam1: 12 to 36KeV and Beam2: 0-12 KeV)

Zinc is essential for catalytical activity and cellular metabolism, deficiency of zinc is associated with diabetes and disturbed immunity as it has no specialized storage system in our body, hence daily intake is crucial (Rink and Gabriel 2000; Hayter 1980). Zn was detected within tolerable limits of 27.4 ppm in all the tested APH, except for DB while calculated THQ was lower than unity for all APH tested, hence might not be considered as toxic for human health supporting previously reported values (Kulhari et al. 2013; WHO 2010). Molybdenum, an essential microelement is a cofactor for four enzymes, sulfite oxidase, xanthine oxidase, aldehyde oxidase, and mitochondrial amidoxime reducing component (mARC), toxicity is unusual with Mo intake (Hernández Rod et al. 2019). Mo was detected in MH (7ppm), DT (7ppm), and BG (6ppm) which was far below than the previous investigation on daily dietary intake(DDI) of 198.26 μg/day where major contributor for DDI was considered as legumes and cereals (Filippini et al. 2019). Chromium an essential element that is associated with enhanced glucose and insulin response was detected in MH (30 ppm) higher than the permissible limit of 20 ppm, Similar findings were reported in Haripur basin, Pakistan where the range of Cr detected was from 1.2–29.49 ppm (FAO/WHO 1984; Abdul et al. 2012). Higher level of Cr, when exposed for a prolonged period, can cause a severe health hazard, THQ of Cr was lower than unity which was an unexpected finding, hence can be concluded that the time of exposure and also dosage advised will not cause health hazard (Kohzadi et al. 2018).

In the present study, silicon was detected in all formulations except for MH at a range of (8960 ppm in BG to 430 ppm in SN) which was lower when compared to reported DDI of 40mg/day to 19mg/day for men and women respectively (Pennington 2009). Si has limited data on dietary and toxicities studies hence oral reference dose (RfD) and upper tolerable limit (Ul) were not set therefore THQ was not

**Table 4** Estimated daily intake of the elements detected in six APH

| Elements | DT | DB | BG | MA | MH | SN |
|---|---|---|---|---|---|---|
| **Mg** | 292571 | ND | ND | ND | ND | ND |
| **Al** | 82857 | 37143 | ND | 300000 | ND | 128571 |
| **Si** | 167429 | 225400 | 279496 | 274285.7 | ND | 36857 |
| **P** | 61429 | 61429 | 50308.6 | 445714 | 11142.8 | 199714 |
| **S** | 41485.7 | 32228.6 | 34649.1 | 172071 | ND | 43457 |
| **K** | 296000 | 272000 | 296182.9 | 2245714 | 9028.6 | 858857 |
| **Ca** | 217429 | 288571 | 368102.8 | 954428.6 | 290143 | 878571 |
| **Ti** | 14857 | 6857.1 | 7794.3 | ND | ND | ND |
| **Mn** | 4029 | 3257 | 3330.3 | 29357 | 400 | 6514 |
| **Fe** | 146857 | 249714 | 22426.3 | 204429 | 1429 | 56486 |
| **Zn** | 657 | 445714 | 637.7 | 4286 | 300 | 2229 |
| **Rb** | 229 | 429 | 212.6 | 2143 | 42.8 | 600 |
| **Sr** | 514 | 1257 | 460.6 | 2143 | 85.7 | 2143 |
| **Zr** | 200 | 429 | ND | 1714.3 | 57 | 429 |
| **Nb** | 114 | ND | 177.1 | 857.1 | 128.6 | 257 |
| **Mo** | 200 | ND | 212.6 | ND | 100 | ND |
| **Cd** | 857 | ND | 779.4 | 6857 | ND | 2657 |
| **Th** | 286 | ND | ND | ND | 100 | ND |
| **Cr** | ND | ND | ND | ND | 429 | ND |
| **Pb** | ND | 200 | ND | ND | ND | 600 |
| **Bi** | ND | 1371.4 | ND | ND | ND | ND |
| **U** | ND | ND | ND | ND | 57 | ND |

**Table 5** Target Hazard quotient (Risk level >1)

| Elements | DT | DB | BG | MA | MH | SN |
|---|---|---|---|---|---|---|
| **Mg** | 0.0005 | ND | ND | ND | ND | ND |
| **Al** | 0.0064 | 0.0289 | ND | 0.156 | ND | 0.01 |
| **P** | 6.80E-05 | 0.0007 | 5.50E-05 | 0.0033 | 2E-04 | 0.0002 |
| **S** | 7.10E-05 | 0.0005 | 5.90E-05 | 0.002 | ND | 7.40E-05 |
| **K** | 7.60E-05 | 7E-04 | 7.60E-05 | 0.004 | 4.60E-05 | 2E-04 |
| **Ca** | 0.0002 | 0.002 | 3E-04 | 0.0049 | 0.005 | 7E-04 |
| **Ti** | 2.30E-05 | 0.0001 | 1.20E-05 | ND | ND | ND |
| **Mn** | 0.001 | 0.011 | 0.001 | 0.067 | 0.003 | 0.002 |
| **Fe** | 0.014 | 0.243 | 0.002 | 0.133 | 0.003 | 0.006 |
| **Zn** | 4.60E-05 | 0.315 | 4.50E-05 | 0.002 | 4E-04 | 2E-04 |
| **Rb** | 0.034 | 0.629 | 0.031 | 2.108 | 0.126 | 0.088 |
| **Sr** | 7E-04 | 0.016 | 6E-04 | 0.019 | 0.002 | 0.003 |
| **Nb** | 1E-04 | ND | 0.004 | 0.007 | 0.003 | 3E-04 |
| **Mo** | 0.003 | ND | 0.01 | ND | 0.035 | ND |
| **Cd** | 0.002 | ND | 0.002 | 0.119 | ND | 0.007 |
| **Cr** | ND | ND | ND | ND | 0.333 | ND |
| **Pb** | ND | 0.389 | ND | ND | ND | 0.117 |
| **U** | ND | ND | ND | ND | 0.741 | ND |

calculated for Si (Institute of Medicine, Food and Nutrition Board 2001).

Titanium was detected in DT, DB, and BG (520ppm, 220ppm, and 240ppm respectively) which was in accordance with the previous study (Filippini et al. 2019). Scattered data on Ti intake has no toxicity reports, as Ti is not absorbed by the gastrointestinal track, therefore, might not pose any health-related risk (Filippini et al. 2019; Reilly 2002). Rubidium was detected in all the samples with THQ less than unity except for MA where THQ was calculated to be 2.1082. The biochemical and physiological foundation of Rb bears resemblance to potassium, compounds of Rb has been used in the treatment of antidepressant and goiter (Wagner 2011; USEPA 2016). Strontium was detected in all the six formulations at a range of 2142 ppm in SN to 85.7 ppm in MH comparable with a previous study (Millour et al. 2012) whereas our findings were lower than the reported DDI of 1.93mg/day (Filippini et al. 2019). Sr is associated with impaired bone formation and mineralization, THQ was lower than 1 in all tested APH therefore can be considered safe from health risk (Farsalinos et al. 2015; Koubová et al. 2018). Zirconium was detected in all the APH except for BG, which was observed to be lower than the permissible limit of 5000 μg/m$^3$ established by NIOSH (Farsalinos et al. 2015). THQ was not calculated due to the lack of studies on RfD and upper tolerable limits. Niobium has not been reported as toxic to any of the human studies as it is reported to be excreted in the urine, it has been detected in the range of 9 ppm (MH) to 3 ppm (SN) which is contrary to the reported DDI of 620μg and no chronic toxicities to human (Carson Bonnie 2018).

Cadmium has no role in human health benefits but it is of major concern as it can cause common food poisoning, osteopenia, anemia, severely affects brain metabolism, prostate cancer, liver disorder, lung damage, kidney failure, and a disease Itai-itai (Renal tubular induced osteomalacia) (Singh et al. 2014). Cd was detected in DT (30 ppm), MA (32ppm), BG (22 ppm), and SN (31ppm), which was contradictory to the previous report (Mensah et al. 2019). Our findings were within the maximum residual limit (MRL) of Cd (60 ppm) which was obtained from the literature (Mensah et al. 2019). Thorium was detected in DT and MH which was contradictory to previous reports (Iyengar et al. 2004). Due to the lack of previous studies on human intake, Th THQ was not calculated. Lead is considered as highly toxic heavy metals that can accumulate in tissues including blood and bone, also cause behavioral abnormalities, and hence tagged as a neurotoxin (Tülay et al. 2009). Pb is detected in SN and DB at a concentration of 7ppm which was in accordance with previous reports of Haripur basin, Pakistan (Abdul et al. 2012). APH tested were found to be within permissible limits of 10 ppm, also THQ was lower than unity therefore can be considered as devoid of Pb associated health risk (WHO 2010). Uranium was detected in MH (4ppm) within permissible range and THQ lower than one (Filippini et al. 2019). Bismuth was detected at 48 ppm in DB. It is used in the treatment of ulcers and can be toxic to the human when exposed to overdose for a prolonged time. Due to the lack of scientific data, RfD was not set for Bi, therefore, THQ was not calculated (Dolara 2014).

The percentage contribution of the elements detected is represented in Fig 2. Among all elements, the maximum percentage of Th, Cr, and Pb were detected in DT, MH, and SN respectively whereas Rb accounts for the highest percentage in DB, BG, and MA and hence can be concluded as major contaminants in the respective APH.

Though there is increased usage of these polyherbal formulations, the safety and efficacy pose a great concern as they contain different impurities including heavy metals and trace elements in higher concentrations which are regarded as contaminants. Collection and unscientific processing conditions of raw material might lead to heavy metal contamination (Kohzadi et al. 2018). For valuation of herbal formulation WHO in 1998 has laid detailed guiding principle in effective production, which includes elemental assessment of the products. As the Indian population is predominantly affected by DM, it is necessary to assess the quality of antidiabetic herbal formulations. Lack of regular pre and post-preparative surveillance of polyherbal formulations in India results in data gaps regarding the same (Mensah et al. 2019). Therefore, the present study is focused to evaluate the level of elemental concentration and its health risk assessment in selected APH to assure their quality.

## Conclusion

In India, a large number of people relies on herbal source of medicine for management of DM; therefore, the present study was set to assess levels of macro-elements, micro-elements, and heavy metals in six selected APH. The results revealed presence of a wide range of elements in APH tested indicating

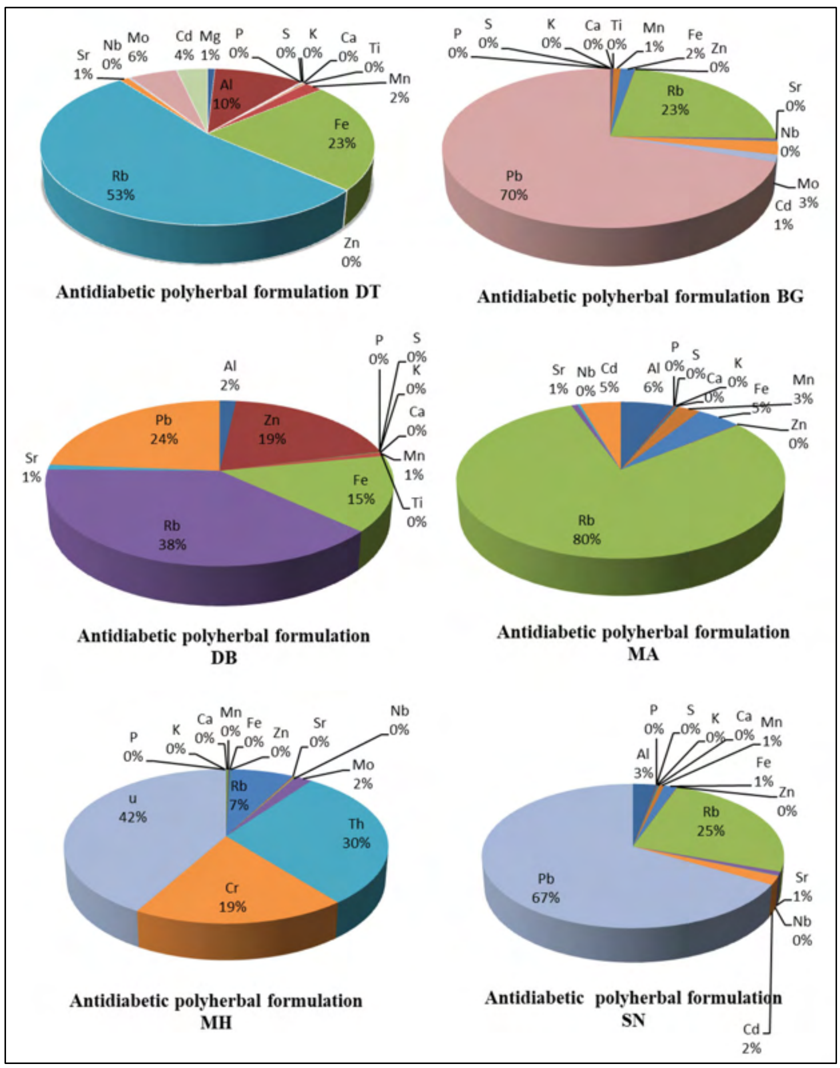


**Fig 2** Percentage contribution of each element to the Target Hazard Quotient of six APH

mainly on environmental pollution and lack of safety assessment for commercial herbal formulations. Among the six tested APH, MH, DB, DT, SN, and BG were found to be devoid of any health risk associated with reference to THQ. The presence of elements such as K, Ca, Mn, Zn and Cr are one of the most significant findings of our study as these elements are associated with stimulation of insulin action and hence might help in management of DM. THQ for Rb in MA was found to be more than unity which can pose threat when exposed for a longer duration. Therefore, stringent guidelines are vital for the preparation of herbal formulation to avoid a high concentration of elements and their related toxicities. A premarketing safety screening of these herbal formulations should be made mandatory. For evaluating the quality of herbal formulations, health risk assessment regarding elements present in the formulation can be considered as essential criteria that would give a valuation regarding the formulations.

**Authors Contribution** Authors confirms all research are done by authors. Saptadipa Paul carried out the health risk assessment and constructed the manuscript; Daisy joseph has assessed the samples for elemental analysis using HH-XRF; Mala Majumdar supervised the work and edited the manuscript.

**Availability of Data and Material** Authors support their claim and comply with field standards

## Declarations

**Ethics approval** Not applicable

**Consent to participate** Not applicable

**Consent to publish** Not applicable

**Conflict of interest** The authors declare that they have no conflict or competing interest.

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