Research Article

Pilot Study of Trace Elements in the Infusion of Medicinal Plants Used for Diabetes Treatment

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1.Introduction

The existence of many essential human nutrients, including elements in plants, enables them to significantly affect human health. It is known that the excess or deficiency of essential elements critically affects biochemical processes within the human body. The amount of elements varies among plants; thus, plants with considerable content are termed ‘medicinal plants.’ Medicinal plants are used as starting materials to produce medications. In addition, they can be used directly prior to any chemical therapy to treat certain diseases [1]. This direct usage of fresh plants has a long history in human medicine. It has been reported that 70–80% of the global population use medicinal plants as an alternative medicine to treat some types of diseases [2]. Therefore, medicinal plants are important for pharmacological research and drug production, and many diseases are treated with alternative medicine today, especially in areas enriched with medicinal plants.

One of the major and growing contemporary health concerns is diabetes mellitus (DM). The figures of affected people are widely debated; however, according to World Health Organization (WHO) data, the disease affects about 200 million of the world’s population. In Saudi Arabia, a recent study concluded that about 30% of the population were afflicted with diabetes [3]; hence, the disease represents a global as well as a local health problem. The disease is associated with unnatural levels of glucose in the blood, as a result of the unusual function of beta cells in the pancreas [4]. Glucose levels in the blood are controlled through the
hormone insulin. Therefore, the deficiency of insulin and/or the ineffectiveness of the insulin produced are the main causes that disturb the metabolic process in diabetes; this results in the sugar present in the blood [5]. It has been claimed that deviations in the metabolism of some trace elements, such as Cu, Zn, Mg, and Mn, are associated with diabetes [6]. Researchers have concluded that some trace elements, such as copper, zinc, selenium, and manganese, may help in protecting the insulin-secreting pancreatic β-cells [7]. Therefore, the quantification of trace elements in medicinal plants used by local diabetic people can provide useful information about the safety of utilization and the effectiveness of such herbal medicine.

In the present study, fourteen trace elements concentrations were determined in five antidiabetic medicinal plants used by local diabetic residents in the Asir region using the inductively coupled plasma mass spectrometry (ICP-MS) technique. The purpose of this study was to determine both essential and toxic trace elements in five antidiabetic medicinal plants. Additionally, they were evaluated as sources of both types of elements, and the efficacy of their use was based on elemental analysis.

2. Methods

2.1. Samples’ Collection and Pretreatment. Five types of medicinal plants were collected from local markets (Attar’s shops) in the cities of Khamis Mushait and Abha, Saudi Arabia. These medicinal plants are traditionally used for diabetic treatments. The types of medicinal plants sampled were Tut leaves (Mulberry), olive leaves (Olea europaea), clove (Syzygium aromaticum), Luban Dhakar (Boswellia carterii), and Karela or bitter melon (Momordica charantia). In total, nine samples were collected and pretreated for elemental measurements. All plants are presented in Table 1.

2.2. Infusion of the Samples. One gram from each plant type was boiled in deionized water for 10 minutes and made up to 50 mL. The infusion (filtrate solution) was filtered with a 0.45 µm filter millipore before elemental analysis. Only Karela was dried in an oven overnight at 70°C and then powdered, before following the same procedure. This is because Karela’s samples were wet, while other plants’ samples were dry.

2.3. Chemicals and Reagents. A single-stock solution mixture of 27 elements at a concentration of 10 µg/mL (Agilent Technologies, USA) was used for standards preparation. Calibration standards 2, 10, 20, 40, and 100 µg/L were prepared by dilution with 1% HNO3.

2.4. Elemental Analysis Using Inductively Coupled Plasma Mass Spectrometry (ICP-MS). In total, fourteen elements were measured in all collected samples. Concentrations of the fourteen elements—aluminum (Al), chromium (Cr), manganese (Mn), iron (Fe), cobalt (Co), nickel (Ni), copper (Cu), zinc (Zn), arsenic (As), selenium (Se), strontium (Sr), cadmium (Cd), barium (Ba), and lead (Pb)—were measured in each sample by Agilent 7900 ICP-MS at De Montfort University, United Kingdom. Samples were divided into two parts and analyzed in duplicate (n = 4). Oxide ratios and double-charge ratios were 2.5% and 1.1%, respectively. The Agilent 7900 ICP-MS operating conditions are presented in Table 2.

2.5. Quality Control. A method was validated for all measured elements; limits of detection (LODs) and limits of quantification (LOQs) were calculated. LOD = Xb1 + 3Sb1 and LOQ = Xb1 + 10Sb1, where Xb1 is the mean concentration of the blank and Sb1 is the standard deviation of the blank (deionized water). LODs and LOQs (expressed in µg/L) for the measured elements were Al (6.24 and 20.8), Cr (0.09 and 0.3), Mn (1.26 and 4.2), Fe (15.1 and 49.5), Co (0.04 and 0.11), Ni (0.38 and 1.15), Cu (1.05 and 3.5), Zn (1.38 and 4.6), As (0.17 and 0.45), Se (0.27 and 0.9), Sr (3.54 and 11.8), Cd (0.03 and 0.08), Ba (2.31 and 7.7), and Pb (0.66 and 2.2).

The LODs and LOQs for elements were treated the same as samples ((µg/L * 0.05 L)/1g). Therefore, the LODs and LOQs for the real samples (expressed in µg/g) are as follows: Al (0.312 and 1.04), Cr (0.005 and 0.015), Mn (0.063 and 0.21), Fe (0.755 and 2.475), Co (0.002 and 0.006), Ni (0.019 and 0.058), Cu (0.053 and 0.175), Zn (0.069 and 0.23), As (0.009 and 0.023), Se (0.014 and 0.045), Sr (0.177 and 0.59), Cd (0.002 and 0.004), Ba (0.116 and 0.385), and Pb (0.033 and 0.11).

Quality control checks were performed by measuring 50 µg/L of mixed elements three times after each batch of five samples. Recoveries (%) of triplicate measurements of each element were as follows: Al (92.7), Cr (103.7), Mn (102.9), Fe (115.9), Co (107.6), Ni (110.3), Cu (108.6), Zn (149.2), As (125.7), Se (110.7), Sr (115.3), Cd (117.2), Ba (131.6), and Pb (115.5). High recoveries revealed from Zn, As, and Ba are not surprising, since measurements were spread over 15 samples (3x after each batch of 5 samples).

2.6. Quality Assurance. A 50 µg/L mixed standard was spiked in a sample and the obtained recoveries (%) were as follows: Al (93.3), Cr (92.4), Mn (92.9), Fe (85.6), Co (94.4), Ni (92.8), Cu (108.6), Zn (95.3), As (97.9), Se (96.5), Sr (93.7), Cd (93.6), Ba (95.8), and Pb (93.4). Actually, we had no CRM to be used to assess the accuracy of the method, specifically for infusion method. Therefore, recoveries range between 93 and 109% are used instead.

| Table 1: The studied plant species and the parts used for both diabetes treatment and analysis |
|---------------------------------|-----------------|----------------|
| Scientific name                  | Common name     | Used part   |
| Mulberry                        | Tut             | Leaves      |
| Olea europaea                   | Olive           | Leaves      |
| Syzygium aromaticum            | Clove           | Seeds       |
| Boswellia carterii              | Luban Dhakar    | Gum         |
| Momordica charantia             | Karela          | Fruit       |

| Scientific name                  | Common name     | Used part   |
|---------------------------------|-----------------|-------------|
| Olive                           | Olive           | Leaves      |
| Syzygium aromaticum            | Clove           | Seeds       |
| Boswellia carterii              | Luban Dhakar    | Gum         |
| Momordica charantia             | Karela          | Fruit       |

| Scientific name                  | Common name     | Used part   |
|---------------------------------|-----------------|-------------|
| Olive                           | Olive           | Leaves      |
| Syzygium aromaticum            | Clove           | Seeds       |
| Boswellia carterii              | Luban Dhakar    | Gum         |
| Momordica charantia             | Karela          | Fruit       |

| Scientific name                  | Common name     | Used part   |
|---------------------------------|-----------------|-------------|
| Olive                           | Olive           | Leaves      |
| Syzygium aromaticum            | Clove           | Seeds       |
| Boswellia carterii              | Luban Dhakar    | Gum         |
| Momordica charantia             | Karela          | Fruit       |

| Scientific name                  | Common name     | Used part   |
|---------------------------------|-----------------|-------------|
| Olive                           | Olive           | Leaves      |
| Syzygium aromaticum            | Clove           | Seeds       |
| Boswellia carterii              | Luban Dhakar    | Gum         |
| Momordica charantia             | Karela          | Fruit       |

| Scientific name                  | Common name     | Used part   |
|---------------------------------|-----------------|-------------|
| Olive                           | Olive           | Leaves      |
| Syzygium aromaticum            | Clove           | Seeds       |
| Boswellia carterii              | Luban Dhakar    | Gum         |
| Momordica charantia             | Karela          | Fruit       |

| Scientific name                  | Common name     | Used part   |
|---------------------------------|-----------------|-------------|
| Olive                           | Olive           | Leaves      |
| Syzygium aromaticum            | Clove           | Seeds       |
| Boswellia carterii              | Luban Dhakar    | Gum         |
| Momordica charantia             | Karela          | Fruit       |

| Scientific name                  | Common name     | Used part   |
|---------------------------------|-----------------|-------------|
| Olive                           | Olive           | Leaves      |
| Syzygium aromaticum            | Clove           | Seeds       |
| Boswellia carterii              | Luban Dhakar    | Gum         |
| Momordica charantia             | Karela          | Fruit       |

| Scientific name                  | Common name     | Used part   |
|---------------------------------|-----------------|-------------|
| Olive                           | Olive           | Leaves      |
| Syzygium aromaticum            | Clove           | Seeds       |
| Boswellia carterii              | Luban Dhakar    | Gum         |
| Momordica charantia             | Karela          | Fruit       |

| Scientific name                  | Common name     | Used part   |
|---------------------------------|-----------------|-------------|
| Olive                           | Olive           | Leaves      |
| Syzygium aromaticum            | Clove           | Seeds       |
| Boswellia carterii              | Luban Dhakar    | Gum         |
| Momordica charantia             | Karela          | Fruit       |

| Scientific name                  | Common name     | Used part   |
|---------------------------------|-----------------|-------------|
| Olive                           | Olive           | Leaves      |
| Syzygium aromaticum            | Clove           | Seeds       |
| Boswellia carterii              | Luban Dhakar    | Gum         |
| Momordica charantia             | Karela          | Fruit       |
The frequency of use was considered as one. Each plant as mentioned above. We considered the number of grams in one dose of different quantities (g) of elements included in the specific medicinal plants. We inferred that Karela is a natural accumulator of both essential and toxic elements. Therefore, Karela is considered a major source of exposure to both types of elements. One dose of Karela contained high percentages of Al (120%), Mn (64%), Co (73%), Cu (101%), As (125%), Se (214%), Cd (304%), and Pb (1157%), calculated against the PMTDI. Therefore, an infusion of Karela contains high concentrations of essential and toxic elements, which lead to health harm if used for treatment. A recent study suggested the use of Karela for diabetic treatment due to the high Zn contents [20]. However, the limitation of this study was that it was not comprehensive and only focused on the investigation of one essential element. The study did not investigate the contents of toxic elements in Karela, which cause adverse health effects in humans. Holistic studies including both types of elements are always required to ensure the safe use of such medicinal plants, regarding the levels of toxic metals [21]. Notably, high levels of both essential and toxic elements can cause negative health implications, such as mutagenic effects in humans, reduced growth, morphological abnormalities, and increased mortality [22]. Therefore, paper [20] is suitable for pharmacological research, to extract and use specific protein fractions of the plant. However, their study approach is only suitable for conventional uses of medicinal plants, whereas diabetic patients use the whole plant.

Our results showed that one dose (1.98 g) of ground clove contributed to 66.3% of Mn of the PMTDI. This agrees...
Table 3: Average concentrations (µg/g) of fourteen measured elements in five types of medicinal plants, mean ± SD (n = 4) with a 95% confidence level. The infusion was one gram of each plant boiled in deionized water for ten minutes.

| Element | Karela | Clove | Luban Dhakar | Olive leaves | Tut leaves |
|---------|--------|-------|--------------|--------------|------------|
| Al      | 39.18 ± 1.27 | 4.21 ± 0.34 | 2.94 ± 1.13 | 3.13 ± 1.50 | 2.73 ± 0.85 |
| Cr      | 3.85 ± 0.22  | 0.05 ± 0.01 | 0.08 ± 0.00 | 0.06 ± 0.01 | 0.07 ± 0.02 |
| Mn      | 251.40 ± 8.41 | 736.36 ± 40.42 | 3.13 ± 0.22 | 14.44 ± 2.64 | 12.20 ± 2.27 |
| Fe      | 671.13 ± 11.02 | 4.26 ± 0.15 | 6.98 ± 0.03 | 4.87 ± 1.93 | 6.64 ± 1.39 |
| Co      | 1.20 ± 0.02  | 0.03 ± 0.00 | 0.02 ± 0.00 | 0.06 ± 0.05 | 0.08 ± 0.03 |
| Ni      | 64.39 ± 4.63  | 4.25 ± 0.39 | 1.62 ± 0.12 | 3.06 ± 1.24 | 7.31 ± 2.12 |
| Cu      | 54.64 ± 4.28  | 3.55 ± 0.22 | 12.70 ± 0.53 | 1.65 ± 0.12 | 2.55 ± 0.40 |
| Zn      | 103.78 ± 7.59 | 5.97 ± 4.49 | 2.30 ± 1.74 | 5.80 ± 3.94 | 9.09 ± 6.68 |
| As      | 0.57 ± 0.02  | 0.05 ± 0.01 | 0.04 ± 0.01 | 0.04 ± 0.01 | 0.12 ± 0.05 |
| Se      | 2.18 ± 0.16  | 0.11 ± 0.01 | 0.09 ± 0.05 | 0.12 ± 0.07 | 0.21 ± 0.03 |
| Sr      | 60.97 ± 1.44  | 4.74 ± 0.06 | 61.72 ± 4.25 | 3.85 ± 1.30 | 67.39 ± 5.86 |
| Cd      | 0.33 ± 0.01  | < LOD      | 0.02 ± 0.01 | 0.01 ± 0.01 | < LOD      |
| Ba      | 13.10 ± 0.32 | 3.57 ± 0.23 | 56.95 ± 1.37 | 1.25 ± 0.38 | 3.38 ± 0.92 |
| Pb      | 4.48 ± 0.02  | 0.36 ± 0.05 | 0.93 ± 0.01 | 0.15 ± 0.03 | 0.20 ± 0.01 |

Table 4: Exposure (µg) to each element related to a specific plant, based on the number of grams used in each dose of a plant. Provisional maximum tolerable daily intake (PMTDI).

| Element | Karela | Clove | Luban Dhakar | Olive leaves | Tut leaves | PMTDI (µg/day) | Reference |
|---------|--------|-------|--------------|--------------|------------|----------------|-----------|
| Al      | 361.27 ± 9.90 | 8.33 ± 0.68 | 22.97 ± 16.59 | 12.63 ± 11.74 | 6.48 ± 2.02 | 143–7000       | [8]       |
| Cr      | 35.53 ± 1.71 | 0.10 ± 0.03 | 0.59 ± 0.04  | 0.23 ± 0.06  | 0.17 ± 0.04 | 100            | [9]       |
| Mn      | 2317.94 ± 65.63 | 1458.00 ± 80.04 | 24.38 ± 1.75 | 58.35 ± 20.62 | 28.91 ± 5.39 | 1800–2200      | [10]      |
| Fe      | 6187.86 ± 85.99 | 8.44 ± 0.30 | 54.45 ± 0.25 | 19.66 ± 15.08 | 15.74 ± 3.29 | 11000         | [11]      |
| Co      | 11.04 ± 0.17 | 0.06 ± 0.01 | 0.16 ± 0.01  | 0.24 ± 0.35  | 0.19 ± 0.08 | 5–8            | [12]      |
| Ni      | 593.68 ± 36.15 | 8.41 ± 0.76 | 12.62 ± 0.97 | 12.38 ± 9.65 | 17.33 ± 5.04 | 1000          | [13]      |
| Cu      | 503.78 ± 33.40 | 7.02 ± 0.43 | 99.07 ± 4.16 | 6.68 ± 0.96  | 6.04 ± 0.95 | 500            | [14]      |
| Zn      | 956.81 ± 59.21 | 11.82 ± 8.90 | 17.98 ± 13.57 | 23.43 ± 30.73 | 21.54 ± 15.83 | 1000          | [15]      |
| As      | 5.26 ± 0.18  | 0.09 ± 0.02 | 0.28 ± 0.06  | 0.18 ± 0.06  | 0.28 ± 0.12 | 0.42           | [16]      |
| Se      | 20.12 ± 1.23 | 0.21 ± 0.03 | 0.68 ± 0.36  | 0.47 ± 0.55  | 0.49 ± 0.08 | 70             | [17]      |
| Sr      | 562.17 ± 11.23 | 9.38 ± 0.13 | 481.43 ± 33.19 | 15.57 ± 10.13 | 159.72 ± 13.88 | 1900          | [18]      |
| Cd      | 3.04 ± 0.08  | 0.00 ± 0.00 | 0.13 ± 0.06  | 0.03 ± 0.08  | 0.01 ± 0.01 | 1              | [19]      |
| Ba      | 120.80 ± 2.47 | 7.07 ± 0.46 | 444.24 ± 10.67 | 5.06 ± 2.99  | 8.00 ± 2.19 | 750 (200)      | [18, 19]  |
| Pb      | 41.31 ± 0.17 | 0.70 ± 0.11 | 7.25 ± 0.07  | 0.60 ± 0.27  | 0.48 ± 0.02 | 3.57           | [9]       |

Figure 1: Amount (µg) of each element in each dose of a plant: (a) essential elements and (b) toxic elements.
with other reports, which have stated that this plant contributes to 55–63% of the daily value (DV) in one teaspoon (≥2 g) of ground cloves [23, 24].

Many studies have suggested that Mn, Cu, Zn, and Cr are responsible for the secretion of insulin from the beta cells of the islets of Langerhans and are involved in increasing the ability of insulin action [25, 26].

Mn was found in high concentrations in Karela and clove (Table 3). This requires further investigation; as in a previous study [27], it is indicated that manganese plays a role in immunity through the regulation of blood sugar and cell energy. In addition, Mn is essential for the synthesis and secretion of insulin, and a lack of this element may reduce insulin discharge and alter carbohydrate and lipid metabolism [28]. The contents of Mn in the five medicinal plants in decreasing order were as follows: clove > Karela > olive leaves > Tut leaves > Luban Dhakar (Table 3).

Zinc, copper, and chromium play significant roles, along with calcium and manganese, in glucose tolerance factor (GTF), which affects the level of glucose in the blood by regulating insulin [29]. Interestingly, the levels of Zn in olive leaves and cloves were about the same, whereas Tut leaves presented the highest and Luban Dhakar presented the lowest levels. The plant contents of elemental copper were similar for clove, olive leaves, and Tut leaves, with Karela presenting the highest levels, followed by Luban Dhakar, as shown in Table 4. For chromium, the highest concentration was found in Karela, which was 50–80-fold higher than Cr contents in the other four plants, all of which had similar concentrations (Table 4). Therefore, our results showed that the highest concentration of Cr was in the Karela infusion, which is promising for it to be suitable for diabetes treatment, due to the role of Cr in reducing glyced hemoglobin (HbA1c) in type 2 diabetic patients [30].

A recent study encouraged the use of Karela as an antidiabetic treatment due to high Cr contents [31]. Moreover, based on their speculation analysis, they reported that high Cr contents are bound to protein fractions. However, more speculation analysis is needed to determine which species (Cr (III) or Cr (VI)) of Cr is most present in Karela’s protein fractions. This is because exposure to Cr (VI) poses a toxic risk to human health [32], whereas Cr (III) is essential for human health, improving glucose tolerance [33].

Elemental selenium is a well-known antioxidant and thus may help in reducing the health risks associated with insulin irregularities [34]. Selenium content was found to be high in Karela, up to 22-fold greater than the other four plant contents. However, the concentration of Se in all plants was lower than the guidelines set by the WHO. It has been reported experimentally that some Se compounds behave similarly to insulin, demonstrating a positive link between higher selenium levels and the prevalence of diabetes [35, 36]. A recent study investigated the effects of Se supplements on glucose homeostasis. The study concluded that Se might affect the control of blood sugar at different levels of regulation, associated with insulin signaling, glycolysis, and pyruvate metabolism [37]. Jablonska et al. concluded their study with an open question; the exact effects of selenium supplementation on glucose homeostasis and diabetes risk remain unclear.

The presence of large quantities of toxic elements (As, Al, Cd, and Pb) in Karela and Luban Dhakar exceeded the PMTDI, the allowance level recommended by the WHO (Table 4). These high levels of toxic elements represent a serious health risk for patients who use these plants for diabetic treatment. It has been reported that heavy metals such as lead, arsenic, and cadmium contribute toward the binding of β-cells in the pancreas and thus stimulate an autoimmune reaction to β-cells through the actual destruction of β-cells. In particular, lead is bonded to proteins that could induce morphological changes in the body [29]. A previous study [38] reported a significant positive correlation between blood lead concentrations and fasting blood glucose, which led them to infer that there is a possible association between Pb exposure and diabetes. A recent study [39] investigated the association between arsenic exposure and diabetes; the authors concluded that exposure to arsenic was linked to the development of diabetes. Another study [40] suggested that exposure to arsenic causes oxidative stress, which, in turn, causes β-cell dysfunction and glucose homeostasis, and then induces diabetes, although this remains a hypothesis. It was found that aluminum toxicity causes adverse diabetic effects, in a study that investigated the effects of diabetes mellitus and aluminum toxicity [41]. A previous study [42] investigated the effect of aluminum exposure on rats’ testicular tissue. This study concluded that the exposure to aluminum exacerbated diabetes-induced testicular lesions and impaired male reproductive variables in Wistar rats. A recent study [43] investigated the effects of cadmium exposure in rats and concluded that Cd exposure might increase the risk of diabetes. It was also inferred that exposure to cadmium decreased the activity of liver glucokinase, which affects sugar regulation. In a review article [44], groups of studies demonstrated that exposure to Cd affects adipose tissue, which leads to insulin resistance and enhances diabetes.

We measured two elements (Ba and Sr) considered as nonessential in medicinal plants. However, strontium is essential for bone metabolism [45]. Our results showed that Ba exceeded the PMTDI (200 ug) set by the Scientific Committee on Health and Environmental Risks [46] in Luban Dhakar (Table 4). Barium salts (BaSO4 and BaCO3) have a role in diabetes therapy. As concluded by a very recent study [47], an in vivo study on rats has proven the effectiveness of barium salts in controlling hyperglycemia after oral ingestion. This leads us to conclude that Luban Dhakar is an effective traditional treatment for diabetes based on its high Ba content, which could be used to manage blood sugar...
levels. Another study [48] concluded that plasma strontium was inversely associated with diabetes and impaired glucose regulation. Their study was yet to explore the mechanism which linked high Sr contents with low blood glucose levels in diabetic patients. Another study showed that strontium has anti-diabetic effects by reducing blood glucose levels and improving the tolerance to insulin in diabetic mice [49]. Based on the conclusions of these studies, we can infer that Ba and Sr can be considered for diabetes treatment.

In fact, a comprehensive analysis is needed, including compound and speciation analyses, to guarantee the safety of the global community using these medicinal plants. Our conclusion is based on an elemental analysis point of view; however, more research is required to confirm our findings and to enhance the understanding of the health benefits and harmful effects of these medicinal plants. We recommend that future studies investigating such plants should cultivate them in clean soil supplied with water free from contamination (i.e., a controlled growth area) to ensure that results are not influenced by external parameters.

5. Conclusion

This study measured fourteen elements, including essential, nonessential, and toxic elements, in five medicinal plants. In a traditional dose of these plants for diabetes treatment, some plants exhibited high concentrations of some elements, exceeding the PMDTI. Karela displayed the highest contents for both essential (Mn, Co, Cu, and Se) and toxic elements (Al, As, Cd, and Pb), followed by clove for Mn and Luban Dhakar for Pb. Therefore, we advise against the use of Karela, clove, and Luban Dhakar as traditional anti-diabetic treatments. However, we cautiously recommend the use of the two other medicinal plants (olive leaves and Tut leaves) based on their low levels of essential and toxic elements, which did not exceed the guideline values. Further studies, including compound analysis, are required for these medicinal plants to confirm the safety of the continued traditional usage of these plants for diabetes treatment. Also for future studies, the physiochemical properties of soil where these plants grow such as soil pH and organic matter will be of interest to assess and their extent to uptake from soil.

Data Availability

By sharing the data included in our manuscript, we help in sharing knowledge with researchers in the wider scientific community.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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