***Original Research Article***

**Quantitative Estimation of Chromium, Zinc and Manganese in Anti-Diabetic Plants: A Novel Approach to Diabetic Treatment**

**ABSTRACT**

**Background:**

The goal is to assess the levels of manganese, zinc, and chromium in ten antidiabetic plants and assess their potential in improving glucose metabolism via interactions with bioactive compounds.

**Methods:**

Plant specimens were collected from the Sathuragiri hill area and the Kalasalingam University campus, followed by drying, grinding, and ashing. The elemental analysis was performed using Atomic Absorption Spectroscopy (AAS) to quantify the concentrations of manganese, zinc, and chromium in the plant materials. Calibration standards were utilized to ensure precision in the measurements. The study analyzed trace element levels across different plant species.

**Results:**

The analysis of trace element concentrations revealed that *Hygrophila auriculata*, *Withania somnifera*, *Phyllanthus amarus*, *Careya arborea*, and *Andrographis paniculata* exhibited the highest levels of manganese. Additionally, *Syzygium cumini*, *Withania somnifera*, *Phyllanthus amarus*, *Aerva lanata*, and *Andrographis paniculata* showed the highest concentrations of zinc. In terms of chromium, *Caesalpinia bonducella*, *Andrographis paniculata*, *Gymnema sylvestre*, *Aerva lanata*, and *Careya arborea* demonstrated the greatest levels of this element. These trace elements are recognized for their roles in enhancing insulin sensitivity, glucose uptake, and metabolic regulation.

**Conclusions:**

The elevated concentrations of manganese, zinc, and chromium found in *Withania somnifera, Andrographis paniculata, Phyllanthus amarus*, *Aerva lanata*, *and Careya arborea* indicate their increased potential for diabetes management. These trace metals, when combined with the plants' phytoconstituents, may work together to improve glycemic control. Additional research is necessary to clarify the molecular mechanisms behind these effects and to investigate the possibility of developing natural plant-based treatments for diabetes management.

**Keywords:** Trace element, Manganese, Diabetic mellitus, Chromium, Zinc, Atomic absorption spectroscopy.

# INTRODUCTION

Diabetes mellitus (DM) is the most common endocrine condition impacting over 100 million individuals globally (6% of the population). It occurs due to a deficiency or ineffective production of insulin by the pancreas, leading to fluctuations in blood glucose levels. This condition can harm multiple body systems, especially the blood vessels, eyes, kidneys, heart, and nerves (Deshmukh and Jain, 2015). The International Diabetes Federation (IDF) approximates that there are around 40.9 million people with diabetes in India, a figure expected to rise to 69.9 million by 2025 (Singh et al., 2016). Type 1 diabetes can develop at any age, though it is uncommon within the first year of life. In most demographics, the incidence gradually rises with age until puberty, with an increased occurrence observed in individuals aged 35 years and older. Globally, around half (50%) of people aged 20 to 79 years with diabetes are unaware of their condition, although this statistic varies by region, with systematic or opportunistic screening opportunities ranging from a third undiagnosed in high-income countries to over 75% undiagnosed in low-income countries (Forouhi and Wareham, 2019). In terms of undiagnosed cases, India ranked first worldwide in 2011, with 31 million individuals. In Europe, the top five countries with undiagnosed cases include Russia with 4.5 million, followed by Germany with 1.8 million, Italy with 1.3 million, Turkey with 1.2 million, and France with 1.1 million (Vlad and Popa, 2012). Projections indicate that the number of people living with diabetes will rise to 300 million by 2025 and 366 million by 2030, up from 171 million in 2000. Most of these increases will take place in developing nations. Type 2 diabetes mellitus accounts for more than 90% of diabetes cases, with a higher percentage observed among older and urban populations (Animaw and Seyoum, 2017; Lovic et al., 2019; Zimmet et al., 2016).

The risk factors for developing diabetes include overweight or obesity, physical inactivity, sedentary lifestyle, dietary habits, smoking, previously identified glucose tolerance issues (IGT and/or IFG), abnormal lipid levels (elevated triglycerides, low HDL cholesterol), hypertension, age, gender, ethnicity, family history, and polycystic ovary syndrome(Chen et al., 2012; Uloko Baba M Musa Mansur A Ramalan Ibrahim D Gezawa Fabian H Puepet Ayekame T Uloko Musa M Borodo Kabiru B Sada, n.d.) . Several medications can induce diabetes mellitus, particularly type 2, including statins, thiazide diuretics, antipsychotic drugs, beta-blockers, ACE inhibitors, antihypertensives, antiarrhythmics, glucocorticoids, oral contraceptives, antineoplastic agents, and immunosuppressants(Anyanwagu et al., 2016; Fathallah et al., 2015) .

Various insulin preparations are administered to patients, alongside oral hypoglycemic agents such as Biguanides (Metformin), Sulfonylureas (first generation: Acetohexamide, Chlorpropamide, Tolazamide, Tolbutamide; second generation: Glibenclamide/Gliburide, Glipizide, Glimepiride, Gliclazide), Meglitinides (Repaglinide, Nateglinide), Thiazolidinediones (Rosiglitazone, Pioglitazone), α-Glucosidase inhibitors (Acarbose, Miglitol), Incretin agonists (Exenatide, Liraglutide), and DPP-4 inhibitors (Sitagliptin, Vildagliptin, Saxagliptin) (Bastaki, 2005; Chatterjee and Davies, 2015; George and Copeland, 2013; Kelley et al., 2015; Lorenzati et al., 2010). Oral hypoglycemic agents may cause several adverse effects, including gastrointestinal problems, lactic acidosis, and vitamin B12 deficiency (associated with biguanides), hypoglycemia, weight gain, skin rashes, and potential cardiovascular risks (linked to Sulfonylureas), as well as fluid retention, weight gain, heart failure, and heightened risk of bladder cancer (associated with Thiazolidinediones) (Arun and Vettath, 2024).

Severe deficiency in chromium (Cr) can lead to fasting hyperglycemia, glucosuria, and stunted growth. Enhancing muscle mass and reducing fat associated with exercise can be achieved through Cr supplementation, which also promotes better glucose metabolism and improves the lipid profile in both diabetic and non-diabetic patients. A lack of dietary Cr is linked to an increased likelihood of developing risk factors associated with non-insulin-dependent diabetes. Zinc (Zn) is crucial for the effective processing, storage, release, and functioning of insulin in the pancreatic cells of mammals. A deficiency in Zn exacerbates cytokine-induced damage during autoimmune attacks, leading to the destruction of islet cells in Type 1 Diabetes Mellitus (T1DM). Sufficient manganese (Mn) levels are necessary for normal insulin production and release. Diabetic patients who are insulin-resistant showed positive responses to oral manganese supplementation. Manganese acts as a cofactor for various enzymatic systems, including arginase, which has been found at elevated levels in diabetic rodents (Dubey et al., 2020; Kazi et al., 2008; Kibiti and Afolayan, 2015).

Ethnobotanical studies have identified about 1,000 plants that may have antidiabetic properties, leading many individuals to prefer herbal remedies for managing diabetes mellitus due to their fewer side effects (Preethi, 2013; Rao et al., n.d.). Secondary metabolites from plants, including alkaloids, phenols, anthocyanins, flavonoids, stilbenoids, saponins, tannins, polysaccharides, coumarins, and terpenes, have the potential to influence the cellular and molecular mechanisms related to carbohydrate metabolism. Additionally, these compounds can protect pancreatic beta cells from damage, restore abnormal insulin signalling, reduce oxidative stress and inflammation, activate AMP-activated protein kinase (AMPK), and inhibit carbohydrate digestion and absorption (Shehadeh et al., 2021). Several plants known for their anti-diabetic properties include *Phyllanthus Amarus, Withania somnifera, Syzygium cumini, Hygrophila auriculata, Senna auriculata, Careya arborea, Andrographis paniculata, Aerva lanata, Caesalpinia bonducella and Gymnema sylvestre (Abdul Khaliq, 2016; Adedapo et al., 2014; Agrawal et al., 2013; Bhuyan et al., 1970; Devi and Soris, n.d.; Hossain et al., 2007; Jena, 2013; Kannur et al., 2006; Mishra et al., 2009; Vijayakumar et al., 2006)*.

This study aims to assess the concentrations of chromium, zinc, and manganese in ten selected anti-diabetic plants. This evaluation is based on the important role that these mineral concentrations play in the anti-diabetic properties of plants. Moreover, the study seeks to determine the most effective anti-diabetic plant by analysing the levels of these three minerals.

# METHODS AND MATERIALS

## Plant Collection and initial preparation:

The plant material samples were freshly gathered from the Sathuragiri hill area and the campus of Kalasalingam University. The different parts of the plant samples were separated and thoroughly rinsed with distilled water to eliminate any sand, dust, or other surface impurities. The plant materials were then dried in the shade at room temperature. Once dried, all plant parts were mechanically crushed and ground into a fine powder. The resulting powdered samples were stored at room temperature in tightly sealed dry plastic containers for subsequent elemental analysis.

## Sample Digestion **procedure**

The dried plant material powder was weighed and kept in ceramic crucible. This is subjected to heating in an electric Muffle furnace at a temperature of 450°C for a duration of 5 hours. During the ashing process, all organic components in the sample were completely eliminated. After ashing, the crucibles with the resulting ash were removed from the muffle furnace and placed in a desiccator. Once cooled, the ash was weighed. Subsequently, a solution comprising HNO3, HCl, and H2SO4 in a 1:2:4 ratio was gradually added to the ash sample. The mixture was then digested on an electric hot plate in a porcelain basin for approximately 2 hours until the dark color of the residue disappeared, resulting in a pasty, colorless residue. The weights of both the crude sample and the ash are summarized in Table 1.

## Sample Preparation

A measured amount (10 mg) of the pasty colorless residue was dissolved in approximately 20% Hydrochloric Acid. The resulting mixture was permitted to stand overnight and then filtered into a 100 mL volumetric flask using Whatman 40 filter paper to eliminate any remaining trace of colorless insoluble solids. The volume was then adjusted to the 100 mL mark. From this solution, 1 mL was extracted and placed into a 100 mL volumetric flask, and the flask was filled with deionized water. The resulting solution was subsequently utilized for Atomic Absorption Spectroscopy analysis.

## Standard Preparation

The manufacturer provided the standard stock solution for the elemental analysis of manganese, zinc, and chromium. (Shimadzu & Co.)

## Atomic Absorption Spectroscopical Study

A diluted filtrate sample was prepared for element analysis using Atomic Absorption Spectroscopy (AAS). The Shimadzu AA-7000 model was utilized for the AAS analysis. An appropriate hollow cathode lamp was employed for the measurements. The concentrations of various elements were determined through a relative method that used analytical reagent-grade solutions of the target elements. The standard measurement conditions for atomic absorption can be found in Table 2.

Once the AAS instrument was calibrated for each specific element, the corresponding standard and sample solutions were aspirated into the flame alternately to measure their absorbance. A minimum of four standard solutions were aspirated for accurate readings. The absorbance values for both the sample and standard solutions were calculated and recorded using WizAArd software (Version 1.03). Calibration curves for each element were created by plotting the absorbance against the concentrations of the standard solutions. In every case, the resulting graphs were linear, and the optimal fitting straight line was determined. The software directly provided the concentration values for the diluted samples. The concentration values obtained for the diluted samples were adjusted by multiplying with the corresponding dilution factor.

**Table No - 1 : Weight of the crude sample and ash**

|  |  |  |  |
| --- | --- | --- | --- |
| **S.No.** | **Plant Name** | **Weight of dried sample powder taken** | **Weight of ash obtained** |
| 01. | *Phyllanthus amarus* | 2g | 0.168g |
| 02. | *‎Withania somnifera* | 2g | 0.105g |
| 03. | *Syzygium cumini* | 2g | 0.152g |
| 04. | *Hygrophila auriculata* | 2g | 0.148g |
| 05. | *‎Senna auriculata* | 2g | 0.192g |
| 06. | *Careya arborea* | 2g | 0.137g |
| 07. | *Andrographis paniculata* | 2g | 0.117g |
| 08. | *Aerva lanata* | 2g | 0.138g |
| 09. | *‎ Gymnema sylvestre* | 2g | 0.147g |
| 10. | *Caesalpinia bonducella* | 2g | 0.162g |

**Table No – 2 : Spectroscopical Parameters**

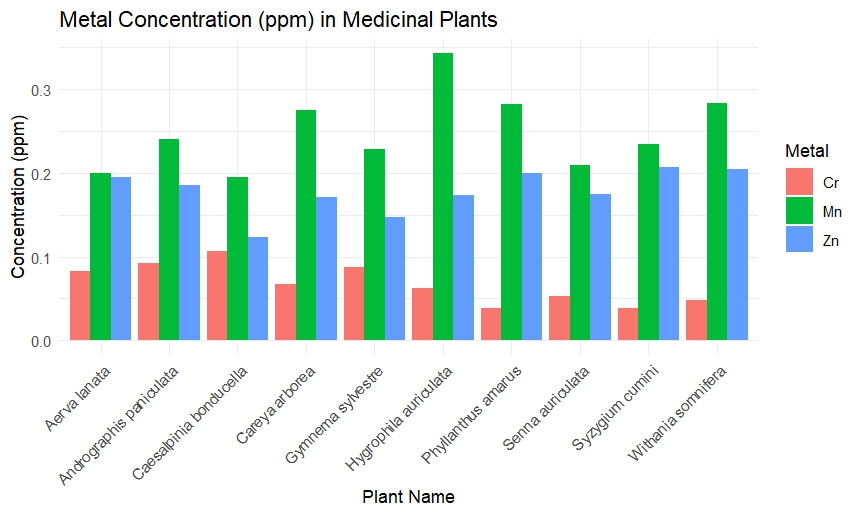
|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **S.No** | **Parameter** | **Manganese (Mn)** | **Zinc (Zn)** | **Chromium (Cr)** |
| 01. | Wavelength | 279.5nm | 213.9nm | 357.9nm |
| 02. | *Lamp Current Low (peak) (mA)* | 10Ma | 8mA | 10Ma |
| 03. | *Slit width (nm)* | 0.2nm | 0.7nm | 0.7nm |
| 04. | *Lamp Mode* | BGC-D2 | BGC-D2 | BGC-D2 |
| 05. | *Working Range* | 0.01 to 2.0 ppm | 0.1 to 1.0 ppm | 0.2 to 2.0ppm |

# RESULTS

Upon analysis of trace elemental composition of the Ten ant diabetic medicinal plants, it was found that zinc, manganese and chromium were present in the following quantities in all the ten plants at varying levels as as presented in Table 3 and figure 1. The plant species *Hygrophila auriculata, Withania somnifera, Phyllanthus amarus, Careya arborea, and Andrographis paniculata* exhibited the highest levels of manganese, with respective concentrations of 0.3430, 0.2836, 0.2817, 0.2746, and 0.2401. The most elevated levels of zinc were detected in the plant species *Syzygium cumini, Withania somnifera, Phyllanthus amarus, Aerva lanata, and Andrographis paniculata*, with concentrations measuring 0.2073, 0.2045, 0.1996, 0.1947, and 0.1849, respectively. The greatest levels of chromium were identified in the plant species *Caesalpinia bonducella, Andrographis paniculata, Gymnema sylvestre , Aerva lanata, and Careya arborea*, with concentrations of 0.1072, 0.0924, 0.0875, 0.0825, and 0.0677, respectively.

**Table No – 3 : Analysis of Concentration of Manganese, Zinc, Chromium.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **S.No.** | **Plant Name** | **Conc of Manganese in ppm** | **Conc of Zinc in ppm** | **Conc of Chromium in ppm** |
| 01. | *Phyllanthus amarus* | **0.2817** | **0.1996** | 0.0381 |
| 02. | *‎Withania somnifera* | **0.2836** | **0.2045** | 0.0479 |
| 03. | *Syzygium cumini* | 0.2343 | **0.2073** | 0.0382 |
| 04. | *Hygrophila auriculata* | **0.3430** | 0.1732 | 0.0628 |
| 05. | *‎Senna auriculata* | 0.2094 | 0.1751 | 0.0529 |
| 06. | *Careya arborea* | **0.2746** | 0.1715 | **0.0677** |
| 07. | *Andrographis paniculata* | **0.2401** | **0.1849** | **0.0924** |
| 08. | *Aerva lanata* | 0.1998 | **0.1947** | **0.0825** |
| 09. | *‎ Gymnema sylvestre* | 0.2286 | 0.1472 | **0.0875** |
| 10. | *Caesalpinia bonducella* | 0.1954 | 0.1234 | **0.1072** |



**Figure 1:- Analysis of Concentration of Manganese, Zinc, Chromium**

# DISCUSSION

The most elevated levels of zinc were detected in the plant species *Syzygium cumini, Withania somnifera, Phyllanthus amarus, Aerva lanata, and Andrographis paniculata*, with concentrations measuring 0.2073, 0.2045, 0.1996, 0.1947, and 0.1849, respectively. Various pathways through which zinc exhibits insulin-mimetic effects on glucose and lipid metabolism have been recoreded (Ilouz et al., n.d.; Moniz et al., 2011). As a second messenger within cells, Zn regulates insulin signaling and maintains glucose balance(Yamasaki et al., 2007). Zinc also promotes the uptake of glucose, the formation of fat in fat cells, and the phosphorylation of tyrosine in both the insulin/IGF-1 receptor and insulin receptor substrate-1. Furthermore, it activates the epidermal growth factor receptors. Zinc also facilitates the absorption of glucose, the production of fat within adipocytes, and the phosphorylation of tyrosine in both the insulin/IGF-1 receptor and insulin receptor substrate-1. Moreover, it initiates the activation of epidermal growth factor receptors(Pandey et al., 2010). This promotes the formation of glycogen by inhibiting glycogen synthase kinase-3 (Ilouz et al., n.d.). These mechanisms help reduce the buildup of glucose in the blood in individuals with diabetes.

The plant species *Hygrophila auriculata, Withania somnifera, Phyllanthus amarus, Careya arborea, and Andrographis paniculata* exhibited the highest levels of manganese, with respective concentrations of 0.3430, 0.2836, 0.2817, 0.2746, and 0.2401. Manganese serves as both an activator and a component of various enzymes, and the enzymes involved in oxidative phosphorylation. Its action enhances insulin release, which aids in improving glucose tolerance in diabetic conditions. Manganese activates enzymes related to the metabolism of fatty acids, nucleic acids, thyroid hormones, and cholesterol. Thus, manganese is crucial for the utilization of glucose (Dubey et al., 2020; Kazi et al., 2008; Kibiti and Afolayan, 2015).

The greatest levels of chromium were identified in the plant species *Caesalpinia bonducella, Andrographis paniculata, Gymnema sylvestre , Aerva lanata, and Careya arborea*, with concentrations of 0.1072, 0.0924, 0.0875, 0.0825, and 0.0677, respectively. Chromium (Cr) acts as a cofactor in regulating insulin activities and is a component of the low-molecular weight chromium (LMWCr)-binding substance, commonly referred to as chromodulin. The relationship between Cr and LMWCr, along with how this complex impacts insulin metabolism, is extensively established (Hepburn and Vincent, 2003). Consequently, Cr is significant in managing diabetes mellitus. It aids in insulin binding and promotes glucose uptake by cells, thereby lowering fasting glucose levels. This enhances glucose tolerance, reduces insulin levels, and decreases total cholesterol in individuals who are normal, elderly, or have type 2 diabetes. In the absence of chromium, insulin's functionality is impaired, resulting in elevated glucose levels. Cr also hinders phosphotyrosine phosphatase, the enzyme responsible for removing phosphate from the insulin receptor, leading to reduced insulin sensitivity (Kibiti and Afolayan, 2015).

The herbs *Withania somnifera, Andrographis paniculata,* and *Careya arborea* possess elevated levels of manganese, zinc, and chromium, which, together with their abundant phytoconstituents, demonstrate improved antidiabetic effects. The potential antidiabetic effects of *Withania somnifera* can be linked to its bioactive components, which include withanine, somnine, withaferin, and withanolides. These compounds may significantly aid in lowering blood glucose levels through various mechanisms, such as improving insulin sensitivity, regulating glucose uptake, and demonstrating antioxidant properties. The presence of these phytoconstituents, along with the plant’s elevated levels of essential trace elements like manganese, zinc, and chromium, could enhance its combined effectiveness in diabetes management. Additional research is needed to clarify the specific molecular pathways involved (Makhlouf et al., 2024; Shanti Bhushan and V, 2010).

The diterpenoid lactone andrographolide, a significant constituent of *Andrographis paniculata*, could be essential in improving glucose metabolism, thus contributing to its potential as an antidiabetic agent. Research indicates that andrographolide can influence pathways involved in glucose uptake and utilization, which may enhance insulin sensitivity and foster effective metabolic functions. The effectiveness of *Andrographis paniculata* in managing diabetes might be further enhanced by its trace metal elements, such as manganese, zinc, and chromium, known to aid in the regulation of glucose balance. These observations highlight the plant's diverse role in glycemic control and call for more research to uncover its underlying molecular mechanisms (Shanti Bhushan and V, 2010; Zhang et al., 2009).

*Phyllanthus amarus* has shown considerable ability to lower blood glucose levels, mainly due to its alkaloid content. The alkaloids present in this plant are known to possess hypoglycemic properties by affecting glucose metabolism, potentially resulting in lowered blood glucose levels. Furthermore, the elevated levels of chromium and manganese found in *Phyllanthus amarus* may enhance this effect. Chromium is crucial for enhancing insulin sensitivity and glucose absorption, while manganese plays a key role in the effective functioning of enzymes that manage glucose metabolism. Collectively, these trace elements are probably going to work in conjunction with the alkaloids to enhance the plant's hypoglycemic effect, providing a potential therapeutic strategy for regulating blood glucose levels (Shanti Bhushan and V, 2010; Shetti et al., n.d.).

*Aerva lanata* is particularly abundant in zinc and chromium, both of which play a significant role in its anti-diabetic properties. Zinc has been found to boost insulin secretion and enhance insulin sensitivity, whereas chromium is essential for glucose metabolism by improving the effectiveness of insulin. Furthermore, the presence of phenolic acids in *Aerva lanata* supports its anti-diabetic capabilities. These phenolic acids demonstrate strong α-glucosidase inhibitory effects, which effectively reduce the breakdown of carbohydrates into glucose during digestion. This inhibition slows down glucose absorption, thus contributing to lower postprandial blood sugar levels. Altogether, the array of trace elements and bioactive compounds in *Aerva lanata* likely increases its potential as a therapeutic agent for diabetes management (Pieczykolan et al., 2021; Vetrichelvan and Jegadeesan, 2002).

# CONCLUSION

This research presents a thorough examination of the levels of manganese, zinc, and chromium in ten selected antidiabetic plants, emphasizing their significant contributions to the antidiabetic effects of these species. Among the analyzed plants, *Withania somnifera, Phyllanthus amarus, Aerva lanata, Andrographis paniculata, and Careya arborea* stood out as the most effective due to their high concentrations of these trace elements. These metals are crucial for improving insulin sensitivity, facilitating glucose uptake, and regulating overall metabolism.

Moreover, the phytochemical constituents found in these plants, including withanine, somnine, withaferin, and withanolides in *Withania somnifera*, alongside andrographolide in *Andrographis paniculata*, also enhance their antidiabetic properties by mechanisms such as boosting glucose metabolism and decreasing oxidative stress. The identification of a metformin-like compound in *Careya arborea*, along with its substantial manganese and chromium levels, highlights its exceptional potential for natural diabetes treatment.

These results indicate that the combined effects of trace metals and phytochemical constituents in these plants provide a multifaceted strategy for managing glycemic levels. Future research that investigates the molecular pathways and synergistic interactions of these elements and compounds is crucial for realizing their complete therapeutic potential in diabetes treatment.

# DECLARATIONS

**Ethics approval and clinical trial registration**

Not applicable.

**Consent for publication**

Not applicable.

**Data availability of data and material**

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

**Disclaimer (Artificial Intelligence)**

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

# REFERENCE

Abdul Khaliq, H., 2016. Pharmacognostic, physicochemical, phytochemical and pharmacological studies on Careya arborea Roxb.; A review, The Journal of Phytopharmacology.

Adedapo, A., Ofuegbe, S., Oguntibeju, O., 2014. The Antidiabetic Activities of the Aqueous Leaf Extract of Phyllanthus Amarus in some Laboratory Animals, in: Antioxidant-Antidiabetic Agents and Human Health. InTech. https://doi.org/10.5772/57030

Agrawal, R., Sethiya, N.K., Mishra, S.H., 2013. Antidiabetic activity of alkaloids of Aerva lanata roots on streptozotocin-nicotinamide induced type-II diabetes in rats. Pharm Biol 51, 635–642. https://doi.org/10.3109/13880209.2012.761244

Animaw, W., Seyoum, Y., 2017. Increasing prevalence of diabetes mellitus in a developing country and its related factors. PLoS One 12. https://doi.org/10.1371/journal.pone.0187670

Anyanwagu, U., Idris, I., Donnelly, R., 2016. Drug-Induced Diabetes Mellitus: Evidence for Statins and Other Drugs Affecting Glucose Metabolism. Clin Pharmacol Ther. https://doi.org/10.1002/cpt.274

Arun, N., Vettath, R.E., 2024. Adverse Events Due to Oral Hypoglycemic Drugs, in: Management of Diabetic Complications. Springer Nature Singapore, Singapore, pp. 285–300. https://doi.org/10.1007/978-981-97-6406-8\_21

Bastaki, S., 2005. Review Diabetes mellitus and its treatment, Int J Diabetes & Metabolism.

Bhuyan, Z.A., Rokeya, B., Masum, N., Hossain, S., Mahmud, I., 1970. Antidiabetic effect of syzygium cumini l. Seed on type 2 diabetic rats. Dhaka University Journal of Biological Sciences 19, 157–164. https://doi.org/10.3329/dujbs.v19i2.8959

Chatterjee, S., Davies, M.J., 2015. Current management of diabetes mellitus and future directions in care. Postgrad Med J 91, 612–621. https://doi.org/10.1136/postgradmedj-2014-133200

Chen, L., Magliano, D.J., Zimmet, P.Z., 2012. The worldwide epidemiology of type 2 diabetes mellitus - Present and future perspectives. Nat Rev Endocrinol. https://doi.org/10.1038/nrendo.2011.183

Deshmukh, C.D., Jain, A., 2015. Diabetes Mellitus: A Review, Int. J. Pure App. Biosci.

Devi, K. V, Soris, T.P., n.d. Antidiabetic, antihyperlipidaemic and antioxidant activity of Senna auriculata (L.) Roxb. leaves in alloxan induced diabetic rats, International Journal of PharmTech Research CODEN.

Dubey, P., Thakur, V., Chattopadhyay, M., 2020. Role of minerals and trace elements in diabetes and insulin resistance. Nutrients. https://doi.org/10.3390/nu12061864

Fathallah, N., Slim, R., Larif, S., Hmouda, H., Ben Salem, C., 2015. Drug-Induced Hyperglycaemia and Diabetes. Drug Saf. https://doi.org/10.1007/s40264-015-0339-z

Forouhi, N.G., Wareham, N.J., 2019. Epidemiology of diabetes. Medicine (United Kingdom). https://doi.org/10.1016/j.mpmed.2018.10.004

George, M.M., Copeland, K.C., 2013. Current treatment options for type 2 diabetes mellitus in youth: Today’s realities and lessons from the TODAY study. Curr Diab Rep 13, 72–80. https://doi.org/10.1007/s11892-012-0334-z

Hepburn, D.D.D., Vincent, J.B., 2003. Tissue and subcellular distribution of chromium picolinate with time after entering the bloodstream. J Inorg Biochem 94, 86–93. https://doi.org/10.1016/S0162-0134(02)00623-2

Hossain, M.A., Roy, B.K., Ahmed, K., Sarwaruddin Chowdhury, A.M., Rashid, M.A., 2007. Antidiabetic activity of Andrographis paniculata. Dhaka University Journal of Pharmaceutical Sciences 6, 15–20. https://doi.org/10.3329/dujps.v6i1.338

Ilouz, R., Kaidanovich, O., Gurwitz, D., Eldar-Finkelman, H., n.d. Inhibition of glycogen synthase kinase-3b by bivalent zinc ions: insight into the insulin-mimetic action of zinc.

Jena, S., 2013. ANTI-DIABETIC EFFECTS OF Withania somnifera ROOT AND LEAF EXTRACTS ON STREPTOZOTOCIN INDUCED DIABETIC RATS. Journal of Cell and Tissue Research 13, 3597–3601.

Kannur, D.M., Hukkeri, V.I., Akki, K.S., 2006. Antidiabetic activity of Caesalpinia bonducella seed extracts in rats. Fitoterapia 77, 546–549. https://doi.org/10.1016/j.fitote.2006.06.013

Kazi, T.G., Afridi, H.I., Kazi, N., Jamali, M.K., Arain, M.B., Jalbani, N., Kandhro, G.A., 2008. Copper, chromium, manganese, iron, nickel, and zinc levels in biological samples of diabetes mellitus patients. Biol Trace Elem Res 122, 1–18. https://doi.org/10.1007/s12011-007-8062-y

Kelley, K.W., Carroll, D.G., Meyer, A., 2015. A review of current treatment strategies for gestational diabetes mellitus. Drugs Context. https://doi.org/10.7573/dic.212282

Kibiti, C.M., Afolayan, A.J., 2015. The biochemical role of macro and micro-minerals in the management of diabetes mellitus and its associated complications: A review. International Journal for Vitamin and Nutrition Research. https://doi.org/10.1024/0300-9831/a000226

Lorenzati, B., Zucco, C., Miglietta, S., Lamberti, F., Bruno, G., 2010. Oral hypoglycemic drugs: Pathophysiological basis of their mechanism of action. Pharmaceuticals. https://doi.org/10.3390/ph3093005

Lovic, D., Piperidou, A., Zografou, I., Grassos, H., Pittaras, A., Manolis, A., 2019. The Growing Epidemic of Diabetes Mellitus. Curr Vasc Pharmacol 18, 104–109. https://doi.org/10.2174/1570161117666190405165911

Makhlouf, E.A., AlamElDeen, Y.K., El-Shiekh, R.A., Okba, M.M., 2024. Unveilling the antidiabetic potential of ashwagandha ( *Withania somnifera* L.) and its withanolides—a review. Nat Prod Res 1–16. https://doi.org/10.1080/14786419.2024.2439009

Mishra, P.K., Prakash, V., Kumar, G., 2009. Antidiabetic and Hypolipidemic Activity of Gymnema sylvestre in Alloxan Induced Diabetic Rats, Global Journal of Biotechnology & Biochemistry.

Moniz, T., Amorim, M.J., Ferreira, R., Nunes, A., Silva, A., Queirós, C., Leite, A., Gameiro, P., Sarmento, B., Remião, F., Yoshikawa, Y., Sakurai, H., Rangel, M., 2011. Investigation of the insulin-like properties of zinc(II) complexes of 3-hydroxy-4-pyridinones: Identification of a compound with glucose lowering effect in STZ-induced type I diabetic animals. J Inorg Biochem 105, 1675–1682. https://doi.org/10.1016/j.jinorgbio.2011.09.005

Pandey, N.R., Vardatsikos, G., Mehdi, M.Z., Srivastava, A.K., 2010. Cell-type-specific roles of IGF-1R and EGFR in mediating Zn2+-induced ERK1/2 and PKB phosphorylation. JBIC Journal of Biological Inorganic Chemistry 15, 399–407. https://doi.org/10.1007/s00775-009-0612-7

Pieczykolan, A., Pietrzak, W., Gawlik-Dziki, U., Nowak, R., 2021. Antioxidant, Anti-Inflammatory, and Anti-Diabetic Activity of Phenolic Acids Fractions Obtained from Aerva lanata (L.) Juss. Molecules 26, 3486. https://doi.org/10.3390/molecules26123486

Preethi, P.J., 2013. Herbal medicine for diabetes mellitus: A Review. https://doi.org/10.7439/ijpp

Rao, M.U., Sreenivasulu, M., Chengaiah, B., Reddy, K.J., Chetty, C.M., n.d. Herbal Medicines for Diabetes Mellitus: A Review, International Journal of PharmTech Research CODEN (USA): IJPRIF ISSN.

Shanti Bhushan, M., V, R.C., 2010. AN ANALYTICAL REVIEW OF PLANTS FOR ANTI DIABETIC ACTIVITY WITH THEIR PHYTOCONSTITUENT & MECHANISM OF ACTION, Available online on www.ijpsr.com.

Shehadeh, M.B., Suaifan, G.A.R.Y., Abu-Odeh, A.M., 2021. Plants secondary metabolites as blood glucose-lowering molecules. Molecules. https://doi.org/10.3390/molecules26144333

Shetti, A.A., Sanakal, R.D., Kaliwal, B.B., n.d. Antidiabetic effect of ethanolic leaf extract of Phyllanthus amarus in alloxan induced diabetic mice. Pelagia Research Library Asian Journal of Plant Science and Research 2012, 11–15.

Singh, N., Kesherwani, R., Kumar Tiwari, A., Kumar Patel, D., Arun Kumar Tiwari, C., 2016. A review on diabetes mellitus, The Pharma Innovation Journal.

Uloko Baba M Musa Mansur A Ramalan Ibrahim D Gezawa Fabian H Puepet Ayekame T Uloko Musa M Borodo Kabiru B Sada, A.E., n.d. Prevalence and Risk Factors for Diabetes Mellitus in Nigeria: A Systematic Review and Meta-Analysis. Diabetes Therapy 9. https://doi.org/10.6084/m9.figshare.6216518

Vetrichelvan, T., Jegadeesan, M., 2002. Anti-diabetic activity of alcoholic extract of Aerva lanata (L.) Juss. ex Schultes in rats. J Ethnopharmacol 80, 103–107. https://doi.org/10.1016/S0378-8741(01)00412-3

Vijayakumar, M., Govindarajan, R., Rao, G.M.M., Rao, C. V., Shirwaikar, A., Mehrotra, S., Pushpangadan, P., 2006. Action of Hygrophila auriculata against streptozotocin-induced oxidative stress. J Ethnopharmacol 104, 356–361. https://doi.org/10.1016/j.jep.2005.09.030

Vlad, I., Popa, A.R., 2012. Epidemiology of diabetes mellitus: A current review. Rom J Diabetes Nutr Metab Dis 19, 433–440. https://doi.org/10.2478/v10255-012-0050-0

Yamasaki, S., Sakata-Sogawa, K., Hasegawa, A., Suzuki, T., Kabu, K., Sato, E., Kurosaki, T., Yamashita, S., Tokunaga, M., Nishida, K., Hirano, T., 2007. Zinc is a novel intracellular second messenger. J Cell Biol 177, 637–645. https://doi.org/10.1083/jcb.200702081

Zhang, Z., Jiang, J., Yu, P., Zeng, X., Larrick, J.W., Wang, Y., 2009. Hypoglycemic and beta cell protective effects of andrographolide analogue for diabetes treatment. J Transl Med 7, 62. https://doi.org/10.1186/1479-5876-7-62

Zimmet, P., Alberti, K.G., Magliano, D.J., Bennett, P.H., 2016. Diabetes mellitus statistics on prevalence and mortality: Facts and fallacies. Nat Rev Endocrinol. https://doi.org/10.1038/nrendo.2016.105