Polyherbal Formulations in the Management of Diabetes Mellitus: Phytochemical Basis, Standardization, and In Vitro Antidiabetic Evaluation

Akshay Sagar Gosavi[1], Prof Amol G Jadhao[2]
[1]*Research Scholar, Gawande College of Pharmacy, Sakharkherda, Maharshtra, India, 443202*
[2]*Research Guide, Gawande College of Pharmacy, Sakharkherda, Maharshtra, India, 443202*

***Abstract*—Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Despite the availability of synthetic antidiabetic drugs, their long-term use is often associated with adverse effects and limited efficacy. Polyherbal formulations, derived from medicinal plants with complementary mechanisms of action, have gained increasing attention as safer and effective alternatives for diabetes management. This review focuses on the role of polyherbal formulations in diabetes control, emphasizing phytochemical constituents, analytical standardization, chromatographic fingerprinting, and in vitro antidiabetic evaluation methods such as α-amylase and α-glucosidase inhibition assays. The review highlights the importance of marker-based standardization, particularly corosolic acid, and discusses stability and safety aspects necessary for the development of scientifically validated herbal antidiabetic formulations.**

***Index Terms*—Diabetes mellitus, Polyherbal formulation, Antidiabetic activity, Phytochemical screening, α-Amylase inhibition**

I. INTRODUCTION

Diabetes mellitus is a complex and multifactorial metabolic disorder that has emerged as a major global public health challenge. Its prevalence is increasing at an alarming rate worldwide, primarily due to rapid urbanization, sedentary lifestyles, unhealthy dietary habits, obesity, and genetic susceptibility. Persistent hyperglycemia, the hallmark of diabetes mellitus, results in long-term damage and dysfunction of various organs, leading to serious microvascular and macrovascular complications such as cardiovascular diseases, diabetic neuropathy, nephropathy, and retinopathy. These complications significantly reduce the quality of life and increase morbidity and mortality among diabetic patients. Although several classes of synthetic antidiabetic agents, including sulfonylureas, biguanides, and α-glucosidase inhibitors, are widely used for glycemic control, their long-term use is often associated with undesirable side effects such as hypoglycemia, gastrointestinal disturbances, weight gain, and reduced patient compliance. These limitations have prompted continuous exploration for safer and more effective therapeutic alternatives. Traditional systems of medicine, particularly Ayurveda, have extensively utilized medicinal plants for the prevention and management of diabetes mellitus for centuries. In recent years, polyherbal formulations have gained considerable scientific interest due to their ability to target multiple pathological pathways simultaneously. The combination of herbs in polyherbal systems is believed to produce synergistic and additive therapeutic effects, enhance efficacy, minimize adverse reactions, and improve overall safety compared to single-herb formulations. Consequently, polyherbal antidiabetic formulations represent a promising and rational approach for the development of effective, safe, and standardized herbal therapies for diabetes management.

II. RATIONALE FOR POLYHERBAL FORMULATIONS

The concept of polyherbalism is based on the principle that multiple herbs, when combined in optimized proportions, produce enhanced therapeutic efficacy through synergistic mechanisms. In diabetes management, polyherbal formulations may act by:

- Inhibiting carbohydrate-digesting enzymes
- Enhancing insulin secretion and sensitivity
- Improving glucose uptake
- Providing antioxidant protection

Plants such as Costus igneus, Lagerstroemia speciosa, and Gymnema sylvestre are widely reported for their antidiabetic potential due to the presence of bioactive phytoconstituents like corosolic acid, gymnemic acids, flavonoids, and phenolic compounds.

III. PHYTOCHEMICAL CONSTITUENTS RESPONSIBLE FOR ANTIDIABETIC ACTIVITY

Phytochemical screening is a fundamental step in the scientific evaluation of medicinal plants, as it enables the identification of bioactive secondary metabolites responsible for their pharmacological effects. In the context of antidiabetic herbal formulations, qualitative phytochemical analysis provides critical insight into the therapeutic potential and mechanism of action of plant extracts. Numerous studies have demonstrated that the antidiabetic efficacy of medicinal plants is closely associated with the presence of specific classes of secondary metabolites. Alkaloids are known to play an important role in glucose homeostasis by stimulating insulin secretion from pancreatic β-cells and improving peripheral glucose utilization. Flavonoids constitute another major group of phytoconstituents that contribute significantly to antidiabetic activity through multiple mechanisms, including enhancement of insulin sensitivity, modulation of glucose transporters, and potent antioxidant effects that protect pancreatic β-cells from oxidative stress–induced damage. Saponins are reported to reduce intestinal glucose absorption by forming complexes with dietary carbohydrates and by modulating membrane permeability, thereby lowering postprandial blood glucose levels. Tannins and other phenolic compounds exhibit strong inhibitory effects on key carbohydrate-digesting enzymes such as α-amylase and α-glucosidase, resulting in delayed carbohydrate digestion and reduced glucose absorption. Additionally, these compounds possess antioxidant properties that further contribute to the prevention of diabetes-associated oxidative stress. Glycosides are also implicated in the regulation of carbohydrate metabolism and insulin signaling pathways, thereby supporting overall glycemic control. The presence of these phytochemical constituents in individual herbal extracts as well as in the final polyherbal formulation confirms the scientific basis of their antidiabetic potential. Moreover, the coexistence of multiple bioactive compounds suggests possible synergistic interactions, which may enhance therapeutic efficacy while reducing adverse effects. Thus, phytochemical screening not only validates the traditional use of these medicinal plants but also provides a rational foundation for their inclusion in standardized polyherbal antidiabetic formulations.

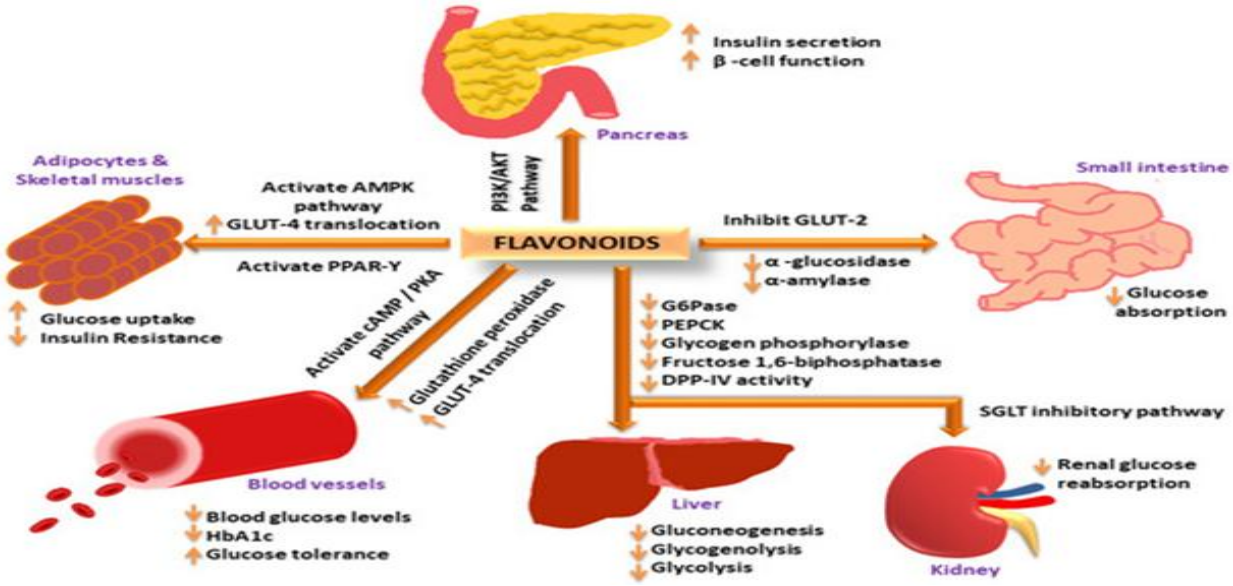

Figure: Mechanism of Antidiabetic Action of Polyherbal Formulation

IV. ANALYTICAL STANDARDIZATION AND CHROMATOGRAPHIC FINGERPRINTING

Standardization is a fundamental requirement in the development of herbal formulations to ensure their quality, safety, efficacy, and reproducibility. Unlike synthetic drugs, herbal products are complex mixtures of multiple phytoconstituents, and their therapeutic performance can vary significantly due to differences in raw material quality, processing methods, and storage conditions. Therefore, the evaluation of physicochemical parameters such as moisture content, pH, extractive values, and solubility is routinely performed as part of standardization protocols. These parameters provide essential information regarding the stability, purity, and suitability of the formulation for pharmaceutical use, as well as its shelf-life and patient acceptability. In addition to physicochemical evaluation, chromatographic fingerprinting has emerged as a reliable and indispensable tool for quality control of herbal formulations. High-performance liquid chromatography (HPLC) and UV spectrophotometry are widely employed to generate characteristic chemical profiles of individual plant extracts and finished polyherbal products. The quantification of specific marker compounds, such as corosolic acid, plays a crucial role in standardization. Corosolic acid is well recognized for its insulin-mimetic activity, enhancement of glucose uptake, and overall glucose-lowering effects, making it a suitable phytomarker for antidiabetic herbal formulations. The presence and retention of characteristic chromatographic peaks corresponding to marker compounds from individual extracts within the polyherbal formulation confirm chemical compatibility among the components and indicate that the formulation process does not adversely affect the stability of active constituents. Furthermore, consistent retention times and peak areas across different batches ensure batch-to-batch uniformity, thereby reinforcing the reliability and therapeutic consistency of the formulation. Collectively, physicochemical evaluation and chromatographic standardization provide a robust scientific framework for the quality assurance and regulatory acceptance of standardized polyherbal antidiabetic formulations.

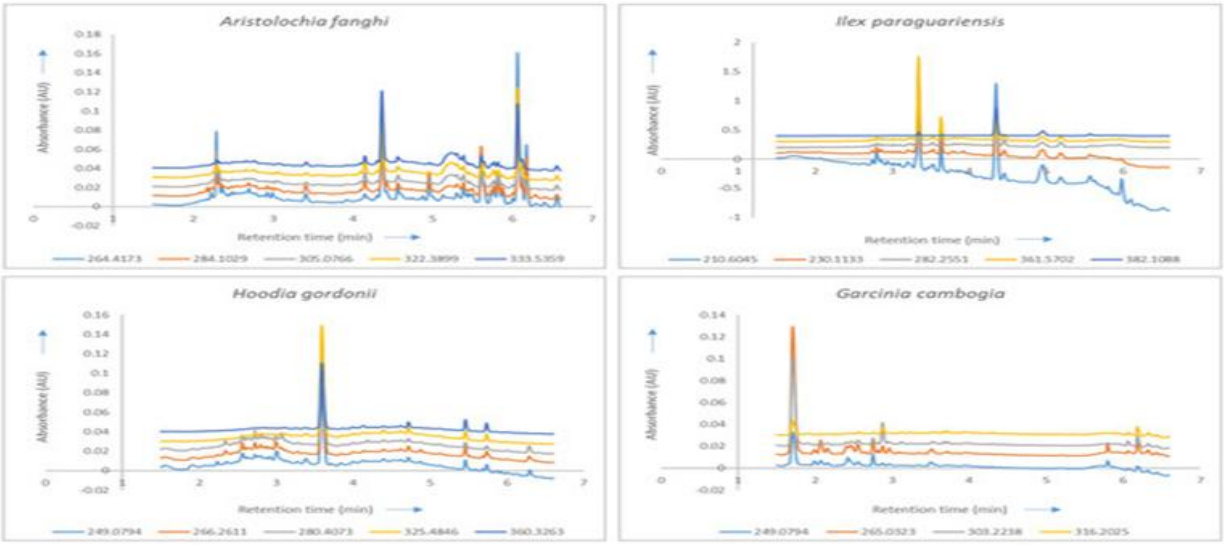

Figure: Analytical Standardization and Chromatographic Fingerprinting

V. IN VITRO ANTIDIABETIC EVALUATION

In vitro enzyme inhibition assays are widely employed as preliminary screening tools to assess the antidiabetic potential of herbal extracts and formulations. These assays are simple, reproducible, and cost-effective, and they provide valuable insight into the possible mechanisms by which herbal formulations may regulate blood glucose levels. Among the various in vitro models, inhibition of carbohydrate-digesting enzymes such as α-amylase and α-glucosidase is considered particularly

important, as these enzymes play a key role in postprandial hyperglycemia.

VI. A-AMYLASE INHIBITION

α-Amylase is a digestive enzyme responsible for the hydrolysis of complex carbohydrates into smaller oligosaccharides and glucose, which are subsequently absorbed into the bloodstream. Inhibition of α-amylase slows down carbohydrate digestion and reduces the rate of glucose release, thereby preventing sudden postprandial spikes in blood glucose levels. This mechanism forms the basis for the therapeutic action of clinically used α-amylase inhibitors such as acarbose. Polyherbal formulations, owing to the presence of multiple bioactive phytoconstituents including flavonoids, tannins, phenolic compounds, and glycosides, often demonstrate significant α-amylase inhibitory activity. These phytochemicals interact with the active site of the enzyme or alter its catalytic efficiency, resulting in reduced enzymatic activity. Several studies have reported that standardized polyherbal formulations exhibit α-amylase inhibition comparable to or moderately lower than that of acarbose, but with a potentially improved safety profile. Thus, the ability of polyherbal formulations to inhibit α-amylase supports their role in controlling postprandial hyperglycemia and highlights their therapeutic relevance in the management of type 2 diabetes mellitus. In vitro α-amylase inhibition assays therefore serve as an important indicator of the antidiabetic potential of herbal formulations prior to in vivo evaluation.

VII. A-GLUCOSIDASE INHIBITION

α-Glucosidase is a key intestinal enzyme involved in the final step of carbohydrate digestion, where disaccharides and oligosaccharides are hydrolyzed into absorbable glucose molecules. Inhibition of this enzyme effectively delays glucose absorption from the intestine, thereby attenuating postprandial hyperglycemia. This mechanism is clinically exploited by α-glucosidase inhibitors such as acarbose, which are commonly prescribed in the management of type 2 diabetes mellitus. Herbal extracts rich in phenolic compounds, flavonoids, tannins, and glycosides have demonstrated notable α-glucosidase inhibitory activity through competitive and non-competitive mechanisms. When such extracts are combined in polyherbal formulations, enhanced inhibitory effects are often observed due to synergistic interactions among diverse phytoconstituents. These interactions allow simultaneous modulation of multiple enzyme binding sites, resulting in improved enzyme inhibition compared to individual plant extracts. Several studies have reported that standardized polyherbal formulations exhibit significant α-glucosidase inhibition in a concentration-dependent manner, with inhibitory potential approaching that of standard synthetic drugs but with a lower risk of adverse gastrointestinal effects. The dual inhibition of α-amylase and α-glucosidase by polyherbal systems provides a comprehensive strategy for controlling postprandial blood glucose levels. Therefore, α-glucosidase inhibition represents an important in vitro parameter for evaluating the antidiabetic efficacy of polyherbal formulations and supports their therapeutic relevance in the dietary and pharmacological management of diabetes mellitus.

VIII. ANTIOXIDANT ACTIVITY

Oxidative stress is widely recognized as a critical factor in the onset and progression of diabetes mellitus and its associated complications. Chronic hyperglycemia leads to excessive generation of reactive oxygen species (ROS), which contributes to pancreatic β-cell dysfunction, insulin resistance, and tissue damage. Therefore, the antioxidant potential of antidiabetic agents plays a crucial role in mitigating oxidative damage and improving glycemic control. The DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging assay is one of the most commonly employed in vitro methods for evaluating the antioxidant capacity of herbal extracts and formulations. This assay measures the ability of test samples to donate hydrogen atoms or electrons to neutralize free radicals. Polyherbal formulations enriched with phenolic compounds and flavonoids generally exhibit strong DPPH radical scavenging activity in a concentration-dependent manner. These phytoconstituents effectively reduce oxidative stress by scavenging free radicals, inhibiting lipid peroxidation, and protecting cellular components from oxidative damage. The pronounced antioxidant activity of polyherbal formulations not only supports their protective role against diabetes-induced

oxidative stress but also contributes synergistically to their overall antidiabetic efficacy by preserving pancreatic β-cell integrity and enhancing insulin sensitivity.

IX. STABILITY AND SAFETY CONSIDERATIONS

Stability assessment is an essential component in the development of herbal formulations to ensure the maintenance of quality, safety, and therapeutic efficacy throughout their shelf life. Stability studies conducted in accordance with International Council for Harmonisation (ICH) guidelines evaluate changes in physical appearance, moisture content, pH, phytochemical composition, and biological activity under accelerated and long-term storage conditions. Such studies help establish appropriate storage conditions and shelf-life specifications for standardized polyherbal formulations. Safety evaluation is equally important for confirming the suitability of herbal formulations for prolonged use. Acute oral toxicity studies performed as per Organisation for Economic Co-operation and Development (OECD) guidelines provide critical information on the toxicological profile of the formulation. The absence of mortality, adverse behavioral changes, or significant body weight alterations at therapeutic doses indicates a favorable safety margin. These findings support the traditional use of polyherbal antidiabetic formulations and reinforce their potential as safe and effective alternatives or adjuncts to conventional antidiabetic therapies.

X. CONCLUSION

Polyherbal formulations represent a scientifically robust and promising therapeutic strategy for the management of diabetes mellitus. The presence of multiple bioactive phytoconstituents acting through complementary and synergistic mechanisms offers a distinct advantage over single-herb or monotherapy approaches. Proper standardization through physicochemical evaluation, chromatographic fingerprinting, and marker-based quality control ensures formulation consistency, safety, and reproducibility. In vitro validation using enzyme inhibition and antioxidant assays further substantiates the antidiabetic potential of these formulations. The integration of traditional herbal knowledge with modern analytical and pharmacological techniques facilitates the development of evidence-based herbal antidiabetic therapies. Stability assessment and safety evaluation are essential components for ensuring product reliability and patient acceptability. Although existing findings strongly support the therapeutic relevance of polyherbal formulations, comprehensive in vitro investigations and well-designed clinical trials are necessary to establish their long-term efficacy, safety, and clinical applicability. Such studies will play a critical role in the successful translation of polyherbal antidiabetic formulations from traditional practice to mainstream therapeutic use.

REFERENCES

[1] World Health Organization, WHO Global Report on Diabetes. Geneva, Switzerland: WHO, 2016.

[2] S. Kumar, R. Malhotra, and D. Kumar, “Antidiabetic and free radical scavenging potential of Costus igneus,” Journal of Ethnopharmacology, vol. 131, no. 2, pp. 452–456, 2010.

[3] N. Jothivel, S. P. Ponnusamy, M. Appachi, S. Singaravel, D. Rasilingam, and K. Deivasigamani, “Antidiabetic activity of Costus igneus leaves in streptozotocin-induced diabetic rats,” Journal of Health Science, vol. 53, no. 6, pp. 655–663, 2007.

[4] G. Gireesh, S. K. Thomas, B. Joseph, and C. S. Paulose, “Antihyperglycemic and insulin secretory activity of Costus igneus,” Journal of Ethnopharmacology, vol. 123, no. 3, pp. 470–474, 2009.

[5] P. Kanetkar, R. Singhal, and M. Kamat, “Gymnema sylvestre: A memoir,” Journal of Clinical Biochemistry and Nutrition, vol. 41, no. 2, pp. 77–81, 2007.

[6] K. Baskaran, B. Kizar Ahamath, K. Radha Shanmugasundaram, and E. R. Shanmugasundaram, “Antidiabetic effect of a leaf extract from Gymnema sylvestre,” Journal of Ethnopharmacology, vol. 30, no. 3, pp. 295–300, 1990.

[7] M. Ayyanar and P. Subash-Babu, “Syzygium cumini (L.) Skeels: A review of its phytochemical constituents and traditional

uses," Asian Pacific Journal of Tropical Biomedicine, vol. 2, no. 3, pp. 240–246, 2012.

[8] K. Ravi, B. Ramachandran, and S. Subramanian, "Protective effect of Syzygium cumini seed kernel on tissue antioxidants in streptozotocin-induced diabetic rats," Biological and Pharmaceutical Bulletin, vol. 27, no. 8, pp. 1212–1217, 2004.

[9] A. K. Tiwari and J. M. Rao, "Diabetes mellitus and multiple therapeutic approaches of phytochemicals," Journal of Ethnopharmacology, vol. 83, no. 1–2, pp. 109–121, 2002.

[10] Y. M. Kim, Y. K. Jeong, M. H. Wang, W. Y. Lee, and H. I. Rhee, "Inhibitory effect of pine extract on α-glucosidase activity and postprandial hyperglycemia," Nutrition, vol. 21, no. 6, pp. 756–761, 2005.

[11] G. L. Miller, "Use of dinitrosalicylic acid reagent for determination of reducing sugar," Analytical Chemistry, vol. 31, no. 3, pp. 426–428, 1959.

[12] W. Brand-Williams, M. E. Cuvelier, and C. Berset, "Use of a free radical method to evaluate antioxidant activity," LWT – Food Science and Technology, vol. 28, no. 1, pp. 25–30, 1995.

[13] J. B. Harborne, Phytochemical Methods: A Guide to Modern Techniques of Plant Analysis, 3rd ed. London, U.K.: Chapman and Hall, 1998.

[14] C. K. Kokate, A. P. Purohit, and S. B. Gokhale, Pharmacognosy, 50th ed. Pune, India: Nirali Prakashan, 2014.

[15] Indian Pharmacopoeia Commission, Indian Pharmacopoeia. Ghaziabad, India: IPC, 2018.

[16] International Council for Harmonisation (ICH), ICH Q1A(R2): Stability Testing of New Drug Substances and Products. Geneva, Switzerland, 2003.

[17] Organisation for Economic Co-operation and Development (OECD), Guidelines for the Testing of Chemicals, Section 4: Test No. 423 – Acute Oral Toxicity. Paris, France: OECD Publishing, 2001.

[18] H. P. Rang, M. M. Dale, J. M. Ritter, and R. J. Flower, Rang and Dale's Pharmacology, 8th ed. London, U.K.: Elsevier, 2016.

[19] S. D. Sarker, Z. Latif, and A. I. Gray, Natural Products Isolation, 2nd ed. Totowa, NJ, USA: Humana Press, 2006.

[20] E. M. Williamson, "Synergy and other interactions in phytomedicines," Phytomedicine, vol. 8, no. 5, pp. 401–409, 2001.

[21] M. Modak, P. Dixit, J. Londhe, S. Ghaskadbi, and T. P. A. Devasagayam, "Indian herbs and herbal drugs used for the treatment of diabetes," Journal of Clinical Biochemistry and Nutrition, vol. 40, no. 3, pp. 163–173, 2007.

[22] D. K. Patel, S. K. Prasad, R. Kumar, and S. Hemalatha, "An overview on antidiabetic medicinal plants having insulin mimetic property," Asian Pacific Journal of Tropical Biomedicine, vol. 2, no. 4, pp. 320–330, 2012.

[23] M. Jung, M. Park, H. C. Lee, Y. H. Kang, E. S. Kang, and S. K. Kim, "Antidiabetic agents from medicinal plants," Current Medicinal Chemistry, vol. 13, no. 10, pp. 1203–1218, 2006.

[24] W. L. Li, H. C. Zheng, J. Bukuru, and N. De Kimpe, "Natural medicines used in the traditional Chinese medical system for therapy of diabetes mellitus," Journal of Ethnopharmacology, vol. 92, no. 1, pp. 1–21, 2004.

[25] P. Daisy, J. Eliza, and K. A. Mohamed Farook, "A novel dihydroxy gymnemic triacetate isolated from Costus igneus leaves possessing antidiabetic activity," Journal of Ethnopharmacology, vol. 126, no. 2, pp. 282–285, 2009.

[26] K. Shilpa, K. N. Sangeetha, V. S. Muthusamy, and S. Sujatha, "Hypoglycemic and antioxidant effect of Costus igneus leaves in experimental diabetes," Indian Journal of Pharmaceutical Sciences, vol. 75, no. 1, pp. 84–88, 2013.

[27] N. Jothivel, S. P. Ponnusamy, and M. Appachi, "Evaluation of antidiabetic potential of Costus igneus leaves in animal models," International Journal of Pharmaceutical Sciences Review and Research, vol. 8, no. 2, pp. 36–41, 2011.

[28] S. J. Persaud, H. Al-Majed, A. Raman, and P. M. Jones, "Gymnema sylvestre stimulates insulin release in vitro by increased membrane permeability," Journal of Endocrinology, vol. 163, no. 2, pp. 207–212, 1999.

[29] E. R. B. Shanmugasundaram, G. Leela, K. Radha Shanmugasundaram, and V. M. Rajendran, "Possible regeneration of the islets of Langerhans in streptozotocin-diabetic rats given Gymnema sylvestre leaf extracts," Journal of Ethnopharmacology, vol. 30, no. 3, pp. 265–279, 1990.

[30] S. B. Sharma, A. Nasir, K. M. Prabhu, P. S. Murthy, and G. Dev, "Antihyperglycemic effect of fruit pulp of Syzygium cumini in diabetic rats," Journal of Ethnopharmacology, vol. 85, no. 2–3, pp. 201–206, 2003.

[31] A. Helmstadter, "Antidiabetic drugs used in Europe prior to the discovery of insulin," Pharmazie, vol. 62, no. 10, pp. 717–720, 2007.

[32] J. K. Grover, S. Yadav, and V. Vats, "Medicinal plants of India with antidiabetic potential," Journal of Ethnopharmacology, vol. 81, no. 1, pp. 81–100, 2002.

[33] E. Apostolidis, Y. I. Kwon, and K. Shetty, "Inhibitory potential of herb, fruit, and fungal extracts against key enzymes linked to type 2 diabetes," Innovative Food Science and Emerging Technologies, vol. 8, no. 1, pp. 46–54, 2007.

[34] P. P. McCue and K. Shetty, "Inhibitory effects of rosmarinic acid extracts on porcine pancreatic amylase in vitro," Asia Pacific Journal of Clinical Nutrition, vol. 13, no. 1, pp. 101–106, 2004.

[35] R. L. Prior, X. Wu, and K. Schaich, "Standardized methods for the determination of antioxidant capacity and phenolics in foods and dietary supplements," Journal of Agricultural and Food Chemistry, vol. 53, no. 10, pp. 4290–4302, 2005.

[36] V. L. Singleton, R. Orthofer, and R. M. Lamuela-Raventós, "Analysis of total phenols and other oxidation substrates by means of Folin–Ciocalteu reagent," Methods in Enzymology, vol. 299, pp. 152–178, 1999.

[37] P. K. Mukherjee, Quality Control and Evaluation of Herbal Drugs. New Delhi, India: Business Horizons, 2002.

[38] O. F. Kunle, H. O. Egharevba, and P. O. Ahmadu, "Standardization of herbal medicines – A review," International Journal of Biodiversity and Conservation, vol. 4, no. 3, pp. 101–112, 2012.

[39] S. Parasuraman, "Toxicological screening," Journal of Pharmacology and Pharmacotherapeutics, vol. 2, no. 2, pp. 74–79, 2011.

[40] D. Lorke, "A new approach to practical acute toxicity testing," Archives of Toxicology, vol. 54, no. 4, pp. 275–287, 1983.