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Green Synthesis and Antidiabetic Evaluation of Metal-Complexes Derived from Schiff Bases

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ABSTRACT

The lack of therapeutic alternatives that are effective, safe and environmentally sustainable has been heightened by the spread of Type 2 diabetes in the global realm. Emerging candidates include the Schiff base metal complexes synthesized through green chemistry strategies that have presented interest due to their multifunctional antidiabetic capability. The high stability, biocompatibility, and environmental non-toxicity of these complexes produced by environment-friendly synthesis protocols based on plant extracts, ethanol or water, and facilitated by microwave- or ultrasonic irradiation points out to the feasibility and economic viability of their application in the synthesis of biodegradable complexes in general. Cu(II), Zn(II), Co(II) and Ni(II) transition metals bearing the cations of electron-rich and aromatic Schiff base ligands are potent hypoglycemics in experimental models that are insulin-like, carbohydrate-metabolizing enzyme (i.e. - -alpha-glucosidase, glycogen-6-phosphatase) inhibitors, reducing oxidative stress, and pancreatic -beta-cell regenerators. Biological analysis such as OGTT, ELISA, oxidative stress and histopathological analysis show that glucose tolerance collected, insulin secretion and integrity of the islet cells have greatly improved. Although they proved to be promising in preclinical studies, poor pharmacokinetic profiling, inability to standardize synthesis protocols, as well as an inability to compare proportions to conventional drugs limits their clinical transfer. In the future, more attention should be paid to the whole scope of toxicological analysis, novel drug delivery, and optimization attempts based on suitable Structure-Activity constituents. On the whole, Schiff base metal complexes synthesized through a green method of synthesis have a potential future as multi-targeted, environmentally-friendly, diabetes management drugs.

Key Words:

Schiff Base, Metal Complexes, Green Synthesis, Antidiabetic Activity, Oxidative Stress, Insulin Mimicry, B-Cell Regeneration, Enzyme Inhibition

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1. INTRODUCTION

The high number of patients with diabetes mellitus across the globe, in terms of Type 2 diabetes, has triggered a lot of research on novel therapies that are not only effective but also environmentally friendly. Although traditional pharmacology intervention is effective, there are undesirable side effects associated with this type of treatment, its weakened effectiveness

in the long term, and its high economic rates[1]. Metal-based drugs that have been suggested as prospective medications in recent years have become viable, because of their relevance biologically and multifaceted redox states. Schiff bases and their metal complexes among them have elicited a lot of interest due to their ability in the formation of stable and bioactive structures that bind various biological targets. Schiff bases are the organic compounds that are usually made by using condensation reactions (with aldehydes or ketones) with a primary amine and possess ease of synthesis, functional tunability and can also serve as a chelating agenst of various metal ions including Cu(II), Zn(II) and Co(II). These complexes have possessed a range of pharmacological potencies such as antimicrobial, anticancer and some pharmacological activities have been found in particular valence as being of antidiabetic nature, thus donning relevance into drug developments program.

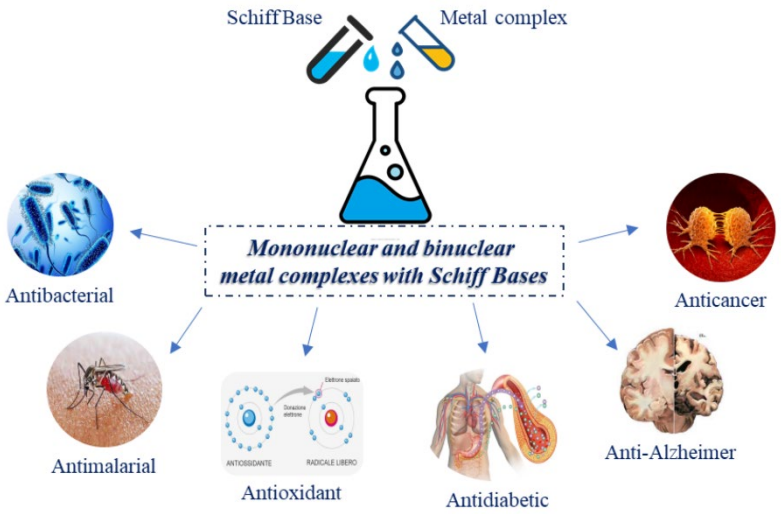

Figure 1: Metal Complexes With Schiff Bases[2]

The current trend in this aspect is the introduction of green chemistry principles in the development of Schiff base metal complex synthesis. Traditional synthetic pathways tend to use non-friendly chemicals, hazardous solvents and energy-intensive preparations, and this begs the question of their sustainability and safety. These limitations are overcome through green synthesis, in which natural plant extracts are used, with both water-based and ethanol solvents, and energy saving methods (such as microwave or ultrasonic methods) are employed. Such environmental-friendly strategy is not only compatible with the efforts of the world community aimed at providing sustainable pharmaceutical development, but it can also improve biocompatibility and decrease the risk of toxicology[3]. These green-synthesized Schiff base complexes have been studied on animal models of diabetes and showed improvement in glucose homeostasis, reduction of oxidative stress and regeneration of pancreatic tissue. This review summarizes the existing development in this promising interception of medicinal and green chemistry with particular attention to animal-based testing to facilitate a sound preclinical insight of their potential therapeutic value.

1.1.Background Information and Context

Diabetes is a complicated type of metabolic disturbance with an increasing trend of its prevalence in the world and its development has severe consequences that include such complications as nephropathy, neuropathy, and cardiovascular diseases. The most common

barriers to standard therapy options may include side effects of hypoglycemia, gastrointestinal side effects and lack of patient compliance as is the case with other common medications such as metformin, sulfonylureas and injections of insulin. In the meantime, Schiff base metal complex could be used to overcome these disadvantages with specific qualities about their physicochemical characteristics, like redox prioritization and ligating agility. The metal ions such as copper and zinc are reported to play the roles in the biosynthesis and secretion of insulin, and the ligand system of the Schiff bases provides the sort of manipulation of the metal biological activity. With a growing need to have safe, economically efficient and ecologically sound solutions in therapeutic applications, the study of green-synthesized metal complexes will be an interesting field of knowledge to investigate in the upcoming years[4].

1.2.Objectives of the Review

The main objectives of this review are:

- To review green synthesis methods of Schiff base metal complexes.
- To summarize antidiabetic effects in animal models.
- To analyze mechanisms like insulin mimicry and antioxidant action.
- To study structure–activity relationships of metal-ligand systems.
- To identify gaps and suggest future research directions.

1.3.Importance of the Topic

The subject of interest falls at the intersection of green chemistry, coordination chemistry and antidiabetic pharmacotherapy all of which are attracting growing worldwide interest. With the help of green synthesis and toxicity testing in animal models, this review backs the sustainable drug discovery innovation. It further adds to the initiative to find workable and safer substitutes to traditional antidiabetic agents. Due to the need to treat diabetes based on new approaches, practical candidates are in short supply, and this purpose will become a useful measure of pharmaceutical innovation and the introduction of green technologies in medicine[5].

2. GREEN SCHIFF BASE METAL COMPLEXES FOR ANTIDIABETIC APPLICATIONS

Schiff base metal complexes can be prepared through green synthesis which is economical, environmentally friendly, and the use of water, ethanol, or plant extracts produces high yields and efficiency which is also made possible through the use of a process such as microwave assisted reactions. These complexes especially those of Cu (II), Zn (II), Ni (II) and Co (II), exhibit an important antidiabetic potentiality on STZ or alloxan- induced diabetic model in rat by enhancing insulin release, glucose holdup, enzyme inhibition and antioxidant protection[6]. These can be characterized as FTIR, UV-Vis, XRD, TGA and CV, followed by pharmacological testing (blood glucose concentrations, insulin ELISA, oral glucose tolerance tests, markers of oxidative stress and histopathology). Although it shows prospective outcomes, there are still problems in terms of pharmacokinetics, bioavailability, species particularity, and the ability to compare them with standard drugs.

2.1.Green Synthesis of Schiff Base Metal Complexes

Green synthesis of Schiff base metal complexes will recapitulate the green chemistry principles, which are associated with reduced production of hazardous wastes and the use of renewable resources and environment-friendly reagents[7]. The formation of Schiff bases The Schiff bases are prepared via a condensation reaction involving primary amines and alde- hydes or ketones to generate imine (-C=N-) linkages (covalent bond). This is followed by the chelation of metal ions such as (Cu2+), (Zn2+), (Ni 2+), and (Co) 2+. The customary solvents are substituted with water, ethanol or natural plant extracts (e.g., green tea, neem, tulsi) that serve as reducing/stabilizing agents as well as a solvent in green synthesis schemes.

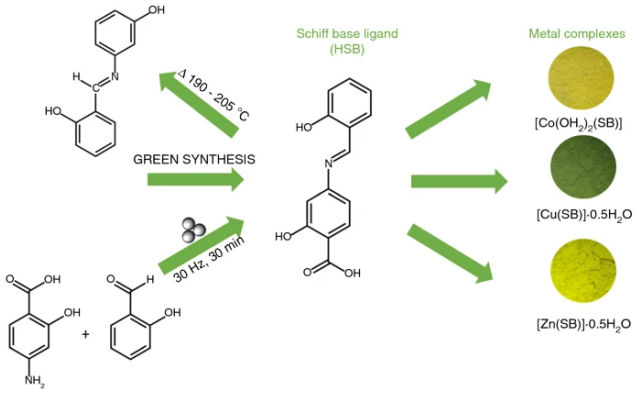

Figure 2: Green Synthesis of Schiff Base Metal Complexes[8]

There are also methodologies in having increased reaction rates, yields, energy consumption such as the microwave-assisted and ultrasonic irradiation techniques. The procedure described has great atom economy and process efficiency in line with the vision of sustainable development[9].

2.2.Antidiabetic Evaluation in Animal Models

These group of metal compounds have been estimated greatly as antidiabetic agents in vivo most specifically streptozotocin (STZ) or alloxan induced diabetic rats. These models are helpful to emulate the insulin deficient or insulin resistant conditions, and are therefore comfortable in testing the efficiency of antidiabetic drugs[10].

- **Cu (II)-Schiff Base Complexes:** Shown to have significant levels of hypoglycemic activity, significantly lowering fasting blood glucose (FBG) quantum. They stimulated the secretion of insulin, preserved the pancreatic 2-beta-cells as well as reversed the hepatic-pancreatic tissue levels of antioxidant enzymes. The two mechanisms of action include scavenging reactive oxygen species and maintenance of islet architecture.

- **Zn(II) Complexes:** These complexes had an insulin-mimetic effect and they were found to regenerate β-cells, increase glucose tolerance and augment insulin sensitivity. Research demonstrated the islet of the pancreatic histological regeneration and the restoration of glucose homeostasis[11].

- **Co (II) and Ni (II) Complexes:** Had inhibitory effects against alpha-glucosidase and glucose-6-phosphatase enzymes indicating slow carbohydrate breaking down and

diminished hepatic gluconeogenesis. This process supplements insulin free pathways, which are appropriate in combination treatment such as the one that incorporates it with carcinoma pathways.

In all cases, metal chelation enhanced the bioavailability and stability of the Schiff base ligands, further supporting their antidiabetic effects.

2.3.Methodologies and Biological Assays

These complexes of metals are checked biologically by the use of standard approaches to inspect metabolism of glucose and mechanism of insulin reaction, antioxidant guard and organs preservation:

- **Blood Glucose Estimation:** Measured in the procedure of glucose oxidase-peroxidase in order to determine the fasting and postprandial glucose levels in the blood[12].
- **Serum Insulin levels:** Measured through enzyme-linked immunosorbent assay (ELISA) kits that are sensitive in monitoring endogenous secretions of insulin.
- **Oral Glucose Tolerance Test (OGTT):** A set of tests done to measure how glucose moves out of the blood in a period of time after an oral dose of glucose, which is an assessment of insulin sensitivity and metabolism of blood glucose.
- **Oxidative stress markers:** The activities of superoxide dismutase (SOD), catalase (CAT) and malondialdehyde (MDA) are measured as homogenates of liver and pancreas. The markers indicate the residual antioxidant potential and antidiabetes protection of the complexes to diabetes-induced oxidative damage.
- **Histopathological Analysis:** It examines pancreatic tissue under the microscope to establish the status of islet cells stability and necrosis, inflammation or regeneration following treatment.

All these assays contribute to a complete picture of pharmacodynamics and therapeutic potential of the complexes[13].

2.4.Critical Evaluation of Research Findings

- **Strengths**
  - **Cost-Effective and Eco-Friendly:** Green synthetic pathways reduce hazards to the environment by avoiding or limiting non-toxic reagents, as well as toxic and hazardous solvents. These strategies also reduce the cost of producing pharmaceuticals, and thus they are quite appropriate in sustainable development of pharmaceuticals particularly in the low resource setting.
  - **Biological Significance:** Schiff base derived metal complexes have a multi pronged biological effect. They usually work by means of antioxidant mechanisms, insulinotropic effects and inhibition of carbohydrates-metabolizing enzymes and hence hit multiple diabetes coping levels[14].
  - **Scarce Ability to Scale or Reproduce:** In general, green chemical synthesis methods are not complex and have few steps involving less advanced instrumentation. This easy scalability allows it to be easily created in large scale production, and it is also easy to repeat in various research environments.
- **Weaknesses**

- **Failure in the Mechanism of Action:** The mechanism of action of these metal complexes is unknown, with little information available regarding the absorption, distribution, metabolism, excretion (ADME) and chronic-toxicity of these lead-containing metal complexes. This discrepancy prevents their advancement towards the clinical trials.
- **Restricted Standard Comparisons:** They are not always compared with normal antidiabetic medications such as metformin or glibenclamide. Such irregularity hampers the benchmarking of the efficacy as well as safety of metal complexes prepared through the green synthesis method[15].
- **Species and Model Limitations:** Most of pharmacological tests are carried out in species like rodents which do not exactly resemble the human metabolic and physiological environments. Therefore, their extrapolation to human applications has to be done with caution and has to be validated.
- **Solubility and Bioavailability problems:** Some metal complexes have problems with solubility, stability or bioavailability in biological systems. These restrictions can therefore require progressive formation means, e.g. encapsulation with nanocarriers, in order to boost treatment efficacies[16].

3. STRUCTURE–ACTIVITY RELATIONSHIP AND MECHANISTIC INSIGHTS INTO METAL-SCHIFF BASE COMPLEXES

The antidiabetic activity of metal complexes of Schiff bases is highly dependent upon the metal ion, as well as the ligand structure and synergistic or additive effects of both to ameliorate oxidative stress. The characteristic action of complexes of Cu (II), Zn (II), Co (II), Ni (II) is the antioxidant activity, mimicking insulin, enzyme inhibition and glucose control. The electron donating and aromatic ligands increase metal binding, antioxidant effects, and bioaccessibility. They increase tissue insulin sensitivity, endogenous antioxidant enzymes, and protect the β-cells and minimize oxidative damage to the β-cells. They are multi-targeted and this is reflective of their potential in the treatment of diabetes as a result of redox or metabolic modulation applications[17].

3.1.Theme 1: Metal-Ion Specific Effects

The central metal ion- The pharmacological effectiveness of Schiff base metal complexes in antidiabetic procedures is highly determined by the nature of the central metal ion since each metal has unique biochemical assets that influence numerous metabolic routes. The high antioxidant activity of complexes of copper (Cu (II)) is especially marked. They mimic the effect of superoxide dismutase (SOD), the main enzyme involved in the reduction of oxidative stress, hence contain reduced proportions of reactive oxygen species (ROS) and oxidative stress indicators such malondialdehyde (MDA). Cu (II) complexes have beneficial effects in diabetes management by protecting 8-cells and hepatocyte tissue against oxidative damage that would otherwise destroy these cellular components and impair insulin secretion[18].

Inherent biological importance Zinc (Zn(II)) complexes have intrinsic biological importance because of the naturally occurring importance of zinc in insulin production, storage, and secretion. In β-cells, zinc is required to crystallize insulin to maintain its structure as well as readiness to be secreted. The Zn(II)-Schiff base complexes have also been found to exhibit

insulin-mimetic properties improving the glucose uptake and stimulating the endogenous insulin release. They are also shown to preserve the building up of islets, and enhance glucose tolerance in diabetic models, which emphasizes their ability to control the course of both insulin-dependent and independent patterns[19].

Action of cobalt (Co(II)) complexes is due to their similarity with insulin action and their effect on important enzymes of gluconeogenesis. Such complexes were found to suppress the activities of enzyme including glucose-6-phosphatase and phosphoenolpyruvate carboxykinase (PEPCK) involved in the manufacture of glucose in the liver. Inhibition of hepatic gluconeogenesis by Co(II) complexes is also likely to reduce fasting blood glucose and thus, the complexes have potential as hyperglycemia treatment agents.

Less investigated are nickel (Ni(II)) complexes with displayed inhibitory effect on digestive enzymes, notably the a-glucosidase, which retards the process of carbohydrate break down to glucose. It leads to a decrease in the rate at which glucose is assimilated as well as a decrease in postprandial (after-meal) rises in blood glucose levels. They are useful in balancing acute changes in glucose, and may supplement the effects of the insulin or other anti-hyperglycemic agents[20].

3.2.Theme 2: Ligand Structure and Activity

The structure and design of ligands Schiff base play a very important role in ascertaining the biological activity of their metal complexes. The nucleophilicity of imine nitrogen increases in the presence of hydroxyl (-OH) and methoxy (-OCH 3) electron donating groups, which explains the stronger and more stable binding of the metal ions. Antioxidant activity is also achieved through these substituents because they enter into electron transfers of the neutralization of ROS thus increasing the therapeutic effect of the complexes[21].

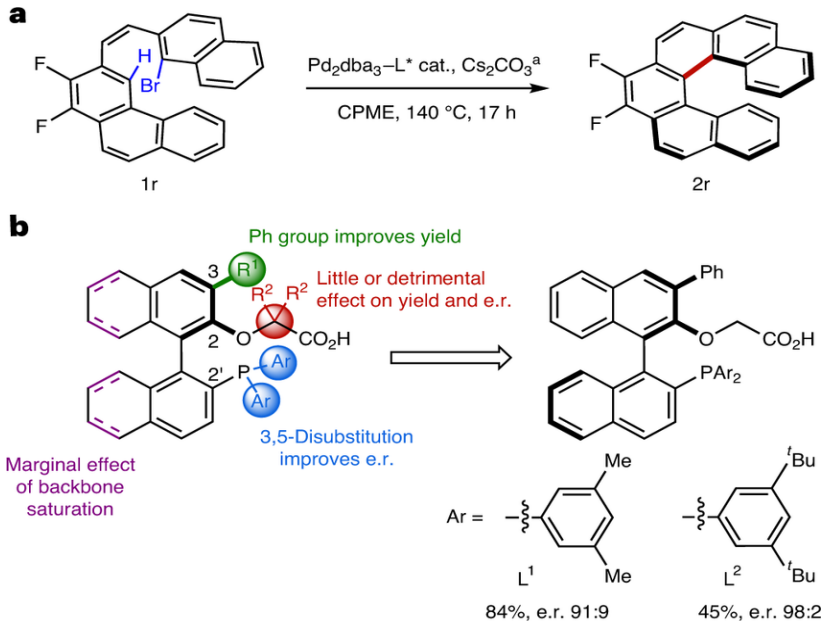

Figure 3: Ligand Structure and Activity[22]

Adding aromatic or heteroaromatic rings to the ligand backbone enhances the PI-conjugation stabilizing the complex; further it helps it engage with biological macromolecules (enzymes, transporters and receivers). This is also a structural property that amplifies the binding of the

complex to glucose-regulating biomolecules and the probability of excellent pharmacodynamics[23].

Moreover, bidentate or tridentate ligands, i.e, agents that have the property of forming chelate rings by coordinating with the metal atom through 2 or 3 donor atoms, respectively (typically N, O, or S), form chelate rings with a high degree of stability. The presence of those rings enhances the total stability, solubility, and hydrolytic degradation resistance by physiological conditions. Plane ligands facilitate 0-π interactions with biomolecular targets, flexibility optimizes binding inside enzyme pockets and the hydrophobicity promotes uptake through cell membranes. Collectively, such features guarantee the successful intracellular transport and the extended pharmacological effect of the metal complexes[24].

3.3.Theme 3: Oxidative Stress and Antidiabetic Effect

Central to the pathogenesis of Type 1 and Type 2 diabetes is oxidative stress which plays a significant role in the damage of pancreatic 2 cells and facilitating insulin resistance in extra pancreatic tissues[25]. The Schiff base metal complexes because of their redox-active metal centers and antioxidant ligand structure can have proven great free radical scavenging activity to prevent this damage.

The experimental studies have repeatedly demonstrated that the use of these complexes lowers the markers of oxidative stress e.g. MDA, at the same time increasing the concentrations of endogenous antioxidant enzymes e.g. SOD, catalase (CAT), and glutathione peroxidase (GPx). It is the primary line of defense against ROS and these enzymes play a vital role in redox homeostasis of the cells[26]. The increase in the levels of these enzymes are signs of activation of protective cellular processes and maintenance of tissue integrity.

This antioxidant effect maintains the functional integrity of islet cells by averting apoptosis and facilitating insulin production by stimulating regeneration of islet cell s in the pancreatic tissue. The result in the peripheral tissues (pediatrics), like liver, skeletal muscle and adipose tissue is a rise in insulin sensitivity and glucose uptake and utilization. Notably, antioxidant properties are frequently related with the existence of phenolic or polyphenolic functional groups in Schiff base ligating, which have a direct role in the free radical neutralizing attribute of the complex. The combination of both processes, i.e., a decrease in oxidative stress and metabolic enzyme modulation, highlights the extensive antidiabetic potential of Schiff base metal complexes and qualifies them as interesting candidates in multi-target drug development strategies[27].

4. MECHANISTIC INSIGHTS INTO ANTIDIABETIC ACTION OF SCHIFF BASE METAL COMPLEXES

The mechanism of action of Schiff base metal complexes in antidiabetic activities is multifactorial and has interdependent effects on various pathways of glucose homeostasis, insulin signaling cascade, oxidative stress and preservation of 8 cells. These mechanisms are not mere hypoglycemic functions, but provide an integrated treatment of diabetes.

4.1.Insulin Mimetic and Sensitizing Effects

Some Schiff base metal complexes particularly those involving vanadium and zinc and chromium ions have been shown to have an insulin like activity by stimulating important

molecular elements of the insulin signal pathway. Among them are insulin receptor substrates (IRS-1 and IRS-2), phosphatidylinositol 3-kinase (PI3K), protein kinase B (Akt) that influence the uptake and usage of glucose on insulin sensitive tissues. It has also been demonstrated by experimental work with diabetic rats that such complexes encourage glycogen production within the liver and the increase of GLUT4 movement to the cell membrane within the muscle and fat tissues, which allows increasing cellular glucose uptake. This insulin-sensitizing effect aids to enhance systemic insulin reactivity especially to insulin-resistance conditions like Type 2 diabetes[28].

4.2.Inhibition of Carbohydrate-Metabolizing Enzymes

The other important mechanism would be is--inhibition of special enzymes which causes the carbohydrate digestion and glucose manufacturing in the liver. The metal complexes of Schiff bases have demonstrated significant inhibitory effect on a pair of enzymes of complex carbohydrate digestion process, that is, on α-amylase and α-glucosidase. Blocking of these enzymes slows down the digestion of the carbs that also slows down their absorption of glucose in the blood hence reducing the spiking of blood glucose after food. There are metal complexes which inhibit enzyme glucose-6-phosphatase, in the liver, which plays important role in gluconeogenesis and glycogenolysis. These complexes also help to further lower the concentration of glucose in the blood during fasting and better glycemic control by inhibiting hepatic glucose production[29].

4.3.Antioxidant and Anti-inflammatory Mechanisms

The main contributors to the development of a β-cell dysfunction and insulin resistance are oxidative stress and long-term low-grade inflammation. Schiff base metal complexes resist these reactions by very strong antioxidant behavior, partly brought about by the metal complex (e.g. Cu(II) or Zn(II)) and partly by the phenolic or polyphenolic ligand. These complexes are suitable scavengers of reactive oxygen species (ROS), stimulate the increases of endogenous antioxidant enzymes including superoxide dismutase (SOD), catalase (CAT) and glutathione (GSH). Moreover, a number of studies have also shown that they are able to downregulate pro-inflammatory cytokine such as tumor necrosis factor-alpha (TNF-a) and interleukin-6 (IL-6), which is known to interfere with insulin signaling pathways. These complexes reverse the weight loss caused by low insulin action levels in the body by regulating oxidative and inflammatory stress associated with metabolic imbalances in the body.

4.4.Pancreatic β-Cell Regeneration and Protection

One hallmark pathophysiology of diabetes is that there is decay or collapse of insulin-secreting beta cells of the pancreas. These schiff base metal complexes have demonstrated the potential to shield the pancreatic 8-cells against the cytotoxicity caused by STZ, or alloxan and histopathological study has been used to prove that effect in diabetic animal models. The use of such complexes triggers rebuilding of the islet structure, the augmented production of β-cells, and better insulin secretion. This factor that promotes healing or cell survival is termed regenerative or cytoprotective effect and is due to their antioxidative nature, enzyme inhibition and due to their influence in cellular repair mechanisms. Therefore, not only can these complexes stop the destruction of β-cells, but also stimulate the restoration of their functioning, which becomes a lasting therapeutic advantage.

Table 1: Summary of Selected Studies on Schiff Base Metal Complexes and Their Biological Activities[30]

Author(s)	Study	Focus Area	Methodology	Key Findings
Shukla et al. (2018)[31]	Synthesis, characterization, in vitro anti-diabetic, antibacterial and anticorrosive activity of some Cr (III) complexes of Schiff bases derived from isoniazid	Antidiabetic, antibacterial, anticorrosion activity of Cr(III) Schiff base complexes	Synthesis of Cr(III) complexes, spectral characterization (UV-Vis, FTIR, NMR), in vitro assays	Cr(III) complexes exhibited promising in vitro antidiabetic and antibacterial activity along with anticorrosive potential
Shukla et al. (2019)[32]	Biochemical relevance of Cr (III) complexes of isoniazid: synthesis, characterization, DFT, antibacterial screening, antioxidant activity and glucose-lowering effect in STZ-induced diabetic rats	Antidiabetic and antioxidant effects in vivo	Synthesis, spectral analysis, DFT studies, in vivo testing in STZ-diabetic rats	Cr(III) complexes showed strong antioxidant and glucose-lowering effects; DFT supported stability and bioactivity
Sinicropi et al. (2022)[33]	Metal complexes with Schiff bases: Data collection and recent studies on biological activities	Comprehensive review of biological activities of Schiff base metal complexes	Literature survey and data analysis	Broad range of metal complexes showed antimicrobial, anticancer, and antidiabetic effects, highlighting versatility
Sudha (2022)[34]	Investigation of new Schiff base transition metal (II) complexes: theoretical, antidiabetic and	Antidiabetic activity and molecular modeling	Synthesis, FTIR, UV-Vis, NMR, in vivo studies, molecular docking	Complexes demonstrated antidiabetic efficacy and good binding affinity to

	molecular docking studies			insulin-related targets in docking studies
Swathi & Ayodhya (2024)[35]	Design, structural characterization, DNA interaction, antibacterial, antioxidant, and cytotoxicity studies of Co(II), Ni(II), Cu(II), Zn(II) complexes	Multifunctional evaluation (antioxidant, cytotoxic, antibacterial)	Synthesis, spectral studies, DNA interaction, antioxidant and cytotoxicity assays	

5. DISCUSSION

The review points out that the Schiff base metal complexes prepared by green strategies, more so, those of Cu(II), Zn(II) and Co(II) metal possess considerable antidiabetic effects in animal models acting via some mechanisms, such as insulin mimicry, enzyme inhibition and antioxidant agent[36]. Such environmentally friendly complexes do not only enhance the control of glucose level, but they are also in line with the postulates of green chemistry. Nevertheless, disadvantages are given by the lack of the long-term toxicity, pharmacokinetic data and direct comparison with standardized drugs. Future studies are to be concentrated on mechanistic studies, further drug delivery techniques, or uniform protocols to improve clinical translation and therapeutical use.

5.1.Interpretation and Analysis of the Findings

The literature thus analyzed in this paper reflects that the prospect of the Schiff base metal complexes synthesized by employing green techniques as the potential antidiabetic agent is very high, particularly in the preclinical animal model[37]. The complexes, and especially those that include Cu(II), Zn(II) and Co(II), exhibit multifaceted modes of action, including insulin mimicry, glucose-metabolizing enzyme inhibition and antioxidant protection. The activities help in enhancing glucose tolerance, reduction of fasting blood glucose levels, and regeneration of pancreatic beta cells. The strategy of using plant extracts and environmentally friendly solvents makes the process synthetic more biocompatible and sustainable and suits in the objectives of green chemistry. Moreover, structure activity relationship (SAR) analysis implies that the presence of electron-donating and aromatic groups in ligands have a large influence over stability and biological activity of these complexes. In general, the evidence confirms the therapeutic capability of these green-synthesized complexes in the management of diabetes at pre-clinical level.

5.2.Implications and Significance

The results of the given review are widely applied to related spheres of green chemistry, coordination chemistry, pharmacotherapy of diabetes. The incorporation of sustainability in the

designing of drugs implies that these metal complexes overrule the commonly raised environmental and toxicological issues linked with traditional drug synthesis. Future implementation of them in drug development pipelines as part of standalone drugs or an adjunct to current antidiabetic medications is justified by their effectiveness in animal models. This can be discussed in terms of integrative management of diabetes because of the capacity of these complexes to provide their overall effects in various biochemical pathways such as reduction of oxidative stress and inhibition of enzymes among others. The improved bioavailability, as well as pharmacodynamic properties as a result of metal-ligand coordination, also indicate a way ahead of addressing the challenges posed by traditional small-molecule drugs[38].

5.3.Gaps and Future Research Directions

Though it has promising results, there are also a few limitations that should be dealt with. To begin with, the lack of the comprehensive pharmacokinetics and long-term toxicological investigations in animal models are essential to the clinical translation. The available research merely investigates the short term effect and bio-distribution characteristics or patterns of waste are not adequately discussed or investigated. Secondly, efficacy is difficult to benchmark because a very few studies have conducted head-to-head comparisons with standard antidiabetic medications[39]. These complexes also need to be evaluated in other animal models other than rodents to know animal specific responses. Moreover, the problems of solubility and bioavailability in physiological conditions should be addressed, perhaps with the help of nanocarrier-delivery systems. The next step in future research should be on mechanistic studies at molecular level with molecular biology tools, comparative pharmacology and enhanced formulations to increase delivery and therapeutic efficacy. Reproducibility will also be enhanced and the progress to clinical evaluation boosted with a more standardised approach in synthesis, characterisation and biological testing[40].

6. CONCLUSION

Schiff base metal complexes green-synthesized especially including metals such as Cu (II), Zn (II), and Co (II) have been shown to have good antidiabetic outcome in animals with enhanced glucose homeostasis through different ways, such as insulin-mimetic activity, and halting of carbohydrate-metabolizing enzymes, and prevention of oxidative stress. In a green approach, synthesis in these complexes with biocompatible solvents like plant extracts and solvents makes sure that the complex provides a sustainable platform to the traditional methods of drug synthesis besides providing enhanced biocompatibility. The existence of electron-donating and aromatic groups in ligand structures also enhance their efficacy and stability in a biological process, as evidenced by structure-activity relationships analysis. Nevertheless, there are still unfilled knowledge gaps within the pharmacokinetics, long-term safety and efficacy versus the standard treatment. Most of them are short-term studies in which toxicological profiling or biodistribution data are very limited and any clinical translation is limited. Future studies are warranted to be conducted on more mechanistic study, animal testing in various animal models and using formulation advance delivery systems to transcend the problem of bioavailability. Synthesis and biological assessment standardization will be necessary to move closer to clinical use as well as achieve full therapeutic potential.

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