RES MILITARIS
REVUE EUROPEENNE D ETUDES EUROPEAN JOURNAL OF MILITARY STUDIES
Social Science Journal

Innovative synthetic strategies for dual action antidiabetic and neuroprotective drugs: Addressing diabetes-induced neuropathy

[1*]Dr. Bhuvaneshwari Y. Rane, [2]Gaurav G. Jagtap, [3]Rahulsing U. Khairnar, [4]Dr. Samikha P. Warke, [5]Dr. Parag R. Patil
Department of Pharmaceutical Chemistry, KYDSCT'S College of Pharmacy Sakegaon Bhusawal 425201

Corresponding author: ranebhuvaneshwari718@gmail.com

Abstract
The chronic metabolic disorder known as diabetes mellitus is linked to a wide range of complications, the most prominent of which is diabetic neuropathy, which has a significant impact on the quality-of-life people who have diabetes experience. The current treatment strategies frequently fail to be effective and require the utilization of distinct therapies for the control of glycemic levels and the protection of nerves. This results in difficulties in patient compliance and maintenance of the condition. The potential of dual-action drugs, which are drugs that combine neuroprotective and anti-diabetic properties into a single formulation, is investigated. The mechanistic synergy that exists between the regulation of glucose and the health of nerves, we bring to light the rationale behind a combined therapeutic approach. As a means of developing effective compounds that are tailored to diabetic environments, a number of novel synthetic strategies are being discussed. These strategies include multifunctional drug design, pharmacophore hybridization, and the prodrug approach. Additional support for the development of this field comes from the identification of important chemical scaffolds, as well as from the utilization of contemporary synthetic techniques. The shift toward dual-action therapies represents a significant advancement in the management of complications related to diabetes. This advancement has the potential to improve patient outcomes as well as the overall quality of life.
Keywords: *diabetes, neuropathy, dual-action drugs, antidiabetic, neuroprotective, pharmacophore hybridization, multifunctional design, patient compliance.*

1. Introduction

The neuropathy that is caused by diabetes is a serious complication that occurs when high blood sugar levels are maintained for an extended period of time, which ultimately involves nerve damage. Pain, numbness, and difficulty with motor functions are all symptoms that patients typically experience. When it comes to long-term efficacy and patient compliance, traditional treatments frequently concentrate on controlling blood glucose and managing neuropathy in a separate manner. However, this approach has limitations. Innovative dual-action drugs that can simultaneously offer neuroprotective and anti-diabetic benefits are currently being developed by researchers in order to address these challenges. By addressing two essential facets of diabetes management, dual-action drugs showcase a promising approach to the disease. These medications not only help to regulate blood sugar levels but also assist in the repair of nerves and protect them from damage. They accomplish this by combining the control of glucose with neuroprotective effects. The creation of hybrid molecules is one method that is being investigated in relation to the process of synthesis. The structure of these molecules is such that they possess both neuroprotective and anti-diabetic properties under one roof. An example of this would be the combination of neuroprotective agents that have antioxidant or anti-inflammatory effects with existing glucose-lowering medications such as biguanides and thiazolidinediones. The combination of these pharmacophores results in the creation of a single medication that is capable of regulating glucose levels and protecting nerves for the same time. Another developing field is the application of nanotechnology to the development of drug delivery systems. Because of this, it is possible to precisely target the tissues that are affected, which increases the effectiveness of the drug while simultaneously reducing any unwanted side effects. Nanoparticles have the potential to enable more efficient delivery of the drug to regions that are afflicted with both neuropathy and diabetes, thereby improving the outcomes of therapeutic interventions. With their ability to react to diabetic environments, enzyme-activated prodrugs provide a novel solution. Inactive until they are exposed to high glucose levels or oxidative stress, these medications then release active compounds that address both blood sugar and nerve health. As a result, they are highly targeted and effective in treating both conditions.

1.2 Neuropathy prevalence

Diabetes is a major and often disabling condition that can cause diabetic neuropathy, also known as diabetes-induced neuropathy. The risk rises with the length of the disease and affects approximately 50% of those with diabetes. Extended periods of uncontrolled hyperglycemia lead to peripheral nervous system damage, which is the main cause of the condition. Peripheral neuropathy, which affects the legs and feet, is the most prevalent kind of neuropathy. Neuropathy caused by diabetes can cause mild to severe symptoms such as burning sensations, tingling, numbness, sharp pain, and weakness in the muscles. Injury detection becomes more challenging as the disease worsens because patients may lose feeling in impacted areas, especially in the feet. In severe situations, this can result in amputations from undetected wounds, infections, and foot ulcers. Increasing the risk of falls and other injuries is the development of motor dysfunction, which affects mobility and balance. Diabetic neuropathy has more than just uncomfortable physical effects. Patients quality of life is greatly diminished by their ongoing pain and loss of autonomy. The diminishing capacity to carry out daily tasks causes many to face emotional and psychological difficulties, including depression, anxiety, and frustration. Individuals with diabetes may experience a decline in work productivity and social interactions due to this condition, which is a primary cause of disability. Diabetic neuropathy is a major resource-intensive condition for healthcare providers. Medical costs are raised when neuropathy-related complications are managed, including wound care, pain management, physical therapy, and hospital stays. To manage symptoms and stop additional nerve damage, patients frequently need lifetime care [1,2,3].

1.3 Need for dual drugs

The complicated nature of diabetes-induced neuropathy has resulted in the requirement for dual-action drugs that are capable of providing both neuroprotective and anti-diabetic effects. The management of blood sugar levels is one of the most important factors in preventing further complications; however, it does not directly address the nerve damage that is caused by hyperglycemia that is prolonged. The current treatment options are frequently insufficient, necessitating the use of separate medications for the control of glucose levels and the relief of neuropathy. Taking this approach can result in an increase in the number of adverse effects, interactions between medications, and a decrease in patient adherence due to the complexity of treatment regimens. Both the metabolic and neurological aspects of diabetes can be simultaneously targeted by dual-action drugs, which offer a promising solution to the problem. The nerves that have been damaged by diabetes would be protected or repaired by these medications, in addition to helping to regulate blood glucose levels. Managing diabetes while addressing the underlying cause of nerve damage is possible through the synergy between glucose control and neuroprotection, which has the potential to slow or even stop the progression of diabetic neuropathy. Dual-action drugs simplify treatment for patients, leading to a reduction in the number of medications that are required to treat their condition. Patients are more likely to adhere to a regimen that is simplified, which can lead to an improvement in compliance. The challenge that lies ahead in terms of the development of drugs is the creation of compounds that successfully combine neuroprotective and anti-diabetic activity. On the other hand, recent developments in drug synthesis and molecular design, such as hybrid molecules and enzyme-activated prodrugs, are paving the way for the development of these dual-action therapeutic modalities. In the long run, these medications might be able to offer a more all-encompassing and effective method of managing diabetes as well as the complications that are associated with it, thereby giving patients a notably better quality of life [4,5].

2. Current Treatment of Diabetes-Induced Neuropathy

2.1 Limited treatment success

The effectiveness of current therapies for diabetes-induced neuropathy in treating nerve damage and blood sugar regulation is limited, which results in less than ideal patient outcomes. Conventional therapies usually address only one aspect either neuropathic pain is treated with painkillers, antidepressants, or anticonvulsants, or blood glucose is controlled with antidiabetic drugs such as insulin, metformin, or sulfonylureas. Nevertheless, neither strategy sufficiently treats the underlying nerve damage brought on by long-term hyperglycemia. While crucial for regulating blood sugar, anti-diabetic medications are ineffective at preventing or reversing nerve damage. They do not actively repair or shield the peripheral nervous system from the long-term effects of diabetes, even though they may lower the risk of developing new problems. Consequently, patients may still be susceptible to the development of neuropathy even with carefully controlled blood sugar levels. Neuropathic painkillers, on the other hand, mostly treat symptoms without treating the underlying cause. These medications cover up the discomfort but don't stop the nerve deterioration. As nerve damage worsens over time, higher dosages of painkillers may be necessary. However, these drugs frequently have serious side effects, like dependency or drowsiness. Patients who take multiple medications for their neuropathy and antidiabetic treatments are said to be polypharmacy. Because it becomes more difficult to manage multiple medications, there is a greater chance of drug interactions, side effects, and decreased treatment adherence [6].

2.2 Separate drugs for diabetes & neuropathy

The current treatment methods frequently depend on the administration of distinct drug therapies to alleviate the symptoms of nerve damage and regulate blood sugar levels. Metformin and insulin are examples of antidiabetic medications that effectively regulate glucose levels; however, they do not address the underlying nerve deterioration. Although these medications are essential for metabolic regulation, they impair nerve function and render individuals susceptible to complications. However, analgesics, antidepressants, or anticonvulsants are the most common treatments for nerve pain. in contrast. Symptom relief is the primary objective of these medications; however, they do not repair or safeguard the nervous system. While patients may experience temporary pain relief, the progression of nerve damage persists, resulting in a cycle of escalating medication dosages and supplementary side effects. Drug interactions and potential adverse reactions are exacerbated by the dependence on multiple medications, which complicates treatment regimens. The treatment of multiple prescriptions can be overwhelming, resulting in ineffective overall management of the condition and decreased adherence. The necessity for a more comprehensive approach is emphasized by the fragmentation of therapy. By integrating the functions of metabolic control and nerve protection into a single agent, the development of dual-action drugs could simplify treatment. This type of innovation would not only improve therapeutic efficacy but also improve patient compliance by reducing the number of medications required. In the final analysis, a unified treatment strategy could more effectively address both aspects, providing a comprehensive solution to enhance quality of life and health outcomes [7,8].

2.3 Side effects, compliance issues

A patient's compliance is frequently impacted by the serious side effects that can arise from taking multiple medications to control blood sugar levels and relieve nerve pain. Adverse reactions are more likely to occur when patients take multiple medications at once, as each drug has a unique risk profile.

Weight gain, gastrointestinal problems, and hypoglycemia are common side effects of antidiabetic drugs, whereas sleeplessness, vertigo, and cognitive impairment are common effects of painkillers. It may be difficult for people to follow their recommended regimens because of these side effects. Maintaining consistency in treatment becomes more difficult for patients due to the complexity of managing multiple prescriptions, which can complicate daily routines. When managing multiple prescriptions becomes more difficult, some people may unintentionally forget to take their medications or quit completely. Noncompliance can worsen symptoms and raise the risk of complications in addition to impeding effective management. A common factor influencing adherence is the psychological toll that managing chronic conditions takes. A patients motivation to adhere to treatment plans may be further weakened by feelings of frustration, anxiety, or depression. A more simplified approach to therapy is required, as evidenced by this cycle of side effects and decreasing compliance. Due to their ability to minimize side effects, simplify treatment regimens, and require fewer medications overall, dual-action drugs may help address these problems. Such medications would probably improve patient adherence and overall health outcomes because they address nerve protection and blood sugar control in a single formulation [9].

3. Dual-Action Therapeutic Approach

3.1 Combined glucose control & neuroprotection

Combining antidiabetic and neuroprotective effects makes sense because glucose metabolism and nerve health are regulated by similar pathways. Hyperglycemia can cause metabolic dysregulation, oxidative stress, and inflammation all of which aggravate nerve damage. Treatments that target both aspects at the same time can more successfully address the underlying causes of complications. Mechanistic synergy is achieved via multiple important pathways. Oxidative stress a major contributing factor to nerve degeneration is lessened when glucose levels are stable. Reactive oxygen species (ROS), which harm nerve cells, can be produced in greater quantities when there is a high concentration of glucose. Antidiabetic medications can reduce oxidative damage and support nerve health by enhancing glycemic control. An important factor in diabetic complications is inflammation. Persistently high blood sugar levels can set off inflammatory reactions that exacerbate damage to nerve tissue. This inflammatory burden can be decreased and nerve function preserved by combining neuroprotective agents with antidiabetic medications that have anti-inflammatory qualities. Neuronal health is directly impacted by some glucose metabolism-related pathways, such as the insulin signaling pathway. Insulin supports neuronal growth and survival by having neuroprotective effects. Improved glucose control and neuronal cell protection are two advantages of increasing insulin sensitivity with antidiabetic drugs. The pathways that facilitate neuronal regeneration and repair are frequently targeted by neuroprotective agents. Better results in managing nerve damage result from the combination of drugs that regulate blood sugar with an overall therapeutic effect [10].

3.2 Advantages over current treatments

Dual-action drugs are superior to conventional therapies for complex conditions like diabetes. A key benefit is their comprehensive treatment approach are as shown in the figure 1. These drugs can treat diabetes and its complications by targeting metabolic regulation and neuroprotection, potentially improving outcomes. These drugs can improve patient compliance and convenience. With multiple therapeutic effects in one formulation, patients are less likely to miss doses or struggle with multiple prescriptions. For chronic disease management, this simplified approach can boost treatment adherence. Dual-action drugs may optimize dose. Combining two therapeutic effects allows lower doses of each component, reducing side effects and toxicity while maintaining efficacy[11]. This may also reduce polypharmacy side effects. Dual-action therapies spur drug design and formulation innovation, enabling new compounds to meet patient needs. This forward-thinking approach makes dual-action drugs a major chronic disease treatment advancement.

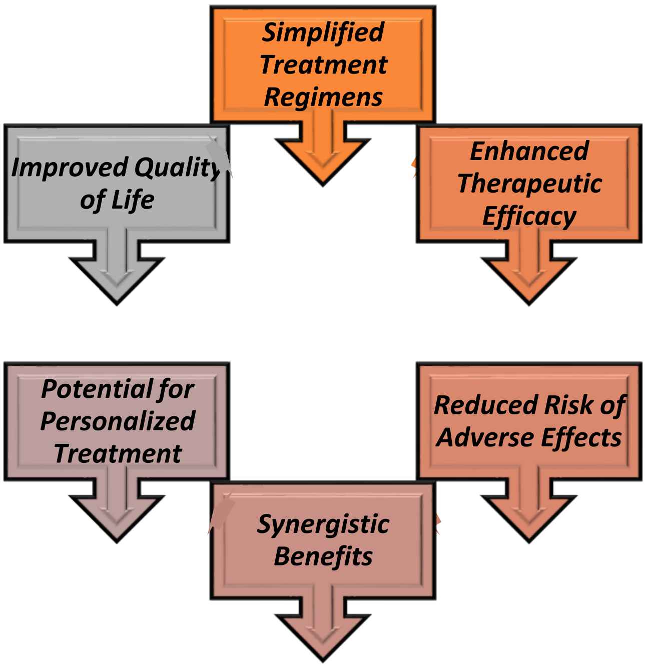

Figure 1: Advantages of dual-action drugs over conventional therapies

- *Simplified Treatment Regimens*: Dual-action medications combine neuroprotection and glucose regulation into one formulation. For patients who frequently find it difficult to manage several prescriptions, this method greatly lessens the complexity of their treatment. Patients are more likely to follow their medication regimens when they have to take fewer pills, which leads to improved control of their blood sugar levels and nerve health. By making things simpler, caregivers who help with medication management may find it easier.

- *Enhanced Therapeutic Efficacy*: Dual-action medications can more successfully address the underlying causes of complications because they simultaneously target neurological and metabolic factors. Patients may be exposed to additional nerve damage as a result of conventional therapies, which may only manage one aspect of the condition or relieve symptoms. Dual-action drugs have the ability to effectively control blood sugar levels and potentially slow or reverse the advancement of nerve damage, improving long-term results and general health [12].

- *Reduced Risk of Adverse Effects*: Drug interactions and the cumulative effect of side effects make patients who take multiple medications more susceptible to adverse effects. Dual-action medications reduce the need for multiple medications, hence minimizing this risk. A more controllable side effect profile and a decreased chance of adverse interactions result from using fewer medications. Patients may find it easier to adhere to their recommended regimens as a result of the substantial improvements in treatment comfort and safety that can result from this.

- *Synergistic Benefits*: Dual-action medications can take advantage of the interrelated pathways that are involved in nerve and glucose metabolism. Enhancing insulin sensitivity with anti-diabetic ingredients may also have neuroprotective effects. Through the reduction of oxidative stress and inflammation, two major factors contributing to nerve damage, these drugs can work in concert to improve neurological and metabolic health, providing more thorough management of complications associated with diabetes.

- *Potential for Personalized Treatment*: The creation of dual-action medications creates new opportunities for tailored healthcare. Medical professionals can customize these drugs to meet each patient's specific needs by considering things like the degree of nerve damage, coexisting conditions, and general health profiles. By taking a focused approach, a more successful management strategy can be implemented, which raises the possibility of favorable health outcomes and enhances the patient experience.

- *Improved Quality of Life*: Dual-action medications can greatly improve patients' quality of life by meeting several treatments needs with a single prescription. Reducing the burden of treatment not only facilitates adherence but also lessens the psychological and emotional strain that comes with managing long-term illnesses. Patients may feel less anxious and frustrated, which would increase their level of satisfaction with their treatment regimens overall. In the end, this all-encompassing method of treatment has the potential to empower patients and motivate them to take a more active role in their own health care.

4. Synthetic Strategies for Dual-Action Drugs

4.1 Multifunctional Drug Design

Innovative multifunctional drug design targets multiple therapeutic areas. This method is becoming popular for managing diabetes and nerve damage. Molecular engineering molecules that regulate blood sugar and protect neuronal health is the main goal. Simplifying treatment protocols improves adherence and patient outcomes. Science uses computational modeling and high-throughput screening to create dual-action agents. These methods find therapeutic candidate compounds. Technology allows more nuanced analysis of drug candidate-target interactions. This helps researchers optimise molecule structures for antidiabetic and neuroprotective effects. This novel method uses pharmacophore hybridization. Merging pharmacophores the structural features that give drugs their biological activity is this process. Researchers can combine existing antidiabetic and neuroprotective agents to create novel entities that combine their benefits by identifying their key components. For example, a compound with insulin-sensitizing and neuroprotective properties could be combined to manage blood glucose levels and protect nerve cells. Medical chemistry and structural biology are crucial to pharmacophore hybridization. To optimize hybrid compound effectiveness, researchers use molecular docking simulations to predict target binding. Structure-activity relationship (SAR) studies help refine these hybrids by showing how chemical structure changes affect biological activity. Iteratively selecting promising candidates for development and testing helps scientists identify the best candidates. Develop dual-action compounds for more than efficacy and patient compliance. By targeting multiple pathways simultaneously, researchers can reduce medication side effects. Treatment as a single entity reduces the risk of side effects from each drug. Patients quality of life improves as safety and management are simplified. Understanding disease mechanisms is essential to drug design, along with technical challenges. Identifying how elevated glucose levels cause oxidative stress, inflammation, and nerve damage helps researchers find intervention targets. The design process uses this comprehensive pathology view to develop compounds that treat symptoms and root causes. This innovative approach may revolutionize diabetes management as the field evolves. This method can create safe, effective, and easy-to-use medications, improving patient care. Scientists can develop new treatments for chronic diseases by combining cutting-edge chemical design with disease mechanisms. This paradigm shift leads to more integrated and effective therapeutic approaches in modern medicine [13,14].

4.2 Activation of neuroprotective compounds in diabetic environments

Drug development using the prodrug approach is promising, especially for diabetic therapies. Chemically modified prodrugs are metabolically converted into active drugs. This approach improves neuroprotective agent efficacy while reducing side effects. Diabetes can damage nerves due to high glucose levels and metabolic disturbances. Prodrugs designed for such environments can remain inactive until biochemical conditions indicate elevated glucose or oxidative stress. Uncontrolled diabetes tissues contain high levels of glucose and reactive oxygen species (ROS), which can activate certain prodrugs. Selectivity releases neuroprotective compounds where they are needed, improving efficacy and reducing systemic exposure. Improved safety is a major benefit. By releasing the active drug only in the target environment, off-target effects and toxicity are reduced. This is especially important for diabetics who are taking multiple medications and have other health issues. Controlled release of active compounds can also stabilize therapeutic levels in tissues, improving treatment outcomes. The prodrug strategy also allows the addition of functionalities to the chemical structure, improving neuroprotective agents' therapeutic profile. Neuroprotective, anti-inflammatory, and antioxidant moieties can be added to prodrugs. This multifaceted approach can benefit multiple diabetes-related nerve damage pathways. Researchers are looking for biochemical triggers to activate these prodrugs in diabetic environments. This involves studying hyperglycemic enzymatic pathways and metabolic changes. Researchers can optimize prodrug targeting and efficacy by understanding these mechanisms [15].

Conclusion

A revolutionary chance to treat diabetes and the neuropathy it causes is provided by the research into dual-action medications. The current therapeutic landscape frequently fails to adequately address the complexities of this illness, giving patients limited options for care that might not offer them complete protection or relief. Diabetes-induced neuropathy is highly prevalent, and its effects are profound, underscoring the urgent need for novel treatments that can successfully address the disease's neurological and metabolic components. The justification for merging neuroprotective and antidiabetic effects points to a potential mechanistic synergy that could improve treatment results. Researchers can develop compounds that are specifically tailored to the distinct biochemical environments found in patients with diabetes by concentrating on prodrug strategies, pharmacophore hybridization, and multifunctional drug design. By focusing on the important concerns of patient compliance and safety, this targeted approach has the potential to reduce side effects while also increasing efficacy. The development of these dual-action agents also heavily depends on the adoption of sophisticated synthetic techniques and the identification of critical chemical scaffolds. By utilizing current knowledge and creative approaches, the pharmaceutical sector can open the door for a new class of drugs that fully address the problems caused by diabetes and its aftereffects.

References

1. Prasad, N. Influence of Curcumin on Pioglitazone Metabolism and Pk/Pd: Diabetes Mellitus. Conference Proceedings of 3rd World Congress on Diabetes & Metabolism, Hyderabad, India, September 24. *J. Diabetes Metab.* **2012**, *3*, 80.

2. Khayatnouri, M.; Bahari, K.; Safarmashaei, S. Study of the Effect of Gliclazide and Garlic Extract on Blood Sugar Level in STZ-Induced Diabetic Male Mice. *Adv. Environ. Biol.* **2011**, *5*, 1751–1755.
3. Rani, T.; Sujatha, S.; Veeresham, C. Pharmacokinetic and Pharmacodynamic Interaction of Curcumin with Glimepiride in Normal and Diabetic Rats. *Pharmacogn. Commun.* **2012**, *2*, 14–21.
4. Jyothi, P.; Babu, R.B.; Narsimha, R.Y. Effect of repaglinide and curcumin combination on oxidative stress and biochemical parameters in stz induced diabetic rats. *Eur. J. Biomed. Pharm. Sci.* **2017**, *4*, 384–388.
5. Gao, J.; Xu, P.; Wang, Y.; Wang, Y.; Hochstetter, D. Combined Effects of Green Tea Extracts, Green Tea Polyphenols or Epigallocatechin Gallate with Acarbose on Inhibition against α-Amylase and α-Glucosidase in Vitro. *Molecules* **2013**, *18*, 11614–11623.
6. Pathak, N.M.; Millar, P.J.B.; Pathak, V.; Flatt, P.R.; Gault, V.A. Beneficial Metabolic Effects of Dietary Epigallocatechin Gallate Alone and in Combination with Exendin-4 in High Fat Diabetic Mice. *Mol. Cell. Endocrinol.* **2018**, *460*, 200–208.
7. Sun, X.; Cao, Z.; Ma, Y.; Shao, Y.; Zhang, J.; Yuan, G.; Guo, X. Resveratrol Attenuates Dapagliflozin-Induced Renal Gluconeogenesis via Activating the PI3K/Akt Pathway and Suppressing the FoxO1 Pathway in Type 2 Diabetes. *Food Funct.* **2021**, *12*, 1207–1218.
8. Kannappan, S.; Anuradha, C.V. Insulin Sensitizing Actions of Fenugreek Seed Polyphenols, Quercetin & Metformin in a Rat Model. *Indian J. Med. Res.* **2009**, *129*, 401–408.
9. Poonam, T.; Prakash, G.P.; Kumar, L.V. Influence of Allium Sativum Extract on the Hypoglycemic Activity of Glibenclamide: An Approach to Possible Herb-Drug Interaction. *Drug Metabol. Drug Interact.* **2013**, *28*, 225–230.
10. Williamson, G.; Sheedy, K. Effects of Polyphenols on Insulin Resistance. *Nutrients* **2020**, *12*, 135.
11. Villa-Rodriguez, J.A.; Aydin, E.; Gauer, J.S.; Pyner, A.; Williamson, G.; Kerimi, A. Green and Chamomile Teas, but Not Acarbose, Attenuate Glucose and Fructose Transport via Inhibition of GLUT2 and GLUT5. *Mol. Nutr. Food Res.* **2017**, *61*, 1700566.
12. González-Abuín, N.; Martínez-Micaelo, N.; Margalef, M.; Blay, M.; Arola-Arnal, A.; Muguerza, B.; Ardévol, A.; Pinent, M. A Grape Seed Extract Increases Active Glucagon-like Peptide-1 Levels after an Oral Glucose Load in Rats. *Food Funct.* **2014**, *5*, 2357–2364.
13. Amadi, C.N.; Orisakwe, O.E. Herb-Induced Liver Injuries in Developing Nations: An Update. *Toxics* **2018**, *6*, 24.
14. Ríos, J.L.; Francini, F.; Schinella, G.R. Natural Products for the Treatment of Type 2 Diabetes Mellitus. *Planta Med.* **2015**, *81*, 975–994.
15. Adeshirlarijaney, A.; Gewirtz, A.T. Considering Gut Microbiota in Treatment of Type 2 Diabetes Mellitus. *Gut Microbes* **2020**, *11*, 253–264.