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REVIEW: INTERACTION OF GLIMEPIRIDE WITH HERBAL PLANTS

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ABSTRACT

Glimepiride is a commonly prescribed oral antidiabetic drug for the management of type 2 diabetes mellitus (T2DM). However, extensive simultaneous use of herbal plants increases the risk of notable interactions between herbs and drugs. This systematic review analyzed the pharmacokinetic and pharmacodynamic interactions between glimepiride and various medicinal plants, based on 20 selected studies published between 2014 and 2024. The results show that several herbs including *Berberine hydrochloride*, *Licorice*, *Quercetin*, *Aloe vera*, *Ocimum sanctum*, and *Fenugreek* can alter glimepiride's metabolism, enhance its bioavailability, and increase insulin secretion, potentially amplifying its hypoglycemic effect. Although these interactions may improve therapeutic outcomes, they also increase the risk of hypoglycemia, indicating that careful monitoring and professional supervision are essential when using herbal supplements alongside glimepiride.

Keywords: Pharmacokinetic pharmacodynamics, glimepiride interaction, herbal plants.

INTRODUCTION

The use of modern medications in the management of chronic diseases such as diabetes mellitus (DM) has rapidly advanced alongside medical technology. Diabetes mellitus (DM) is a global health challenge characterized by glucose metabolism disorders caused by insulin deficiency or insulin resistance. Data from the World Health Organization (WHO) show that the number of DM patients continues to rise and is currently among the top eight leading causes of death worldwide, especially type 2 Diabetes Mellitus (T2DM), which is closely related to income, lifestyle, and dietary patterns (World Health Organization, 2024).

Glimepiride is a second-generation sulfonylurea that promotes insulin secretion from the pancreatic β-cells. Furthermore, it exerts its effects through various extrapancreatic pathways. It is commonly prescribed as a standalone treatment for individuals with type 2 diabetes mellitus, who are unable to achieve adequate glycemic control through dietary adjustments and lifestyle changes. Additionally, glimepiride can be used in combination with other antihyperglycemic medications, such as metformin and insulin, in patients whose blood sugar levels remain uncontrolled with sulfonylurea therapy alone. Studies have generally linked glimepiride to a lower incidence of hypoglycemia and reduced weight gain compared to other sulfonylureas. It is also considered a safer option for patients with cardiovascular conditions, as it does not negatively impact pre-existing ischemic diseases. This medication is effective in reducing fasting plasma glucose, postprandial glucose, and glycated hemoglobin levels, making it a practical and cost-efficient choice for managing type 2 diabetes mellitus (Basit *et al.*, 2022).

It is estimated that one-third of adults in developed countries and more than 80% of the population in many developing countries use herbal medicines to improve health and manage common diseases, such as colds, inflammation, heart disease, diabetes, and central nervous system disorders (Chhabra, Singh and Upadhyay, 2020). Traditional medicines are often used to treat diabetes because they are believed to be safer, more affordable, and have fewer side effects than conventional drugs. Numerous scientific studies have indicated that

the phytochemicals present in medicinal plants, such as *Allium sativum*, *Momordica charantia*, *Hibiscus sabdariffa L.*, and *Zingiber officinale*, exhibit anti-hypoglycemic effects and hold potential for the prevention and/or treatment of diabetes mellitus (DM) (Mierza V., 2023). The combined use of herbal plants and therapeutic drugs may lead to herb and drug interactions, which could have important clinical consequences, as suggested by the growing number of clinical reports documenting such occurrences (Chhabra, Singh and Upadhyay, 2020).

Drug interactions arise when the effect of a drug is modified by the presence of other substances, including herbal remedies, foods, drinks, or environmental chemicals. This definition applies to both conventional and herbal medicines. This effect can be harmful if the interaction leads to increased drug toxicity. A potential example is the experimental increase in toxicity observed when amikacin is administered together with ginkgo. A reduction in efficacy due to interactions can sometimes be as dangerous as the excessive enhancement of the effect of a drug. These interactions can occur through various mechanisms, namely:

1. Pharmacokinetic Interactions: These include the influence of herbal substances on drug absorption, distribution, metabolism, and excretion (ADME). Such interactions can lead to an increase or decrease in the plasma drug levels. For example, herbal products can affect gastrointestinal motility, which may alter the transit time of drugs and impact their absorption. In terms of distribution, interactions may affect plasma protein binding, which can change the distribution of drugs within the body. Displacement from protein binding sites can increase the proportion of active drugs. Herbal-related interactions in the metabolism process can influence metabolic enzymes, particularly those in the cytochrome P450 (CYP) family. The induction or inhibition of these enzymes can alter drug metabolism, potentially increasing side effects or reducing the effectiveness of synthetic drugs.
2. Pharmacodynamic Interactions: These interactions occur when the effect of a drug is altered by the use of another drug. Sometimes, these drugs directly compete for the same receptors, but more often, the interaction is indirect and involves disruptions in physiological mechanisms (Williamson Driver and Baxter, 2009).

Therefore, understanding the interaction between glimepiride and herbal plants is crucial, especially in the context of clinical practice involving combination therapies. This review examines several pieces of literature related to the interaction between glimepiride and herbal plants, covering the mechanisms, clinical impacts, and implications in the management of T2DM. This review is expected to be beneficial for clinical healthcare professionals as a reference for providing healthcare services to patients.

RESEARCH METHOD

This study was based on a systematic literature review approach. Data were obtained from scientific journals in databases, such as PubMed, ResearchGate, and Google Scholar. The selection criteria for this review encompassed articles that examined interactions between glimepiride and herbal plants, were published within the last 10 years (2014–2024), were written in English or Indonesian, and involved experimental studies or clinical trials. The exclusion criteria were articles that did not mention specific herbal plants, articles without full-text access, and journals not indexed in Scopus or Sinta. The search was conducted using keywords such as *"glimepiride herbal interaction," "interaction glimepiride herb,"* and *"pharmacokinetic and pharmacodynamic glimepiride herbal."* The initial screening process involved reviewing the titles and abstracts of articles to determine their relevance to the research topic. Articles that met the inclusion criteria were analyzed to identify the mechanisms of interaction, clinical effects, and their implications.

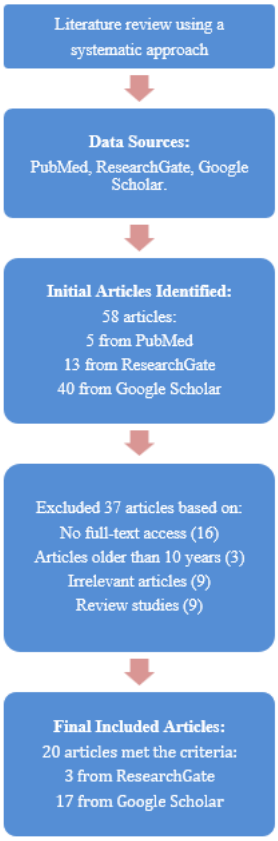

Figure 1. Systematic Review Flow Diagram

The article search yielded a total of 58 articles, consisting of 5 articles from PubMed, 13 articles from ResearchGate, and 40 articles from Google Scholar. After the initial screening based on the exclusion criteria, 16 articles were excluded due to the unavailability of full-text access, 3 articles were excluded for being over 10 years old, 9 articles were not specific to the topic under review, and 9 articles were review-type studies. This resulted in the exclusion of 37 studies. The articles that met the inclusion criteria amounted to 20, comprising 1 article from PubMed, 3 articles from ResearchGate and 17 articles from Google Scholar. Hence, these 20 articles were selected as the basis for the systematic review because they were considered relevant and met the established research criteria.

RESULTS AND DISCUSSION

Table I. Summary of the Review on the Interaction Pharmacokinetics Between Glimepiride and Herbal Plants

No	Herbal Plant	Interaction Mechanism	Study Type	Implications	Reference
1.	*Berberine hydrochloride*	*Berberine hydrochloride* can increase the concentration and bioavailability of glimepiride in the body by enhancing AUC_{0-t} and Cmax, as well as reducing CLz (clearance), most likely through the inhibition of glimepiride metabolism mediated by the	*In vivo* (dogs)	*Berberine hydrochloride* can enhance the pharmacological effects of glimepiride. Therefore, it is important to be	(Li, Zhao and Zhao, 2021)

		CYP2C9 enzyme in the liver.		aware of the potential drug interactions that may increase the risk of hypoglycemia.	
2.	*Licorice*	*Licorice* significantly increases the AUC-6, Cmax, and t1/2 of glimepiride while reducing its clearance and elimination.	*In vivo* (rats)	A significant reduction in blood glucose levels.	(Hamad et al., 2017)
3.	*Coriandrum Sativum* L	Animals administered a combination of *Coriandrum sativum* and glimepiride demonstrated notable changes in pharmacokinetic parameters, including an increase in maximum serum concentration (Cmax), time to reach peak concentration (Tmax), and volume of distribution (Vd).	*In vivo* (rats)	A notable interaction between *Coriandrum sativum* and glimepiride has been identified, with *Coriandrum sativum* potentially increasing the bioavailability of glimepiride.	(Spandana, Sreedevi and Sruthi, 2021)
4	*Quercetin*	In both normal and Streptozotocin (STZ)-induced diabetic rats, the co-administration of glimepiride with quercetin resulted in a significant increase in pharmacokinetic parameters such as Cmax, AUC_{0-n}, AUCtotal, $t_{1/2}$, and MRT. This enhancement may be attributed to modifications in glimepiride metabolism, possibly through improved absorption or inhibition of CYP2C9, the enzyme responsible for its metabolism. However, the Tmax of glimepiride remained unchanged in both groups, suggesting that the rate of absorption was not affected. Additionally, glimepiride exhibits a high serum albumin binding affinity of 99.5%. Acidic drugs have a greater potential to displace sulfonylureas from protein	*In vivo* (rats)	This combination can enhance the effectiveness of glimepiride but also increases the risk of hypoglycemia.	(Samala, 2015)

		binding sites compared to glimepiride, which is less affected due to its non-ionic binding nature. This indicates that the decreased volume of distribution may not be due to displacement of glimepiride by *quercetin*. As there is no plasma protein binding interactions between *quercetin* and glimepiride, the decreased volume of distribution may be due to meta- bolic inhibition of glimepiride by *quercetin*.			
5	*Boswellic Acids*	Co-administration of glimepiride with BSE (*Boswellia serrata* extract) and BA (*Boswellic acid*) enhances the bioavailability of glimepiride by inhibiting the CYP2C9 enzyme.	*In vivo* (rats)	Enhances the effectiveness of blood glucose reduction.	(Samala, 2013)
6	*Pterocarpus marsupium*	Glimepiride shows a reduced percentage of protein binding when combined with green synthesized silver nanoparticles from *Pterocarpus marsupium*. This indicates that the interaction with nanoparticles can affect the drug's distribution in the body, as the amount of drug bound to plasma proteins decreases, resulting in more free-form drug with pharmacological activity.	*In vivo* (rats)	Enhances the effectiveness of blood glucose reduction.	(Bavya, 2021)
7	*Andrographolide*	The co-administration of glimepiride and metformin with *Andrographolide* (AD) led to a significant increase in pharmacokinetic parameters such as Cmax, AUC_{0-n}, AUCtotal, $t_{1/2}$, and MRT. This effect may be due to alterations in the metabolism of both drugs, possibly through improved absorption or inhibition of the CYP2C9 and CYP3A enzymes involved in their metabolic pathways. Nevertheless, the Tmax for glimepiride and metformin remained unchanged in both normal and diabetic rats, indicating that	*In vivo* (rats)	The combination of glimepiride and metformin with *Andrographolide* (AD) notably enhances the glucose-lowering effects of both medications. As a result, careful dose adjustment of glimepiride and metformin may be necessary when	(Dav, 2015)

		the absorption rate of these drugs was not affected. The reduced volume of distribution is unlikely to be caused by AD displacing glimepiride and metformin, as no plasma protein binding interactions were found between AD, glimepiride, and metformin. Instead, the decreased volume of distribution may be due to the metabolic inhibition of these drugs by AD.		administered together with AD.	
8	*Ferulic Acid (*FA*) (Ligusticum chuanxiong, Angelica Sinensis, and Cimicifuga racemosa)*	A low dose of FA did not influence the metabolism of glimepiride. However, when administered with a high dose of FA, it resulted in a reduction of glimepiride plasma levels, an increase in its metabolism to hydroxy glimepiride, and changes in several pharmacokinetic parameters of both glimepiride and hydroxy glimepiride. This effect is attributed to the inhibitory action on the activity of CYPs, UGTs, and P-gp.	*In vivo* (rats)	A significant reduction in blood glucose levels.	(Lin et al., 2021)
9	*Ashwagandha*	*Ashwagandha* markedly increases the oral bioavailability of glimepiride. Additionally, diabetic rats pretreated with *Ashwagandha* exhibited a significantly greater reduction in blood glucose levels compared to those treated with glimepiride alone. This enhanced effect of *Ashwagandha* may be linked to its inhibition of the CYP2C9 drug-metabolizing enzyme in liver microsomes.	*In vivo* (rats)	Increased hypoglycemic activity.	(Nagaraj and Veeresham, 2018)
10	*Neem Leaf* extract	All the pharmacokinetic parameters such as Cmax, AUC0-n, AUCtot, t1/2 are increased and clearance and Vd are decreased when compared with control group.	*In vivo* (rats)	Increase hypoglycemic action of concomitant administration of Glimepiride with *Neem Leaf Extract.*	(Sumalatha, Vidyavathi and Thirupathi, 2017)

Table II. Summary of the Review on the Interaction Pharmacodynamic Between Glimepiride and Herbal Plants

No	Herbal Plant	Interaction Mechanism	Study Type	Implications	Reference
1.	*Capsicum frutescens* L.	A significant elevation in serum insulin levels was observed in diabetic rats following treatment with a combination of Caps*icum frutescens* and glimepiride (C. frutescens 400 mg/kg with glimepiride 2 TD (0.144 mg/200 g, p.o.) when compared to single drug/herb treated groups. It is possible that C.frutescens may initiate cell proliferation, since it has been reported that pancreatic endocrine cells have the potential to proliferate after induction of diabetes with STZ (11). It was reported that glimepiride has effect on the β- cells and increase the insulin secretion.	*In vivo* (rats)	Elevates the likelihood of hypoglycemic events.	(Raja et al., 2020)
2.	*Aloe vera*	The co-administration of Aloe vera and glimepiride leads to higher serum insulin levels in diabetic rats compared to those treated with either *Aloe vera* or glimepiride alone. This suggests that *Aloe vera* may play a role in enhancing pancreatic β-cell proliferation or stimulating insulin release, as previously reported in studies indicating that glimepiride has a direct effect on β-cells, promoting insulin secretion.	*In vivo* (rats)	Enhances the hypoglycemic effect by increasing serum insulin levels.	(Mondal et al., 2020)
3	*Ocimum s anctum*	The current study demonstrated a dose-dependent enhancement in the anti-diabetic effects of *Ocimum sanctum* and glimepiride when given individually. Moreover, the hypoglycemic effect of glimepiride was further amplified when combined with varying doses of *Ocimum*	*In vivo* (rats)	When administered together, the blood glucose-lowering effect increases significantly compared to the administration of each drug	(Ahmad, Keservani and Babu, 2015; Singh, Swati and Karunakar, 2023)

		sanctum, indicating a positive herb-drug interaction between the two.		separately.	
4	Herbs Mixture *(Roselle, Marjoram, Chamomile and Doum)*	The hypoglycaemic effect of the herbal mixture aqueous extract in the present study resulted from initiating secretion of insulin from pancreatic β cells as they improved the structure of islets, and also may be due to the enhancement of peripheral metabolism of glucose.	*In vivo* (rats)	Promising effects in controlling diabetic hyperglycaemia.	(Ibrahim et al., 2020)
5	*Fenugreek*	The combination group of glimepiride with *Fenugreek* showed a significant reduction in blood glucose levels compared to all other treatment groups at the end of the 4th and 8th weeks. This was further supported by an improvement in the histology of the pancreas.	*In vivo* (rats)	Enhances the effectiveness of blood glucose reduction.	(Haritha et al., 2015)
6	*Fenugreek*	The aqueous extract of fenugreek seeds functions as an insulin secretagogue. Its hypoglycemic effect is likely due to the stimulation of insulin production and enhanced secretion from pancreatic β-cells.	*In vivo* (rats)	The combined use of aqueous fenugreek seed extract and glimepiride yields more effective control of hyperglycemia in STZ-induced diabetic rats. Additionally, this combination eliminates the need to increase the glimepiride dosage, thereby reducing the risk of potential side effects in diabetic patients.	(Elghazaly, 2019)
7	*Stevia* extract	The combined administration of *Stevia* extract (300 mg/kg/day) and glimepiride (1 mg/kg/day) to diabetic rats over the same duration	*In vivo* (rats)	Increase hypoglycemic action of concomitant administration.	(Assi et al., 2020)

		resulted in a greater reduction in blood glucose levels compared to those treated with glimepiride alone. Diabetic rats receiving the glimepiride and stevia extract combination also showed increased insulin secretion, which contributed to the observed decrease in blood glucose levels.			
8	*Gymnema sylvestre* extract	Concomitant administration of extract and glimepiride exhibits significant increase insulin level and not show any significant change when compared with pharmacokinetic parameters	*In vivo* (rats)	Beneficial pharmacodynamic interactions whereas no major alterations in the pharmacokinetics parameters.	(Kamble et al., 2016)
9	*Azadirachta indica leaf* extracts	In this study, the interaction occurring between the leaf extracts of *Azadirachta indica* and the two second-generation sulfonylureas, glibenclamide and glimepiride, is characterized as an antagonistic interaction. This means that when the *A. indica* extract is administered concurrently with glibenclamide, the hypoglycemic effect of glibenclamide is reduced, which can affect patient treatment outcomes. The research indicates that this interaction could be more significant when the extract is given for 10 days prior to co-administration with these drugs. This interaction is linked to potential changes in calcium channels that may affect the hypoglycemic effects of the sulfonylureas.	*In vivo* (rats)	Increase hypoglycemic action of concomitant administration.	(Nduka et al., 2015)

The concurrent use of glimepiride with various herbal plants has been shown to significantly influence its pharmacokinetics and pharmacodynamics, often enhancing its antidiabetic effects. However, these interactions also increase the potential for adverse outcomes, particularly hypoglycemia, due to increased bioavailability or synergistic pharmacological effects.

Pharmacokinetic interactions primarily involve changes in the metabolism, absorption, and distribution of drugs. Several herbal plants, such as *berberine hydrochloride*, *Licorice***,** and *Quercetin*, have been found to increase the plasma concentration and prolong the half-life of glimepiride, largely through the inhibition of cytochrome P450 enzymes, especially CYP2C9 (Samala, 2015; Hamad et al., 2017; Li, Zhao and Zhao, 2021). These interactions elevate glimepiride therapeutic efficacy but simultaneously increase the risk of hypoglycemia.

Likewise, *Coriandrum sativum***,** *boswellic acid*, and *Pterocarpus marsupium* improve glimepiride bioavailability or alter its protein binding and volume of distribution, further intensifying its glucose-lowering activity (Samala, 2013; Bavya, 2021; Spandana, Sreedevi and Sruthi, 2021). Notably, *Ferulic acid* exhibited a dose-dependent effect, whereas lower doses had minimal impact; higher doses accelerated glimepiride metabolism, suggesting the importance of dosage in modulating herb-drug interactions (Lin et al., 2021).

In terms of pharmacodynamic interactions, the addition of herbal agents such as *Aloe vera*, *Ocimum sanctum*, *Stevia***,** and *Fenugreek* significantly increased serum insulin levels and enhanced β-cell activity in diabetic rats, producing a greater hypoglycemic response when combined with glimepiride (Ahmad, Keservani and Babu, 2015; Haritha et al., 2015; Assi et al., 2020; Mondal et al., 2020). *Capsicum frutescens* and a mixture of herbs, including *Roselle*, *Marjoram*, and *Chamomile*, also demonstrated promising pharmacodynamic synergy with glimepiride by improving pancreatic islet structure and stimulating insulin secretion (Ibrahim et al., 2020; Raja et al., 2020).

However, not all the interactions were synergistic. *Azadirachta indica* (Neem) exhibited a potential antagonistic interaction by reducing the hypoglycemic effect of glimepiride, likely through the modulation of calcium channels (Nduka et al., 2015). This highlights the complexity of herb-drug interactions and the need for a tailored approach based on specific herbal profiles.

Given the prevalence of herbal supplements in diabetic populations, particularly in regions such as Southeast Asia, understanding these interactions is clinically significant. Enhanced glucose-lowering effects may reduce the required dose of glimepiride, but vigilant monitoring is necessary to avoid hypoglycemic episodes. Additionally, these findings suggest the need for patient education and awareness among healthcare providers regarding the concurrent use of herbal remedies and antidiabetic medications.

Overall, while the combination of glimepiride with herbal plants presents opportunities for improved diabetes management, it also requires careful therapeutic monitoring and further research through clinical trials to validate the safety and efficacy of such combinations in human populations.

CONCLUSION

In conclusion, the interaction between glimepiride and various herbal plants such as *Berberine hydrochloride*, *Licorice*, *Quercetin*, *Aloe vera*, *Ocimum sanctum*, and *Fenugreek* can significantly enhance the drug's hypoglycemic effect through both pharmacokinetic mechanisms like increased bioavailability and enzyme inhibition and pharmacodynamic mechanisms such as stimulation of insulin secretion. While these interactions may offer therapeutic advantages in managing type 2 diabetes mellitus, they also pose a heightened risk of hypoglycemia if not properly monitored. Therefore, the combined use of glimepiride and herbal remedies should be approached with caution and guided by clinical supervision to ensure safe and effective treatment of diabetes.

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