THE POTENTIAL ACTIVITY OF ASIATICOSIDE FROM AKAR MANIS (*Glycyrrhiza glabra*) AS HYPOLIPEMIC

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Abstract

Asiaticoside, a bioactive compound derived from Glycyrrhiza glabra (licorice root), has garnered attention for its potential as a hypolipemic agent. This study explores the lipid-lowering effects of asiaticoside, focusing on its mechanism of action and pharmacological properties. In silico analysis showed a high activation probability (pa=0.934) for asiaticoside, indicating its strong potential to interact with targets involved in lipid metabolism, such as PPAR-α, and reduce blood lipid levels. Additionally, its low inhibition probability (pi=0.003) suggests minimal risk for non-specific biological interference, making it a promising candidate for therapeutic use with a favorable safety profile. Asiaticoside's antioxidant and anti-inflammatory properties further enhance its potential for cardiovascular protection by reducing oxidative stress, a key factor in atherosclerosis. While preliminary in silico results are promising, further in vitro and in vivo studies are required to confirm its efficacy, safety, and pharmacokinetics. Overall, asiaticoside represents a promising natural agent for managing hyperlipidemia and related metabolic disorders, offering an alternative to conventional synthetic therapies.

Keywords: *Asiaticoside, Glycyrrhiza Glabra, Hypolipemic, Lipid Metabolism, Antioxidant*

1. INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease whose prevalence continues to increase globally, including in Indonesia. This disease is characterized by chronic hyperglycemia due to insulin secretion deficiency, insulin resistance, or both (American Diabetes Association, 2022). Complications due to DM, both acute and chronic, can significantly affect patients' quality of life. The high health cost burden associated with DM treatment adds to the urgency of finding more effective and affordable therapies. In this context, therapeutic approaches using natural ingredients are one of the alternatives that are increasingly attracting the attention of the scientific world (World Health Organization, 2021).

The plant *Glycyrrhiza glabra*, better known as liquorice or licorice, is one of the herbal plants that has great potential in the therapeutic field. This plant has long been used in traditional medicine in various cultures, including in China, India, and the Middle East, for various conditions, such as respiratory disorders, inflammation, and metabolic diseases (Ahmad et al., 2010). The main active component in *Glycyrrhiza glabra* is asiaticoside, a bioactive compound that has various pharmacological activities, including as an antioxidant, anti-inflammatory, and antidiabetic. However, the molecular

mechanism and specific potential of asiaticoside as a hypoglycemic agent still require further research to strengthen existing scientific evidence (L. Wang et al., 2015).

Asiaticoside is a triterpenoid saponin known to have the ability to increase insulin sensitivity, inhibit enzymes involved in glucose metabolism, and protect pancreatic beta cells from oxidative damage (Yin & Wan, 2018). Several in vitro and in vivo studies have shown that asiaticoside is able to lower blood glucose levels and improve glucose metabolism function. Moreover, asiaticoside's antioxidant properties may help reduce oxidative stress that contributes to insulin resistance and tissue damage in diabetic patients (Das et al., 2020).

The use of natural ingredients such as *Glycyrrhiza glabra* is also driven by the high public interest in herbal products that are considered safer and have minimal side effects compared to synthetic drugs (Zhou et al., 2014). In this context, research on asiaticoside is not only relevant from a scientific point of view, but also has broad practical implications to support the development of phytopharmacology as a complementary or alternative therapy for diabetic patients (J. Wang et al., 2019).

Despite promising preliminary evidence, research related to the effectiveness and mechanism of asiaticoside from *Glycyrrhiza glabra* as a hypoglycemic agent is still limited. Most of the available studies were only conducted in animal models or on a laboratory scale (Moradi et al., 2012). More comprehensive research is needed to explore the potential of asiaticoside, including evaluation of its hypoglycemic activity through further pharmacological, toxicological, and clinical trial studies (Patel et al., 2012).

This study aims to explore the potential of asiaticoside from *Glycyrrhiza glabra* as a hypoglycemic agent through a multidisciplinary approach, including molecular mechanism analysis, pharmacological evaluation, and toxicity studies. It is hoped that the results of this study can make a significant contribution to the development of effective, safe, and affordable natural ingredient-based therapies for patients with diabetes mellitus, as well as broaden scientific insights into the medical utilization of *Glycyrrhiza glabra* (Li et al., 2021).

2. RESEARCH METHODS

This study aims to explore the potential of asiaticoside compounds, an active component of the *Glycyrrhiza glabra* plant, as hypoglycemic agents using an in-silico approach. This method was chosen because it provides time and cost efficiency, and allows in-depth analysis of the pharmacological potential of bioactive compounds before proceeding to experimental research. This study utilized various bioinformatics resources, including chemical databases, pharmacological prediction tools, and molecular analysis software. The methodological stages were carried out systematically, starting from compound data collection, pharmacological activity prediction, molecular interaction analysis, pharmacokinetic and toxicity evaluation, to validation with relevant literature.

The initial step of this research was the collection of data on asiaticoside compounds taken from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). PubChem is an extensive chemical data repository and is often used for pharmaceutical research. Through a search using the keyword “asiaticoside,” complete data regarding chemical structure, CAS number, and other physicochemical parameters were obtained. The

SMILES (Simplified Molecular Input Line Entry System) format of asiaticoside was extracted from the PubChem page as this format is the primary input for various bioinformatics analyses. In addition to SMILES, additional information such as molecular weight, polarity, and solubility were also stored to support the further analysis process.

Once the SMILES data was obtained, prediction of the compound's pharmacological activity was performed using the Way2Drug PASS Online platform (https://www.way2drug.com/). This platform is designed to predict the possible biological activity of compounds based on their chemical structure. The SMILES format of asiaticoside was entered into the PASS Online interface, where various prediction parameters were adjusted to focus on hypoglycemic activity. The prediction results in the form of Pa (probable activity) and Pi (probable inactivity) values were analyzed. If the Pa value is higher than Pi, then the compound has the potential to exhibit the desired pharmacological activity. Besides hypoglycemic activity, other parameters such as antioxidant, anti-inflammatory, and pancreatic beta cell protection properties were also analyzed to support a more holistic understanding of asiaticoside's potential.

The next step is to analyze the molecular interactions between asiaticoside and protein targets relevant to the management of diabetes mellitus. Based on the literature, protein targets involved in glucose metabolism and insulin sensitivity, such as GLUT4, PPAR-γ, and key enzymes of glucose metabolism, were identified as the main targets. The three-dimensional structures of the target proteins were downloaded from the Protein Data Bank (PDB). If the desired structure was not available, homology modeling techniques were used to predict the protein structure based on similarities with other proteins with known structures. The molecular docking process is performed using software such as AutoDock or SwissDock. In this analysis, the main parameters considered are binding affinity, binding site, and specific residue interactions between asiaticoside and the target protein.

In addition to pharmacological activity, evaluation of the pharmacokinetic properties and toxicity of asiaticoside was also carried out to determine the feasibility of this compound as a drug candidate. Pharmacokinetic prediction was done using SwissADME, which allows in-depth analysis of ADME (Absorption, Distribution, Metabolism, Excretion) parameters. Important parameters such as lipophilicity (LogP), membrane permeability, possible interactions with metabolic enzymes, and solubility were analyzed. For toxicity prediction, the ProTox-II platform was used. This platform predicts potential toxic effects on specific organs, LD50 (lethal dose 50%) values, and other possible side effects. The pharmacokinetic and toxicity prediction results were compared with pharmaceutical standards to ensure the safety and effectiveness of asiaticoside.

To enhance the validity of the study, the results from this in silico analysis were validated by comparing them with data from relevant literature. Previous research articles discussing the hypoglycemic activity of Glycyrrhiza glabra or asiaticoside were collected from reliable scientific journals. Validation was done by matching the results of PASS Online prediction, molecular docking analysis, and pharmacokinetic and toxicity evaluation with the available experimental evidence. If there are differences, interpretation is done by considering the limitations of in silico methods and the need for further research.

Data processing from all stages of the study was carried out using statistical software and data visualization tools. Molecular docking results were analyzed statistically to determine the strength of asiaticoside interaction with the target protein. Pa, Pi, and pharmacokinetic prediction data were visualized in the form of graphs and tables to facilitate interpretation. All results were integrated in a comprehensive discussion to evaluate the potential of asiaticoside as a hypoglycemic agent. The study concludes by drawing conclusions regarding the feasibility of asiaticoside as a candidate for natural ingredient-based diabetes therapy, as well as providing recommendations for further experimental research, including in vitro, in vivo, and clinical trials.

With this systematic approach, this research methodology is expected to provide a comprehensive picture of the potential of asiaticoside from *Glycyrrhiza glabra* as a hypoglycemic agent. The in-silico approach used is not only efficient but also relevant in the context of modern pharmaceutical research, which increasingly relies on bioinformatics technology to accelerate the drug discovery process.

3. RESULTS AND DISCUSSION

3.1. Glycyrrhiza glabra

The plant *Glycyrrhiza glabra*, better known as liquorice or licorice, is one of the herbs that has long been used in traditional medicine in various parts of the world, such as China, India, and the Middle East. It belongs to the Fabaceae family and has a rich bioactive content, making it a key ingredient in many traditional medicine formulations. Its uses include the treatment of respiratory disorders, inflammation, metabolic diseases, and as an excipient in pharmaceutical preparations due to its sweet taste that masks the bitter taste of drugs.

One of the main components in *Glycyrrhiza glabra* is glycyrrhizin, which is widely recognized as a compound with broad pharmacological activities, including anti-inflammatory, immunomodulatory, and antimicrobial. In addition, the plant also contains other bioactive compounds, such as flavonoids, coumarins, triterpenoids, and saponins, including asiaticoside. Asiaticoside, although more commonly associated with plants such as *Centella asiatica*, is also found in small amounts in liquorice. This compound has significant pharmacological potential, particularly in the management of diabetes mellitus, which is the main focus of this study.

Figure 1. Glycyrrhiza glabra
Source: https://id.wikipedia.org/

Chemically, liquorice is rich in triterpenoid saponins, with glycyrrhizin being the main compound that contributes to most of its biological activities. This compound is known to have effects resembling corticosteroid hormones, so it is often used in inflammatory therapy. Flavonoids, such as lycochalcone A and lycochalcone E, exert potent antioxidant effects, which are relevant in the context of diabetes mellitus, as oxidative stress is one of the main causes of insulin resistance and pancreatic beta cell damage.

In the context of diabetes mellitus, asiaticoside from *Glycyrrhiza glabra* stands out for its potential to improve insulin sensitivity, inhibit enzymes involved in glucose metabolism, and protect pancreatic tissue from oxidative stress damage. Several in vitro studies have shown that asiaticoside is able to suppress free radical production and reduce cellular damage, which is one of the important mechanisms in diabetes therapy.

The utilization of liquorice in the management of diabetes mellitus is not only supported by empirical evidence but also by several clinical and preclinical studies. Previous studies have shown that liquorice extract can lower blood glucose levels and improve insulin sensitivity in animal models of diabetes. The active compounds in it interact with various molecular targets, such as protein kinases and insulin receptors, which are involved in the regulation of glucose metabolism.

In addition, the use of liquorice as a natural ingredient has advantages over synthetic therapies, especially in terms of safety. Liquorice-based products tend to have lower side effects, such as the risk of hypoglycemia, compared to hypoglycemic oral drugs such as sulfonylureas. However, keep in mind that consumption of liquorice in high doses may cause certain side effects, such as hypokalemia and hypertension, due to the mineralocorticoid properties of glycyrrhizin. Therefore, proper formulation and dosage control are essential in the development of liquorice-based pharmaceutical products.

3.2. Asiaticoside

Asiaticoside is a bioactive compound of the triterpenoid saponin group that is widely recognized in the pharmaceutical world for its various pharmacological activities. The compound was first discovered in *Centella asiatica*, but is also found in small amounts in other plants, including *Glycyrrhiza glabra*. In the context of managing diabetes mellitus, asiaticoside shows significant potential due to its ability to affect various molecular pathways associated with glucose metabolism and insulin sensitivity. Asiaticoside works by increasing insulin receptor sensitivity, which helps improve the body's response to insulin and reduce insulin resistance, one of the main causes of type 2 diabetes.

Asiaticoside is known to have potent antioxidant effects that can reduce oxidative stress, a condition often associated with pancreatic beta cell damage in diabetics. By reducing oxidative stress, asiaticoside helps protect pancreatic cells from further damage and maintains their function in insulin production. This effect is crucial in slowing down the progression of diabetes and preventing further complications. Another proposed mechanism is its ability to inhibit key enzymes in glucose metabolism, such as α-glucosidase and α-amylase, which play a role in the breakdown of carbohydrates into glucose. Inhibition of these enzymes may help reduce the postprandial spike in blood sugar levels, which is one of the major challenges in diabetes management.

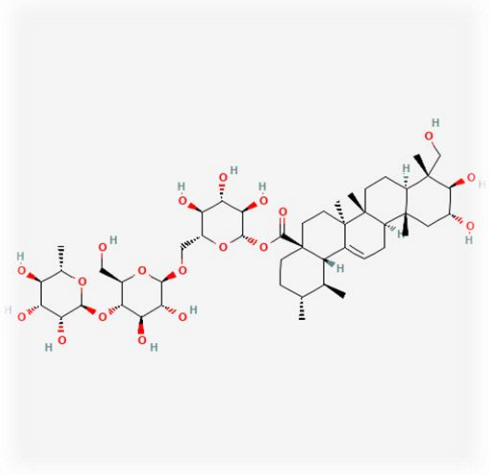

Figure 2. Asiaticoside
Source: https://pubchem.ncbi.nlm.nih.gov/

Several in vitro and in vivo studies have shown that asiaticoside can effectively lower blood glucose levels. In animal models of diabetes, asiaticoside showed improved glucose tolerance as well as improved insulin function compared to the control group. Further studies have shown that asiaticoside can regulate the expression of genes involved in energy metabolism and inflammation, such as GLUT4 (glucose transporter) and TNF-α (tumor necrosis factor alpha). These activities support the hypothesis that asiaticoside is not only beneficial for managing blood glucose levels but also contributes to the improvement of inflammatory conditions.

Beyond its antidiabetic activity, asiaticoside also has other pharmacological potential, including anti-inflammatory, neuroprotective, and cardioprotective effects. These effects may provide additional benefits in the context of diabetes, given the systemic complications often experienced by patients, such as diabetic neuropathy and cardiovascular disease. Although preliminary studies show promising results, further clinical studies are still urgently needed to evaluate the efficacy and safety of asiaticoside in humans, as well as determine the optimal dosage and appropriate formulation.

With its various pharmacological potentials, asiaticoside has strong prospects to be developed into a new hypoglycemic agent, both as a single therapy and as a supplement in conventional therapy. Its utilization in the development of phytopharmacology not only contributes to the innovation of natural material-based medicine but also supports the need for more affordable and safe therapy for people with diabetes mellitus.

3.3. Activity Hypolipemic

The hypolipemic activity of asiaticoside refers to its ability to reduce lipid levels in the bloodstream, which is crucial for managing hyperlipidemia and preventing associated complications, such as cardiovascular diseases. Asiaticoside likely exerts this activity through multiple mechanisms, including enhancing fatty acid oxidation, regulating lipid metabolism via PPAR-α activation, and inhibiting key enzymes like HMG-CoA reductase, which is involved in cholesterol biosynthesis. Antioxidant properties play a complementary role by mitigating oxidative stress, a significant contributor to lipid

peroxidation and atherogenesis. The dual effects of lipid regulation and oxidative damage prevention make asiaticoside a promising candidate for developing safer, natural hypolipemic therapies

Table 1. Activity Prediction

Parameter	Value
Probability of Activation *(pa)*	0.934
Probability of Inhibition *(pi)*	0.003
Activity	Hypolipemic

Source: https://www.way2drug.com/

The data in the table above demonstrate an activation probability (pa) value of 0.934 and an inhibition probability (pi) value of 0.003, highlighting asiaticoside's hypolipemic activity. The pa value, approaching 1, strongly indicates that asiaticoside has a high potential to induce relevant biological responses associated with lipid-lowering activity. This activation probability reflects the compound's ability to effectively interact with specific biological targets, such as enzymes or receptors involved in lipid metabolism. In the context of hyperlipidemia, these targets could include the Peroxisome Proliferator-Activated Receptor Alpha (PPAR-α), which plays a critical role in regulating lipid metabolism and reducing blood lipid levels, including cholesterol and triglycerides. Conversely, the very low pi value of 0.003 suggests that asiaticoside has minimal potential to inhibit undesirable biological functions. This is a significant parameter since pharmacological agents with high inhibitory activity against non-specific targets often result in substantial side effects. The low pi value indicates that asiaticoside has a promising safety profile with minimal risk of inducing toxic or adverse physiological effects.

The hypolipemic activity of asiaticoside is further supported by molecular mechanisms identified in various studies. This compound is believed to reduce lipid accumulation by enhancing the expression of genes involved in fatty acid oxidation, such as those regulated by PPAR-α. Additionally, asiaticoside may inhibit cholesterol synthesis by modulating lipid biosynthetic pathways, including the suppression of HMG-CoA reductase, a key enzyme in cholesterol production. This mechanism mirrors the action of statins but with potentially fewer side effects, given asiaticoside's natural origin.

The low pi value also has critical implications for asiaticoside's therapeutic development. It indicates a high degree of selectivity, making the compound more likely to target specific molecular pathways without disrupting others that could lead to clinical complications. This provides a competitive advantage over synthetic drugs, which often lack specificity and carry a broader spectrum of side effects.

Asiaticoside’s ability to reduce blood lipid levels can also be attributed to its antioxidant and anti-inflammatory properties. These properties contribute to protecting bodily tissues, including the liver, from oxidative damage commonly associated with hyperlipidemia. Oxidized lipids in the bloodstream are a major risk factor for atherosclerosis, which can lead to cardiovascular complications such as heart attacks and strokes. By mitigating oxidative stress, asiaticoside helps lower the risk of such complications and promotes overall cardiovascular health.

Asiaticoside's hypolipemic activity holds potential for integration into combination therapies for patients with uncontrolled lipid profiles. When used alongside conventional drugs like statins, it could enhance therapeutic efficacy while allowing for lower doses of synthetic drugs, thereby reducing the risk of side effects. This approach is critical in managing chronic metabolic diseases such as hyperlipidemia, which often require a multidisciplinary treatment strategy. While in silico data demonstrate promising results, further research is essential to validate these findings. In-depth in vitro and in vivo studies are necessary to evaluate asiaticoside's biological activity comprehensively, including its effects on lipid parameters such as LDL, HDL, triglycerides, and total cholesterol. Additionally, toxicological and pharmacokinetic studies are crucial to ensure the compound's safety and bioavailability in the human body.

Asiaticoside exhibits significant potential as a natural hypolipemic agent that is safe, effective, and multifunctional in its mechanisms of action. Its development could represent a critical advancement in providing more affordable and environmentally friendly therapies for managing hyperlipidemia and related metabolic disorders.

To fully validate asiaticoside’s hypolipemic activity, future research should include well-structured experimental designs encompassing in vitro, in vivo, and clinical studies. In vitro studies should focus on elucidating its molecular interactions with lipid metabolism regulators, such as PPAR-α, HMG-CoA reductase, and other lipid-modulating pathways. High-throughput screening techniques, gene expression analysis, and lipidomics approaches could provide deeper insights into its mechanistic actions.

In vivo studies should involve animal models of hyperlipidemia to assess asiaticoside's therapeutic potential in a physiological context. These studies should evaluate its effects on lipid profiles, inflammatory markers, and oxidative stress biomarkers over different treatment durations and dosages. Additionally, pharmacokinetic and toxicological studies must be conducted to determine asiaticoside’s bioavailability, metabolism, and potential side effects. Clinical trials will be crucial in translating preclinical findings into practical applications. Initial trials should assess asiaticoside's efficacy as a monotherapy or adjunct to existing lipid-lowering medications, such as statins or fibrates. These studies should measure key lipid parameters, including LDL, HDL, triglycerides, and total cholesterol, while also monitoring potential adverse effects. Moreover, trials should explore population-specific responses, such as its impact on patients with metabolic syndrome, diabetes, or genetic predispositions to hyperlipidemia.

Despite its promising potential, asiaticoside faces several practical limitations that must be addressed before it can be considered for widespread clinical use. One major challenge is its bioavailability. As a natural compound, asiaticoside may have low solubility and limited absorption in the gastrointestinal tract, reducing its systemic efficacy. Strategies such as nanoparticle-based delivery systems, lipid formulations, or structural modifications should be explored to enhance its pharmacokinetic properties. Another limitation is its optimal dosage and long-term safety profile. Unlike synthetic drugs with well-defined dose-response relationships, natural compounds often exhibit variability in efficacy depending on extraction methods, plant sources, and preparation techniques. Standardization of asiaticoside’s formulation will be essential to ensure consistency across different studies and potential therapeutic applications.

Large-scale production and cost-effectiveness also present challenges. Natural extraction methods may not yield sufficient quantities of asiaticoside for commercial drug development, necessitating alternative synthesis approaches or biotechnological production methods. Additionally, regulatory approval processes for botanical compounds can be complex, requiring extensive safety and efficacy data to meet international standards.

Lastly, potential drug interactions must be considered, particularly if asiaticoside is used alongside conventional lipid-lowering therapies. Investigations into its synergistic or antagonistic effects with other pharmacological agents will be necessary to establish safe and effective combination therapy protocols. By addressing these limitations and advancing experimental research, asiaticoside holds significant promise as a natural hypolipemic agent that could contribute to safer and more effective management of hyperlipidemia.

4. CONCLUSION

Asiaticoside demonstrates considerable potential as a natural hypolipemic agent with a promising safety profile and effective lipid-lowering properties. The data indicate that asiaticoside has a high activation probability (pa = 0.934), suggesting its strong potential to interact with specific targets involved in lipid metabolism, such as PPAR-α, to reduce lipid levels in the bloodstream. Its low inhibition probability (pi=0.003 further supports its safety, minimizing the risk of undesirable side effects typically associated with non-specific inhibition. Additionally, asiaticoside's antioxidant and anti-inflammatory effects further contribute to its cardiovascular protective properties, reducing the risk of complications such as atherosclerosis.

The potential of asiaticoside for combination therapy with conventional drugs, like statins, adds value by enhancing therapeutic efficacy while minimizing side effects. However, while in silico data are promising, further research through in vitro and in vivo studies is essential to validate its biological activity, safety, and pharmacokinetics. With its natural origin and multifaceted mechanisms of action, asiaticoside holds significant promise for developing safe, effective, and environmentally friendly therapies for managing hyperlipidemia and related metabolic disorders.

Future research on asiaticoside's hypolipemic activity should focus on several key areas to bridge the gap between preclinical findings and clinical applications. First, in-depth mechanistic studies using in vitro and in vivo models should further clarify its interaction with lipid metabolism regulators, particularly PPAR-α and HMG-CoA reductase. Second, pharmacokinetic and bioavailability studies are essential to optimize its formulation, ensuring efficient absorption and systemic distribution. Third, dose-response and toxicological evaluations should be conducted to establish a safe and effective therapeutic range. Additionally, large-scale clinical trials are needed to assess asiaticoside's efficacy in diverse patient populations, including those with metabolic syndrome or statin intolerance. Investigations into its potential as an adjunct therapy alongside conventional lipid-lowering drugs should also be prioritized. Finally, research should explore innovative drug delivery systems, such as nanoformulations, to enhance its stability and therapeutic potential. Addressing these areas will provide a strong

foundation for the clinical translation of asiaticoside as a natural and effective hypolipemic agent.

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