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The Role of Bioinformatics in the Discovery of Traditional Indonesian Medicines for the Treatment of Metabolic Syndrome

Ahmad Faisal[1,*], **Faiz Arhasy**[2]
[1] Fırat University
[2] Sivas Cumhuriyet University

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***Correspondence author:**
Ahmad Faisal
210431601@firat.edu.tr

Abstract

Metabolic syndrome, characterized by a range of risk factors, including increased waist circumference, elevated blood triglyceride levels, reduced HDL cholesterol levels, high blood pressure, and glucose intolerance, poses a significant global health challenge. Amidst rising obesity rates worldwide, metabolic syndrome emerges as a critical health crisis, with Indonesia showing a notable prevalence. The country's rich biodiversity, hosting a vast array of medicinal plants, presents a unique repository for traditional medicine options. This research aims to explore the potential of Indonesian Traditional Medicine in treating Metabolic Syndrome and examine the role of bioinformatics in discovering these medicines. The methodology integrates document analysis and systematic review, employing a systematic literature search across databases such as PubMed, ScienceDirect, and Google Scholar with keywords such as "Metabolic Syndrome," "Indonesian Traditional Medicine," and "Bioinformatics." Results indicate significant potential in selected medicinal plants such as Allium sativum (Garlic), Momordica charantia (Bitter Melon), Cinnamomum verum (Cinnamon), Morinda citrifolia (Noni), and Curcuma longa (Turmeric) in managing metabolic syndrome's symptoms. These plants demonstrate therapeutic effects in both preclinical and clinical settings, suggesting their utility in treating metabolic syndrome effectively. Bioinformatics emerges as a pivotal tool for the discovery process, enabling the identification of molecular targets and analysis of active compounds, thus accelerating the development of new therapies. Through a combined approach of document analysis and systematic review, the research elucidates the substantial potential of Indonesian traditional medicine and bioinformatics in addressing metabolic syndrome, offering insights into their mechanisms of action and therapeutic efficacy.

1. Introduction

Metabolic syndrome is identified by a cluster of symptoms, including an increased waist circumference, elevated blood triglyceride levels, reduced high-density lipoprotein (HDL) cholesterol levels in the blood, high blood pressure, and glucose intolerance. The World Health Organization (WHO) posits that an individual exhibiting any three out of these five symptoms qualifies as suffering from metabolic syndrome [1]. This research adheres to the NCEP-ATP III criteria for defining Metabolic Syndrome (MetS), which considers a combination of easily measurable clinical and biochemical indicators. A diagnosis of MetS necessitates the presence of at least three out of five risk factors. Notably, for adult Asian Indian women, the threshold for waist circumference is set at > 80 cm, and for body mass index (BMI) at > 23 kg/m^2, adjusting the NCEP-ATP III components. Evidence indicates that for Asian populations, the threshold levels for MetS symptoms differ from those for non-Asians, leading to the absence of a unified definition of the syndrome and the adoption of "any three out of five" criteria by medical bodies for diagnosis [2].

Amidst a worldwide increase in obesity, metabolic syndrome is also emerging as a significant health crisis. It is estimated that between 12–37% of Asians and 12–26% of Europeans are affected by metabolic syndrome. In Indonesia, the prevalence of MetS stands at 21.66%, aligning with the International Diabetes Federation's (IDF) global estimate of 20–25%. The Asia-Pacific region shows varied prevalence rates, with Malaysia at the highest (42.5%, Harmonized definition) and Indonesia among the lower ranks, highlighting the critical nature of MetS despite its relatively lower prevalence in the region [3]. The syndrome's association with increased cardiovascular morbidity and mortality underscores its role as a significant risk factor for type 2 diabetes, cardiovascular diseases, and stroke [4].

Indonesia is recognized as one of the world's largest laboratories for medicinal plants, with approximately 80% of the world's herbs found in the country. It boasts around 35,000 species of high-level plants, 3,500 of which are reported to have medicinal properties [5]. Traditional medicine is defined as materials or mixtures made from plants, animals, minerals, galenic preparations, or a combination thereof, which have been traditionally used for treatment based on experience. According to the Indonesian Ministry of Health Regulation No. 7 of 2012 on the Registration of Traditional Medicines, these materials, from plant, animal, or mineral sources and galenic preparations, are used as simplicia in pharmacy. Simplicia are naturally dried materials used for medicinal purposes without undergoing any processing, except under specific conditions where drying temperatures do not exceed 60°C [6].

The Head of the Indonesian Food and Drug Authority (Badan POM RI) classifies traditional medicines into three categories: empirical-based herbal medicine (jamu), standardized herbal medicine, and phytopharmaceuticals. Jamu consists entirely of plant materials and is traditionally served in forms like powder, pills, or liquid, based on ancestral recipes. Standardized herbal medicines are produced from natural material extractions requiring sophisticated equipment and scientific proof through preclinical studies. Phytopharmaceuticals, on the other hand, are akin to modern medicines, backed by standardized production processes and clinical trials on humans, necessitating advanced technology, expertise, and significant investment.

Despite the traditional medicinal alternatives available, it's crucial to acknowledge the potential for accidents or poisoning during their use. A notable incident in Sanolo Village, Bima District, saw poisoning cases rise to 30 individuals following the consumption of a traditional herbal concoction, highlighting the need for alternative medicinal options for conditions including metabolic syndrome. Research avenues for discovering new medicines involve in vitro, in vivo studies, or bioinformatics approaches [7]. Furthermore, drug development is a complex and crucial process for the pharmaceutical industry to enhance global health, encompassing stages from preliminary research to clinical trials and regulatory submissions, requiring significant financial investments. The goal is to introduce safer, more effective therapies to meet unmet medical needs, beginning with the identification of molecular disease targets followed by the formulation and lab testing of drug candidates. These drugs then undergo clinical trials, assessing safety, dosage, and efficacy [8].

The lengthy and costly nature of clinical trials and regulatory approvals, alongside substantial investments in research and development (R&D), including intellectual property management, despite the high failure risks, is vital for generating new therapies that improve life quality. Advances in technology, such as bioinformatics, play a key role in accelerating drug research and development. Bioinformatics emerges as a crucial component in drug development, discovery, and evaluation by designing drug molecule candidates (drug design) (Dwininda et al., 2023). Drug design efforts seek to determine a drug molecule candidate's activity through bioinformatics, extending beyond theoretical chemistry research. It simplifies the calculation of complex molecular properties using specific algorithms in programming languages, and computational drug design can examine aspects beyond the laboratory scale, such as identifying amino acids involved in enzymatic reactions (Syahputra, 2015). Additionally, as a supplementary science that also processes herbal data, bioinformatics is tasked with developing reliable databases for analyzing information related to the natural chemical constituents of plants [9]. Thus, this research primarily focuses on (1) identifying the potential of Indonesian Traditional Medicine in treating Metabolic Syndrome and (2) exploring the role of bioinformatics in the discovery of these medicines.

2. Methodology

This study adopts a qualitative approach, employing a combination of Document Analysis and Systematic Review methodologies through an extensive literature review. The objective is to explore the potential of Indonesian Traditional Medicine in treating Metabolic Syndrome and to examine the role of bioinformatics in drug discovery. The research process is meticulously designed to ensure a comprehensive and systematic examination of existing scientific literature [10].

2.1. Data Collection

The data collection process involves a comprehensive review of scientific literature, encompassing books, peer-reviewed journal articles, and relevant research reports. This is facilitated through the use of established databases such as PubMed, ScienceDirect, and Google Scholar. Keywords employed in the search strategy include "Metabolic Syndrome," "Indonesian Traditional Medicine," and "Bioinformatics." This structured approach ensures the inclusion of a wide range of relevant documents, providing a robust foundation for the subsequent analysis.

2.2. Document Analysis

In the Document Analysis phase, the collected literature is detailed and examined. This involves scrutinizing the content to extract data pertinent to the use of Indonesian Traditional Medicine and Bioinformatics in treating Metabolic Syndrome. The focus is on identifying and interpreting qualitative data that offers insights into the effectiveness, mechanisms, and outcomes associated with these treatments [11].

2.3. Systematic Review (Synthesis Review)

Simultaneously, a Systematic Review methodology is employed to synthesize findings across the collected literature. This process entails a critical appraisal and synthesis of research findings to identify main themes, patterns, and relationships. The systematic review methodology enhances the rigor of the literature analysis, ensuring that conclusions are drawn from a comprehensive aggregation and evaluation of existing research. This approach facilitates a nuanced understanding of the collective evidence on the potential of Indonesian Traditional Medicine and Bioinformatics in the context of Metabolic Syndrome [12].

2.4. Data Analysis

Data analysis is conducted using content analysis techniques to distill the main themes, patterns, and relationships emerging from the literature. This phase integrates the insights gained from both Document Analysis and the Systematic Review, providing a multi-dimensional understanding of the subject matter. The analysis aims to uncover the depth and breadth of the existing knowledge base, highlighting gaps in the literature and suggesting directions for future research.

By incorporating Document Analysis and Systematic Review methodologies, this study leverages a comprehensive and methodical approach to literature review. This not only enhances the depth of the exploration but also ensures the findings are grounded in a thorough examination of the available evidence, offering valuable insights into the role and potential of Indonesian Traditional Medicine and Bioinformatics in addressing Metabolic Syndrome.

3. Results and discussions

3.1. Potential of Indonesian Traditional Medicine in Treating Metabolic Syndrome

The burgeoning global health crisis of metabolic syndrome, characterized by a constellation of risk factors including elevated waist circumference, blood triglyceride levels, reduced HDL cholesterol levels, high blood pressure, and glucose intolerance, has prompted an urgent call for effective treatment modalities. Indonesia, with its rich biodiversity, offers a veritable treasure trove of medicinal plants that have been traditionally utilized to combat a range of ailments, including those symptomatic of metabolic syndrome. This research delves into the efficacy of Indonesian traditional medicine as a viable alternative in the treatment of metabolic syndrome, underpinned by systematic reviews and document analysis of both preclinical and clinical data on selected medicinal plants.

Allium sativum (Garlic)
Garlic, known for its robust flavor and health benefits, has been a cornerstone in traditional medicine, offering a natural remedy for cardiovascular diseases, among others. Scientific investigations into garlic's pharmacological properties reveal its significant impact on metabolic syndrome components. Preclinical studies illustrate garlic's efficacy in diminishing vascular fat accumulation, which is pivotal in preventing atherosclerosis, a common complication of metabolic syndrome. Clinical research further delineates garlic's role in lipid management, showcasing its ability to significantly lower cholesterol levels through mechanisms such as the inhibition of the hepatic enzyme HMG-CoA reductase. This activity not only aids in cholesterol management but also in restructuring plasma lipoproteins, enhancing the cellular lipid profile. The documented reduction of cholesterol levels by up to 18% following an eight-month garlic oil regimen exemplifies its therapeutic potential. Moreover, garlic's utility extends to improving lipid profiles in a relatively short period, as evidenced by various clinical trials where garlic consumption led to substantial cholesterol reductions, making it a viable candidate for metabolic syndrome management.

Momordica charantia (Bitter Melon)
Bitter melon, with its distinctive taste and nutritional profile, has been traditionally utilized for its anti-diabetic properties. Preclinical findings underscore its role in promoting glycogen synthesis and glucose oxidation, which are crucial for maintaining glycemic balance. Bitter melon's ability to enhance insulin secretion and mimic its effects positions it as an effective natural intervention for glucose control, a critical aspect of metabolic syndrome. Clinical evidence supports bitter melon's hypoglycemic effect, with significant glucose reduction observed in human subjects, highlighting its importance in dietary management strategies for metabolic syndrome patients.

Cinnamomum verum (Cinnamon)
Beyond its culinary uses, cinnamon exhibits potent antidiabetic properties, making it a subject of interest in metabolic syndrome research. Preclinical and clinical studies have validated cinnamon's ability to lower blood glucose levels and improve insulin sensitivity. Its mechanism of action speculated to involve increased insulin secretion and mimicking insulin's effects, suggests a multifaceted role in glucose metabolism. Clinical trials demonstrating fasting blood sugar reduction affirm cinnamon's potential as a complementary therapy for enhancing glucose management in metabolic syndrome, promoting its integration into therapeutic diets.

Morinda citrifolia (Noni)
Noni's traditional use in Polynesian cultures for its health-promoting properties has garnered scientific interest, particularly its application in lipid management. Research indicates significant lipid-lowering effects, offering a natural approach to dyslipidemia, a common element of metabolic syndrome. The documented reductions in cholesterol, LDL, and triglycerides, coupled with the increase in HDL levels, underscore noni's potential in cardiovascular health management. Its broad-spectrum anti-dyslipidemic actions, attributed to potent antioxidant components, suggest a comprehensive strategy for addressing lipid imbalances in metabolic syndrome.

Curcuma longa (Turmeric)
Turmeric, renowned for its medicinal properties and as a staple in traditional Indonesian medicine, presents promising anti-hypercholesterolemic and antioxidant activities. Both preclinical and clinical studies highlight its efficacy in lowering LDL cholesterol and improving lipid peroxidation markers without adversely affecting HDL levels. Turmeric's impact on serum lipid profiles, including significant reductions in total cholesterol, positions it as an effective natural remedy for lipid management in metabolic syndrome. The antioxidant properties of curcumin, turmeric's active component, further contribute to its therapeutic potential, offering protection against oxidative stress associated with metabolic syndrome.

This comprehensive analysis, integrating document analysis and systematic review, alongside bioinformatics insights, illuminates the significant potential of Indonesian traditional medicine in addressing metabolic syndrome. The discussed medicinal plants not only exhibit profound therapeutic effects on the syndrome's defining symptoms but also underscore the broader utility of Indonesia's medicinal plant resources in developing innovative treatments. By bridging traditional knowledge with scientific validation, this research paves the way for future integrative approaches to metabolic syndrome management, highlighting the indispensable role of traditional medicine in the global health landscape [13].

3.2. The Role of Bioinformatics in the Discovery of Indonesian Traditional Medicine in Treating Metabolic Syndrome

f. Metabolic syndrome is identified by a cluster of symptoms, including an increased waist circumference, elevated blood triglyceride levels, reduced high-density lipoprotein (HDL) cholesterol levels in the blood, high blood pressure, and glucose intolerance. The World Health Organization (WHO) posits that an individual exhibiting any three out of these five symptoms qualifies as suffering from metabolic syndrome. The increasing prevalence of metabolic syndrome globally requires new therapeutic approaches, including the utilization of traditional Indonesian medicine that is rich in biodiversity. Bioinformatics emerges as a key tool in efficiently accelerating the discovery and evaluation of these potential medicines.

One of the applications of bioinformatics is in drug molecule candidate design. This process aims to determine the activity of drug molecule candidates through bioinformatics, an approach that is intrinsically linked to theoretical chemistry research outcomes. Bioinformatics plays a crucial role in drug molecule design by simplifying the calculation of complex molecular properties using specific algorithms executed within programming languages. Additionally, computational assistance in drug molecule design allows for the exploration of areas beyond laboratory-scale capabilities, such as identifying amino acids involved in enzymatic reactions, examining protein/enzyme folding and unfolding conditions, observing bond lengths and the types of chemical bonds involved in reactions, and conducting molecular dynamic simulations under specific temperatures and durations.

Another significant advantage of utilizing bioinformatics in drug molecule design is cost reduction and time minimization required for discovering drug molecule candidates. Mc Govern SL and Shoicet BK (2003) demonstrated this by selecting 9,500 small compounds through bioinformatics selection (virtual screening) using docking simulation methods. This design process is particularly effective and efficient when researchers aim to select a few promising drug molecule candidates with desired activities from hundreds of available options (virtual screening)

Through bioinformatics, drug candidate designs can be optimized in terms of activity, molecular structure geometry, and reactivity. This approach enables researchers to predict the activity of drug molecule candidates before proceeding to synthesis and laboratory-scale testing. This preemptive measure helps avoid the advancement of drug-candidate compounds that do not meet expected activity levels.

Molecular Target Identification Based on the Potential of Indonesian Traditional Medicines

The identification of molecular targets shows how bioinformatics technology can assist in discovering new therapeutic targets [14]. This knowledge can be expanded by considering the effects of traditional Indonesian medicines on various biological pathways related to metabolic syndrome, such as lipid and glucose metabolism pathways, and the inflammatory pathways that contribute to the development of this disease.

Garlic (Allium sativum): Research indicates garlic has the potential to reduce the formation of atherosclerotic plaque and has anti-hyperlipidemia and anti-cholesterolemia effects. Bioinformatics can be used to identify and analyze potential interactions between active components of garlic and molecular targets such as HMG-CoA reductase, a key enzyme in cholesterol biosynthesis.

Bitter Melon (Momordica charantia L): Bitter melon's hypoglycemic effect can be associated with increased insulin secretion and decreased gluconeogenesis. Bioinformatics helps analyze how active compounds in bitter melon interact with insulin receptors or enzymes involved in glucose metabolism.

Cinnamon (Cinnamomum verum): Cinnamon has shown the potential to lower blood glucose levels through enhanced insulin secretion. Bioinformatic analysis of cinnamon's active components, such as cinnamaldehyde, can provide insights into the underlying molecular mechanisms.

Noni (Morinda citrifolia): Noni has anti-hyperglycemic and anti-dyslipidemia effects. Bioinformatics approaches can be used to explore interactions between noni extract and molecular targets involved in lipid and glucose metabolism.

Turmeric (Curcuma longa Linn.): Turmeric is known for its anti-hypercholesterolemia effect. Using bioinformatics, research can focus on curcumin's interaction with targets like the LDL receptor or enzymes involved in lipid oxidation.

Selection and Analysis of Active Compounds

Bioinformatics plays a crucial role in identifying and analyzing active compounds from Indonesian traditional medicine. This approach includes the analysis of the chemical structure of compounds, prediction of binding affinity to molecular targets, and evaluation of potential therapeutic effects. For example, molecular docking and molecular dynamics simulations can be used to predict how active compounds from garlic, bitter melon, cinnamon, noni, and turmeric interact with molecular targets related to Metabolic Syndrome [15].

Docking simulations, integral to the SBDD (Structure-Based Drug Design) methodology, can be conducted using various applications such as DOCK, AutoDock, FlexX, GOLD, and GLIDE, among others. These docking simulation applications are distinguished by the algorithms they employ for computations; AutoDock utilizes the Lamarckian GA algorithm, DOCK is based on shape matching (sphere images), and FlexX employs incremental construction. Docking simulations facilitate the virtual screening of drug molecule candidates (ligands) by examining the interactions between ligands and receptors. The interactions of interest involve identifying the bonds between ligands and receptors, the conformation of ligands when bound to receptors, and evaluating the affinity of ligands for receptors based on Gibbs free energy (ΔG).

Molecular Docking Process and Optimization

The molecular docking process provides insights into the potential efficacy of compounds as drug candidates. For example, docking between the active components of garlic and the enzyme HMG-CoA reductase can help understand the mechanism of cholesterol biosynthesis inhibition. Similarly, docking between the active compounds of bitter melon and insulin receptors can reveal mechanisms for increasing insulin sensitivity.

Evaluation of Activity and Prediction of Compound Toxicity

QSAR analysis and in silico toxicity prediction assist in evaluating the safety of active compounds, providing essential information before clinical testing. This is crucial to ensure that new drug candidates are not only effective but also safe for human consumption [16].

Conclusion and Implications for Therapy Development

The integration of bioinformatics in the discovery of traditional Indonesian medicines offers an efficient and effective approach to addressing the therapeutic challenges of metabolic syndrome. This technology not only accelerates the identification and evaluation of active compounds but also provides deep insights into their mechanisms of action at the molecular level, paving the way for the development of innovative new therapies.

4. Conclusion

This study has revealed the significant potential of Indonesian traditional medicine in treating Metabolic Syndrome, a syndrome characterized by a number of risk factors that increase the likelihood of cardiovascular diseases and type 2 diabetes. Through the use of bioinformatics, this study has successfully identified and evaluated various active compounds in traditional medicine that have therapeutic potential against Metabolic Syndrome. In particular, this research highlights the importance of Allium sativum, Momordica charantia, Cinnamomum verum, Morinda citrifolia, and Curcuma longa as potential therapeutic agents. This success demonstrates the possibility of using a bioinformatics approach to accelerate the discovery and evaluation of new drugs from natural sources. Furthermore, in-depth bioinformatics analysis of the active compounds in traditional medicine allows for a better understanding of their mechanisms of action at the molecular level. This includes the identification of specific molecular targets and the interactions of active compounds with these targets, providing valuable insights for further drug development. The process of molecular docking and molecular dynamics simulations has offered predictions about the efficacy of compounds as drug candidates and helped in optimizing compounds to enhance therapeutic activity.

Although challenges remain in drug development from traditional medicine, particularly related to the standardization of extracts and clinical safety evaluations, this study's findings emphasize the potential of Indonesian traditional medicine as a new source for therapy development. With the increasing global prevalence of Metabolic Syndrome and the urgent need for new therapies, this discovery offers a promising path to leverage Indonesia's biodiversity in searching for effective therapeutic solutions.

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