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Prediction of Sennosides from Senna Leaves (*Cassia angustifolia*) for Management of Constipation in Hemodialysis Patients

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Abstract: Constipation is a common issue among hemodialysis patients, significantly impacting their quality of life. Factors such as a low-fiber diet and fluid restrictions contribute to the worsening of this condition. Herbal laxatives, particularly senna leaves (Cassia angustifolia), which contain sennosides, have shown potential as a safe and effective alternative for managing constipation. This study utilized an in silico approach to predict the biological activity of sennosides using PASS Online. The results indicate that sennosides have a high probability of functioning as a laxative, with an activity probability value (Pa) of 0.921 and an inactivity probability (Pi) of 0.001. These values suggest a strong potential for laxative activity. Additionally, the pharmacokinetic predictions show that sennosides have favorable clearance rates, allowing for efficient elimination from the body and reducing the risk of drug accumulation. However, dose adjustments remain necessary based on the patient's residual renal function. The findings from this in silico study provide valuable insights into the biological interactions and cost efficiency of sennosides as a natural laxative, supporting their potential use in hemodialysis patients suffering from constipation..

Keywords: Sennosides, Laxative, Constipation, Hemodialysis

Introduction

Constipation is a common problem in hemodialysis patients that can affect quality of life. Constipation is a condition characterized by difficulty in defecating (BAB) and usually involves a reduction in the frequency of bowel movements to less than three times a week. Many factors cause this condition, including a low-fiber diet, fluid restriction, reduced physical activity, and side effects of medications. Managing constipation properly is essential to improve the comfort and quality of life of hemodialysis patients, so attention to diet and physical activity is essential. Interventions such as increasing fiber consumption, adjusting fluid intake, and physical exercise programs can help reduce constipation symptoms and improve patient well-being (Lailiyah, 2021).

According to the World Health Organization (WHO) in 2020, around 15% of the global population suffers from chronic kidney failure (CKD), which causes around 1.2 million deaths. In 2021, the number of deaths due to CKD reached 254,028 people, and is expected to increase to 843.6 million people in 2022. WHO also noted that currently there are around 1.5 million chronic kidney failure patients worldwide undergoing hemodialysis, with the incidence increasing by 8% each year (Pratiwi, 2024). In Indonesia, based on data from the Ministry of Health in 2023, there were around 499,800 people suffering from chronic kidney

failure. Of that number, around 66,433 people were actively undergoing hemodialysis. In a study conducted at Sanglah General Hospital, the prevalence of constipation in chronic kidney failure patients undergoing hemodialysis was reported to reach 36% of the total patients studied. This study involved 45 patients and showed that gastrointestinal complications, including constipation, are a common problem among hemodialysis patients (Utami et al., 2020).

The use of herbal laxatives such as senna leaves with bioactive sennosides can be a safe and effective alternative. However, the use of high doses is at risk of causing dependency and electrolyte disturbances. Consideration for dialysis patients with the right dose, because the way it works is to increase intestinal peristalsis and regulate water absorption in the large intestine so that it helps soften stool and helps prevent constipation without disturbing critical electrolyte balance (Lailiyah, 2021). However, it is important to closely monitor electrolyte levels and kidney function, and consult a doctor to determine a safe dose, given the patient's health condition which may be more sensitive to changes in the digestive system, a study to determine the effect of giving senna leaves on the quality and quantity of defecation in people with constipation. The results showed that giving senna leaves significantly improved the quality and quantity of defecation. Data were analyzed using the Wilcoxon test, with significant results ($p < 0.05$) indicating the effectiveness of senna leaves as a natural laxative (Aguilika, 2016).

This journal aims to investigate the safe herbal laxative activity for dialysis patients from Sennosides compounds from senna leaves (Cassia angustifolia) using an in silico approach (Salsabila, 2020). The in silico method, which utilizes computational tools to simulate and analyze biological interactions, offers several advantages, including cost efficiency, time efficiency, and the ability to predict the pharmacological mechanisms of candidate compounds (Purnomo & Tilaqza, 2022). The results of this prediction are expected to provide a better understanding of the potential safe herbal laxative activity for hemodialysis patients from Sennosides compounds from senna leaves (Cassia angustifolia) (Salsabila, 2020). In addition, this journal also contributes to efforts to preserve and utilize Indonesian biodiversity in the development of modern medicine (Khasanah et al., 2022).

Methods

Information on the molecular structure of reserpine was accessed through the PubChem database (https://pubchem.ncbi.nlm.nih.gov/), which is a trusted chemical library portal providing extensive information on various chemical compounds, including their molecular structures, physicochemical properties, biological activities, safety profiles, and pharmacokinetics. Through PubChem, complete data was obtained regarding the molecular structure and Simplified Molecular Input Line Entry System (SMILES) code of the reserpine compound (Pratiwi & Sutrisna, 2021).

Reserpine, classified as an indole alkaloid derived from the Rauwolfia serpentina plant, has been widely studied due to its potent pharmacological activities, particularly as an antihypertensive and antipsychotic agent. The molecular structure of reserpine consists of a complex arrangement of indole, yohimbane, and ester functional groups, which contribute to

its unique pharmacodynamic and pharmacokinetic properties. The acquisition of its molecular structure and SMILES code through PubChem serves as an essential step in further computational and predictive analyses, allowing researchers to investigate its interactions, metabolism, and potential toxicity in silico.

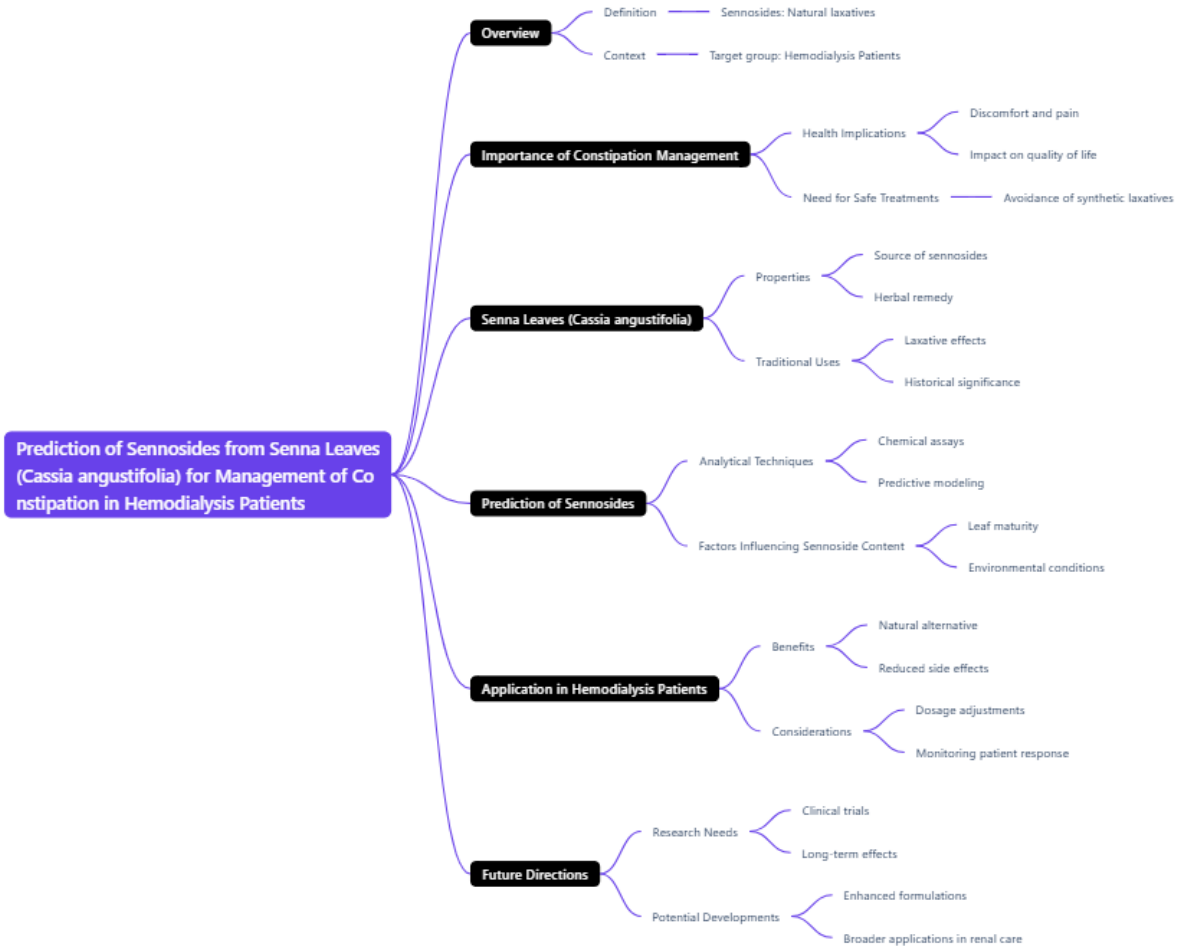

Figure 1. Mind Maps

Furthermore, predictive analysis of the pharmacokinetic profile and reserpine toxicity was performed using the Prediction of Activity Spectra for Substances (PASS Online) platform, which is available through the Way2Drug website (https://www.way2drug.com/passonline/predict.php). PASS Online is a widely recognized tool used for in silico predictions of various biological activities, mechanisms of action, and potential toxic effects based on structural similarity and machine-learning algorithms. By inputting the obtained SMILES code from PubChem into PASS Online, researchers can assess the likelihood of reserpine exhibiting specific pharmacological and toxicological properties, including hepatotoxicity, cardiotoxicity, and neurotoxicity (Muslikh et al., 2024).

In addition to toxicity predictions, an in-depth pharmacokinetic analysis was conducted using the SwissADME tool (http://www.swissadme.ch/index.php), which provides a comprehensive evaluation of absorption, distribution, metabolism, and excretion (ADME) properties of a given drug. The SwissADME platform allows researchers to predict various

pharmacokinetic parameters, such as gastrointestinal absorption, blood-brain barrier penetration, P-glycoprotein (P-gp) interactions, and metabolic pathways involving cytochrome P450 enzymes. One crucial aspect examined through SwissADME is the clearance rate of reserpine, which is directly related to its elimination from the body. Clearance is a vital pharmacokinetic parameter that influences drug dosing regimens, potential accumulation, and overall therapeutic efficacy.

By integrating data from multiple computational platforms such as PubChem, PASS Online, and SwissADME, a more comprehensive understanding of reserpine's pharmacokinetics, toxicity risks, and potential therapeutic applications can be obtained. These predictive tools facilitate early-stage drug discovery and development by allowing researchers to assess crucial drug-likeness properties before conducting extensive in vitro and in vivo experiments. The application of computational methods also supports the refinement of drug formulations, identification of safer analogs, and minimization of adverse effects associated with reserpine treatment.

Further research is needed to validate the computational predictions obtained from PASS Online and SwissADME through experimental studies, including in vitro cytotoxicity assays, in vivo pharmacokinetic profiling, and clinical trials. By combining in silico, in vitro, and in vivo methodologies, a more holistic approach to understanding reserpine's pharmacological properties can be achieved, ensuring its safe and effective therapeutic use in clinical settings.

Result and Disscusion

Senna leaves (*Cassia angustifolia*)

Senna leaves have long been recognized for their medicinal properties, particularly as a natural laxative. This effect is primarily attributed to their anthraquinone content, which ranges between 1.5% and 3%. Anthraquinones are a class of organic compounds known to stimulate bowel movements by increasing peristaltic activity in the intestines, thereby facilitating defecation. However, beyond their anthraquinone content, senna leaves also contain approximately 10% mucilage. Mucilage is a polysaccharide-based substance that can retain water, leading to increased stool bulk and softness. The combined effects of anthraquinone-induced peristalsis and mucilage-induced bulk laxation likely contribute to the overall efficacy of senna leaves in treating constipation.

In traditional medicine, senna leaves have been utilized for centuries to alleviate constipation, a condition characterized by infrequent or difficult bowel movements. In Javanese, these leaves are commonly referred to as "godong seno." The primary active components responsible for their laxative effect are sennosides, a type of glycoside that undergoes enzymatic hydrolysis in the colon to produce active metabolites. These metabolites stimulate colonic motility, accelerating the transit of stool through the intestines. Due to this mechanism of action, senna leaves are widely used as an herbal remedy for digestive health and are often incorporated into pharmaceutical laxative formulations.

The use of senna leaves is not limited to a specific region; they are recognized and known by different names in various parts of the world. For instance, in many countries, they are referred to as "Senna Alexandria," a name derived from the species commonly utilized as a laxative. In India, where the plant is extensively cultivated, the term "Indian Senna" is frequently used. In some Arab countries, senna leaves are known as "Senna Makki," emphasizing their historical significance in traditional Arabian medicine. In Indonesia, they

are sometimes referred to as "Chinese Teak," possibly due to their resemblance to certain species of teak trees. Additionally, the term "Sennas" is often used as a general reference to plants belonging to the Senna genus, which includes multiple species known for their medicinal properties.

Scientifically, senna leaves are classified under the species Cassia angustifolia. The taxonomic classification of this plant is as follows:

Kingdom	: Plantae
Subkingdom	: Tracheobionta
Superdivision	: Spermatophyta
Division	: Magnoliophyta
Class	: Magnoliopsida
Subclass	: Rosidae
Order	: Fabales
Family	: Fabaceae
Genus	: Senna

The natural habitat of Cassia angustifolia spans multiple geographical regions. Senna leaves are indigenous to several parts of North Africa, particularly Egypt and Sudan, where they grow abundantly in tropical climates. In the Middle East, the plant is also widely cultivated, having been integrated into traditional medicine for centuries. Beyond Africa and the Middle East, senna leaves are found in various Asian countries, including India and Indonesia. In India, Cassia angustifolia is commonly referred to as "Indian Senna" and has been an integral part of Ayurvedic medicine, where it is used not only as a laxative but also for detoxification and digestive support. In Indonesia, senna leaves are often found in herbal markets, where they are sold in dried form for medicinal use.

Morphologically, Cassia angustifolia exhibits distinctive characteristics that allow for easy identification. The plant possesses compound leaves that are even-pinnate, a feature commonly observed in members of the Fabaceae family. The leaves are oval or oblong, with a pointed tip, and typically range in length from 3.5 cm to 15 cm, with widths varying between 2.5 cm and 9 cm. Each leaf comprises multiple leaflets, usually numbering between 8 and 24 pairs. The upper surface of the leaves is green and glossy, while the underside appears duller. Unlike some other medicinal plants, the edges of senna leaves are smooth and not serrated.

Apart from its leaves, other morphological aspects of Cassia angustifolia contribute to its recognition. The stems of the plant are covered in grayish-brown bark and exhibit branching patterns that form a wide crown. The flowers, which emerge from the leaf axils, are bright yellow and consist of five petals arranged in a symmetrical fashion. These flowers attract pollinators, contributing to the plant's reproductive cycle. The fruit of Cassia angustifolia is a long pod, characteristic of many Fabaceae species, and contains multiple seeds that facilitate propagation.

The pharmacological properties of senna leaves extend beyond their laxative effects. Research has shown that the sennosides found in Cassia angustifolia may also possess mild antimicrobial activity, potentially inhibiting the growth of certain bacterial strains. Additionally, some studies suggest that anthraquinones present in senna leaves may exert anti-inflammatory effects, although further research is needed to establish their clinical significance. The presence of mucilage in senna leaves further enhances their therapeutic potential, as mucilage compounds are known to have soothing effects on the gastrointestinal lining, reducing irritation and discomfort associated with constipation.

Given the potent laxative effect of senna leaves, their usage should be approached with caution. Excessive consumption may lead to adverse effects, such as abdominal cramping, diarrhea, and electrolyte imbalances. Chronic use of senna-based laxatives has been associated with dependence, where the intestines become reliant on external stimulation for bowel movements. As a result, healthcare professionals often recommend intermittent use rather than prolonged administration. To minimize potential side effects, senna leaves are commonly combined with other herbal ingredients that promote gastrointestinal health, such as fennel and peppermint.

Senna leaves can be consumed in various forms, including herbal teas, capsules, tablets, and liquid extracts. When preparing senna tea, dried leaves are steeped in hot water to extract the active constituents. The tea is typically consumed before bedtime to induce bowel movements the following morning. In pharmaceutical formulations, senna extracts are often standardized to ensure consistent dosing of sennosides, thereby optimizing efficacy while minimizing variability in therapeutic outcomes.

The cultivation of Cassia angustifolia requires specific environmental conditions to ensure optimal growth. The plant thrives in well-drained sandy or loamy soils and prefers warm temperatures with adequate sunlight. Agricultural practices for senna cultivation involve periodic pruning to encourage leaf production and careful harvesting to maintain the potency of the active compounds. In commercial farming, senna leaves are typically harvested when they reach peak maturity, followed by drying and processing to produce marketable herbal products.

Figure 1. Senna leaves (*Cassia angustifolia*)

Senna leaves (Cassia angustifolia) contain various bioactive compounds that contribute to its laxative effect. The content found in senna leaves: including Sennoside: This compound is the main active component in senna leaves and consists of several types, such as sennosides A, B, C, and D. Sennosides function to stimulate bowel movements, thereby helping to overcome constipation (Mardiyaningsih & Pramono, 2012). The next bioactive is :

1. Anthraquinone: The anthraquinone content in senna leaves ranges from 1.5% to 3%. This compound also has a laxative effect and works by increasing intestinal motility.
2. Mucilage: Senna leaves contain about 10% mucilage, which functions as a bulk laxative, helping to soften stool and facilitate its excretion.
3. Flavonoids and Phenolics: Senna leaves are also rich in flavonoids and phenolic compounds, which have antioxidant properties and may provide additional health benefits.
4. Minerals and Vitamins: Senna leaves contain various important minerals such as

potassium, calcium, magnesium, and iron, as well as vitamin B complex and vitamin C. (Mardiyaningsih & Pramono, 2012).

Sennosides

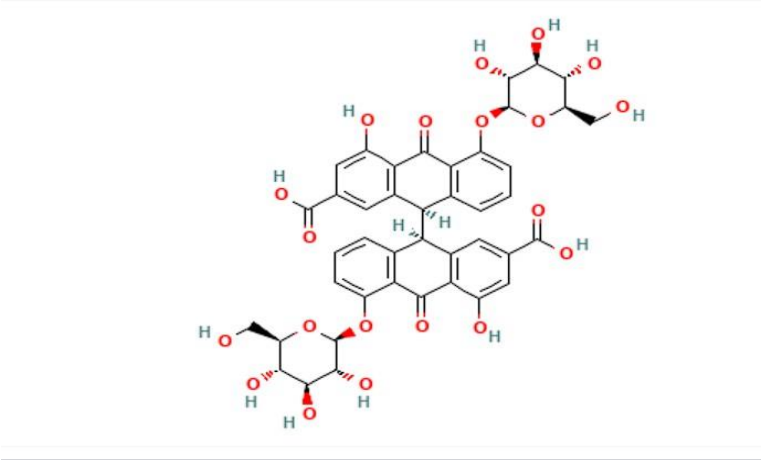

Figure 2. Chemical Structure of Sennosides (https://go.drugbank.com/drugs/DB00206)

*Sennosides*belongs to the glycoside group, which is a compound consisting of two glycoside parts (sugar part) and aglycone (non-sugar part). In this case, sennosides are glycoside compounds derived from anthraquinone, which have a laxative effect. Sennosides consist of several types, such as sennosides A and B, which are isolated from senna leaves (Cassia angustifolia) and function to stimulate intestinal peristalsis, thereby helping to overcome constipation. Identification of Elements This formula shows that the compound consists of three elements carbon (C), hydrogen (H), and oxygen (O). Number of Carbon Atoms (C) There are 42 carbon atoms. Hydrogen (H) there are 38 hydrogen atoms Oxygen (O) there are 20 oxygen atoms (Liu et al., (2021) and DrugBank, (2023). Prediction of Sennosides Activity Prediction from senna leaves (Cassia angustifolia) Management of Constipation in Hemodialysis Patients. Inthis journal, Prediction of Sennosides from senna leaves (Cassia angustifolia) for Constipation Management
in Hemodialysis Patients in silico approach.

Table 1. Prediction of Sennosides Activity in the Management of Constipation in Hemodialysis Patients

Compound	Activity Probability (*pa*)	Probability of Inactivity (*pi*)	Activity Pharmacology
Sennosides	0, 921	0.001	Laxative

The prediction results show that Sennosides has a pa (probability of activity) value of 0.921 and a pi (probability of inactivity) of 0.001, indicating that this compound has the potential to be active as a laxative. The pa value (0.921) approaching 1 indicates that Sennosides has the possibility of interacting with pharmacological targets and showing a significant Laxative effect. Conversely, the relatively small pi value (0.001) indicates that the chance of this compound being inactive is quite low, thus further strengthening the prediction that Sennosides can act as a potential Laxative.

Figure 3. Creatinine Clearance Image Sennosides Management of Constipation in Hemodialysis Patients

Property	Model Name	Predicted Value	Unit
Excretion	Total Clearance	0.68	Numeric (log ml/min/kg)
Excretion	Renal OCT2 substrate	No	Categorical (Yes/No)

The prediction results show that Sennosides have a clearance value of 0.68 log ml/min/kg, the interpretation of which is very different from the usual clearance value in ml/min/kg. Clearance Meaning 0.68 log ml/min/kg. clearance is expressed in logarithms (log), this means the reported value is the base 10 logarithm of the actual clearance value (in ml/min/kg). So, to get the actual clearance value, we need to do the antilog (10 raised to the power of the log value).

Actual Clearance Calculation:

Clearance(ml/min/kg) = 10^(0.68) = 4.79 ml/min/kg (rounded)

*Clearance*is actually about 4.79 ml/min/kg.

With the clearance converted to 4.79 ml/min/kg, we can evaluate its safety in hemodialysis patients more accurately: The value of 4.79 ml/min/kg is much higher than 0.68 ml/min/kg. This indicates that the compound is eliminated from the body at a moderate to relatively rapid rate. The risk of drug accumulation is reduced compared to when the clearance is only 0.68 ml/min/kg. Although lower risk, dose adjustments may still be necessary, depending on other factors such as How much residual kidney function the patient has (even if hemodialysis replaces most of the kidney function). Whether the compound is removed by hemodialysis (dialysability). It is still important to know whether the compound is dialysable. If the compound is dialysable, then some of the drug will be lost during the hemodialysis session, and additional doses may be needed after dialysis. However, this may also help prevent accumulation.

Check whether the compound is primarily metabolized by the liver. If so, impaired liver function (which may occur in some hemodialysis patients) may affect clearance. Be aware of potential interactions with other medications the patient may be taking.

Conclusion

The prediction results using PASS Online show that Sennosides have the potential as a laxative compound with an activity probability value (Pa) of 0.921 and an inactivity probability (Pi) of 0.001. Low Pa and Pi values indicate that Sennosides have a high probability of showing laxative activity.

Constipation is a common problem faced by hemodialysis patients, affecting their quality of life. Various factors, including low-fiber diet and fluid restriction, can worsen this condition. The use of herbal laxatives, especially senna leaves (Cassia angustifolia), with sennosides content, shows potential as a safe and effective alternative to overcome constipation. Research shows that sennosides have a high probability of activity as a laxative.

The in silico method used in this study provides insight into biological interactions and cost efficiency. The prediction results show that sennosides have fairly good clearance values, indicating that these compounds can be eliminated from the body at a relatively rapid rate.

Although the risk of drug accumulation is low, dose adjustments are still needed based on the patient's residual renal function.

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