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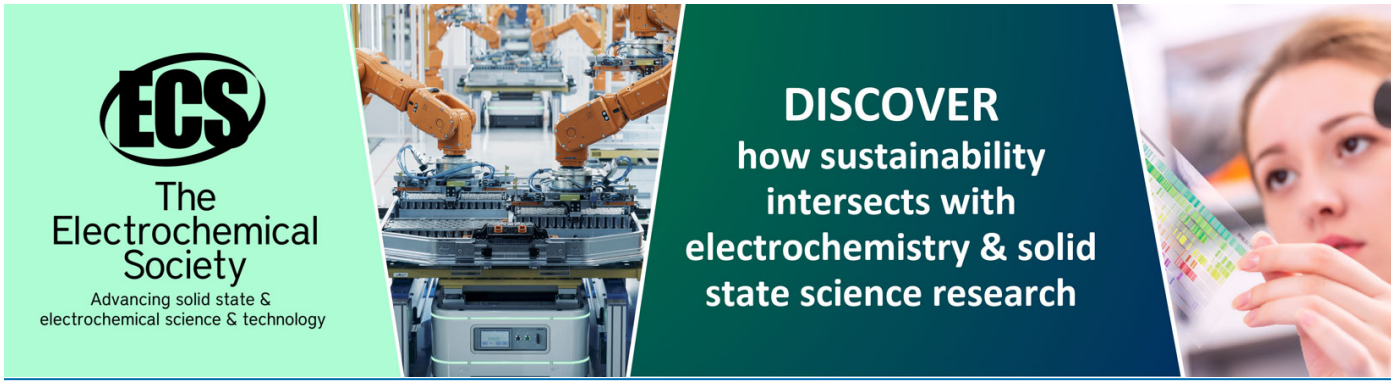

A systematic literature review (SLR): evaluation pharmacokinetic profile of drug combined p-glycoprotein (p-gp) alkaloid inhibitor in white rats (rattus norvegicus)

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Abstract. P-glycoprotein (P-gp) is a protein transporter as an active efflux pump of many xenobiotics. P-gp plays an important role in the pharmacokinetic process that it will affect the bioavailability of the drug. Secondary metabolites of alkaloids are known to be P-gp inhibitors which can modulate P-gp expression so it will increase the bioavailability of various drugs. The aim of this study was to determine the effect of alkaloid administration as a P-gp inhibitor on the pharmacokinetic profile of drugs in white rats (*Rattus norvegicus*). This research is a Systematic Literature Review (SLR). Articles were retrieved from the Science Direct and PubMed databases from 2000 to 2020 with the inclusion criteria are P-gp substrate used as a synthetic drug also has a pharmacokinetic profile measurement and exclusion criteria are articles in English and there were no duplication of articles. SLR research results show that secondary metabolites of alkaloids can significantly change the pharmacokinetic parameters of P-gp substrate such as the area under curve (AUC), peak plasma concentrations (C_{max}) and time to reach Cmax (T_{max}), clearance (Cl), distribution volume (Vd) and half-life ($T_{1/2}$) in white rats (*Rattus norvegicus*). Therefore, it shows that alkaloids can act as P-gp inhibitors.

1. Introduction

The availability of the drug in the workplace for pharmacological effects is characterized by processes of absorption, distribution, metabolism and elimination [1]. One of the transporter proteins in humans that plays a major role in decreasing the absorption of various drugs is P-glycoprotein (P-gp) [2]. P-gp can limit systemic exposure to various xenobiotics by reducing intestinal absorption and increasing renal and biliary excretion [3].The role of P-gp is most likely to protect these susceptible organs from toxic compounds, preventing them from entering the cytosol and excreting them [4].

P-glycoprotein (P-gp) is an ATP-dependent transport protein [5]. P-gp functions as a transmembrane efflux pump with a working mechanism of moving drug molecules from intracellular to extracellular [6]. Several drug molecules are the substrate of P-gp, such as anti-cancer agents, immunosuppressants, steroid hormones, calcium channel blockers (CCB), beta-adrenoreceptor blockers, cardiac glycosides [7]. The mechanism of P-gp with the substrate will lead to decreased absorption and increased excretion of the substrate [8]. P-gp is found in many epithelial cells that have an excretory role [9].

Several compounds derived from plant secondary metabolite products have been widely reported to play a role in changing the expression of P-gp [10]. Any change in the expression and activity of P-gp will result in an increase or decrease in the plasma drug concentration [11]. Alkaloids are effective P-

gp inhibitors by various mechanisms [12]. This compound has been widely used in therapy for health as well as consumption as nutritional support for the body [13]. Alkaloids have various pharmacological effects such as antibiotics, anticancer along with their potential exploitation as narcotics and stimulants [14].

One of the transporter proteins in rats is P-gp which is the same as in humans, which is a transporter protein that is widely expressed in the endothelial capillary cells of the brain [15]. Rats can be used as animal models because between rats and humans have the same level of homology in amino acids and nucleotides with a percentage of 85% [16]. Some in vivo studies using rat test animals have shown that P-gp plays a role in drug disposition, especially in the central nervous system (CNS) [17]. Physiological expression of P-gp in tissues is a determining factor in drug absorption in various cells and tissues [18]. P-gp is considered as one of the main obstacles to the bioavailability of drugs that will decrease the effectiveness of the treatment [11]. Based on the description above, it is necessary to study the literature regarding the effects of alkaloids as P-gp inhibitors on the pharmacokinetic profile of white rats (*Rattus norvegicus*).

2. Experimental

2.1. Materials

All articles on alkaloids as P-gp inhibitors in pharmacokinetics published from 2000 to 2020 were identified through a comprehensive search using the PubMed database and the ScienceDirect database with the following terms and keywords: "rat," "P-glycoprotein," "alkaloid," “pharmacoknetics”. Searches were limited to animal studies.

2.2. Search strategy and selection of articles

The search for articles is based on the formulation of research questions. The formulation of these questions focuses on predetermined research topics. Determination of the formulation of the problem in this study refers to the PICO instrument which aims to make the search method more selective and sensitive **[**19**]**. The PICO instrument consists of four elements, namely:

a. P (Population) : Rat with P-gp substrate
b. I (Intervention) : Alkaloids
c. C (Comparison) : No treatment with alkaloids
d. O (Outcome) : Improved pharmacokinetics of P-gp substrate

2.3. Inclusion and exclusion criteria

All candidate articles were considered eligible for the systematic literature review if they met following criteria: 1) full text from 2000 to 2020 where the subject is a white mouse (*Rattus norvegicus*) with an undetermined rat strain; 2) the P-gp substrate used is a synthetic drug; 3) using alkaloid secondary metabolites in a single form or containing an herbal plant; 4) there are measurements of the pharmacokinetic profile of P-gp substrate with unspecified method and instrumentation. All articles other than English, duplication of articles, and if the entire data in full text cannot be accessed were all excluded.

2.4. Quality assessment

The quality assessment of the article on this SLR study was carried out according to the SYRCLE's risk of bias tool for animal studies. There are 10 question criteria to determine the quality of the article that will be used. On these benchmarks a "yes" rating indicates a low risk of bias, a "no" rating indicates a high risk of bias, and an "unclear" rating indicates ambiguity in the explanation in the article.

2.5. Data extraction

Synthesis of search results data on articles in tabular form is carried out to summarize the data so that information related to predetermined topics will be obtained. In this study, the information that was

synthesized was related to the identity of the article, the type of P-gp substrate, the type of alkaloid and the measurement results of the P-gp substrate pharmacokinetics profile.

2.6. Data analysis

Data obtained from literature studies will be analyzed descriptively to determine the effect of alkaloid administration as a P-glycoprotein (P-gp) inhibitor on drug pharmacokinetics in white rats (*Rattus norvegicus*).

3. Results and Discussions

3.1. Article selection

The process of searching and filtering articles on a systematic literature review (SLR) research refers to the PRISMA guideline. PRISMA guideline is one of the guidelines used in reporting the results of systematic reviews system so that information is obtained in accordance with previously formulated questions **[**20**]**. Outlines the including or excluding procedure of potential studies in a flowchart based on PRISMA guidelines can be seen in Figure 1.

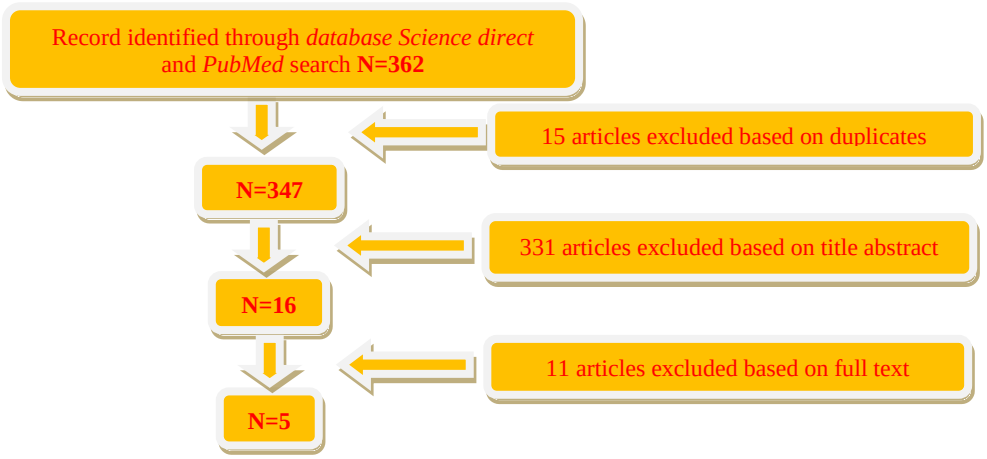

Figure 1. Flow diagram of the article selection process.

Based on the PRISMA flow chart, the selection of articles in this study was carried out through 2 databases, namely Science Direct and PubMed. There were 362 articles that can be accessed with titles and abstracts with details of 233 articles from the Science Direct database and 129 articles from the PubMed database. Meanwhile, there were 15 articles published in Science Direct and PubMed, which were excluded from the selection of articles, bringing a total of 347 articles. Out of 347 articles, 331 articles were excluded because after reviewing the titles and abstracts that were not in accordance with the predetermined problem formulations and keywords, a total of 16 articles were obtained for further study. There were 8 articles from the PubMed database, after being searched as a whole from the full text of the articles there were only 3 articles that matched the inclusion criteria. Meanwhile, there were also 8 articles from the Science Direct database, after a thorough search of the full text of the articles there were only 2 articles that matched the inclusion criteria. In total, 5 articles were obtained from the PubMed and Science Direct databases based on selection using the PRISMA guideline which includes 4 stages, namely identification, screening, eligibility and inclusion. The 5 articles will be assessed for the quality of the literature.

3.2. Quality assessment of article

The literature quality assessment in this study was conducted according to the SYRCLE's risk of bias tool for animal studies [21]. SYRCLE's risk of bias tool for animal studies was chosen as an instrument for assessing the quality of articles because this reference has been widely used in systematic review research in experimental studies with test animals [22]. The resulting RoB tool for experimental studies on animals used in this study contains 10 question criteria. These questions cover 6 types of bias associated with experimental study with test animals. Interpretation of the results of the assessment to assess whether screened articles have a low or high risk of bias with SYRCLE's risk of bias tool for animal studies refers to the Cochrane Collaboration RoB tool [21]. The results of the assessment of articles are shown in Figure 2.

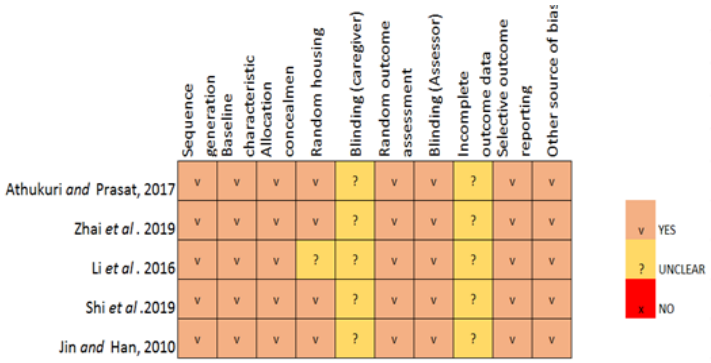

Figure 2. The results of the assessment of articles based on the Syrcle tool.

In the Cochrane Collaboration RoB tool, it is explained by pointing out one of the domains that most influences the results in the study. The selected domain must have a "yes" rating in the relevant article so that it can be concluded that the article has a low risk of bias. In SYRCLE's risk of bias tool for animal studies, there are 10 domains of assessment of articles in preclinical studies, namely: sequence generation, baseline characteristics, allocation concealment, random housing, blinding participants, random outcome assessment, blinding assessors, incomplete outcome data, selective outcome reporting. and other sources of bias. In this study the topic raised was related to alkaloids as inhibitors of P-glycoprotein (P-gp) on the pharmacokinetic profile of drugs in white rats (*Rattus norvegicus*) or in other words related to alkaloid activity tests, so that the most influential domain in this study was baseline characteristics. This can be shown by the results of the assessment on the domain key that have been described previously were the domain key selected is the baseline domain characteristics. The results of the assessment of domain baseline characteristics in all selected articles showed a "yes" rating.

3.3. Data synthesis

The results of the study using alkaloids as P-gp inhibitors against the pharmacokinetic profile of the drug in white rats (Rattus norvegicus) are summarized in Table 1.

No	Article Identity	Alkaloid	P-gp Substrate	Pharmacokinetic Parameters			
				$AUC_{0-\infty}$ (h. ng/ml)		C_{max} (ng/mL)	
				Control	Eksperi-mental	Control	Eksperi-mental
1.	Athukuri *and* Neerati, 2017[23]	Piperin	Domperidon	1641.23 ± 93.90	2493.44 ± 381.8	114.4 ± 15.36	178.22 ± 13.87
2.	Zhai *et al*. 2019 [24]	Capsaicin	Vinblastin	82.28 ± 9.90	101.54 ± 12.78	52.38 ± 9.31	44.43 ± 10.33
3.	Li *et al*. 2016 [25]	Piperin	Docetaxel	868.412 ± 6305.50	1369.915 ± 13157.19	1625.52 ± 355.53	6603.58 ± 1889.89
4.	Shi *et al*. 2019 [26]	*Xiao-Ai-Ping*	Paclitaxel	8682.0 ± 1129.7	12572.3 ± 2173.4	7032.5 ± 522.2	9532.5 ± 2385.6
5.	Jin *and* Han, 2010 [27]	Piperin	Fexofenadine	575 ± 74.5	1020 ± 333	209 ± 92.4	189 ± 53.2

There are 5 articles from the results of the selection process, where all of these articles used the same test animal, namely white rats with healthy conditions and not induced by a particular disease. In the summary of the research results from the 5 articles, the test animals used were divided into 2 test groups, namely the control group and the experimental group. The control group was a group of rats without alkaloid pretreatment, while the experimental group was a group of rats with alkaloid pretreatment. Overall results were obtained in the form of changes in the pharmacokinetic parameters of the drug or the same P-gp substrate, namely the area under the curve (AUC) and the peak plasma concentration (Cmax). The process of inhibition or suppression of the mechanism of action of the P-gp transporter protein can be indicated by an increase in the bioavailability of the drug or P-gp substrate so that it will increase the effectiveness of the treatment.

3.4. Discussion

P-glycoprotein (P-gp) is a member of the ABC transporter super family that is able to hydrolyze ATP so it is also called the ATP-binding cassette (ABC) [5]. P-gp is a product of the MDR1 gene in humans and the mdr1a and mdr1b genes in rats [28]. This protein is mainly expressed in the apical membrane of cells which have excretory functions such as in the liver, kidney, small intestine, stomach, and the blood-brain barrier [9].

The role of herbal plants which contain certain secondary metabolites is currently reported to possess their own activities related to the potential for induction and inhibition of P-gp expression [29]. The inhibitory activity of P-gp can be seen from the alkaloid structure, namely the basic nitrogen atom and two aromatic rings which are important components related to the bonds that occur between alkaloids and P-gp. Alkaloids have been reported to inhibit P-gp activity through various mechanisms [12]. There are 2 mechanisms of secondary metabolites related to activity in P-gp inhibition. The first mechanism is the secondary metabolite as a P-gp substrate and will act like a competitive inhibitor. Meanwhile, the second mechanism is the secondary metabolite as a P-gp inhibitor that will bind P-gp reversibly or irreversibly and it will reduce the efflux activity of P- gp. The existence of 2 mechanisms of P-gp inhibition from secondary metabolites results in a higher P-gp substrate concentration in cells so that it can increase the effectiveness of therapy [30].

In 5 selected articles, it can be seen that alkaloid secondary metabolites can change the pharmacokinetic profile of the drug. This can be seen from changes in the pharmacokinetic parameters of the drug or P-gp substrate The expression of P-gp in the intestines will cause a decrease in the peak

plasma concentration (Cmax) and the area under the curve (AUC) of the P-gp substrate, this can occur because the absorption process decreases as a result of the increase in P-gp in the intestine [31]. In addition, P-gp also affects the renal clearance parameter (Cl), namely the expression of P-gp in the kidney tubules will increase the elimination process from the P-gp substrate [23].

4. Conclusion

The effect of alkaloid administration as a P-glycoprotein (P-gp) inhibitor on the pharmacokinetic profile of drugs in white rats (Rattus norvegicus), which can change the pharmacokinetic profile of drugs with an increase in pharmacokinetic parameters of drugs with an increase in the pharmacokinetic parameters of the drug, namely the area under the curve (AUC), peak plasma concentration (Cmax) and time to reach Cmax (Tmax) as well as a decrease in the volume distribution (Vd) and clearance (Cl) parameters. In white rats (Rattus norvegicus).

Acknowledgments

Great appreciation and acknowledgement to Sebelas Maret University for funding this research.

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