Effect of a decoction of Lophira alata (Banks ex P. Gaertn) on the pharmacokinetics of risperidone: Study of a drug-herb interaction

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Abstract
Drug interactions may cause a drug to be more or less effective (synergism or antagonism), or cause unexpected effects on the body. Risperidone is a second-generation atypical antipsychotic medication while *Lophira alata* is a plant used traditionally to treat psychotic disorders. A large number of patients with psychosis have been reported to simultaneously use both orthodox and traditional medicines in Africa. This research was carried out to determine the effect of concomitant administration of risperidone and *Lophira alata* in healthy human volunteers. The first phase of the research was carried out to establish the baseline pharmacokinetic profile of risperidone 2 mg in 18 male subjects. The second phase was carried out after a 2-week washout period, where the subjects were randomly divided into three equal groups and group A received risperidone 2 mg and decoction of the herb (9.4mg/kg) concurrently, group B received risperidone 2 mg and decoction of the herb (9.4mg/kg) was administered after 1 hour and group C received a decoction of the herb (9.4mg/kg) and risperidone 2 mg was administered after 1 hour. Blood samples were collected at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 24 hours after drug administration, and plasma analyses were carried out using a developed RP-HPLC method to determine the plasma concentrations. Subsequently, Kinetica 5.0 software was used to extrapolate pharmacokinetic parameters from the plasma concentrations. Results show that there was a significant ($p < 0.05$) increase in the rate of absorption (k_a), peak plasma concentration (C_{max}) and measure of drug exposed to the body ($AUC_{0-\infty}$) but significant ($p < 0.05$) decrease in the time to achieve peak plasma concentration (t_{max}), half-life of absorption ($t_{1/2a}$) and extent of drug distribution (Vd) when risperidone and *Lophira alata* were administered concurrently. Drug-herb interaction was observed to be more significant ($p < 0.05$), when *Lophira alata* was administered concurrently with risperidone than when administered one hour before or after *Lophira alata*. Decoction of *Lophira alata* interacts with risperidone tablets when administered together, which may be attributed to alteration in the mechanism of risperidone absorption by *Lophira alata*.

Keywords: Risperidone, *Lophira alata,* Drug-interaction, Pharmacokinetics

Introduction

Drug interactions occur when there is an alteration in a patient's response to a drug due to the effect of another drug, herb, food, formulation excipient, environmental factor or a disease. Drug-herb interactions affect the pharmacokinetic outcomes or the pharmacodynamic activities of medications, resulting in therapeutic failure, toxicity, or increase in pharmacologic action of the drug (Bhargav and Parveen, 2020).

Risperidone, an atypical second-generation antipsychotic is a drug of choice in the management of psychotic symptoms in schizophrenia and bipolar disorders (Meltzer and Gadaleta, 2021).

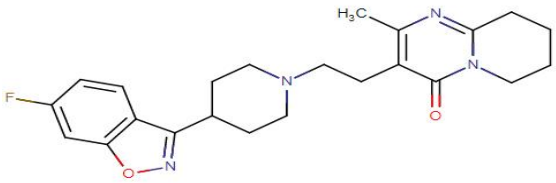

Figure 1 Risperidone

Risperidone is well absorbed after oral administration; however, its absorption in the intestines is largely regulated by p-glycoprotein (p-gp). It is mainly metabolized by cytochrome P450 enzyme (CYP), CYP2D6 into 9-hydroxyrisperione, its active metabolite. It has a half-life of 3 hours in extensive metabolizers and 20 hours in poor metabolizers (Schoretsanitis *et al*., 2018).

The CYP enzymes account for about 70% of drug metabolism in humans, and P-glycoprotein (P-gp), an efflux pump that extrudes drug substrates out of cells into the intestines regulates drug absorption. Herbs regulate the relative activity of both CYP and P-gp, either by inhibiting or inducing their activity. This determines the concentration of drugs at the site of action, thus influencing therapeutic outcomes (Rombola *et al*., 2020).

Lophira alata, locally known as ekki or azobe and commonly as iron red wood, is widely distributed in West Africa where its timber is used for construction purposes (World Agroforestry, 2023). A decoction of *L. alata* stem bark is used for the treatment of a wide range of diseases, including psychotic disorders (Ibrahim *et al.*, 2007; Akwaji *et al*., 2017). Its antipsychotic properties have been evaluated and established in rats (Iniaghe *et al.,* 2015).

The concomitant use of drugs and herbs is common among patients managing psychotic illnesses as well as other diseases. About 45 % of patients attending a tertiary health facility in Northern Nigeria use herbal medicines together with their antipsychotic drugs (Oloyede *et al,* 2017). Concurrent use of herbal and orthodox medicines have also been reported in other parts of Africa, with a prevalence of over 50 % reported in a study carried out in Ghana (Ameade *et al*., 2018). A prevalence of concurrent use of drugs and herbs of 20 % was also reported in a study carried out in the United Kingdom (Agbabiaka *et al*., 2018)

The aim of this research is to determine the effect of concomitant administration of *L. alata* and risperidone (among healthy volunteers) on the pharmacokinetic profile of risperidone and to suggest a mechanism for the pharmacokinetic interaction.

Materials and Methods

Materials

HPLC Agilent 1260 LC System controlled by OpenLab software (Agilent, USA), Centrifuge (Mettler Gallenkamp, England), Risperidone tablets; Risperdal® (Jassen-Cilag,

Germany), Stem barks of *L. alata*, Methanol (HPLC grade; Merck, Germany), Acetonitrile (HPLC grade; Merck, Germany), Ethylacetate (BDH, Germany), EDTA collection tubes (5 ml), Plain collection tubes (5 ml) were used in the experiment.

Methods

Ethical approval

Ethical approval (ABUCUHSR/2016/003) for the research work was gotten from the Ahmadu Bello University Committee on Use of Human Subjects for Research (ABUCUHSR)

Collection of herbal products

The stem barks of *L. alata* were collected in Sabo Wuse, Tafa local government area of Niger state in February 2017. They were authenticated by Namadi Sanusi of Department of Biological Sciences, Ahmadu Bello University, Zaria and assigned voucher number 900269.

Preparation of decoction of L. alata

The stem barks were cleaned dried and reduced to powdered form by milling and 250 g of the stem bark was macerated in 2 L of distilled water for 48 hours, shaking intermittently at room temperature. The extract was decanted, filtered and stored in the refrigerator. A dose of 9.4 mg/kg was adopted based on LD_{50} determined by Iniaghe *et al.* (2015). Subsequently, individual doses were calculated for each volunteer based on mg/kg body weight for each volunteer.

Recruitment of healthy human volunteers

A total of 18 healthy male volunteers (age between 18 and 40 years; body mass index (BMI) in the range of 18 – 25 kg/m^3) were recruited. All volunteers were examined physically. Their vital signs, medical and drug histories were also documented. The exclusion criteria that guided recruitment were: allergic reactions to risperidone or other ingredients in the formulation, subjects having history of diseases that could affect bioavailability of risperidone (such as, gastrointestinal, liver, renal diseases), history of regular alcohol consumption, smoking (more than 10 cigarettes per day) or having participated in other clinical experiments within one month prior to the study. An informed consent was gotten from all volunteers prior to recruitment.

Drug- herb interaction study

The preliminary phase was carried out to determine the pharmacokinetic profile of risperidone 2 mg in the 18 male subjects. Each subject was administered a single dose risperidone 2 mg tablet with 240 ml of water after an overnight fast. They maintained an upright seating position for at least 30 minutes thereafter. Each blood sample (6 ml) was collected into EDTA coated collection tubes via venipuncture at the forearms before dosing and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 24 hours after the drug administration. At 2 hours post-dosing, a standardized sugar drink was given to each subject. The first standardized meal was provided at 4 hours after the drug administration. The blood samples collected were centrifuged at 4500 rpm for 10 minutes and the supernatant collected in plain collection tubes and stored at - 20˚ C. Protein precipitation of 1 ml of the thawed plasma was then carried out by adding 5 ml of acetonitrile and centrifuging at 4000 rpm for 5 minutes. The supernatant was injected into the HPLC for analysis as described by Oloyede, *et al*. (2022). After a 2 weeks washout period, the 18 subjects were randomly divided into three equal groups. Group A subjects received risperidone 2 mg and decoction of the herb (9.4 mg/kg) concurrently. Group B subjects received risperidone 2 mg and decoction of the herb (9.4 mg/kg)

was administered after 1 hour. Group C subjects received a decoction of the herb (9.4 mg/kg) first and then risperidone 2 mg was administered after 1 hour. Blood samples were collected as described earlier and plasma analysis done accordingly.

Pharmacokinetic and statistical analysis
The pharmacokinetic profile for each volunteer was generated using the Kinetica 5.0 software by feeding in the extrapolated plasma concentrations gotten from plasma analysis. The pharmacokinetic parameters generated were analysed statistically using the statistical package for social sciences (SPSS) version 22.0. The Wilcoxon signed-rank test was used to compare the pharmacokinetic parameters obtained before and after administration of herbs, while the Kruskal-Wallis H test was used to compare time modes of herbal administration on the pharmacokinetic parameters.

Results
Table 1, 2 and 3 shows comparison between pharmacokinetic parameters of risperidone when administered alone in healthy human volunteers and when administered with decoction of *L. alata* concurrently, one hour after risperidone and one hour before risperidone respectively. Table 4 shows comparison between pharmacokinetic parameters of risperidone after administration of risperidone 2 mg and *L. alata* by the three different time modes in healthy human volunteers.

Table 1 Comparison of mean ± SEM pharmacokinetic parameters of risperidone after administration of risperidone (2 mg) alone and on concurrent administration with *Lophira alata* in healthy human volunteers (n= 6)

Pharmacokinetic parameters	Risperidone alone	Risperidone + *Lophira alata* (Group A)	*p*-value[#]
C_{max} (ng/ml)	19.46 ± 1.90	64.88 ± 12.16	0.028*
t_{max} (h)	1.75 ± 0.17	1.00 ± 0.00	0.034*
k_a (h^{-1})	1.78 ± 0.21	3.87 ± 0.17	0.028*
$t_{1/2a}$ (h)	0.42 ± 0.04	0.18 ± 0.01	0.028*
k_e (hr^{-1})	0.78 ± 0.26	0.70 ± 0.08	0.917
$t_{1/2e}$ (h)	1.70 ± 0.58	1.05 ± 0.10	0.345
AUC_{0-t} (ng.h/ml)	50.72 ± 12.91	84.18 ± 11.64	0.046*
$AUC_{0-\infty}$ (ng.h/ml)	61.04 ± 18.06	86.79 ± 11.88	0.116
***V*d (L)**	76.56 ± 10.58	37.29 ± 4.64	0.028*
Cl (L/h)	50.30 ± 12.75	26.07 ± 4.76	0.075

[#]Wilcoxon Signed-Rank Test *Significant ($p < 0.05$)

Table 2 Comparison of mean ± SEM pharmacokinetic parameters of risperidone after administration of risperidone (2 mg) alone and *Lophira alata* one (1) hour after risperidone in healthy human volunteers (n= 6)

Pharmacokinetic parameters	Risperidone alone	Risperidone + *Lophira alata* (Group B)	*p*-value[#]
C_{max} (ng/ml)	16.92 ± 1.52	46.27 ± 7.68	0.046*
t_{max} (h)	1.42 ± 0.20	2.00 ± 0.00	0.059
k_a (h^{-1})	2.17 ± 0.33	1.79 ± 0.09	0.463
$t_{1/2a}$ (h)	0.36 ± 0.05	0.39 ± 0.02	0.528
k_e (hr^{-1})	0.64 ± 0.22	0.40 ± 0.01	0.600
$t_{1/2e}$ (h)	1.97 ± 0.60	1.73 ± 0.04	0.753
AUC_{0-t} (ng.h/ml)	49.33 ± 12.34	127.88 ± 20.12	0.028*
$AUC_{0-\infty}$ (ng.h/ml)	59.92 ± 15.03	139.28 ± 21.19	0.028*
***V*d (L)**	93.79 ± 20.62	41.84 ± 8.24	0.046*
Cl (L/h)	47.62 ± 12.26	16.92 ± 3.62	0.028*

[#]Wilcoxon Signed-Rank Test *Significant ($p < 0.05$)

Table 3 Comparison of mean ± SEM pharmacokinetic parameters of risperidone after administration of risperidone (2 mg) alone and *Lophira alata* one (1) hour before risperidone in healthy human volunteers (n= 6)

Pharmacokinetic parameters	Risperidone alone	Risperidone + *Lophira alata* (Group C)	*p*-value[#]
C_{max} (ng/ml)	26.02 ± 3.14	38.07 ± 12.32	0.463
t_{max} (h)	1.83 ± 0.17	3.50 ± 0.85	0.114
k_a (h^{-1})	1.81 ± 0.26	1.33 ± 0.51	0.463
$t_{1/2a}$ (h)	0.41 ± 0.04	1.00 ± 0.27	0.116
k_e (hr^{-1})	0.42 ± 0.13	0.40 ± 0.21	0.600
$t_{1/2e}$ (h)	2.31 ± 0.54	4.02 ± 1.33	0.249
AUC_{0-t} (ng.h/ml)	80.13 ± 12.36	231.02 ± 84.67	0.116
$AUC_{0-\infty}$ (ng.h/ml)	94.62 ± 14.74	300.74 ± 97.60	0.116
***V*d (L)**	57.14 ±7.30	53.16 ± 12.90	0.753
Cl (L/h)	26.81 ± 7.71	22.89 ± 12.97	0.753

[#]Wilcoxon Signed-Rank Test *Significant ($p < 0.05$)

Table 4 Comparison of mean ± SEM pharmacokinetic parameters of risperidone after administration of risperidone (2 mg) and *Lophira alata* by different time modes in healthy human volunteers (n= 6)

	Time mode			Statistical analysis		
	C	DTH	HTD		Post-hoc	
	GROUP			*p*-value[1]	Average rank[2]	Pairwise comparison (Bonferroni adjustment)[3]
Pharmacokinetic parameters	A	B	C			
C_{max} (ng/ml)	64.88 ±	46.27 ±	38.07 ±	0.203	NA	NA

	12.16	7.68	12.32			
t_{max} (h)	1.00	2.00	3.50	0.010*	HTD = 12.50	C- DTH = 0.046*
	±	±	±		DTH = 11.50	C-HTD = 0.017*
	0.00	0.00	0.85		C = 4.50	DTH-HTD = 1.000
k_a (h^{-1})	3.87	1.79	1.33	0.003*	C = 15.50	C- DTH = 0.028
	±	±	±		DTH = 7.50	C-HTD = 0.004*
	0.17	0.09	0.51		HTD = 5.50	DTH-HTD = 1.000
$t_{1/2a}$ (h)	0.18	0.39	1.00	0.003*	HTD = 13.50	C- DTH = 0.028*
	±	±	±		DTH = 11.50	C-HTD = 0.003*
	0.01	0.02	0.27		C = 3.50	DTH-HTD = 1.000
k_e (hr^{-1})	0.70	0.40	0.40	0.011*	C = 14.50	C- DTH = 0.149
	±	±	±		DTH = 8.50	C-HTD = 0.010*
	0.08	0.01	0.21		HTD = 5.50	DTH-HTD = 0.979
$t_{1/2e}$ (h)	1.05	1.73	4.02	0.011*	HTD = 13.50	C- DTH = 0.151
	±	±	±		DTH = 10.50	C-HTD = 0.010*
	0.10	0.04	1.33		C = 4.50	DTH-HTD = 0.983
AUC_{0-t} (ng.h/ml)	84.18	127.88	231.02	0.236	NA	NA
	±	±	±			
	11.64	20.12	84.66			
$AUC_{0-\infty}$ (ng.h/ml)	86.79	139.28	300.74	0.209	NA	NA
	±	±	±			
	11.88	21.19	97.60			
***V*d (L)**	37.29	41.84	53.16	0.700	NA	NA
	±	±	±			
	4.64	8.24	12.90			
Cl (L/h)	26.07	16.92	22.89	0.209	NA	NA
	±	±	±			
	4.76	3.62	12.97			

C= Concurrent administration of herb with drug. DTH= Drug then herb (One hour difference). HTD= Herb then drug (One hour difference). NA= Not applicable *Significant ($p < 0.05$)

[1]Kruskal-Wallis H test (Significance $p < 0.05$). When this is significant, it indicates that the distribution of the pharmacokinetic parameter is not the same across the groups (i.e. reject null hypothesis)

[2]Arranged according to the effect on pharmacokinetic parameter (highest to lowest)

[3] Pairwise comparisons that have $p < 0.05$ indicate that the distribution of compared groups are not the same and vice versa.

Discussion

Administration of a decoction of *L. alata* concurrently with risperidone (2 mg) tablets significantly ($p < 0.05$) increased the rate of absorption (k_a), peak plasma concentration (C_{max}) and measure of drug exposed to the body ($AUC_{0-\infty}$). However, a significant ($p < 0.05$) decrease in the time to achieve this peak plasma concentration (t_{max}), half-life of absorption ($t_{1/2a}$) and extent of drug distribution (Vd) was observed.

An increase in k_a and $AUC_{0-\infty}$ values of risperidone can be an indication of decreased binding of risperidone to P-gp because, the P-gp is an important regulator of drug absorption (k_a) and bioavailability ($AUC_{0-\infty}$) and it is the most critical non-metabolic system that mediates pharmacokinetic drug-drug and drug-herb interactions. Furthermore, risperidone has been reported to have a stronger affinity for P-gp than most atypical antipsychotic drugs thus, its absorption will be affected more by P-gp inhibitors or inductors (Moons *et al*., 2011; Currie, 2018).

Therefore, this study suggests that *L. alata* may have a strong inhibitory effect on P-gp, which results in a decrease in the binding of risperidone for P-gp in the lumen. This led to an observed increase in absorption rate (k_a) of risperidone from the gut into the blood stream, which increased the plasma concentration of risperidone ($AUC_{0-\infty}$). *Ginkgo biloba*, another herb used in the management of psychotic symptoms, has been documented to have inhibitory effect on P-gp and observed to increase drug absorption and plasma concentration of some drugs (Rombola *et al*., 2020; Wasef *et al*., 2022).

L. alata had no significant ($p < 0.05$) effect on the rate of elimination (k_e) of risperidone when administered concurrently. K_e is the major pharmacokinetic parameter that determines drug elimination via metabolism. CYP450 2D6 is a common enzyme in the metabolism of risperidone and clozapine at the hepatic level and this is the primary site of metabolism for antipsychotic drugs (Wang *et al*., 2015; Shnayder *et al*., 2022).

Wang *et al*. (2016) conducted a study on the *in vitro* effects of concomitant use of herbal preparations (that have been documented to be extensively used clinically and have pharmacologic benefits in the treatment of psychotic disorders) on cytochrome P450s involved in clozapine metabolism. Two of the four herbs studied by Wang *et al*. (2016), *Radix rehmanniae* and *Radix bupleuri* had no effect on CYP 2D6, and thus no significant effect was observed on k_e, which is similar to what has been reported about *L. alata* in this study. On the other hand, another herb, *Fructus schisandrae* had a strong inhibitory effect on CYP 2D6 and this translated into a decrease in k_e and an increase in $t_{1/2e}$ while the fourth herb, *Fructus gardenia* had a weak inhibitory effect on CYP 2D6 and this translated into a decrease in k_e and an increase in $t_{1/2e}$ but not as much as what was observed with *Fructus schisandrae.* It can therefore be suggested that *L. alata* may have a weak or no inhibitory effect on CYP 2D6. It is important to note that alterations in the activity of enzymes by enzyme inhibitors and inducers play an important role in drug-herb interactions (Borse *et al.,* 2019).

Administration of a decoction of *L. alata* one (1) hour after administering risperidone (2 mg) tablets significantly ($p < 0.05$) increased C_{max} and $AUC_{0-\infty}$ but significantly ($p < 0.05$) decreased Vd and Cl. The significant ($p < 0.05$)

increase in k_a of risperidone observed on concurrent administration was not observed in this group of delayed administration of the herb. This may be due to risperidone being already absorbed appreciably via the normal mechanisms of absorption by the time the herb was introduced. Thus, the inhibitory effect of the herb on the P-gp would be negligible, because the substrate (risperidone) had been depleted appreciably before the herb got to the intestines to elicit its inhibitory effect.

Administration of a decoction of *L. alata* one (1) hour before administering risperidone (2 mg) tablets had no significant ($p < 0.05$) effect on the pharmacokinetics of risperidone. This may be attributed to the wearing off of most of the effect of the herb before risperidone was administered.

It is important to state at this point that regardless of the time of administration of *L. alata*, no significant ($p < 0.05$) changes were observed in the k_e and $t_{1/2e}$ of risperidone. Thereby, suggesting that the herb probably has negligible effect on the elimination of risperidone which is predominantly mediated CYP 2D6 enzyme.

A further comparison of the effects of time mode of herbal administration on the pharmacokinetics of risperidone in table 4 shows that *L. alata* had more significant ($p < 0.05$) effect on all the pharmacokinetic parameters of risperidone when administered concurrently. This suggests that the alteration of pharmacokinetic parameters of risperidone occurs when administered at the same time as *L. alata*, and that if an hour gap is given between administrations, no pharmacokinetic alteration will occur.

Conclusion

Decoction of *Lophira alata* significantly interacts with risperidone tablet when taken concurrently by increasing risperidone absorption. The mechanism of this pharmacokinetic effect may be due to inhibitory effect of *Lophira alata* on p-glycoprotein, which results in a decreased binding of risperidone to p-glycoprotein in the intestine, resulting in increased absorption of risperidone.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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