ISBN : 978-979-18458-6-1

PROCEEDING

INTERNATIONAL CONFERENCE ON CENTRAL MANAGEMENT OF CENTRAL CYTOTOXIC RECONSTITUTION

Grand Cokro Hotel Yogyakarta
May 25th, 2013

THE INTERNATIONAL CONFERENCE ON CENTRAL MANAGEMENT OF CENTRAL CYTOTOXIC RECONSTITUTION IN PHARMACY PRACTICE YOGYAKARTA, INDONESIA, 2013

Editors :

Dwi Utami M.Si.,Apt

Iis Wahyuningsih M.Si.,Apt

Wahyu Widyaningsih, M.Si., Apt

Nanik Sulistyani, M.Si., Apt

Published by :
Faculty of Pharmacy, Ahmad Dahlan University
Jln. Prof. Dr. Soepomo, Warungboto, Yogyakarta
Indonesia

ISBN : 978-979-18458-6-1

Welcome Address from Chairman of Organizing Committtee

Honorable Rector of Ahmad Dahlan University,
Dean Faculty of Pharmacy of Ahmad Dahlan University,
Honorable Plenary Speakers
Dear Colleague,
Distinguished Participants,
Ladies and Gentlemen

Assalamu'alaikum warahmatullahi wabarakatuh,

Good morning,

First of all, let us give thanks to Allah, the Almighty God, who has allowed us to attend this conference. Secondly, I would like to welcome everyone to Yogyakarta.

Preparation and reconstitution of drug products are an essential function of hospital pharmacy. The hospital pharmacist should also take notice for central intravenous additive service including cytotoxic reconstitution services. Thus, handling cytostatic in hospital is also crusial in hospital practises. In other words, Cytotoxic Handling should to provide protection to patients, the operator and environment.

Ladies and gentlemen,

To celebrate the 17th aniversary faculty of Pharmacy Ahmad Dahlan University, Yogyakarta, in collaboarting with Bethesda Hospital, Yogyakarta, Indonesia hosted The International Conference on Safety Management of Central Cytotoxic Reconstitution in Pharmacy Practice". The conference is held on 25 May, 2013 at The Grand Tjokro Hotel, Yogyakarta, Indonesia. The conference facilitated some of professional that come from world wide such as academia, researchers, hospital pharmacists, policy maker, and health care professionals. The second agenda is Workshop on Basic Cytotoxic Handling for hospital pharmacists and academia. It will hold on 26-27 May, 2013 in Pharmacy Department, Bethesda Hospital.

I do hope this conference will give a new initiative for practicing sorounding cytotoxic handling and team-work. I thank to conference sponsors and committee members for their support.

Wassalamu'alaikum warahmatullahi wabarakatuh,

Yogyakarta, 25 May 2013

Dr.rer.nat. Endang Darmawan, M.Sc., Apotheker
Chairperson of the organizing committee

ISBN : 978-979-18458-6-1

Welcome Address from Dean of Faculty of Pharmacy, Ahmad Dahlan University

Assalamu'alaikum Wr. Wb.

Dear all participants,

Welcome to the International Conference and Workshop on Safety Management of Central Cytotoxic Reconstitution in Pharmacy Practice. Thank you for participating in this great event. Hopefully, you can enjoy the days of International Conference and Workshop.

The topic of this international seminar is very interesting and important for the development of pharmacists' skills in drug reconstitution, since we know that our new perspective of pharmacy practice is patients' care and patients' safety. Dealing with cytotoxic drug is a kind of collaboration among physician, pharmacist, nurse, psychologist, patient and patient's family. However, as the pharmacists, we have unique skills and knowledge related to the preparation, administration and monitoring of cytotoxic drug administration. Therefore, in a team work, pharmacist has some responsibilities as a leader related to the cytotoxic drug reconstitution.

This international conference and workshop are the collaboration between Faculty of Pharmacy, University of Ahmad Dahlan Yogyakarta as academic institution with the Bethesda Hospital of Yogyakarta as one of the central cytotoxic reconstitution. We also invited Prof A.A. Kaptein, from Leiden University Medical Center, Leiden, The Netherlands and Harbans Kaur Dhillon from University Malaya, Medical Centre, Malaysia as speakers, besides Dra. L. Endang Budiarti, M.Pharm., Apt. as practitioners in Bethesda Hospital of Yogyakarta and Dr. Dyah Aryani Perwitasari, Apt., PhD who wants to share about development of pharmacist's skill in medical reconciliation. After the one day seminar, we invite you to joint with us on the workshop of Central Cytotoxic Reconstitution which will be held in Bethesda Hospital of Yogyakarta. This workshop is useful for us, especially when we want to start the Central Cytotoxic Reconstitution in our hospital.

I hope, The International Conference and Workshop on Safety management of Central Cytotoxic Reconstitution in Pharmacy Practice will inspire us to practice our skills and knowledge in our fields. In the future, we can reach one the goal of pharmacy practice, which is patients' safety.

Have a great conference.

Wassalamu'alaikum wr wb

Dean of Faculty of Pharmacy
University of Ahmad Dahlan, Yogyakarta

Dr. Dyah A Perwitasari, Apt., Ph.D

CONTENTS

ISBN : 978-979-18458-6-1

ISBN : 978-979-18458-6-1

ISBN : 978-979-18458-6-1

The Organizing Committee of International Conference on Safety Management of Central Cytotoxic Reconstitution in Pharmacy Practice

Advisory Board :

Rector of Ahmad Dahlan University
Prof. Dr.Achmad Mursyidi, Apt.
Prof. Dr. Mulyadi, Apt.

Steering Committee :

Dean of Faculty of Pharmacy Ahmad Dahlan University

Technical Committee :

Chairperson	:	Dr.rer.nat. Endang Darmawan, Apt
Secretary	:	Andriana Sari, M.Sc., Apt
Treasure	:	Ana Hidayati, S. Far., Apt

Sub-committee :

Secretariat	:	- Imaniar Noor Faridah, M.Sc., Apt
		- Faridah Baroroh, M.Sc.,Apt
Funding, Sponsorship and Exhibition	:	- Arief Budi Setianto, M.Sc., Apt.
		- Nina Salamah, M.Sc.,Apt
		- Vivi Sofia, M.Sc., Apt
Scientific Program	:	- Hendy Ristiono, S.Far., Apt
		- Dr. Laela Hayu Nurani, M.Sc., Apt
		- Moch Saiful Bachri, M.Sc., Ph.D., Apt
		- Nining Sugihartini, M.Sc., Apt
Proceeding Editors	:	- Dwi Utami M.Si.,Apt
		- Iis Wahyuningsih M.Si.,Apt
		- Wahyu Widyaningsih, M.Si., Apt
		- Dra. Nanik Sulistyani, M.Si., Apt
Logistic	:	- Hari Susanti, M.Si., Apt
		- drh. Sapto Yuliani, M.PH

ISBN : 978-979-18458-6-1

		- Aprillia, S.Si.,Apt
		- Warsi, M.Si., Apt
Promotion and Public Relation	:	- Annas Binarjo, M.Sc., Apt
		- Muhammad Muhlis, Sp.FRS., Apt
		- dr. Akrom, M.Kes
Acomodation, Documentation	:	- Azis Ikhsanudin, S.Si., Apt
and Conference Services		- Adnan, S.Si., Apt

ISBN : 978-979-18458-6-1

The Organizing Committee of Workshop on Safety Management of Central Cytotoxic Reconstitution in Pharmacy Practice

Chairperson	:	Anna Purwaning Rahaju, S.Si., Apt.
Secretary	:	Nolen Mayrani Manik, S. Farm., Apt.
Treasure	:	Irine Dyah Widiastuti, S. Si., Apt
Scientific Program	:	Dra. L. Endang Budiarti, M. Pharm., Apt.
		V. Susi Purwanti, S. Si., Apt
Acomodation and Documentation	:	Adhitya Nugraha Arisada, S. Farm., Apt.
Funding, and Sponsorship	:	Dra. P.E. Wardani, MAB., Apt.
Publication	:	Yollita Angela Natasya, S. Farm., Apt.
Logistic	:	Dra. Ning Raswani, Apt.
		Yuliana Sri Suwarti, S.Si., Apt.

THE EFFECT OF INFUSA OF *Zingiber officinale* ROXB TO THE IBUPROFEN TABLET BIOAVAILABILITY IN MALE RABBITS

Iis Wahyuningsih, Joko Priyanto, Erika Diah
Pharmacy Faculty, Ahmad Dahlan University
avinagil@gmail.com, 08122781162

Background. *The tendency to use of herb drug simultaneously with synthetic drug may result in an interaction. Red ginger contains gingerol and shagaol proven to increase gastric emptying time and have antiplatelet activity, which causes the blood becomes more dilute, the heart of the work is lighter, so the smooth blood flow, which in turn may affect the bioavailability of furosemide.*

Objective . *This study aims to determine the difference between the effect of 2 hours before, 4 hours after coadministration with infusa and red ginger (Zingiber officinale Roxb.) on the bioavailability of the tablet furosemida in male rabbits.*

Method. *The cross over design with the same subject was used in this study. The samples consisted of 80 mg furosemide with 0%b/v, 5%b/v, 7,5%b/v and 10%b/v red ginger infusa, 2 hours before administration furosemida tablet, 4 hours after administration of tablets furosemida. Blood sampling is done throught marginalis vein and performed at the 0,5; 0,75; 1; 1,5; 2; 3; 4; 6; 8; and 24. Furosemida levels in blood plasma using the Kelly's method modified by Hakim. Bioavailability parameters are determined directly from the graph the relationship Cp vs t while the AUC determined using the trapezium method.*

Outcome measurement. *The results then were used to evaluated the bioavailability parameters: $t_{maks,}$ $Cp_{maks,}$ and $AUC^{o-\infty}$ and were analyzed using ANOVA test in the same way as well as 95% trust standart.*

Result. *Value $Cp_{max,}$ from treatment respectively for 43.2 ug / ml, 58.3 μg / ml, 182 μg / ml, and 119 μg / ml. Tmax value of treatments A, B, C, and D, respectively for 5.4 hours, 5.2 hours, 5 hours, and 3.6 hours. Value $AUC^{o-\infty}$ of treatments A, B, C, and D, respectively for 668 μg.jam / ml, 867 μg.jam / ml, 1808 μg.jam / ml, and 1459 μg.jam / ml.*

Conclusion : The results showed that infusa red ginger (Zingiber officinale Roxb.) with a variation of the timing of 2 hours before, 4 hours after, and together with the provision may affect the bioavailability of the tablet furosemida, where prices Cp_{maks} and AUC on all three treatments is greater than the control and in each treatment there were significant differences ($P < 0,05$), while the price tmaks did not differ significantly with control or equal to controls ($P > 0,05$).

Key words : *Furosemida, red ginger (**Zingiber officinale** Roxb.) Bioavailability.*

ISBN : 978-979-18458-6-1

INTRODUCTION

Millions of people use herbal medicine in conjunction with synthetic drugs without the doctor's recommendation (Gohil and Patel, 2007). The general public thinks, herbal medicines can reduce the side effects of drugs taken and can improve the effectiveness of treatment (Inamdar *et al.,* 2008). Although considered natural, many medicinal herbs that can interact with other medications causing harmful side effects and or reduce the benefits of the drug (Gohil and Patel, 2007).

The number of pharmacologically active compounds in herbal medicine, the interaction is likely to increase. Theoretically herbal drug interactions with synthetic drugs is higher than synthetic drugs because the interaction of two synthetic drugs usually contain only a single chemical constituents (Izzo, 2004). The use of herbal medicine in conjunction with synthetic drugs is generally not supervised by the physician or practitioner of herbal medicine, it can result in harm to the patient, if they use herbal remedies and potential drug interactions sintetiknya have. This interaction is generally not known until the patient is experiencing pain or serious incident occurs that threatens the patient's life (Gohil and Patel, 2007).

Herbs can interact with medications through pharmacokinetic interactions and synthetic or pharmacodynamic (Rodda et al., 2010). Pharmacokinetic interactions lead to changes in absorption, distribution, metabolism or excretion of synthetic drugs or herbal medicines that can affect drug action quantitatively. Pharmacodynamic interactions qualitatively affect drug action, either through enhancing effect (synergistic or additive action) or antagonist effects (Gohil and Patel, 2007). Interactions between herbal medicines and antibiotics, such as ginger and metronidazole, may increase the toxicity of metronidazole, due to ginger lowers kliren and elimination of metronidazole (Okonta *et al,* 2008). On the other hand, according to Young *et al,* (2006) Ginger has a synergistic effect given together with nifedipine in inhibiting platelet aggregation in hypertensive patients.

Furosemide chosen as a model drug in this study because it is one powerful diuretic drug that is the first line treatment of hypertension according to JNC VII level I (Chobanian *et al,* 2003). Furosemide categorized as BCS class II drug because of poor solubility. Furosemide has a dose-response curve is steep and high protein binding, ie by 95% so that furosemide as a potential drug interactions with objects on drugs, drugs with food (Mc Evoy, 2002). Red ginger contains gingerol and shogaol proven to increase gastric emptying time and have antipletet activity, which causes the blood becomes more dilute, the heart of the work is lighter, so the smooth blood flow, which in turn can affect the bioavailability of furosemide tablets.

MATERIALS AND METHODS

The main material used is a 9 month old red ginger obtained from Bantul area. The chemicals used were pa furosemide powder, furosemide tablets (Indofarma), ethyl acetate pa (E Merck), HCl pa (E Merck), phosphate buffer pH 8 (NaOH and KH2PO4), NaOH pa, heparin (Invicolt), distilled water (Asia Lab.), local strain male rabbits aged 3-4 months weighing 1.5-2 kg (CV <5%). This study used 5 male rabbits of local strain (n = 5) weighing between 1.5-2 kg (CV <5%), were studied using a cross-over design (Table I) with 6 kinds of treatment.

Before the treated rabbits were fasted for 1 day. For each treatment was given 7 days washout (t1 / 2 preliminary experiments (control 1) is 8.15 hours). After drug administration, blood was collected at 0.5 hours, 0.75, 1, 1.5, 2, 3; 3.5; 4; 8 and 24, via Marginal ear vein of rabbits. Blood collected in tubes that had been given heparin ependrof. The blood levels of furosemide in accordance with the method set out Kelly et al. modified by the Judge (1996). Blood plasma (250 mL) plus 0.1 N HCl (50 mL) and then mixed disari with ethyl acetate (3.0 mL) using a vortex for 2 minutes. The organic layer

Table I. The design of Cross Over in determining the bioavailability of the furosemide tablet infusion on coadministration of red ginger

Rabits	Week					
	I	II	III	IV	V	VI
1	F0	F1	F2	F3	F4	F5
2	F1	F2	F3	F4	F5	F0
3	F3	F4	F5	F0	F1	F2
4	F4	F5	F0	F1	F2	F3
5	F5	F0	F1	F2	F3	F4

F0: furosemide 80 mg tablet (control).

F1: Giving with 5 mL of red ginger infusion 5% with furosemide tablets.

F2: Giving with red ginger infusion 5 mL of 7.5% with furosemide tablets

F3: Giving red ginger infusion 5 mL 10% 2 hours before furosemide tablets

F4: Giving with red ginger infusion 5 mL 10% with furosemide tablets.

F5: Giving red ginger infusion 5 mL 10% 4 hours after furosemide tablets Note: delivery volume of 5 mL infusion administered orally.

(2.0 mL) were taken, added to it a solution of 0.1 M phosphate buffer pH 8 (2.50 mL), and then in-vortex for 2 min and in-centrifuged (2500 rpm, 10 min). Buffer layer is taken 2.0 mL acidified with 0.5 N HCl (1.0 mL). Subsequently the solution was measured at a wavelength of excitation intensity and maximum emission using spectrofluorometer (Hitachi F 2500).

Determination of bioavailability parameters of furosemide

Bioavailability parameters include tmax, Cpmaks, and $AUC^{0-\infty}$ obtained directly from the curve relationship between drug concentration and time, and $AUC^{0-\infty}$ obtained by the trapezoidal method.

RESULTS AND DISCUSSION

Determination of furosemide levels in the blood carried by spectrofluorometer that had been previously validated. The result of the excitation and emission wavelengths of furosemide in blood plasma obtained respectively 273 nm and 408 nm. Linear regression equation to calculate the levels obtained: Y = 1.7448 X + 14.5463, with a correlation coefficient of 0.9970 is greater than r table 0.754 (n = 9 and 95% confidence level). Recovery value of 104.84 ± 1.3 to 118.53 ± 2.42%. Value of plasma levels of furosemide in blood at any given time are presented in Table II.

With fluctuating results in Figure 5 has area under the curve (AUC) was determined using the trapezoidal method, the average of the levels obtained, while t_{max} and Cp_{maks} directly from the graph of the results of the assay furosemide in blood plasma for each treatment. More results can be seen in Table III.

From previous experiments on the effect of food on the bioavailability of furosemide, said that the food does not significantly affect the bioavailability of furosemide (Kelly et al, 1974). Unlike the other experiments (McCrindle et al, 1996) that furosemide 40 mg were given and analyzed using HPLC, the food may decrease the

ISBN : 978-979-18458-6-1

Table II. Value of furosemide levels in blood plasma (purata ± SE)

Time (hours)	Consentration (µg/mL) ±SE					
	F0	F1	F2	F3	F4	F5
0	0	0	0	0	0	0
0.5	10.08±3.99	9,71±3.59	16.55±3.10	8.12 ± 0.41	20.13±4.57	38.69 ± 4.72
0.75	12.64±10.87	12,92±3.74	19.33±2.95	8.47 ± 0.64	28.10±5.02	49.76 ± 4.53
1	14.73±4.11	17.77±5.02	22.14±3.47	11.92 ± 1.55	40.54±9.90	53.67 ± 6.82
1.5	25.03±9.23	25.53±10.24	40.89±12.88	14.48 ± 2.37	55.87±15.71	64.84 ± 7.59
2	25.67±9.24	31.12±13.17	49.32±14.30	22.97 ± 1.80	76.32±20.93	77.77 ± 6.30
3	38.84±15.04	47.53±16.76	64.74±14.02	37.25 ± 3.77	100.78±22.27	104.79 ± 11.17
3.5	45.07±14.91	41.27±11.02	72.77±17.36	46.84 ± 2.03	119±19.34	105.65 ± 5.28
4	50.97±14.53	47.99±12.32	82.35±20.28	56.22 ± 5.53	121.85±17.67	71.52 ±4.54
8	58.97±11.27	61.61±9.41	59.57±16.69	44.16 ± 5.29	128.05±29.23	55.52 ± 6.22
24	13.52±2.09	11.13±3.75	9.43±3.34	10.2 ± 1.73	13.26±4.34	18.57 ± 0.79

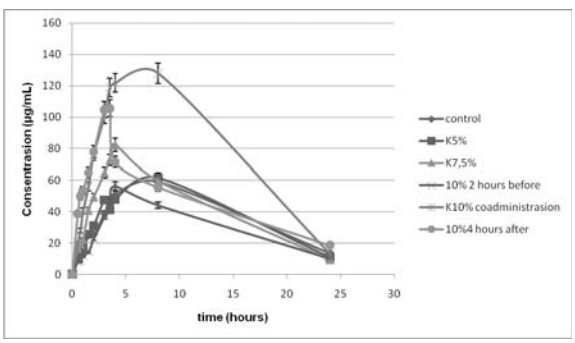

Figure 1. Furosemide concentration curve (purata ± SE) in plasma as a function of time, with each male rabbits treated orally at a dose of 80 mg.

bioavailability of furosemide by 30% and other studies also suggested breakfast can decrease the bioavailability of furosemide by 30%, but is not affected by the long Gastric emptying time (Beerman & Midskov, 1986).

From the results of research conducted, to see the effect of ginger rhizome infusion concentration given that the concentration of 5%, 7.5%, and 10% w / v with furosemide, the price obtained is obtained from the smallest tmax furosemide treatment concentration of 7.5%, which is 4 , 4 hours. This indicated that the coadministration treatment of red ginger infusion concentration of 7.5%, furosemide is absorbed more quickly, made possible because the content of oleoresin of red ginger (gingerol and shogaol) (Yamahara *et al,* 1990) increases the speed of gastric emptying (Hu *et al,* 2011). Speed affects the rate of gastric emptying unstable drug degradation in the stomach (Devissagoet, 1982).

Area Under the Curve ($AUC^{0-\infty}$) largest obtained from coadministration treatment of red ginger infusion concentration of 10%, ie 1996.46 ug / mL.jam, this is due to the possibility of active substance (gingerol and shogaol) highest, which is known to serves as an antiplatelet (Young *et al,* 2006). Next will cause the blood thinner, lighter work of the heart and blood flow to be smooth, so that the displacement of furosemide from the intestine into the systemic circulation has increased.

The maximum concentration (Cp_{maks}) mainly from coadministration treatment of red

ISBN : 978-979-18458-6-1

Table III. Purata furosemide bioavailability parameter values ??in male rabbits

Bioavailability Parameters	Treatment					
	F0	F1	F2	F3	F4	F5
Cpmaks (µg/mL)	61,36± 12,77	70,07±11,48#	87,45±18,05#	58,3 ± 3,9#	154,28±23,49*	119 ± 7,3*
tmaks (Jam)	7,2± 0,80	6,2± 1,11#	4,4± 0,98#	5,2 ± 0,4#	5,5± 1,02#	3,6 ± 0,6*
AUC $0^{-\infty}$ (µg/mL.jam)	1186,26± 150,45	1071,75± 155,22#	1096,58± 194,28#	867 ± 61#	1996,46± 290,08*	1459 ± 64#

Remark s: * No significant difference (p <0.05) with the control treatment
No significant difference (p> 0.05) with the control treatment

ginger infusion concentration of 10%. Cpmaks will increase with an increase in $AUC^{0-\infty}$, because the concentration of the drug will show the amount of drug that will be absorbed by the body.

From the results of the study to see the effect of the timing of the price obtained furosemide smallest tmax obtained from 4 hours after treatment administration is 3.6 hours. Area Under the Curve ($AUC^{0-\infty}$) largest obtained from coadministration treatment of red ginger infusion with furosemide tablet, which is 1996.46 ± 290.08 mg / ml.jam. The maximum concentration (Cp_{maks}) mainly from coadministration treatment of red ginger infusion concentration of 10% concurrently with furosemide tablet, which is 154.28 ± 23.49 mg / ml.jam.

Decrease or increase of Cp_{maks}, t_{max}, and AUC0-∞ possible because of several factors such as the surface area of the intestinal wall that allows the drug to the colon greater contact, the speed in which delay gastric emptying slows gastric emptying and drug absorption furosemide at acidic pH height / base more in the form of ions while the drug is absorbed in the intestine molecular form (Banker and Rhodes, 1996). The movement of the digestive tract and into the blood stream absorption and decreased movement of the drug from the gut can also affect the amount of drug absorbed, and the presence of the drug with mineral complex will also affect drug dissolution rate and amount of drug absorbed becomes smaller, so that everything is not directly affect the bioavailability of the drug. Not only influenced by it alone, the stability of the drug and the disease causes a decrease in organ function in test animals are not known to also affect drug absorption (Devissaguet, 1982).

These results indicate that infusion of red ginger affect the bioavailability parameters Cpmaks and AUC0-∞, but does not significantly affect the parameters tmax, this can happen due to many factors that affect the bioavailability of a drug, among others, note that furosemide in Biofarmasetika Classification System (BCS) including two classes. Ie drugs that have a high permeability while the low solubility or dissolution. The active substance of red ginger rhizome causing increased permeability. This is due to the active substances in addition to increase gastric emptying time, as well as antiplatelet that is a blood thinner and blood flow more smoothly. If the blood flow smoothly shift from gastrointestinal to systemic furosemide increased.

Since the results indicate that furosemide when administered concomitantly with red ginger infusion significantly cause changes in bioavailability parameters Cp_{maks} and AUC0-∞, then the use of furosemide should be careful when consumed with red ginger infusion.

CONCLUSION

At the conclusion of research conducted as follows:

1. There is no significant difference in the effect of red ginger infusion by 5 ml at a concentration of 5% w / v and 7.5% w / v in conjunction with the bioavailability of furosemide tablets furosemide, but the effect on the concentration of 10% Cp_{maks}, and $AUC^{0-\infty}$.

2. There is no significant difference in the timing of the effect of red ginger infusion 5 ml of 10% w / v two hours before, simultaneously, and 4 hours after, the bioavailability of furosemide tablets.

REFERENCES

Banker, G.S.,m Rhodes, C.T., 1996, *Modern Pharmaceutiues*, Volome 72, 3rd edition, revised and expaned, 21-74, Marcel Dekker,Inc,New York.

Beerman, B., dan Midskov, C., 1986, Reduced Bioavailability and Effect of Furosemide Given With Food, *J Clin Pharmacil*, 29:725-727.

Devissaquet, J. Ph, Aiace, J. M., Hermann, A. M. E., 1982, *Farmasetika 2 (Biofarmasi),* Edisi II, Diterjemahkan oleh Widji Soeratri dan Nanizar Zaman, 35, Airlangga University Press, Surabaya.

Gohil, K.J. and Patel, J.A., 2007, Herb-Drug Interactions, *Indian Journal of Pharmacology,* 39(3):129-139.

Hu, M.L., Rayner, C.K., Wu, K.L., Chuah, S.K., Tai, W.C., Chou, Y.P., Chiu, Y.C., Chiu, K.W., Hu, T.H., 2011, Effect of Ginger on Gastric Motility and Symptoms of Functional Dyspepsia, *World J Gastroenterol*, 17(1):105-110.

Inamdar, N., Edalat, S., Kotwal, W.B., Pawar, S., 2008, Herbal Drugs in Milieu of Modern Drugs, *International Journal of Green Pharmacy*, 2(1):2-8.

Izzo, A.A., 2004, Herb-Drug Interactions, *Fundamental & Clinical Pharmacology*, 19: 1–16.

Kelly, M.R., Cutler, R.E., Forrey, A.W., and Kimpel, B.M., 1974, Pharmacocinetics of Orally Administered Furosemid, *J Clin.Pharmacol. ther.,* 15:178-186.

McCrindel,. J.L., Li kam wa, T.C., Barron, W., Prescott, L.F., 1996, Effect of Food on the Absoption of Frusemid and Bumentanide in Man, *J Clin.Pharmacol,* 42:743-746.

McEvoy, G.K., 2002, *American Hospital Formulary Service- Drug Information*, Bethesda, American Society of Health-System Pharmacists.

Okonta, J. M., Uboh, M., Obonga, W.O., 2008, Herb-Drug Interaction : A case Study of Effect of ginger on the Pharmacokinetic of Metronidazole in Rabbit*, J. of Pharmaceutical Sciences*, Department of Pharmaceutical Chemistry, University of Nigeria.

Rodda, H.C., Molmoori, R.K., Samala, S., Banala, N., and Ciddi V., 2010, An Insight into Herb - Drug Interactions, *International Journal of Pharmaceutical Sciences and Nanotechnology*, 2(4): 689-706.

Yamahara, J., Huang, Q.R., Li, Y.H., Xu, L., Fujimura, H., 1990, Gastrointestinal Motility Enhancing Effect of Ginger and its Active Constituent, *Chem Pharm Bull*, 38(2): 430-1.

Young, H.Y., Liao, J.C., Chang, Y.S., Luo, Y.L., Lu, M.C., Peng, W.H., 2006, Synergistic Effect of Ginger and Nifedipine on Human Platelet Agregation: A Study in Hypertensive Patients and Normal Volunteers, *J. Of Chinese Medicine*, Vol. 34, No. 4, 545-