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Phage FR38 Treatment on Sprague Dawley Rat Inferred from Blood Parameters and Organ Systems

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The ability of phage FR38 to lysis indigenous *Salmonella* P38 from feces of diarrheal patient has been studied. However, effects of phage FR38 on organ system were not revealed as yet. This study was conducted to observe the effect of phage FR38 on blood chemistry, kidney functions, and liver functions. Twelve Sprague-Dawley rats were used as a model for this study that were divided into two groups; (i) control and (ii) treated group with phage FR38. For treated phage group, each rat was administered by 5 ml/kg bw of $1.59 \cdot 10^7$ pfu/ml of phage intragastric. The blood parameters were analysed on day 16. The results revealed that body and organs weight, erythrocyte, hematocrit, hemoglobin, leukocyte, total protein, creatinine, SGOT, and SGPT of phage treatment rats were not significantly different with the control rats on day 16 ($P > 0.05$). Therefore, this study showed was no effect of phage FR38 on body weight, blood chemistry, kidney and liver functions of the rat ($P > 0.05$).

Key words: phage FR38, blood chemistry, kidney functions, liver functions

INTRODUCTION

Salmonella is a food borne pathogenic bacteria that cause food borne and water borne disease (Delibato 2006). *Salmonella* were used as an indicator of food hygiene and food safety (Abedon 2008). *Salmonella* P38 that performed antibiotic resistant had been isolated from feces of diarrheal patient.

Contamination of *Salmonella* on food had been reported in orange juice and fresh orange (Castillo *et al*. 2006), apple cider product (Zhuang *et al*. 2005), beverage product (Li & Mustapha 2005), milk (Tadesse *et al*. 2005), apple juice (Izzo & House 2011), and fresh shrimp (Ray (2001). In Indonesia, chemical preservatives mostly were used to decrease microbe, however the chemical preservatives showed toxic effect. Food producers currently used illegal preservative such as, formaldehyde, aluminate and hydrogen peroxyde due to the high price of the legal preservatives. Illegal preservative, such formaldehyde, also cause a negative effect on organ and body cell. Base on presentation upon, other alternative to decrease microbe on food is needed.

Phage lytic is a preservative alternative on food processing (Rode *et al*. 2011), have an environmentally-friendly characteristic (Castro *et al*. 1991), non toxic and is easy to be isolated, such as from humans, cattle, pigs, and chickens (Duijkeren *et al*. 2002) and can be produced (Brenner *et al*. 1991; Maura & Debarbieux 2011). Phage lytic can be isolated from the environment as well such as soil, water, human body, fermented food (Lu *et al*. 2003a), vegetable fermentation (Lu *et al*. 2003b) and food products. Isolate of phage lytic can be taken from various food products e.g. cheese and yoghourt (Binneti & Reinheimer 2000), salad, crisp and lettuce (Kennedy 1986).

Phage application as a biocontrol food had been used to decrease a microbe contaminant on food, such as, *Bacillus cereus* phage in outbreaks of food poisoning (Ahmed *et al*. 1995), psychrotrophic phage to prevent spoilage process on food (Greer 2005), *Xanthomonas* phage to prevent a spot on tomato (Flaherty 2000), *Listeria* phage (Leverentz *et al*. 2004) and *Salmonella enteriditis* phage on melon and apple slices (Leverentz *et al*. 2001). *Staphylococcus aureus* phage also had been applied on milk as well as *Salmonella enteritidis* phage on cheese (Greer 2005), *E. coli* phage on beef steak (O'Neill *et al*. 2001) and on food processing (Rode *et al*. 2011), *Flavobacterium columnare* phage on fish (Laanto *et al*. 2011), *Listeria* and *E. coli* phage on meat (Anani *et al*. 2011), and on milk (ellis *et al*. 1973).

The other application of phage was as a microbe therapy (Chairns & Payne 2009), such as, by using *Salmonella enterica* phage (Pang *et al*. 2011), *Yersinia pestis* (Schofield *et al*. 2009), cancer cell (Browska *et al*. 2010), *Mycobacterium* phage (Foddai *et al*. 2011), *Vibrio cholerae* phage (Chakrabarti *et al*. 2000), *Actinomycetes* phage (Nerney *et al*. 2004), phage of methicillin resistant *S. Aureus* (O'Neill *et al*. 2001; Murchan *et al*. 2004),

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Bacillus antrachis phage (Abshire *et al*. 2005), *Listeria monocytogenes* phage (Kim *et al*. 2012), phage of bacterial resistance to antibiotic (Edgar *et al*. 2011), and *E. coli* O18:K1:H7 phage (Bull *et al*. 2011). Phage therapy on poultry had been done by using of *Salmonella enteriditis* phage Sillankorva *et al*. (2010). The result of Budynek *et al*. (2010) points out that phage therapy on cancer patient can decrease the incident of microbe infection significantly. Ghaemi *et al*. (2010) reported that phage therapy on tumor can be done by use of λ-phage. Budiarti *et al*. (2011) reported that EPEC (Enteropathogenic *Escherichia coli*) can be degraded by phage isolated from the environment.

On preliminary study, phage FR38 had been used to decrease of *Salmonella* P38, an indigenous contaminant, on fresh milk and sausage. Nevertheless, the effect of phage FR38 on body damage was still unrevealed. Therefore, the aim of this study was to observe the effect of *Salmonella* P38 phage (phage FR38) on organs system by use Sprague Dawley's rat as the animal model.

MATERIALS AND METHODS

Phage Production. Palette of *Salmonella* P38 indigenous culture (OD=1) 10^8 cfu/ml were dropped by phage FR38 (1 ml) (collection of the second author), and were incubated at 37 °C for 30 minutes. The cocktail of *Salmonella* P38 phage were cultivated in 49 ml of nutrient broth (NB) medium, and incubated at 37 °C for 24 hours. After 24 hours incubation, bacteria-phage cocktail were centrifugated with 2800 rpm speed (Backman GPR Centrifuge), at 4 °C for 20 minutes. Supernatant (3 ml) were taken by using a 5 ml syringe and filtered by using Millipore membrane 0.22 µm (Whatmann). The supernatant from filtration process were transferred into sterile tube (Clokie & Kropinski 2009). After double overlay process, the phage were counted by use Clokie and Kropinski formula, i.e., phage total = $1.59 \cdot 10^7 \pm 2.449 \cdot 10^7$ pfu/ml (Figure 1).

Experimental Design. A total of 12 *Sprague Dawley* rats, all were in the same two months age rats were obtained from Veterinary Medicine Faculty, Bogor Agricultural University. Experimental rats were aclimitated at rat cage for 15 days, and then divided into two groups. The first group was rats as control and the other group was given by phage treatment. During adaptation, all of rat was fed with Japfa animal feed with standard drink (Table 1).

Research designs were the randomized control group post test design. The treatments of this research were control and phage treatment (5 ml phage FR38/kg bw; 1 ml = 1.59 x 10^7 pfu). Layout of experiment was arranged by coding of the sample, such as, control treatment code (K1, K2, K3, K4, K5, and K6) and phage treatment code (P1, P2, P3, P4, P5, and P6). After treatment coding, rat code were placed in random position (Table 2).

Phage Treatment. All rats were weighed and were labeled with treatment codes. Body weights of rats were measured every two days for 15 days. The doses of treatment were (i) control group and (ii) Phage FR38 group. Each group was administered (5 ml kg^{-1} bw) by phage FR38 every day for 15 days.

Intragastric Administration. Treatment on rat (control group and Phage FR38 group) was carried out using 16 G intra-gastric syringe. For safety intra-gastric administration, the syringes were manipulated and added a bulbed needle.

Data Administration. After given the treatment for 15 days, data collected on day 16 by surgical technique on rat's body. The euthanasia processes of rat were used ether. The blood was taken from the posterior vena cava. The blood chemistry was analyzed for red cell (erythrocyte) and white cell number, hemoglobin, hematocrit, leukocyte differentiation (lymphocyte, neutrophil, eosinophil, and basophil), Serum Glutamic

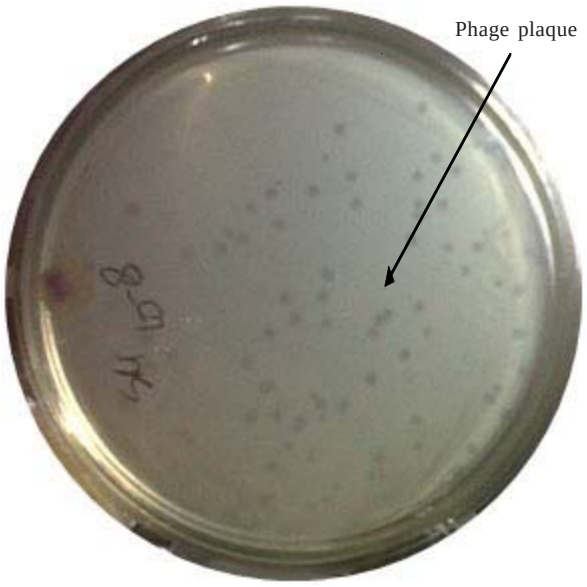

Figure 1. The appearance of plaque phage FR38.

Table 2. Treatment and lay out design

Lay out design			
Location code	Control lay out	Location code	Treatment lay out
1	K4	7	P2
2	K5	8	P1
3	K1	9	P6
4	K6	10	P5
5	K3	11	P3
6	K2	12	P4

Table 1. Feed and treatment given to the rats

Treatment	Adaptation period (for 14 days)	Treatment Period (for 15 days)	
		Feed	Treatment
Control	Feed	Feed	Drink
Phage	Platelet from Jafpa	Platelet from Jafpa	phage = 1 ml/200g bw

Oxaloacetic Transaminase (SGOT), Serum Glutamic Pyruvic Transaminase (SGPT), creatinin, and total protein (Djojosoebagio 2007). The performances (shape and color) of rat feces also were collected for 16 days.

Statistical Analysis. Statistical analysis was carried out using Student's t-test. The results were presented as the mean differences between individual groups with P (less than or equal to) 0.05 consider statistically significant.

RESULTS

Body Weight. Body weights of rat were not significantly different for each group. We found that not significantly different in body weight between the two group treatments (P > 0.05) on day 0, 2, 4, 6, 8, 10, 12, 14, and 16. The average values of the body weight for each group were presented in Table 3. The body weight of phage treatment and control rat showed a normal growth characteristic. On day 1, the mean values of body growth control rat was 214.5 g (n = 6) and the body growth phage treatment rat was 212 g (n = 6). In the fact, the phage and control treatment, on day 1 up to 16, showed not significantly effect on body weight (P > 0.05) with the mean values of control rat was 250.47 g (n = 6) and phage FR38 rat was 255.83 g (n = 6). All of the phage treatment rats shown that the body growth rats were also tend in normal characteristics. The body growth of all controls the same high as all treatment rats. On the last treatment day, the body growth of phage treatment (SD = 8.295) and control (SD = 8.710) rat were uniform (Table 3).

Feces. Data of feces performances on day 0, 2, 4, 6, 8, 10, 12, 14, and 16 showed no difference among rats which had given by phage FR38 treatment and control (Table 4). The feces of phage FR38 rat and control rat were normal on day 0 up to 16.

Organ Weight. Large intestine, spleen, right kidney, left kidney, stomach, small intestine, heart, lung and liver weight the same for the groups (P > 0.05) on day 16 (Table 5). The organ weight of phage treatment was normal as well.

Erythrocyte. Hemoglobin and erythrocyte of rat blood for 16 day were not different for each group (control and phage group). We found not significantly effect in hemoglobin and erythrocyte in the two group treatments (P > 0.05). Hemoglobin number of control rat (n = 6) was similar as the phage treatment rat (n = 6) (P > 0.05) on day 16 day. Erythrocyte of control rat (n = 6) was as much as those in phage treatment rats (n = 6) (P > 0.05) on day 16. Median values of the hemoglobin and erythrocyte for each rat groups were presented in Table 6. Hematocrit value of control rat (n = 6) was also the same as phage treatment rat (n = 6) (P > 0.05).

The research results showed that thrombocyt value was not significantly different in the two group treatment (P > 0.05). Thrombocyt value of control rat (n = 6) was as much as phage treatment rat (n = 6) (P > 0.05) (Table 6) on day 16.

Leukocyte. Leukocyte total number of control rat was not significantly different in the two group treatments (P > 0.05). In this research, we also observed the

Table 3. Effect of phage treatment on body weight of rat

Day	Control (g)	Phage treatment (g)
0	214.5 ± 3.782a	212.00 ± 1.291a
2	217.55 ± 4.579b	219.33 ± 4.308b
4	219.86 ± 5.317c	223.16 ± 2.409c
6	224.19 ± 6.156d	227.17 ± 2.671d
8	227.78 ± 6.494e	232.67 ± 5.153e
10	233.47 ± 7.360f	237.83 ± 4.524f
12	239.05 ± 5.007g	244.33 ± 4.642g
14	244.3 ± 8.335h	248.83 ± 5.757h
16	250.47 ± 8.710i	255.83 ± 8.295i

The same letter in each row indicated not significantly different at P > 0.05.

Table 5. Effect of phage treatment on organ weight values of rat

Organ	Control (g)	Phage FR38 treatment (g)
Large intestine	22.573 ± 2.292a	21.683 ± 1.951a
Spleen	0.702 ± 0.100b	0.673 ± 0.210b
Right kidney	1.852 ± 0.093c	1.842 ± 0.055c
Left kidney	1.822 ± 0.129d	1.840 ± 0.069d
Stomach	9.760 ± 1.615d	7.065 ± 1.845d
Small intestine	7.007 ± 0.776e	6.872 ± 1.529e
Liver	10.103 ± 0.761f	10.002 ± 0.798f
Lung	1.992 ± 0.126g	1.970 ± 0.204g
Heart	0.813 ± 0.065h	0.807 ± 0.070h

The same letter in each row indicated not significantly different at P > 0.05.

Table 4. Effect of phage treatment on rat feces

Treatment	Day								
	0	2	4	6	8	10	12	14	16
	Fs	Fs	Fs	Fs	Fs	Fs	Fs	Fs	Fs
F1	N	N	N	N	N	N	N	N	N
F2	N	N	N	N	N	N	N	N	N
F3	N	N	N	N	N	N	N	N	N
F4	N	N	N	N	N	N	N	N	N
F5	N	N	N	N	N	N	N	N	N
F6	N	N	N	N	N	N	N	N	N
K1	N	N	N	N	N	N	N	N	N
K2	N	N	N	N	N	N	N	N	N
K3	N	N	N	N	N	N	N	N	N
K4	N	N	N	N	N	N	N	N	N
K5	N	N	N	N	N	N	N	N	N
K6	N	N	N	N	N	N	N	N	N

N = Normal.

differentiation of white cell blood, such as, neutrophil, monocyte, eosinophil, lymphocyte, and basophil. The monocyte values of control rat were not significantly different in the two group treatment (P > 0.05). The monocyte value of control rat (n = 6) was as much as phage treatment rat (n = 6) (P > 0.05) on day 16 (Table 6).

The number of neutrophil after given the phage treatment was not increased. The neutrophil values of control rat showed not significantly different in the two group treatment (P > 0.05). The neutrophil value of control rat (n = 6) was as much as phage treatment rat (n = 6) (P > 0.05) on day 16. The result point out that the eosinophil count of controls (n = 6) showed not different value with the phage treatment (n = 6) on day 16 (P > 0.05). The basophil values of control rat also showed not significantly different in the two group treatments (P > 0.05). The neutrophil value of control rat (n = 6) as much as phage treatment rat (n = 6) (Table 6).

Lymphocyte value was not significantly different in the two group treatment (P > 0.05). The lymphocyte value of control rat (n = 6) as much as phage treatment rat (n = 6). Median values of the hemoglobin, hematocrit and erythrocyte for each rat group are presented in Table 6.

Total Protein. The value of protein total shown a total of the globulin and albumin value. Overall structure of the immunoglobulin molecule was determined by the sequence of amino acids. In this research, the protein total value was not significantly different in the two group treatment (P > 0.05). Protein total value of control rat was (n = 6) was as much as phage treatment rat (n = 6) (P > 0.05) (Figure 2) on day 16.

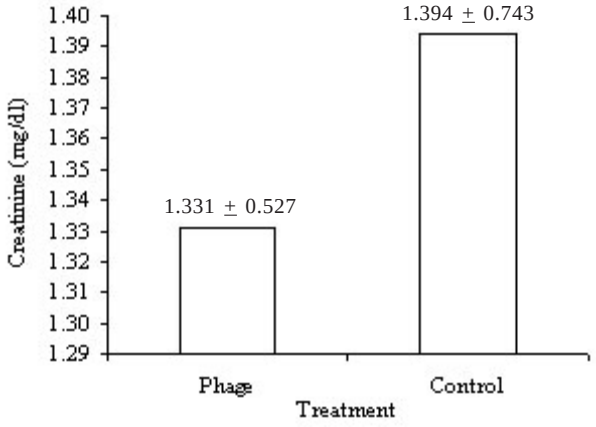

Figure 2. Effect phage FR38 treatment on creatinine value of rat.

Kidney Functions. Kidney functions parameter can be observed from blood, such as, creatinine. Increasingly of creatinine on the blood indicate an abnormal of kidney function. The result showed that the creatinine value was also not significantly different in the two group treatment (P > 0.05). The creatinine value of control rat (n = 6) as much as phage treatment rat (n = 6) on day 16 (P > 0.05) (Figure 3).

Liver Functions. Liver functions parameter can be observed from blood, such as, SGOT and SGPT values. Increasing of SGOT and SGPT on the blood indicate an abnormal of liver function. The result research showed that SGOT and SGPT value were also not significantly different between the two group treatments (P > 0.05). SGOT value of control rat (211.67 ± 65.503 IU L^{-1}) (n = 6) similar to phage treatment rat (193.50 ± 34.735 IU L^{-1}) (n = 6) (P > 0.05) on day 16. SGPT value of control rat (177.00 ± 3 6.630 IU L^{-1}) (n = 6) as much as phage treatment rat (176.67 ± 27.95 IU L^{-1}) (n = 6) (P > 0.05) on day 16 (Table 7).

DISCUSSION

On the last day treatment, all of the treatments (phage and control) had no significantly effect on the body

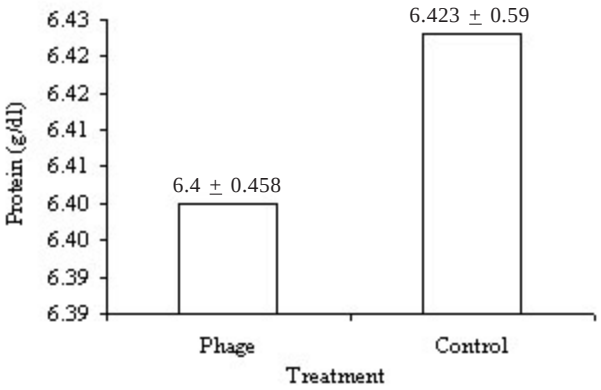

Figure 3. Effect of phage FR38 treatment on total protein values of rat.

Table 7. Effect of phage treatment on SGOT values of rat

Parameter	Phage FR38	Control
SGOT	193.50 ± 34.735a	211.67 ± 65.503a
SGPT	176.67 ± 27.955b	177.00 ± 36.630b

The same letter in each row indicated not significantly different at P > 0.05.

Table 6. Effect of phage treatment on blood cell of rat

Blood cell differentiation	Phage FR38	Control
Erythrocyte (10^6/mm^3)	8.363 ± 0.437a	8.922 ± 1.358a
Hb (%)	12.643 ± 0.798b	12.58 ± 0.776b
PCV (%)	36.125 ± 1.910c	37.125 ± 2.032c
Thrombocyte (10^6/mm^3)	119.167 ± 13.86d	123.5 ± 19.670d
Leukocyte (thousand/mm^3)	8.425 ± 0.687e	8.2 ± 2.905e
Neutrophil (%)	20.667 ± 9.331f	18.167 ± 10.000f
Eosinophils (%)	1.333 ± 1.033g	1.333 ± 0.512g
Basophil (%)	0	0
Lymphocyte (%)	76.167 ± 8.377h	78.167 ± 11.600h
Monocyt (%)	1.833 ± 1.329i	2.333 ± 1.584i

The same letter in each row indicated not significantly different at P > 0.05.

weight (P > 0.05) with the mean values of control was 250.47 g (n = 6) and the body growth phage treatment rat was 255.83 g (n = 6). The mean values of normal body weight of adult rat (for 40-60 days) are 200-250 g, but, it is various depend on strain (Derelanko & Hollinger 2004). The normal body weights of rat (2.5-3.5 month old) are 267-500 g (male) and 225-325 g (female) (Meredith & Anna 2002). All of the phage treatment rat shown that the body growth rat were tend normal trend.

The result showed that organ weight of controls treatment as weight as phage FR38 treatment, at confidence level 99%, on day 16. This result was similar to the previous studies on rat that reported by Derelanko and Hollinger (2004), recorded that normal weight of right kidney were 1.839 $\pm$ 0.222 g and left kidney were 1.717 $\pm$ 0.155 g.

Erythrocyte, Hb, thrombocyte, and PCV values of rat were normal (P > 0.05). Based on research on rat that reported by Meredith and Anna (2002), the normal rat had hemoglobin (Hb) values = (11.1-18) g dl^{-1} and Hematocrit (PCV) = (36-52)%. It was similarly number from the previous study by Derelanko and Hollinger (2004) that the normal Hb of rat = (11-18) g dl^{-1}; Erythrocyte = (6-10) x 10^6 $mm^{-3,}$ and PCV = (34-48)%. This showed that the mean of Hb, erythrocyte, PCV values of phage treatment rat were normal.

The results point out that the differentiation of white blood of control treatment was as much as in the phage treatment, at confidence level 99%, on day 16. It was not significantly different (P > 0.05) than the control treatment. The value was similarly from Derelanko and Hollinger (2004) study showed that a normal rat had values of leukocyte = (7-14) x 10^3 mm^{-3}; neutrophils = (4-50)%; lymphocytes = (40-95)%; monocytes = (0-8)%; eosinophils = (0-2)%; basophils = (0-2)%; and total protein = (5.9-8.4) g dl^{-1}. The results mean that the white blood and total protein values of phage treatment rat were normal; the phage FR38 had no effect on body rat.

Creatinin values of rat that had given phage treatment were not significantly different than control as well. The normal rat had a creatinin values = (0.39-2.29) mg dl^{-1} (Meredith & Anna 2002). The rat that had given phage treatment had SGOT values = (193.50 ± 34.735) IU L^{-1} and SGPT values = (176.67 $\pm$ 27.955) IU L^{-1} were not significantly different than control (P > 0.05).

In conclusion, all parameters studied above showed not significantly different of P value between the two groups of rat (P > 0.05). Therefore, those indicated that the phage FR38 treatment did not effect to the rat body. Paracetamol treatment on rat increased of SGOT and SGPT values (Jawi *et al*. 2008), but natural functional drink did not effect on SGOT and SGPT values (Safithri *et al.* 2012).

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