DOI : 10.18843/rwjasc/v7i1(1)/08
DOI URL : http://dx.doi.org/10.18843/rwjasc/v7i1(1)/08

THE INFLUENCE OF POMELO JUICE (CITRUS MAXIMA VAR NAMBANGAN), VITAMIN C AND LYCOPENE TOWARD MDA LEVEL OF MOUSE (MUS MUSCULUS) HEPATIC TISSUE WHICH EXPOSURE BY OCHRATOXINA

Badriyah,

Chemical Engineering Department,
WR Supratman University, Indonesia

Purwanto,

Economic Department,
WR Supratman University, Indonesia

ABSTRACT

This research is intended on understanding the potency of Pomelo juice (*Citrus var nambangan)*, vitamin C, lycopene, and the combination of vitamin C and lycopene as the antioxidant toward the hepatic tissue of MDA level on mouse (*Mus musculus)* as consequence of Ochratoxin A (OTA). The 35 male mice (*Mus musculus)* aged between two until three months had strain balb/c, they are randomly divided into seven group of treatments (n=5), which are K0, K1, K2, P1, P2, P3, and P4, each of this controlled groups is only given the adjuvant *Olive Oil* (K0), adjuvant CMCNa (K1), ochratoxin A (K2), given the Pomelo juice with dosage of 0,5 ml/30 gram of Weight/day (P1), vitamin C with dosage of 5,85 µg (P2), lycopene dosage as of 0,1025 µg (P3), and the combination of vitamin C dosage as of 5,85 µg of mouse weight with the lycopene as of 0,1025 µg/30g of weight (P4). In group of K0, K1, K2, the treatment ingredients are given for a week which is in the third week, meanwhile for the group of P1, P2, P3, and P4 the antioxidant compound are given for two weeks starting from the second week, which is in the beginning of the third week is given the ochratoxin A with dosage of 1 mg/kg of Weight/day for a week. At the day of 21 all the experimental animals are scarified for the data collecting. The result of statistic analytical within *Kruskal Wallis* test that continued with *Mann-Whitney* test indicate that there is a real different between treatments ($p<0, 05$). It is proven that on all groups which are given the antioxidant (P1, P2, P3, and P4) significantly ($p<0, 05$) is able to prevent the hepatic damage after ochratoxin A exposure, which is indicated from the decreasing of MDA level. The given of Pomelo juice (*Citrus var nambangan)*, vitamin C and lycopene is proven to decreasing the level of mouse *Malondyaldehid* (MDA) tissue which is exposed by ochratoxin A. This research is also proven that the potency of Pomelo juice (*Citrus var nambangan)* is proven to have the same with vitamin C ($p>0, 05$), lycopene, as well as the combination of vitamin C and lycopene in preventing the free radicals reactivity as the consequence of OTA exposure on mouse' hepatic.

Keywords: Pomelo Juice (*Citrus var nambangan)*, Ochratoxin, MDA level of Hepatic cell.

INTRODUCTION:

Ochratoxin (OTA) is the kind of mycotoxins which is produced by the mildew. Mycotoxins is commonly be found as contaminants on the food materials and the processed food, which are in the cereals like corn, wheat, rice, nuts, soybean, coffee bean, cacao bean, spice, grape and fruits (Papachristou and Markaki, 2010).

On the developed countries, regulation that arranges the amount of ochratoxin contaminant in the food ingredients is being implemented and strictly supervised. Ochratoxin level which is permitted inside the food is different in each countries. *European commission committee on food* is recommend the ochratoxin level inside the food should not exceeded than 14 ng/kg inside the food materials, while *World Health Organization (WHO)* sets the maximum limit of ochratoxin in cereals is 5 microgram/kg for the raw nuts and 3 microgram/kg for processed food product (Clark, 2004; O'Brien *et al.,* 2010).

Ochratoxin metabolism in the night is producing the reactive metabolite. This change is being catalysis by P-450 enzyme by oxidize the ochratoxin through the chain reaction of hidroklasi substrate (Hastuti, 2001). This chain reaction will produce O_2 (superoxide) and H_2O_2. $O_2^{\bullet-}$ which is dangerous when there is concurrent with H_2O_2 because it can formed the hydroxyl radical ($OH^{\bullet}$). Besides that, $OH^{\bullet}$ may react with transition metal like Fe^{2+} and Cu^{2+} through the Fenton reaction (Halliwell and Gutteridge, 2007).

The damage cell that caused by free radicals may occur through the lipid peroxide of cell membrane or organelles. Free radicals may cause the peroxide on polyunsaturated fatty acid (*polyunsaturated fatty acid = PUFA)* which constructed the cell membrane. This damage is occurring through the chain reaction which triggered by the free radicals. Lipid peroxidation of membrane cell will produce the final result called aldehyde peroxide like *Malondyaldehid* (MDA) (Setiati, 2003). *Malondyaldehid* is the biggest aldehyde which is produced by free radicals. *Malondyaldehid* is extensively use as the indicator of oxidative stress which can be specifically determined as well as non-specifically in a measurement using tiobarbiturat acid (Winarsi, 2007).

Lipid peroxide on cell membrane will cause the increasing of membrane permeability that resulting in passive mitochondria swelling that lead to the aggravating of cell damage (Hayati, 2011). The damage of mitochondria membrane will cause the decreasing of ATP production which led to disruption of cell membrane permeability and pump of Na^- K, it is lead to the water accumulation inside the cell and organelles (hydropic degeneration). The reversible process of cell will turn to irreversible and triggering the necrosis death of cell if there is increasing of ion calcium intracellular accumulation which incoming to the cell as the result of membrane cell permeability disruption (Gavin, 2007).

Basically several of free radicals like $O_2^{\bullet-}$, H_2O_2, and $OH^{\bullet}$ can be formed in normal metabolic process, but this may mitigates by the antioxidant enzyme such as catalase, *superoxide dismutase* (SOD), glutathione and the other antioxidant compound which is gaining from the food materials, like vitamin C, vitamin E, and selenium. Continuously induction of free radicals and the increasing of free radicals amount which come from outside of the body may cause the balance disorder of antioxidant, this is resulting the oxidative stress.

The addition of antioxidant supplement which is come from the outside of the body is one of the effective ways in reducing the oxidative stress. One of the food materials which are containing antioxidant is the Pomelo fruit that is well known bearing the vitamin C and lycopene. Pomelo fruit (*Citrus maxima*) is proven containing vitamin C and lycopene that having the antioxidant effect. Lycopene is working as antioxidant which catching the free radicals (*Scavenger antioxidant)* and breaking the peroxide chain which triggered by free radicals (*Chain breaking antioxidant*), while the vitamin C working as the antioxidant by catching the free radicals only.

The content of antioxidant vitamin C and lycopene inside pomelo juice is quite enough. The pomelo flesh (*Citrus maxima*) is known containing 43 mg vitamin C and 350 µg lycopene in each of 100 grams of the fruit flesh (Maulida and Zulkarnaen, 2010).

The research on the impact of ochratoxin poisoning toward kidneys has been done, however the ochratoxin impact to the hepatic damage (hepatotoxicity) is very limited. As the tropical country with abundant biodiversity sources, this research is intended to knowing the pomelo (*Citrus var nambangan*) juice potentiality that is a local variety which works as antioxidant in preventing the damage of hepatocyte cells as the result of ochratoxin exposure by observing the MDA level.

FORMULATION OF THE PROBLEM:

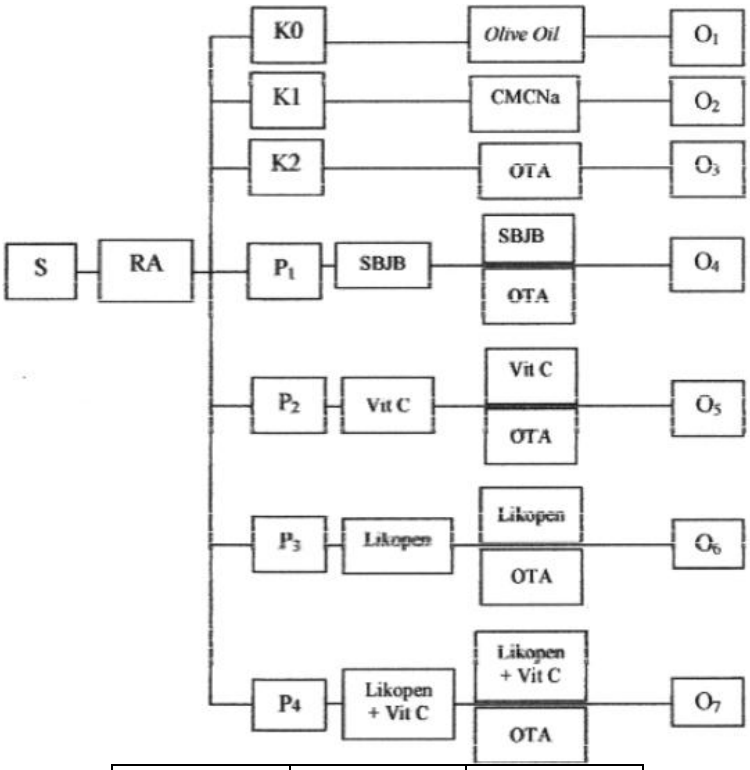
Do the given of pomelo (*Citrus maxima var nambangan*) juice, vitamin C and lycopene may decreasing the *Malondyaldehid* (MDA) level of mouse hepatic tissue as the result of the ochratoxin exposure?

RESEARCH PURPOSES:

To analyze the given influence of pomelo (*Citrus maxima var nambangan*) juice, vitamin C and lycopene toward *Malondyaldehid* (MDA) level of hepatic tissue as the result of ochratoxin exposure.

RESEARCH METHOD
TYPE OF THE RESEARCH:

Type of the research that has been done was the laboratories experimental which using the program of *Random post test only control group design*. Both of sample and treatment are in effort to be controlled and measured, in order to obtain the reliable influence of the treatment.



A	B	C
1 week	1 week	1 week

Explanations:

A	:	The first week of research (the adaptation of experimental animal)
B	:	The second week of research
C	:	The third week of research
CMCNa	:	*Sodium Carboxymethyl Cellulose*
K_0	:	Controlled with the given of Olive Oil adjuvant
K_1	:	Controlled with the given of CMCNa adjuvant
K_2	:	Controlled with the given of ochratoxin A
O	:	Observation
OTA	:	Ochratoxin
P_1	:	Treatment 1 (SBJB + Ochratoxin)
P_2	:	Treatment 2 (Vitamin C + Ochratoxin)
P_3	:	Treatment 3 (Lycopene + Ochratoxin)
P_4	:	Treatment 4 (Vitamin C + Lycopene + Ochratoxin)
RA	:	Random Allocation
S	:	Sample
SBJB	:	Pomelo Juice (PJ)
Vitamin C	:	Vitamin C

UNIT EXPERIMENT, SAMPLE SIZE AND RANDOMIZATION:
UNIT EXPERIMENT:

Unit experiment that has been used for this research was the male mouse (*Mus musculus*), adult strain BALB/C, the age between two until three months and weight between 20 until 30 grams. Experimental animal was gain from experimental animal unit care, Center of Veterinarian Pharma (PUSVETMA) Surabaya.

SAMPLE SIZE:

Sample size was determined based on the number of the repetition or replication which using the Federer calculation formula as follow:
Sample size: Counted using the Federer formula which was (t-1) (n-1) ≥ 15, whereas t was the number of the groups, n was the experimental animal per group.
(6-1) (n-1) ≥ 15
5 (n-1) ≥ 15
n ≥ 20/5
n ≥ 4
Based on the calculation, the number of replication or repetition were four experimental animals as the minimum standard in each group. This research was using 35 male experimental animals whereas there are five individuals in each group of treatments.
The number of male mice as the experimental animals was 35.

VARIABLE CLARIFICATION AND OPERATIONAL VARIABLE DEFINITION:
VARIABLE CLARIFICATION:

Variable was depending on:
- The damage of hepatic cell which was : the number of apoptotic hepatocyte cells

OPERATIONAL VARIABLE DEFINITION:

a. Vitamin C that has been used on this research was the processed product that obtained from PT. SIGMA with catalogue number A 7506 and the given dosage was 5,85 µg / 30g of mouse weight.
b. Lycopene that has been used on this research was the processed product that obtained from PT. SIGMA with catalogue number L 9879 and the given dosage was 0,1025 µg / 30g of mouse weight.
c. The combination of vitamin C and Lycopene
d. Ochratoxin A that has been used on this research was the processed product that obtained from PT. SIGMA with catalogue number O 1877 and the given dosage was 1 mg / kg of mouse weight / day.

MATERIALS RESEARCH:

The material required and used on this research was:

STANDARDIZED POMELO JUICE:

The material required was standardized Pomelo Juice (*citrus maxima var nambangan*) which containing 416, 50 µg/ml of vitamin C and 7, 60 µg/ml of lycopene.
The material for the hepatic tissue examination;
The organs were stored in the media of buffered formalin. The histological making on hepatic tissue was using 70%, 80%, 90%, 100% alcohols, xylol, paraffin, and hemaloxylin eosin staining,

LOCATION AND TIME OF THE STUDY:
LOCATION OF THE STUDY:

The study was conducted in several laboratories. 1) Chemist and Gramik Laboratory of Medical Faculty, Airlangga University. 2) Pathology and Anatomy Laboratory of Veterinary Faculty, Airlangga University. 3) Experimental Animal Cage at Pharmacy Faculty, Airlangga University. 4) Biochemist Laboratory of Mathematic and Natural Sciences Faculty, Brawijaya University Malang.

DATA ANALYSIS:

SPSS.18 was using on statistical analysis toward the obtained data. Normality test was the method that being used to know the normality of variable distribution. Further data will be tested using ANOVA test, when it gets the normal variable data distribution, while if the variable that has been obtain is not normal, it will be tested by *Kruskal Wallis* test. Data collection was conduct in controlled and restrained environment with the assumption that all conditions are in the same manner.

RESEARCH IMPLEMENTATION:
EXPERIMENTAL ANIMAL PREPARATION:

This research has been conduct for three weeks; consist of first week adaptation during one week and two weeks of treatment on the second week. Mouse was adapted for about one week before the treatment conducted and treated as well as divided based on the group as stated on the experimental design.

K_0 : Group of controlled mouse that given the *Olive Oil* adjuvant for one week starts in the third week.
K_1 : Group of controlled mouse that given the CMCNa adjuvant for one week starts in the third week.
K_2 : Group of controlled mouse that given Ochratoxin A for one week starts in the third week.
P_1 : Group of controlled mouse that given the Pomelo juice for two weeks starts in the second week, whereas in the third week, the Ochratoxin A was given for one week.
P_2 : Group of controlled mouse that given vitamin C for two weeks starts in the second week, whereas in the third week, the Ochratoxin A was given for one week.
P_3 : Group of controlled mouse that given lycopene for two weeks starts in the second week, whereas in the third week, the Ochratoxin A was given for one week.
P_4 : Group of controlled mouse that given the combination of vitamin C and lycopene for two weeks starts in the second week, whereas in the third week, the Ochratoxin A was given for one week.

THE DOSAGES AND NUMBERS DETERMINATION OF OCHRATOXIN A AND POMELO JUICE:

The dosage and period in giving ochratoxin and antioxidant level of Pomelo juice were determine on the research that had been conduct formerly. The dosage that has been use in this research for ochratoxin A was suitable with $^1/_5$ *Lethal Dose* (LD 50), which is 1 mg/kg of Weight and 0, 5 ml / 30g of Pomelo juice Weight which is containing vitamin C as much as 5, 85 µg / 30g of mouse weight. The method was by given the Pomelo juice for one week (7 days) and then induced with ochratoxin A for 7 days which still given the Pomelo Juice (Hastuti, 2001; Wahyono, 2006).
Necropsy treatment was conduct after the experimental animals had been anesthetic using ether to decrease the level of consciousness, then necropsy and hepatic excision conducted.
Cytochemistry method was use for the examination of apoptotic.

RESUTL AND DATA ANALYSIS:

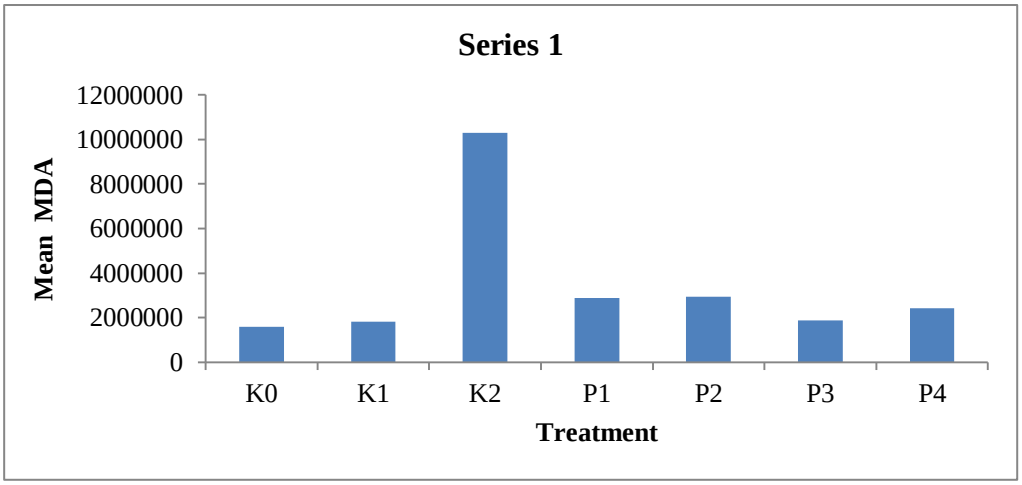
The Influence of Pomelo Juice (*Citrus maxima var nambangan*), Vitamin C and Lycopene toward MDA level of Mouse (*Mus musculus*) Hepatic Tissue which Exposure by Ochratoxin A
The analysis result which is conducted by *Kruskal Wallis* test indicate that the given influence of pomelo juice (*Citrus maxima var nambangan*), vitamin C, lycopene, and the combination vitamin C and lycopene toward the MDA level of mouse tissue which is exposure by ochratoxin A (OTA) there is a significant different ($p<0, 01$) between the treatments. The deviation average and standard of MDA level of tissue in all treatments can be seen on table 1 and picture 1.
The Average Table ± SD of MDA level of hepatic tissue in all treatments

Treatments	Average ± Standard Deviation nmol/g
K_0 (*Olive Oil*)	$158.44^{a} \pm 21.56$
K_1 (CMCNa)	$181.93^{ab} \pm 29.95$
K_2 (Ochratoxin A)	$1028.80^{d} \pm 113.98$
P_1 (SBJB)	$288.97^{bc} \pm 58.94$
P_2 (Vitamin C)	$292.87^{c} \pm 27.72$
P_3 (Lycopene)	$186.21^{ab} \pm 34.16$
P_4 (Vitamin C + Lycopene)	$243.37^{ab} \pm 81.88$

Superscript which is different in each of the same column indicating the significant different on believing degree $\alpha = 0, 05$ ($p < 0, 05$)

From the table, it is knowing that the given of pomelo juice (P1) significantly proven (p < 0, 05) may decrease the MDA level of mouse hepatic tissue which exposure by ochratoxin. The affectivity of pomelo juice (P1) in decreasing the MDA level of mouse hepatic tissue which exposure by ochratoxin in this research is not significantly different (p > 0, 05) with the given of vitamin C (P2), lycopene (P3), also the combination of vitamin C and lycopene (P4). Meanwhile, the MDA average of mouse hepatic tissue in group which given the vitamin C is significantly (p < 0, 05) higher than the group of treatment which given lycopene (P3) also the combination of vitamin C and lycopene (P4).

The average of MDA level on mouse hepatic tissue in the group which given the pomelo juice (*Citrus maxima var nambangan*), vitamin C, lycopene, also the combination of vitamin C and lycopene, are consecutively 288.97 ± 58.94 nmol/g, 292.87 ± 27.72 nmol/g, 186.2 ±34.16 nmol/g, and 243.37 ± 81.88 nmol/g is significantly (p < 0, 05) proven lower than the group which is only given ochratoxin A (K2) in which the average of MDA level on mouse hepatic tissue in the group that given pomelo juice (*Citrus maxima var nambangan*) (P1) and vitamin C (P2), is significantly (p < 0, 05) higher than the negative controlled group that receiving adjuvant *Olive Oil* (K0), but it is slightly different (p > 0, 05) than the negative controlled group that receiving adjuvant CMCNa (K1) and there is different (P > 0, 05) between the group of treatment that given lycopene (P3) also the combination of vitamin C and lycopene (P4) compared to the negative controlled group that receiving adjuvant *Olive Oil* (K0) as well as the group which is receiving adjuvant CMCNa (K1).



Picture 1: The bar chart of MDA average level in hepatic tissue of all treatments. K0: *Olive Oil*, K1: CMCNa, K2: Ochratoxin A, P1/: Pomelo Juice, P2: Vitamin C, P3: Lycopene, P4: Vitamin C + Lycopene.

DISCUSSION:

The Influence of Pomelo Juice (*Citrus maxima var nambangan),* Vitamin C and Lycopene toward MDA level on Mouse (*Mus musculus*) Hepatic Tissue which is Exposure by Ochratoxin A:

The result of this research is to indicate that the given of pomelo juice (*Citrus maxima var nambangan*) as hepatoprotective is proven effective to decrease the MDA level of hepatic cell on mouse which has exposure by ochratoxin A (OTA). On the positive controlled group, this is the group that only given ochratoxin A (OTA), while on the group that exposure by ochratoxin A (OTA) but given the pomelo juice, the MDA level of hepatic cell is only around 30% from the positive controlled group.

MDA as the last product of lipid peroxide is reported to be increased on hepatic of some experiment animals after the exposure with ochratoxin A (OTA). Capraro and Rossi (2012) reported that the exposure of ochratoxin with dosage 3 mg/Kg of Weight as long as 15 days may trigger the increasing of MDA level which varies between 17% to 400% on white mouse. While, on the mouse, the one-time exposure of ochratoxin A (OTA) with dosage 10 mg/Kg of Weight may increasing the MDA level to 150%, meanwhile on the pig, the exposure of ochratoxin A (OTA) with dosage 0.3338 mg/Kg of Weight as long as 15 days lead to the increasing of MDA level in hepatic to 120%.

Even though the damage mechanism of hepatocyte cell as the consequent of ochratoxin A exposure (OTA) had not been known, however it believes that the hepatotoxicity as the consequent of ochratoxin exposure may occur through three main mechanisms which are, protein synthesis disruption, oxidative stress induction through lipid peroxide and the increasing production of free radicals (Ferrantee et al., 2009). The other result

of research reported that the oxidative stress that occurring on hepatocyte cells as the consequent of ochratoxin exposure may cause by the decreasing of antioxidant enzymes (Gagliano et al., 2006).
Biological potency on pomelo juice (*Citrus maxima var nambangan*) in preventing the damage of hepatocyte cell toward various lesions, believes concerning with the antioxidant compounds which contain inside it, which are lycopene and vitamin (Astawan, 2009). The content of vitamin C of pomelo juice (*Citrus maxima var nambangan*) in this research is 416, 50 µg/ml, and the content of lycopene is 7, 60 µg/ml.
The content of lycopene on pomelo flesh is quite high, which is 350 microgram per 100 grams of the flesh (Astawan, 2009), while the content of vitamin C on pomelo fruit is 43 milligram per 100 grams of the fruit flesh (Waljono, 2006). According to Tsai et al., (2007) the antioxidant content on pomelo fruit (*Citrus grandis (L.) Osbeck*) with the red fruit flesh containing phenol of 8.3 mg/mL, also vitamin C and tocopherol, each of it is 472 and 0.35 mg/mL.
Lycopene and vitamin C which are containing in pomelo fruit (*Citrus maxima var nambangan*) believed as two antioxidant which are very potential in preventing the oxidative stress in hepatic cell as the consequent of ochratoxin exposure (Waljono, 2006).
Lycopene is the powerful antioxidant which functions as the scavenger antioxidant; lycopene is also able to bind the radical superoxide (O2-•) which is formed during the ochratoxin exposure (Mackinnon et al., 2011). Lycopene effectively in catching the radical superoxide 100 times stronger than vitamin E, or 12.500 times stronger than glutathione (Mascio et al., 1989). Lycopene is reported having the ability to prevent LDL (Low density lipoprotein) peroxide and decreasing the oxidized LDL level (LDL-ox), therefore it is very potential to be used on preventing the progression of cardiovascular disease (Giovanicci, 2005).
Vitamin C is having the reduction characteristic (reducing agent) the same as vitamin E and working as antioxidant by catching radical superoxide also muffling the activities of hydrogen peroxide, hypochlorite, hydroxyl radical, and peroxyl radical. Vitamin C is effectively hampering lipid peroxide which is initiated by peroxyl radical and preventing the damage of membrane cell (Padayatty, 2003).
The role of antioxidant in preventing the damage of hepatocyte membrane cell during the lipid peroxide may occur through several mechanisms which are by catching the metal ion, catching the free radicals and hampering the peroxide enzymes. The working way of antioxidant in hampering the peroxide usually involves more than one mechanism at a time (Mokbel and Suganuma, 2006).
The special quality of natural antioxidant which is coming from fruits consumption such as pomelo fruit (*Citrus maxima var nambangan*) usually giving the better result than the processed antioxidant or synthetic. The special quality of antioxidant by consumption of natural fruits or vegetables is giving the optimized result since on this natural source, some antioxidant compounds may work together in mutual synergistic (Mokbel and Suganuma, 2006; Singh et al., 2011).

CONCLUSION:

Based on the result of this research, it can be concluded that the given of pomelo juice (*Citrus maxima var nambangan*), vitamin C and lycopene may decreasing *Malondyaldehid* (MDA) level on mouse hepatic tissue as the consequent of ochratoxin exposure.

SUGGESTIONS:

Further research needs to be done on:
1. Further studies of antioxidant potentiality on pomelo juice (*Citrus maxima var nambangan*) toward the ochratoxin toxicity on mouse hepatic with the different doses (chronic).
2. Further studies of antioxidant potentiality on pomelo juice (*Citrus maxima var nambangan*) toward the ochratoxin toxicity on mouse hepatic by measuring SOD, GSH and catalase level.
3. Further studies of antioxidant potentiality on pomelo juice (*Citrus maxima var nambangan*) toward the ochratoxin toxicity on mouse hepatic by measuring free radicals level directly.
4. Further studies of antioxidant potentiality on pomelo juice (*Citrus maxima var nambangan*) toward the ochratoxin toxicity on mouse hepatic by measuring the expression of important proteins through apoptosis induction at the death cell.

REFERENCE:

[1] Ggliano N, Dalle DI, Torri C. Migliori M, Grizzi F, Milzani A, Filippi C, Annoni G, Colombo P, Costa F, Cava Grimaldi G, Bertelli AAE, Giovannini L, Gioia M, (2006). Early cytotoxic effects of Ochratoxin A in rat liver: a morphological, biochemical and molecular study. *Journal Toxicology,* Vol. Pp. 225, 214-224.

[2] Halliwell, B. and Gutteridge, JMC (2007). *Cellular responses to oxidative stress: adaptation, damage, repair, senescence and death. Free Radicals in Biology and Medicine*. 4rd Edition, Oxford University Press, New York, pp. 187-267.
[3] Halliwell, B and Whiteman, M (2004). *Measuring Reactive Species And Oxidative Damage In Vivo And In Cell Culture: How Should You Do It And What Do Theresults Mean? Journal Pharmacol*, Vol.142 pp. 231-55.
[4] Mavati A, (201. *Spermatologi*. Surabaya: pusat penerbitan dan percetakan Unair.
[5] Hill MM, Adrain C, and Martin SJ, (2010). *Portrait of a killer: the mitochondrial apoptosome emerges from the shadows".* Molecular Cell Biology Laboratory, Department of Genetics, Smurfit Institute.
[6] Kataki MS, Murugamani V, Rajkumari A, Singh P, Awasthi D, and Yadav RS, (2012). Antioxidant, Hepatoprotective, and Anthelmintic Activities of Methanol Extract of Urtica dioica. *Journal Leaves Pharmaceutical Crops*, Vol. 3 pp. 38-46.
[7] Kun TD, Sunarmani, (2008). Parameter Likopen Dalam Standarisasi Konsentrat Buah Tomat. Prosiding PPI Standarisasi. Balai Besar Penelitian dan Pengembangan Pascapanen Pertanian.
[8] Kundusen S. Gupta M, Mazumder UP, Haldari PK, Saha P, Bala A, (2011). Antitumor Activity of Citrus maxima (Burm) Merr. Leaves in Ehrlich's Ascites Carcinoma Cell-Treated Mice. *Journal International Scholarly Research Network ISRN Pharmacology.* Article ID 138737, 4 pages.
[9] Kundusen S, Gupta M, Mazumder UP, Haldari PK, Panda SP, Bhattacharya S, (2011), Exploration of *in vivo* antioxidant potential of *Citrus maxima* against paracetamol induced hepatotoxicity in rats. *Journal Der Pharmacia Sinica*, 2 (3): 156-163.
[10] Maulida D dan Zulkarnaen N, (2010). *Ekstraksi Antioksidan (Likopen) dari Buah Tomat denganMenggunakan Solven Campuran, n-Heksana, Aseton, dan Etanol.* Disertation Tehnik Kimia Fakultas Tehnik. Universitas Diponegoro. Semarang.
[11] Mukono HJ, (2005). *Toksikologi Lingkungan Airlangga*. Surabaya: Universitas Airlangga.
[12] Miskiyah C, Winarti, dan Broto W, (2010). Kontaminasi mikotoksin pada buah segar dan produk olahannya serta penanggulangannya. *Jurnal Litbang Pertanian* Vol.29 (3): 79-85.
[13] Mukono HJ, (2005). *Determination of ochratoxin A in virgin olive oils of Greek by immunoaffinity column clean-up and high-performance liquid chromatography. Toksikologi Lingkungan.* Airlangga University Press. Surabaya.
[14] Ringot D, Changoa A, Schneider YJ, Larondelle Y, (2006). Toxicokinetics and toxicodynamics of ochratoxin A, an update. *Journal Chemico-Biological Interactions* Vol. 159. pp. 18-46.
[15] Ross AB, Vuong LT, Ruckle J, Synal HO, Ko'nig TS, Wertz K, Ru'mbeli R, Liberman RG, Skipper PL, Tannenbaum SR, Bourgeois A, Guy PA, Enslen M, Nielsen ILF, Kochhar S, Richelle M, Fay LB, Williamson G, (2011). Lycopene bioavailability and metabolism in humans: an accelerator mass spectrometry study 1-3. *Journal Clin American Society for Nutrition*, Vol. 93 pp. 1263-73.
[16] Wahyono P, (2006). Aktivitas Antioksidan Ekstrak Buah Tomat *(Lycopersicum pyrijorme)* dalam mencegah kerusakan Hepar. Laporan Penelitian Fundamental. Lembaga Penelitian Universitas Muhammadiyah Malang. Wahyono P, 2008. Efek Ekstrak Buah Tomat *(Licopersicum* pyriforme) Terhadap Ekspresi Kolagen Tipe 1, MMP-1, dan MMP-3 Pada Penuaan Kulit. *Jurnal Kedokteran Brawijaya*, Vol.XXIV, No. 3. Malang.
[17] Weidenbach A, Schuh K, Failing K & Petzinger E, (2000). Ochratoxin A induced TNF-a release from the isolated and blood-free perfused rat liver. *Mycotoxin Research*, Vol. 16A, pp. 189-193,
[18] Widodo MA, (2003). Calcium dan generasi Spesies Oksigen Reaktif pada Fungsi mitokondria. *Basic molekular Biology course on mithochondrial medicine*. Vol. 1-2 pp. 15-31.
[19] Wright TL, and Manns MP, (2006). *Pathogenesis and Replication of Hepatitis C Virus:* A Textbook of Liver Disease. Fifth Edition; Volumel;Saunders Elsevier, Vol. 125-147.
[20] Yanwirasti, (2004). *Kajian Biologi Molekuler Kerusakan Sel Hati Sebagai Akibat Proses Oksidatif Pada Biotransformasi Aflatoksin B_1*. Disertation. Universitas Airlangga.
[21] Zakim D, and Boyer TD, (1990). *Hepatology* - A textbook of liver disease Philadelphia: W.B. Saunders Company. pp. 737 - 744.
