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Judul Artikel : Acute Toxicity Level of Pulutan (*Urena lobata*) Leaf Extract on Zebrafish (*Danio rerio*) and its Analysis by *In Silico* Study

Tanggal	Activity	Reviewer Comments
12-07-2020	Submision of article	-
28-07-2020	Revision of article-1	In order to improve the quality of the paper you just go through the below link and cite atleast 10 articles from the list, that have similar works as of yours. The link is http://www.anvpublication.org/Universal_Search.aspx?What=CitationList&tmp_PID= 20619140206123371
05-08-2020	Resubmit the revised article	-
11-08-2021	Revision of article - 2	Pl Resubmit the article after making following corrections. The Ref no. are not mentioned serially in text. The Ref no. are not as per instruction to author. (Model Journal reference)
16-08-2021	Resubmit the revised article	-
01-04-2022	Accepted	Submit final version of article on Web Portal and download acceptance letter
04-05-2022	Galley proof publishing	Final correction of the galley proof of the paper
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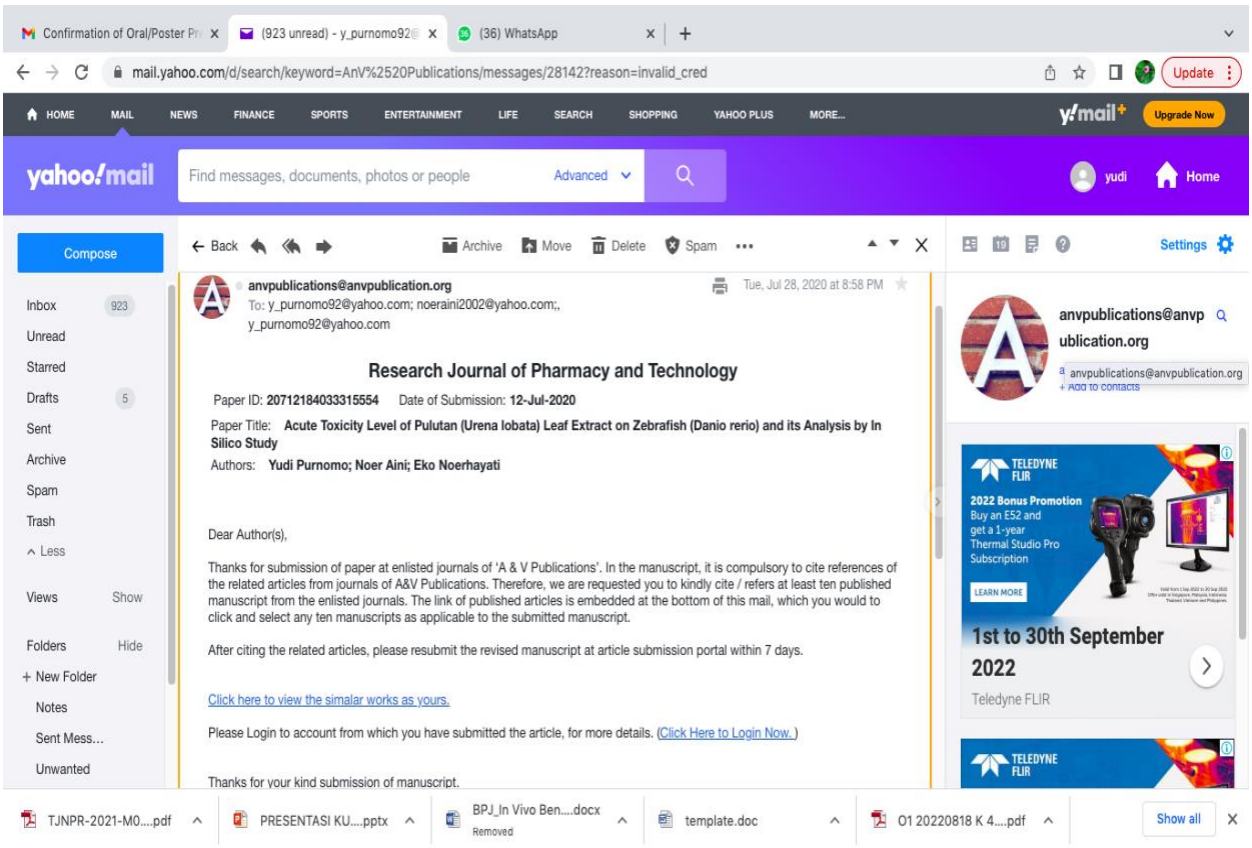

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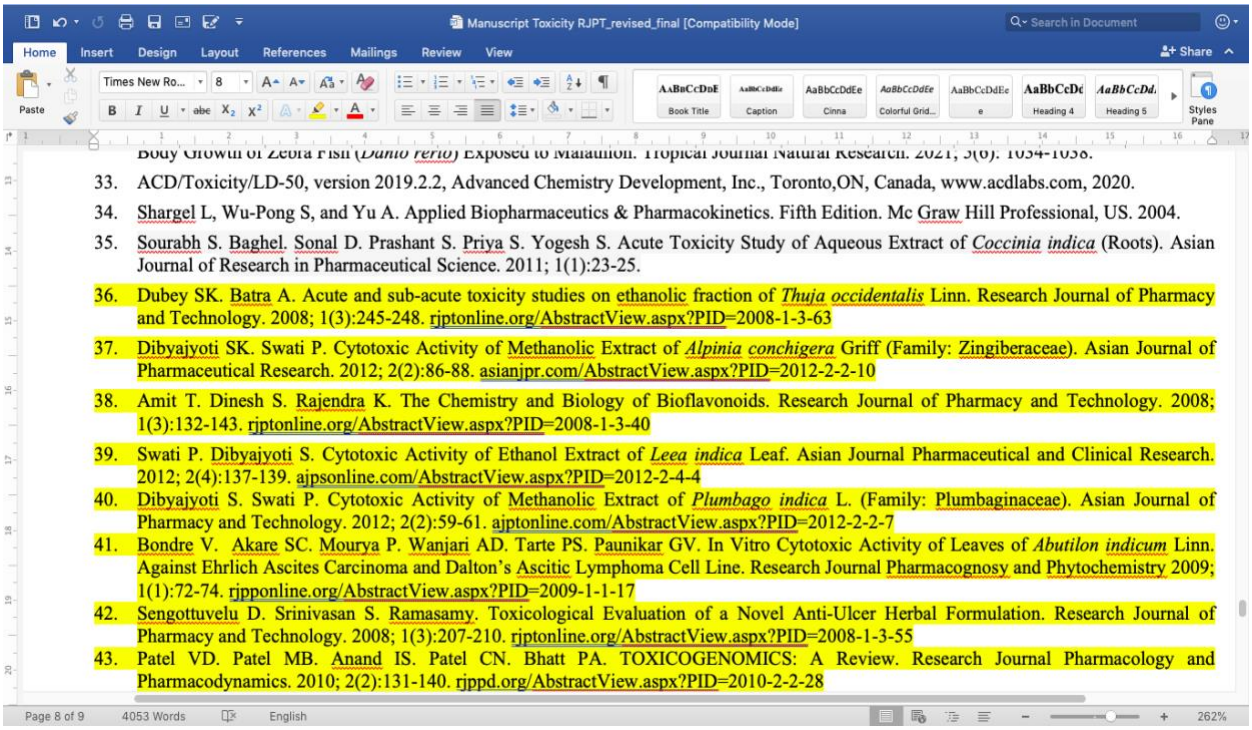

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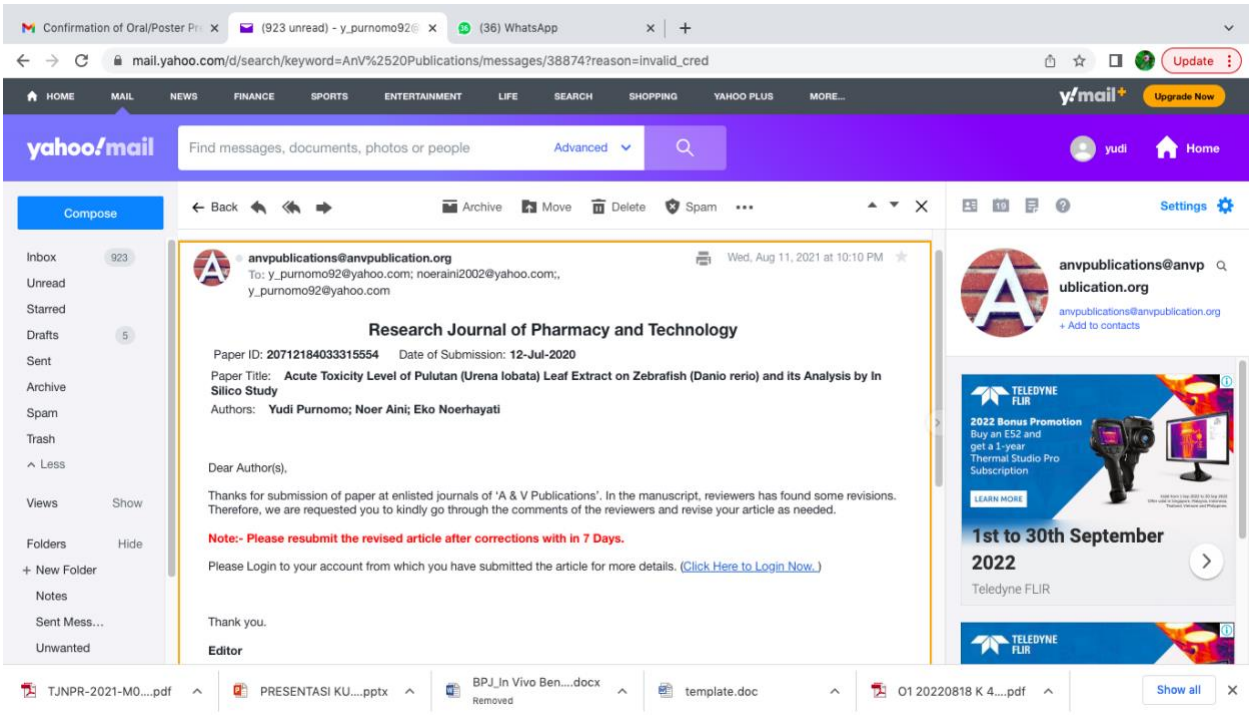

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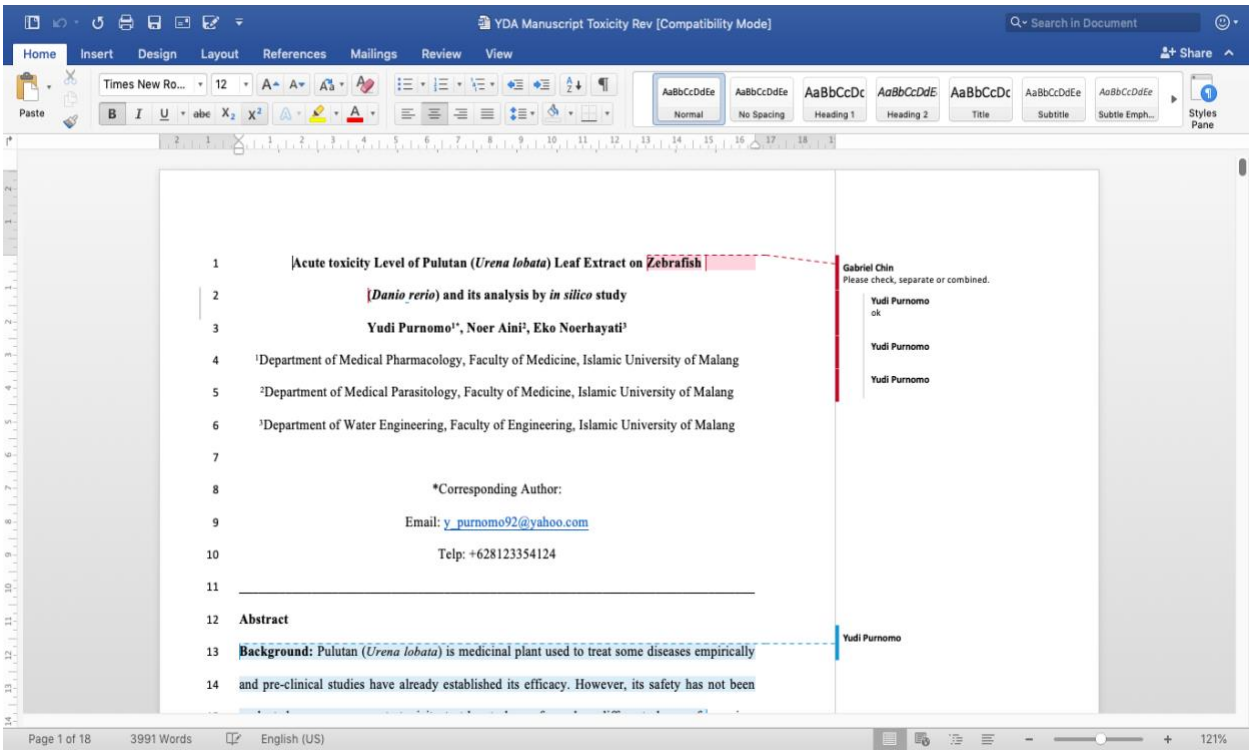

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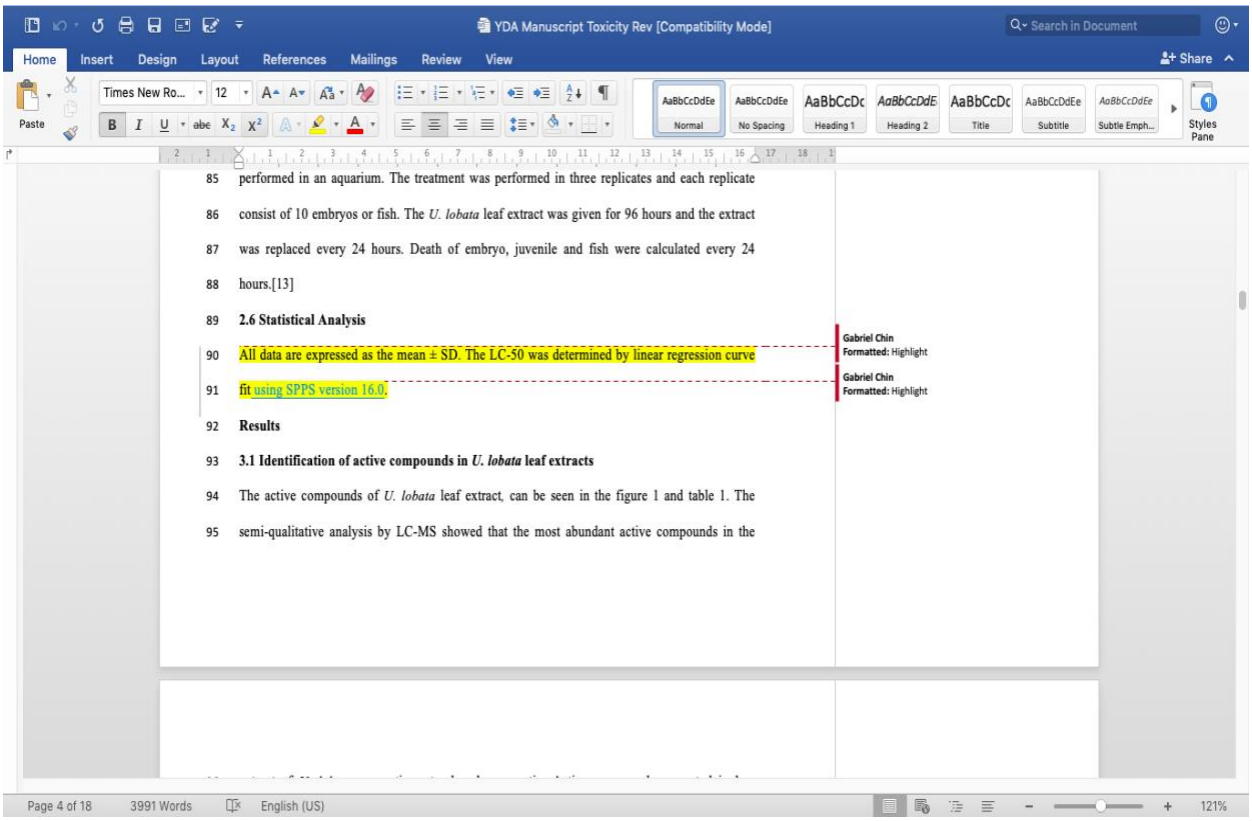

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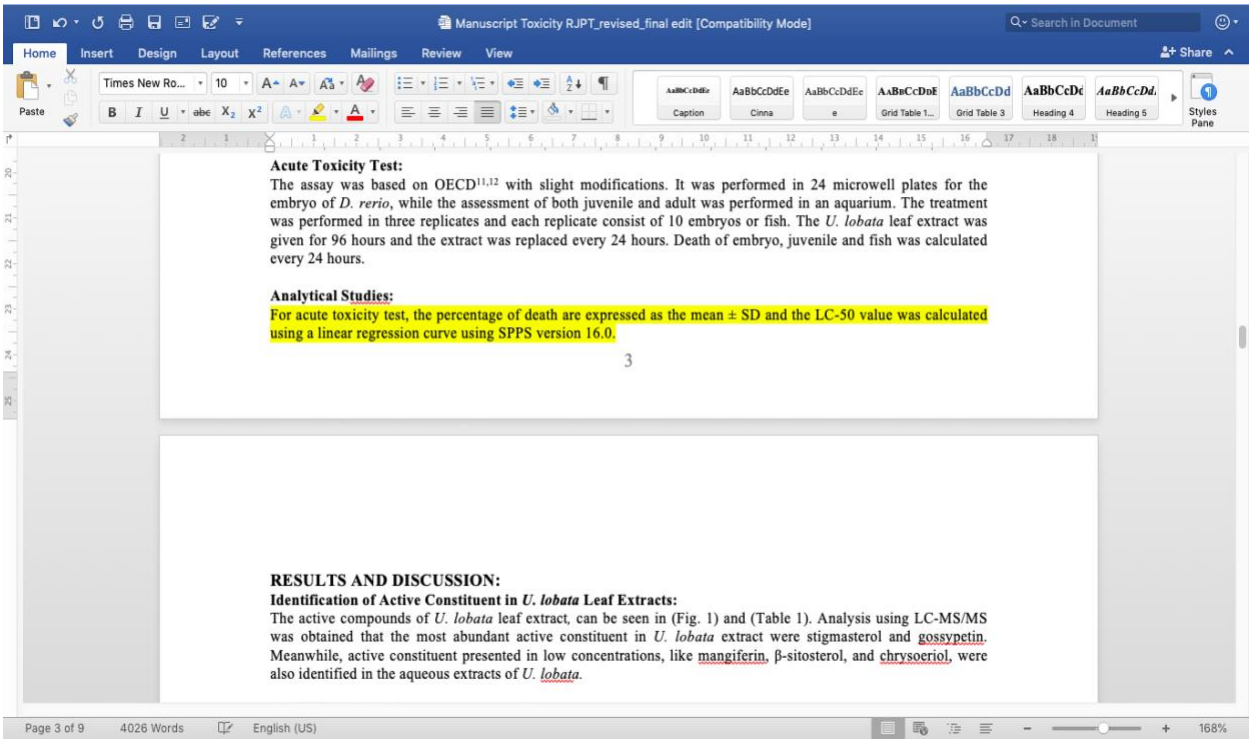

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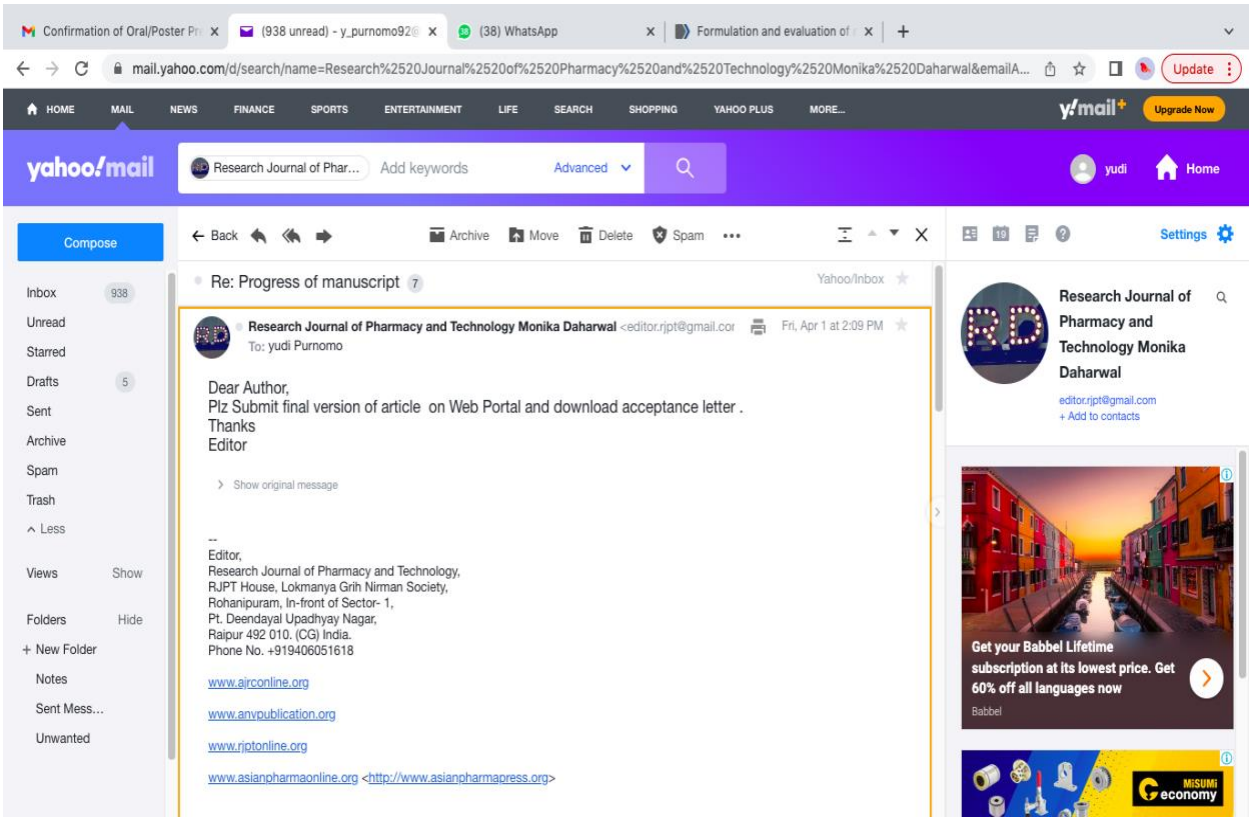

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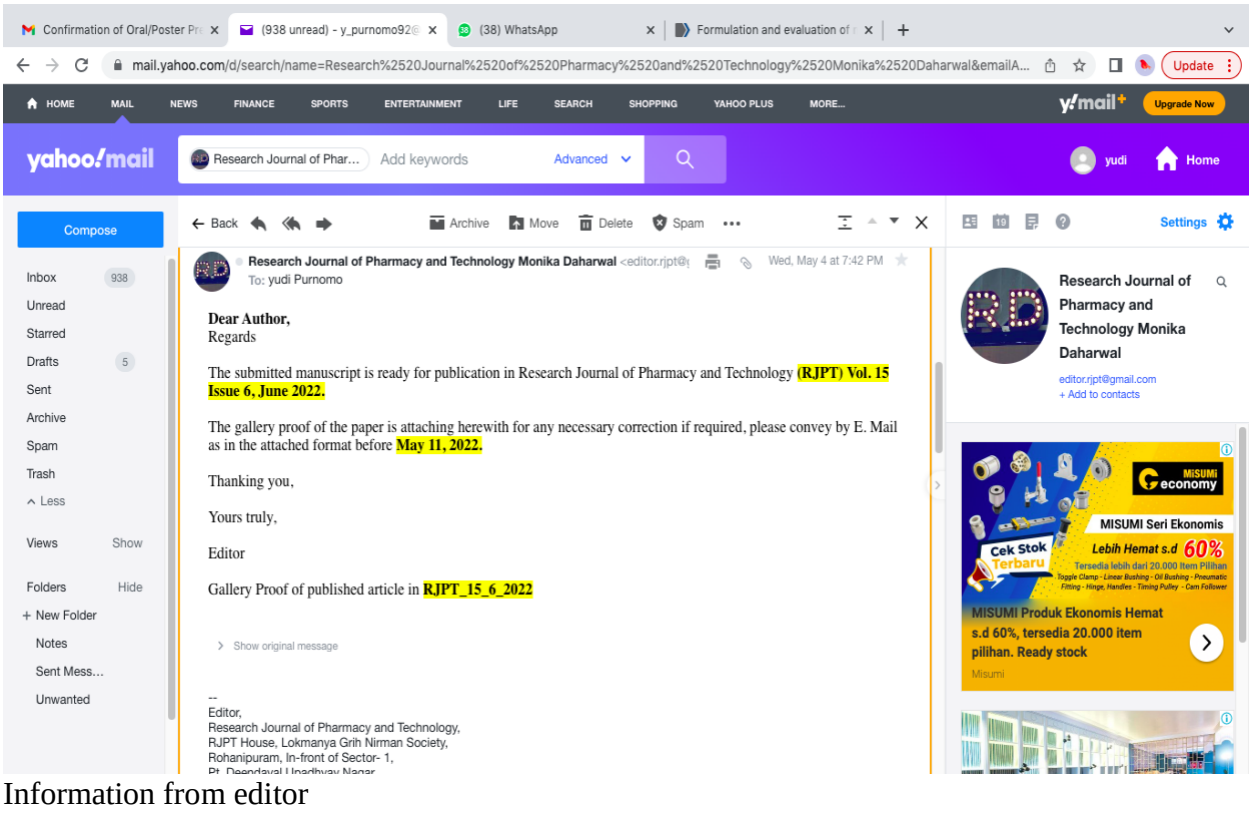

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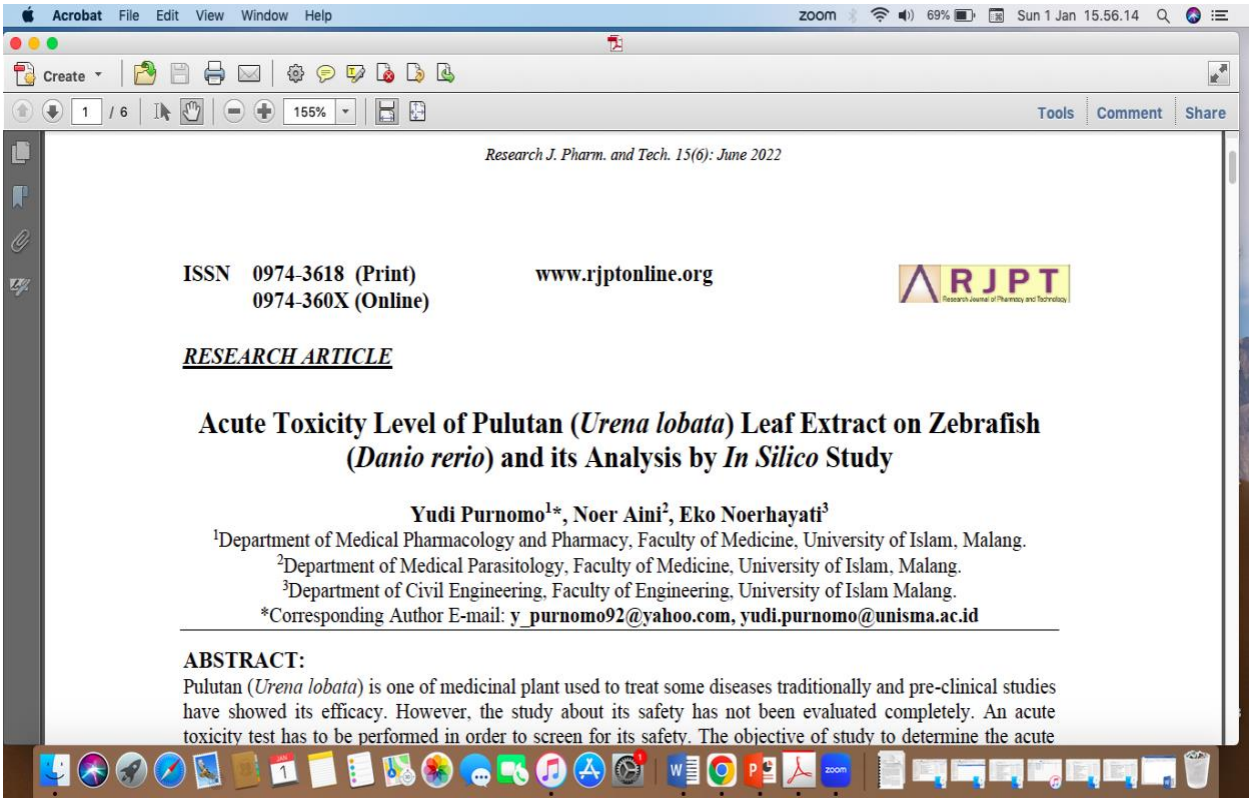

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RESEARCH ARTICLE

Acute Toxicity Level of Pulutan (*Urena lobata*) Leaf Extract on Zebrafish (*Danio rerio*) and its Analysis by *In Silico* Study

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ABSTRACT:
Pulutan (*Urena lobata*) is one of medicinal plant used to treat some diseases traditionally and pre-clinical studies have showed its efficacy. However, the study about its safety has not been evaluated completely. An acute toxicity test has to be performed in order to screen for its safety. The objective of study to determine the acute

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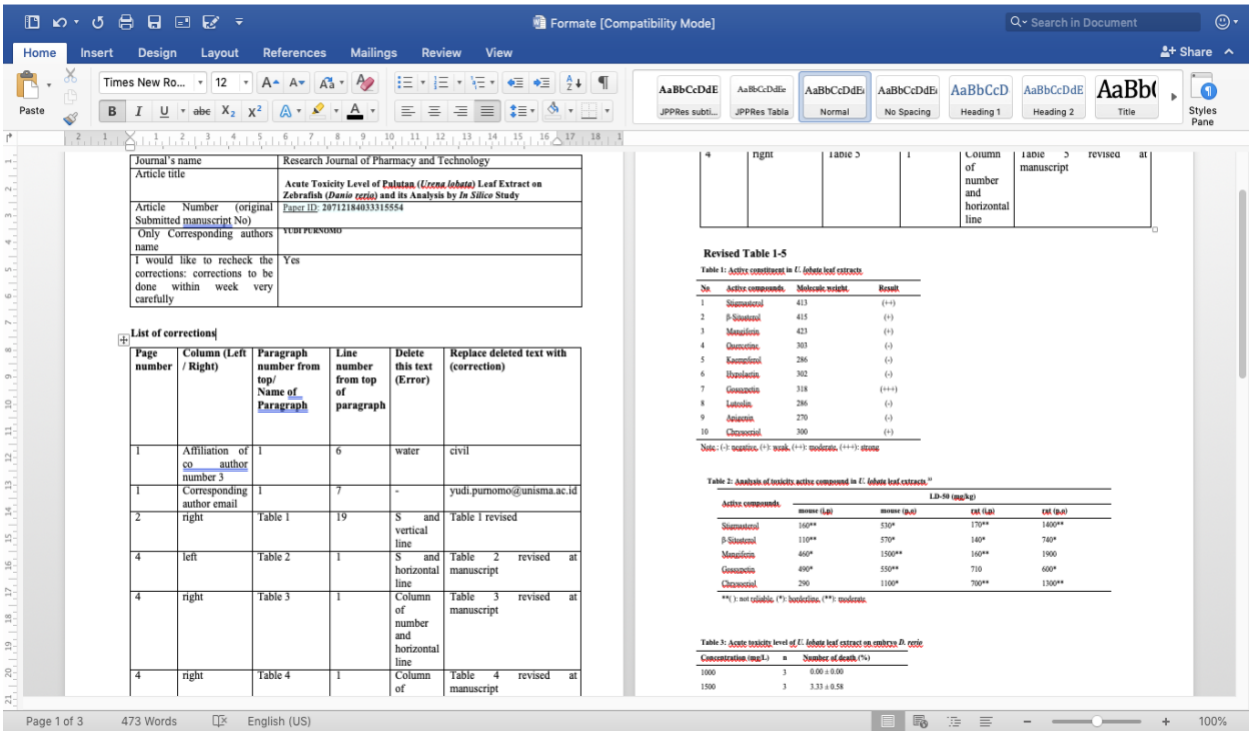

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List of corrections

Page number	Column (Left / Right)	Paragraph number from top/ Name of Paragraph	Line number from top of paragraph	Delete this text (Error)	Replace deleted text with (correction)
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1	Corresponding author email	1	7	-	yudi.purnomo@unisma.ac.id
2	right	Table 1	19	S and vertical line	Table 1 revised
4	left	Table 2	1	S and horizontal line	Table 2 revised at manuscript
4	right	Table 3	1	Column of number and horizontal line	Table 3 revised at manuscript
4	right	Table 4	1	Column of	Table 4 revised at manuscript

Revised Table 1-5

Table 1: Active constituent in *U. lobata* leaf extracts.

No	Active compounds	Molecule weight	Result
1	Stigmasterol	413	(++)
2	β-Sitosterol	415	(+)
3	Mangiferin	423	(+)
4	Quercetin	303	(-)
5	Kaempferol	286	(-)
6	Ursolactin	302	(-)
7	Genistein	318	(+++)
8	Luteolin	286	(-)
9	Apigenin	270	(-)
10	Chrysoeriol	300	(+)

Note: (-) negative, (+): weak, (++): moderate, (+++): strong

Table 2: Analysis of toxicity active compound in *U. lobata* leaf extracts.[a]

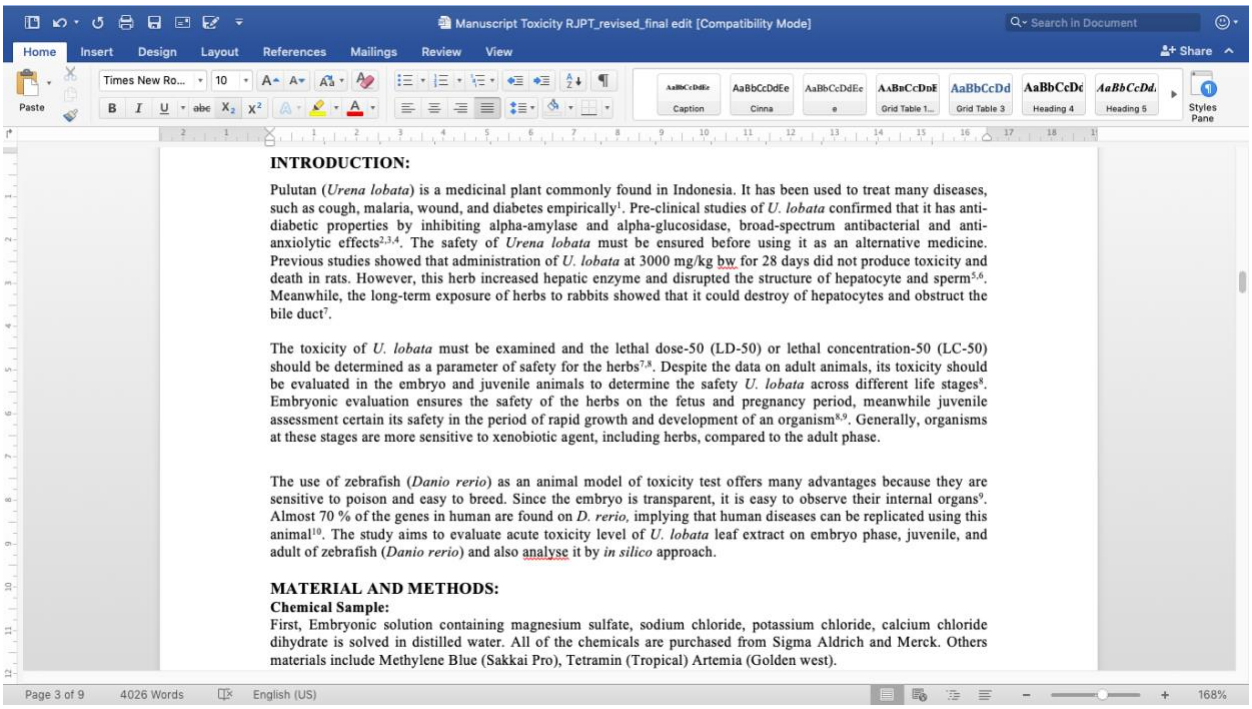
Active compounds	LD-50 (mg/kg)			
	mouse (i.p)	mouse (p.o)	rat (i.p)	rat (p.o)
Stigmasterol	160**	530*	170**	1400**
β-Sitosterol	110**	570*	140*	740*
Mangiferin	460*	1500**	160**	1900
Genistein	490*	550**	710	600*
Chrysoeriol	290	1100*	700**	1300**

**( ): not reliable, (*): borderline, (**): moderate.

Table 3: Acute toxicity level of *U. lobata* leaf extract on embryo *D. rerio*

Concentration (mg/L)	n	Number of death (%)
1000	3	0.00 ± 0.00
1500	3	3.33 ± 0.58

Correction of galley proof from author



INTRODUCTION:

Pulutan (*Urena lobata*) is a medicinal plant commonly found in Indonesia. It has been used to treat many diseases, such as cough, malaria, wound, and diabetes empirically[1]. Pre-clinical studies of *U. lobata* confirmed that it has anti-diabetic properties by inhibiting alpha-amylase and alpha-glucosidase, broad-spectrum antibacterial and anti-anxiolytic effects[2,3,4]. The safety of *Urena lobata* must be ensured before using it as an alternative medicine. Previous studies showed that administration of *U. lobata* at 3000 mg/kg bw for 28 days did not produce toxicity and death in rats. However, this herb increased hepatic enzyme and disrupted the structure of hepatocyte and sperm[5,6]. Meanwhile, the long-term exposure of herbs to rabbits showed that it could destroy of hepatocytes and obstruct the bile duct[7].

The toxicity of *U. lobata* must be examined and the lethal dose-50 (LD-50) or lethal concentration-50 (LC-50) should be determined as a parameter of safety for the herbs[7,8]. Despite the data on adult animals, its toxicity should be evaluated in the embryo and juvenile animals to determine the safety *U. lobata* across different life stages[8]. Embryonic evaluation ensures the safety of the herbs on the fetus and pregnancy period, meanwhile juvenile assessment certain its safety in the period of rapid growth and development of an organism[8,9]. Generally, organisms at these stages are more sensitive to xenobiotic agent, including herbs, compared to the adult phase.

The use of zebrafish (*Danio rerio*) as an animal model of toxicity test offers many advantages because they are sensitive to poison and easy to breed. Since the embryo is transparent, it is easy to observe their internal organs[9]. Almost 70 % of the genes in human are found on *D. rerio,* implying that human diseases can be replicated using this animal[10]. The study aims to evaluate acute toxicity level of *U. lobata* leaf extract on embryo phase, juvenile, and adult of zebrafish (*Danio rerio*) and also analyse it by *in silico* approach.

MATERIAL AND METHODS:

Chemical Sample:

First, Embryonic solution containing magnesium sulfate, sodium chloride, potassium chloride, calcium chloride dihydrate is solved in distilled water. All of the chemicals are purchased from Sigma Aldrich and Merck. Others materials include Methylene Blue (Sakkai Pro), Tetramin (Tropical) Artemia (Golden west).

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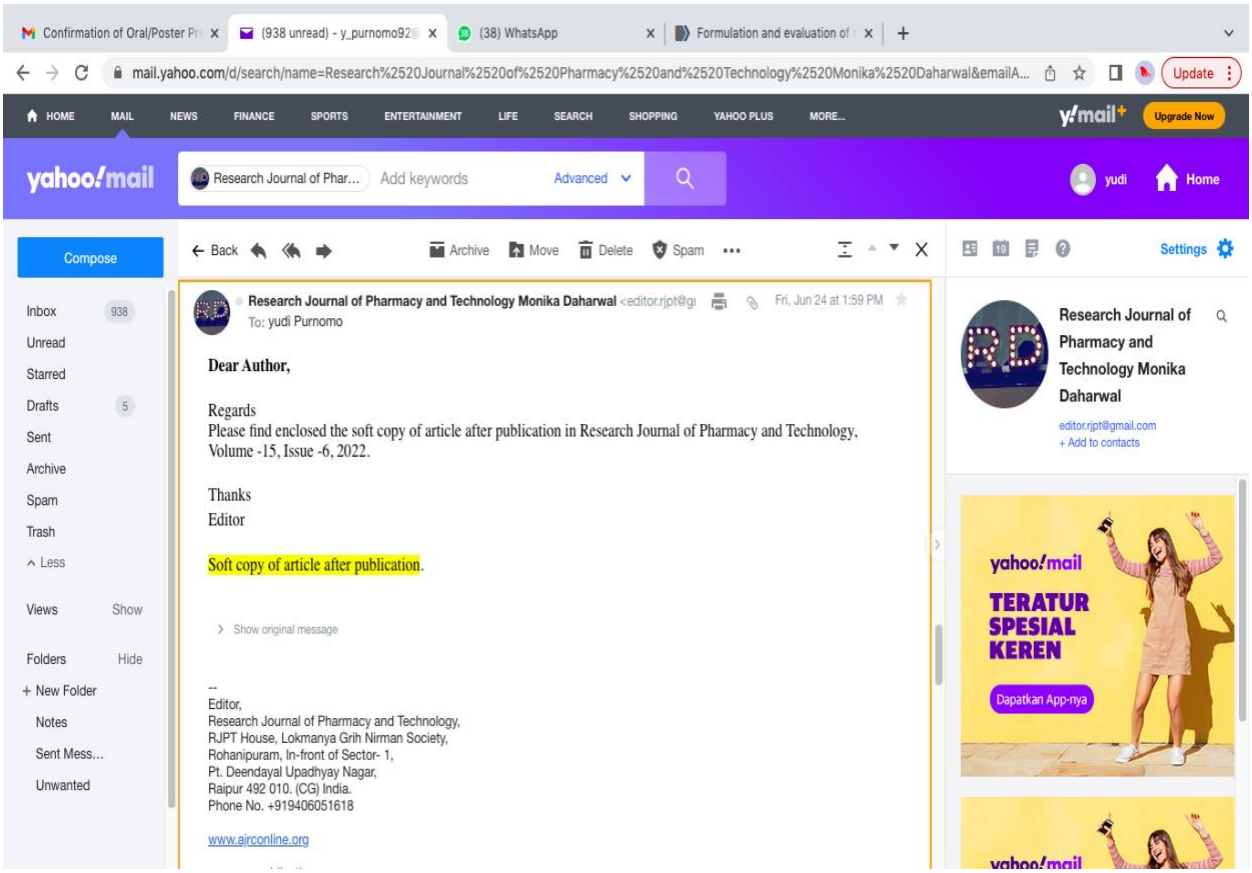

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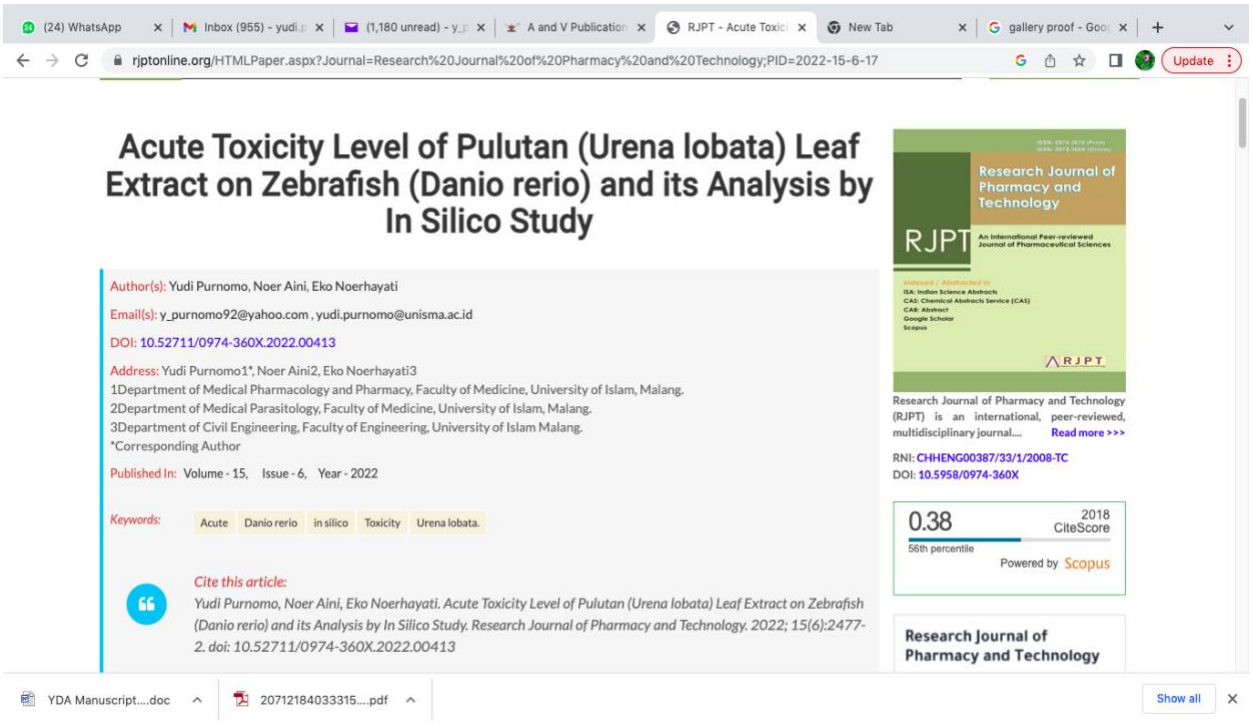

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