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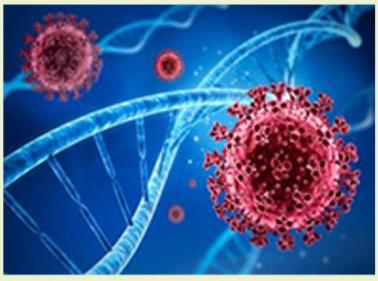

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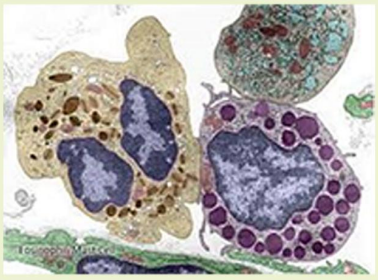

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ORIGINAL ARTICLE

THE EFFECT OF CAULERPA CYLINDRACEA EXTRACT ON HISTOPATHOLOGY DEPICTION OF MALE RATTUS NORVEGICUS GASTER MUCOSA INDUCED BY INDOMETHACIN

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ABSTRACT

Background: A lot of food can repair gastric mucosal damage. For example, sea grapes or the *Caulerpa cylindracea* with its flavonoid content. Anti-inflammatory and anti-ulcer effect can reduce gastric lesions due to ulcerogenic agents. Indomethacin is used to induce gastric ulcers in experimental animals. Based on this background, this study was conducted to analyze the effect of *Caulerpa cylindracea* extract, on the histopathological picture of gastric mucosal damage of *Rattus norvegicus* male rats.

Method: 32 male *Rattus norvegicus* rats were divided into 4 groups, (1) Group K (-), the untreated group, (2) Group K (+) inducedby indomethacin 30 mg/kgBB per head (3) Group P1 inducedbyindomethacin 30 mg/kgBB and *Caulerpa cylindracea* extract 1 gr/100grBB per subject, (4) Group P2, induced by indometacin 30 mg/kgBB and 2 gr/100grBB of *Caulerpa cylindracea* extract per subject for 7 days. At the end of the study, the experimental animals were sacrificed and their stomachs were histopalogicalexamined

Result: There was a significant decrease($p = 0.001$) in the degree of gastric mucosal damage between the P1 group (given Indomethacin and 1 gr/100grBB Caulerpa cylindracea extract) and K + groups (given only indomethacin). There was a significant decrease ($p = 0.001$) in the degree of gastric mucosal damage between K (+) group and group P2 that given Indomethacin and 2 g/100grBB *Caulerpa cylindracea* extract. There was a significant a significant decrease ($p = 0.004$) in the degree of gastric mucosal damage between between group P1 and group P2. Data revealed on group K (-) without any treatment did not obtain significant results ($p = 0.060$) with group P2.

Conclusion: Giving *Caulerpa cylindracea* extract with 1 gr/100grBB dose and 2 gr/100grBB dose can repair mucosal damage in *Rattus norvegicus*male rats induced by indomethacin.

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INTRODUCTION

Gastritis is an inflammation that occurs in the mucosal layer of the stomach. The inflammation may be accompanied by bleeding into the mucosa and in more severe cases epithelial erosions of the mucosal surface may occur. Gastritis can arise due to infection with the Helicobacter pylori bacteria; use of non-steroidal anti-inflammatory drugs (NSAIDs) or severe stress. Usually characterized by mucosal edema and neutrophil infiltration. If this mucosal damage has extended beyond the submucosal layer or deeper, peptic ulcers can appear[1].

According to WHO data in May 2014, peptic ulcer or stomach ulcer has caused 1,081 deaths in Indonesia or 0.08% of total deaths. There are two types of peptic ulcers that are often found, that are gastric ulcer and duodenal ulcer. This naming is based on the location of the ulcer, gastric ulcer in the stomach, while duodenal ulcers in the

duodenum. Peptic ulcers caused by an imbalance between defensive and aggressive factors that maintain the integrity of the gastric mucosa [2].

There are several food ingredients with anti-inflammatory properties that can maintain the integrity of the gastric mucosa, one of which is sea grapes. One type of sea grape is Caulerpa racemosa, a variant of cylindracea, from a group of green algae that lives in several Indonesian waters. The algae variety type C. cylindracea is a species commonly consumed as vegetables or fresh vegetables by people in tropical areas such as in Indonesia. Based on the research of Santoso (2004) extracts of Caulerpa sp. contains three kinds of catechins (fiavanol), namely gallo catechin, epicatechin and catechin gallat. Catechins are the products of plant metabolites which are included in flavonoids. Flavonoids are one of the most effective ingredients that function pharmacologically as anti-bacterial, anti-viral, anti-inflammatory and antioxidant[3,4].

Flavonoids are very effective and have low toxicity as a treatment for gastrointestinal diseases, especially peptic ulcers. Flavonoids act to protect the gastrointestinal mucosa from lesions formed from various ulcer models and can also protect the mucosa from necrotic agents. There are several mechanisms of action involved in the protective effects of flavonoids, the most important of which is their antioxidant properties. Apart from having gastroprotective properties, flavonoids can also improve the healing process of gastric ulcers [5].

Indomethacin is one of the NSAIDs and a group of drugs that is most widely consumed worldwide for its analgesic, antipyretic, and anti-inflammatory effects. This group of drugs has side effects, one of which is aggressive factors that can cause damage or lesions to the gastric mucosa, both locally and systemically, in the form of gastritis and peptic ulcer. Indomethacin induction can be a method to make experimental animals experience gastritis and peptic ulcer. Based on the results of the exploration, it was found that the 30 mg / kgBB dose of Indomethacin is the optimal dose to cause bleeding and peptic ulcer in the stomach.[6,7].

Based on the background, the study was designed to determine the effect of sea grape extract (Caulerpa cylindracea) on the histopathological picture of indomethacin-induced male rats (Rattus norvegicus) gastric mucosal damage.

METHOD

This research was conducted in the Biochemistry laboratory of the Faculty of Medicine, Hang Tuah University, Surabaya for 29 days with the etical clearance number I/027/UHT.KEPK.03/VII/2019. The design of this study was a laboratory experimental study using a post-test only control group design. The study used 32 male white rats (Rattus norvegicus) of the Wistar strain with a body weight of 150-200 grams, divided into Negative control group (K-) ornormal/untreated group, positive control group (K+) : that group was given indomethacin induction at a dose of 30 mg / KgBW per day for 7 days, treatment group 1 (P1) : that group was given Indomethacin at a dose of 30 mg / KgBB and sea grape extract at a dose of 1 gr / 100grBB per day for 7 days, treatment group 2 (P2) : that group was given Indomethacin at a dose of 30 mg / KgBB and sea grape extract at a dose of 2 gr / 100grBB for 7 days.[6]

The sampling technique is simple random sampling. On the 29th day, all groups of rats were anesthetized to take their gastric organs and then made histological preparations with haematoxillin eosin as an addition. The preparation is then viewed using a light microscope with a 40-fold magnification and assessed by looking at the integrity of the gastric mucosal epithelial layer with the following scores:

- normal / no pathological changes found = 0,
- there is desquamation of the gastric mucosal epithelium = 1,
- there is erosion of the epithelial surface of the gastric mucosa (the lesion in the epithelium appears to have peeled off almost half) = 2,
- ulceration of gastric mucosal epithelium (epithelial cell lesions reaching the muscularis lamina) = 3 [8].

The data collected was tested using statistical analysis using the SPSS program in the

form of the Kruskal-Wallis test and then Post Hoc analysis, namely Mann-Whitney.

RESULT

Histopathological examination results with magnification 400X

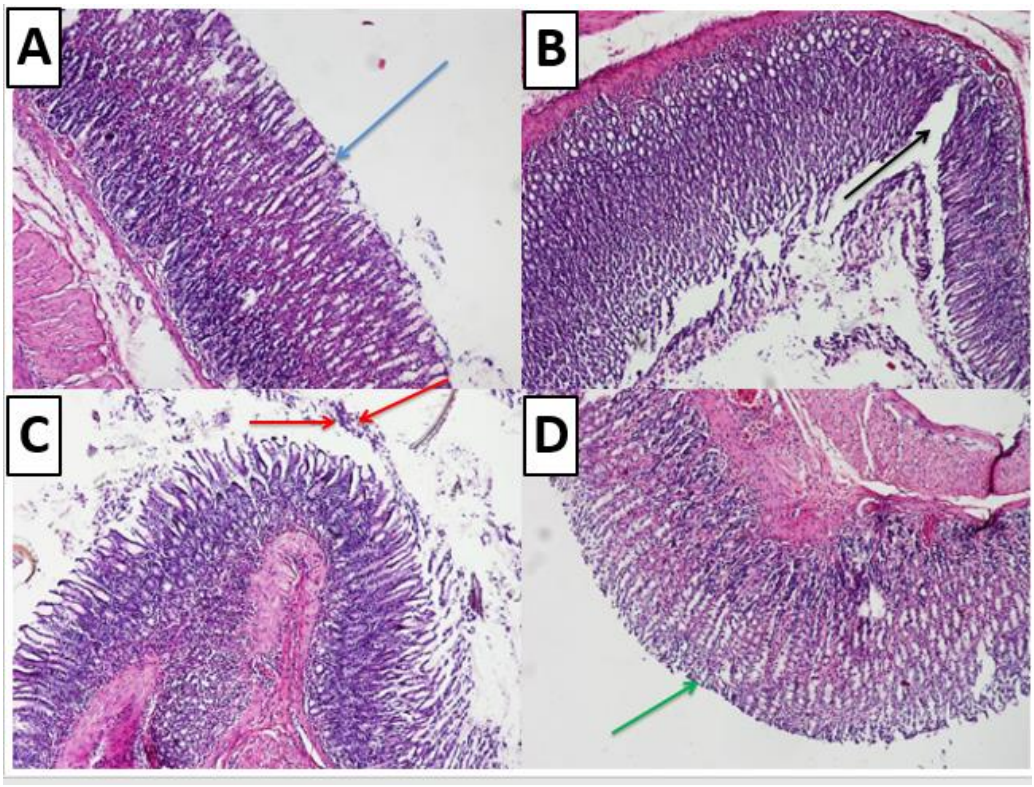

Figure 1. gastric histopathological figure of each group

Note: 1. Figure A : Control negative group;
→ indicates a normal gastric mucosal layer
2. Figure B : Control positive group;
→ indicates gastric ulcer
3. Figure C : Treatment group 1
→ indicates gastric erosion
4. Figure D : Treatment group 2;
→ indicates an improved gastric mucosa

Table 1. Histopatological score the integrity of the gastric mucosal epithelial layer

No	K(-) or normal group	K(+)	P1	P2
1	0	3	2	0
2	0	3	2	0
3	0	3	2	1
4	0	3	2	0
5	0	3	2	1
6	0	3	1	1
7	0	3	1	0
8	0	3	1	0
Mean	0	3	1.71	0.43
SD	0	9	0.49	0.53

The results of the Kruskal Wallis test obtained a significance value of p (0.001 <α (0.05)) so it can be concluded that there is an effect of giving Caulerpa cylindracea extract on the histopathological picture of gastric mucosal damage in indomethacin induced male Rattus norvegicus. Furthermore, the results of the Post Hoc test used Mann-Whitney to determine which groups were different.

Table 2. The results of the Mann Whitney test between groups

Group		P value
K-	K+	0.001
	P1	0.001
	P2	0.060
K+	P1	0.001
	P2	0.001
P1	P2	0.004

The results of data analysis, there is a significant difference between the degree of gastric mucosal damage in the experimental animal group given Indomethacin only (K +) and the experimental animal group given Indomethacin and sea grape extract at a dose of 1gr / 100grBB (P1). There was a significant difference between the degree of gastric mucosal damage in the experimental animal group given Indomethacin only (K +) and the experimental animal group given Indomethacin and sea grape extract at a dose of 2gr / 100grBB (P2). and sea grape extract dose of 1gr / 100grBB (P1) with a group of experimental animals given Indomethacin and sea grape extract with a dose of 2gr / 100grBB (P2). The results of data analysis on the experimental group K (-) without treatment with the P2 experimental group Indomethacin induced and given sea grape extract dose of 2gr / 100grBW did not show any significant results.

DISCUSSION

In group K (-) experimental animals without treatment found no damage or changes in the gastric mucosal histopathological figure of the rats and were given a score of 0 (zero) according to Barthel Manja's criteria. In the K (+) group, experimental animals induced by Indomethacin showed a change in the gastric mucosal histopathological figureof the experimental animals, these changes were in the form of ulcers with a score of 3 (three) according to Barthel Manja's criteria on the gastric mucosal layer of the experimental animals. The results of data analysis between the K (-) group of experimental animals without treatment with the K (+) group of experimental animals induced by indomethacin showed a significant difference with a significance level of p = 0.001.

In the K (+) group, they were given Indomethacin induction at a dose of 30mg / kgBW so that it could cause ulcers to form. The way indomethacin works on the stomach is inhibition of Cox-I and Cox-II. Cox-I in the stomach plays a role in keeping the surface of the stomach healthy by preventing the formation of stomach acid, increasing bicarbonate and mucus production, besides that Cox-I is responsible for maintaining homeostasis. Cox-II is responsible for PG (prostaglandin) formation in acute inflammatory conditions. Inhibition against Cox-II can relieve signs and symptoms of inflammation while inhibition against Cox-I can cause damage or exfoliation (desquamation) of the gastric mucosal layer. Indomethacin is more effective in inhibiting Cox-I than Cox-II, causing erosion of the gastric mucosa which results in peptic ulcers.[9, 10].

There was a significant difference between the K (+) group of experimental animals induced by indomethacin, namely p = 0.001 with the P1 group of experimental animals induced by indomethacin and given Caulerpa extract. cylindracea dose of 1gr

/ 100grBB. On the histopathological examination of the gastric mucosa in group P1, it was found that the gastric mucosal layer of the experimental animals was erosion with a score of 2 (two) according to Barthel Manja's criteria and a small proportion only experienced desquamation with a score of 1 (one) according to Barthel Manja's criteria.

The histopathological examination of gastric mucosa in group P2 experimental animals induced by indomethacin and given 2gr / 100grBB of Caulerpa cylindracea sea grape extract, it was found that changes in the gastric mucosa layer were even better, namely only in the form of desquamation with a score of 1 (one), even some preparations showed a score of 0 (zero).) according to Barthel Manja's criteria. The comparison between the K (+) group of experimental animals induced by indomethacin and the P2 group of experimental animals induced by indomethacin and given Caulerpa cylindracea extract at a dose of 2gr / 100grBB resulted in a significant difference with a significance level of p = 0.001.

This research used Caulerpa cylindracea extract. Caulerpa sp contains three kinds of catechins (fiavanol), namely gallo catechin, epicatechin and catechin gallat. Catechins are the products of plant metabolites which are included in flavonoids. Flavonoids are one of the ingredients of sea grapes which are pharmacologically most effective as anti-bacterial, anti-viral, anti-inflammatory and antioxidant. [10,11, 12]

Flavonoid compounds can also prevent or reduce gastric lesions induced by ulcerogenic agents with an important mechanism that flavonoids have is anti-ulcer activity. The protective effect through its anti-histamine properties can reduce histamine levels and thus prevent the release of histamine from gastric mast cells and inhibit gastric H + / K + proton pump, stimulate mucosubstance synthesis in gastric mucosa and increase prostaglandin levels thereby reducing gastric acid secretion. [5, 10, 13]

The results of the analysis test between the P1 experimental animal groups that were induced by indomethacin and given Caulerpa extract. Cylindracea dose of 1gr / 100grBB with the experimental group P2 indomethacin induced and given Caulerpa cylindracea extract at a dose of 2gr / 100grBB showed significant differences with a significance level of p = 0.004. This shows that there is a significant difference with the addition of the dose of sea grape extract. The results of the data analysis test in the experimental group K (-) without treatment with the P2 experimental group that was induced by indomethacin and given Caulerpa cylindracea extract at a dose of 2gr / 100grBB did not get any significant results. (p = 0.060) so it can be interpreted that the induction in the P2 group was able to improve with results that were close to normal.[12, 13]

The results of thisresearch, the giving Caulerpa cylindracea extract can significantly reduce / repair lesions in the gastric mucosal layer in male rats (Rattus norvegicus) indomethacin induced.

CONCLUSION

Indomethacin inductionin male Rattus norvegicuscaused gastric ulcers. Caulerpa cylindracea extract at a dose of 1gr / 100grBB and 2gr / 100grBB can repair indomethacin-induced damage to the gastric mucosal layer of male Rattus novergicus. 2gr / 100grBB dose of Caulerpa cylindracea extract can repair indomethacin-induced damage to the gastric mucosal layer of male Rattus novergicus better than Caulerpa cylindracea extract at a dose of 1gr / 100grBB.

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ORIGINAL ARTICLE

THE LABOR-INDUCED PREGNANCY CASES IN DR SOETOMO GENERAL HOSPITAL: A DESCRIPTIVE STUDY

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ABSTRACT

Background: Labor induction is a procedure to stimulate uterine contractions during pregnancy before labor begins on its own to achieve a vaginal birth with medical or mechanical intervention to start the labor. This procedure aims to stimulate more extensive contraction in the uterus. The labor induction can reduce the caesarean rate. Prostaglandin E2 (PGE2) and misoprostol are the commonest medicine used to ripen the cervix in the Dr. Soetomo Hospital.

Objective: Our study aim to evaluate the success rate of induction of labor patient

Methods: This study was a descriptive study using the medical record in 2018 in the Dr. Soetomo General Hospital, Surabaya. A total of 183 patient's medical record data who underwent induced labor were used in this study. Inclusion criteria were the women with indication to deliver and have no cephalo-pelvic disproportion. Women with contraindication labor induction were excluded. Data was described using table and narrative approach.

Results: The most range of gestational age was 21-36 weeks (53.01%) followed by 37-42 weeks (42.07%). There were 68 patients (37,1%) primigravida and 115 patients (62,8%) were multipara. The major induced labor was conducted with misoprostol (78.6%), and the most pelvic scores were 2 (58.46%) before underwent induced labor. Vertex delivery was the preferred mode of delivery after the induction of labor with 89 patients (48,62%). The labor induction failure followed with the caesarean operation were 27 patients (14,7%) and one patient (0,54%) with hysterotomy, most of them caused by failure to progress and fetal distress. There were 78 babies (43%) with the weight over 2500 g, 28 babies (31%) were over 2000 g, and the other was below 2000 g. A total of 84.71% with labor induction can be delivered vaginally, and It is a good number to reduce the rate of caesarean operations.

Conclusion: This study concludes that misoprostol uses for the induction of labor than the other. Delivery abdominal is less percentage than the additional delivery finds that as a failure of induction of labor. The Labor induction success to delivered vaginally can reduce the rate of caesarean operation.

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INTRODUCTION

Induction of labor is a procedure to stimulate the uterus contraction before the spontaneous onset of labor condition with pharmacological or mechanical intervention. The indication of labor induction is when the safety and benefits to both mother and fetal is more important than the pregnancy continuation. The indication includes membrane rupture without labor, gestational hypertension, oligohydramnios, non-reassuring fetal status, post-term pregnancy, and various maternal medical conditions such as chronic hypertension and diabetes. The maternal side's contraindications are related to prior uterine incision, contracted or distorted pelvic anatomy, abnor-mally implanted placentas, and uncommon conditions such active genital herpes infection or cervical cancer. The Fetal factors consist of appreciable macrosomia, severe hydrocephalus, malpresentation, or non-reassuring fetal status (1).

The induction of labor can reduce the caesarean section rate. The incidence of labor induction for shortening the duration of pregnancy has risen. In high-income countries, the proportion of infants delivered at term following labor induction is one in four births. (2) In the United States, labor induction incidence rose 2.5 fold from 9.5 percent in 1991 to 23.8 percent in 2015 (3). One-fifth of delivery in the UK is inducing due to safety concerns for the mother or fetus (4). Socioeconomics is one of the risk factors for labor induction in the United Kingdom (5). There is no data labor induction in Indonesia, but there were some data in Bahagia Hospital, Makassar, which were 22,9 percent of all delivery in 2017 and 5,9 percent in 2018 (6).

The induction mechanisms are varying from mechanical to pharmacological or medicinal. The mechanical methods for induction makes cervical ripening and onset of labor by stretching the cervix. They are amongst the oldest methods used to initiate labor. During the last decades, medication such as Prostaglandin E2 (PGE2), misoprostol, and oxytocin have partly replaced mechanical means (7). Previous study by Trihastuti found that oral administration of misoprostol is safe in decreasing the interval to delivery on 40 weeks gestation women (8). There's a research in the UK comparing the usage of misoprostol vaginal inserts (MVI), and dinoprostone vaginal inserts (DVI) which showed that MVI is better than DVI in reducing time, and duration of active labor, leading to estimated reduced resource use in terms of hospital staff shift and length of stay in hospital. Reducing the resource utilization could improve efficiencies and optimize patient care without increasing the burden of hospital resources. (9) Some studies show that labor induction is more beneficial than expectant delivery management improves perinatal outcomes without increasing caesarean section rates (10) (11). In this study we aimed to evaluate of induction of labor in Dr. Soetomo General Hospital.

METHODS

Design and Setting: We studied pregnant women admitted for labor induction in the Department of Gynecology and Obstetrics at Dr. Soetomo General Hospital, Surabaya. This institution is a public medical care center and one of the most important maternal care facilities in East of Java, Indonesia. It receives referrals patients mainly from the peripheral maternities within the East of Java region and also within the surrounding areas. A cross sectional descriptive study was conducted over twelve months form 1st January to 30th December of 2018 using patients medical records. This study was approved the ethical committee from Soetomo Hospital.

Population: we included all women with pregnancy-related complications while pregnant (antenatal complications need urgent delivery), during labor or within immediate postpartum. Inclusion criteria were all pregnant women with an indication of the induction of labor and with no cephalo-pelvic disproportion during the study period. Women with

contraindication labor induction were excluded such as history of previous caesarean section, malposition of aterm fetus, history of myomectomy or uterine rupture.

Data collection and analysis: We used patient's medical records and followed their history including after delivery and during post-natal hospitalization. The following information were extracted: current pregnancy characteristics, management of childbirth, and the outcome of the labor and the babies. For more precision, information about final diagnoses and prognoses were obtained from the receiving midwife at referral hospital, or from the obstetric outpatient clinic. Descriptive analysis was performed using Microsoft excel.

RESULTS

Table 1 – Characteristic patient Induction of Labor

Characteristic	Cases	%
Patients Age Group		
17 - 34 years old	138	75,4
≥ 35 years old	45	24,6
Parity		
Primiparous	68	37,15
Multiparous	115	62,84
Gestational Age		
≤ 20 weeks	9	4,91
21 - 36 weeks	97	53,01
37 - 42 weeks	77	42,07

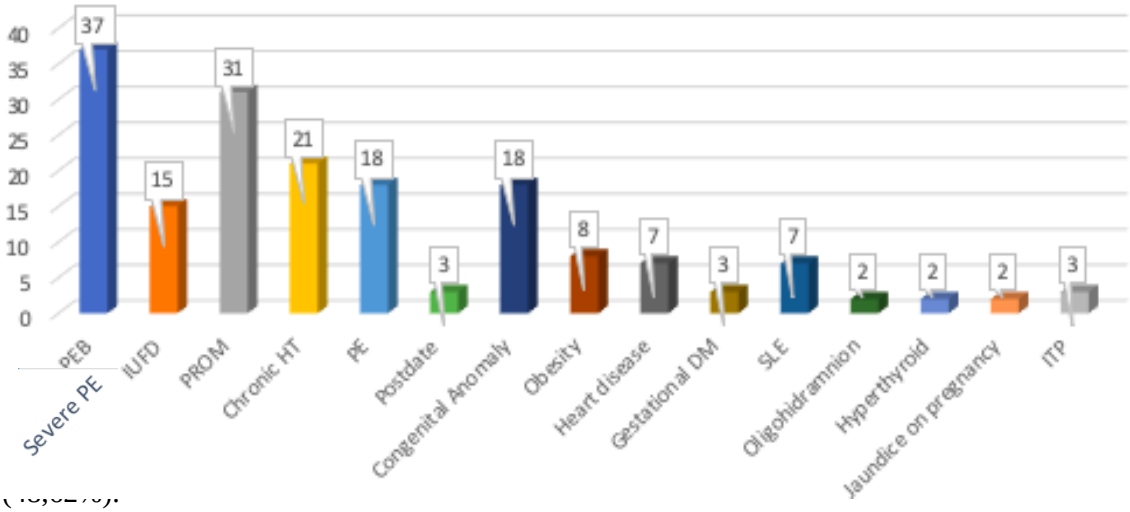
From the data that we gathered throughout 2018, we found a total 1454 birth medical records, and a total of 183 that fulfilled the inclusion criteria, and 92 were excluded due to malposition of the fetus, history of myomectomy, and history of previous caesarean section. Which the majority of the subject (75,4%) was age 17 – 34 years old. The most range of gestational age was 21-36 weeks (53.01%) followed by 37-42 weeks (42.07%). There were 68 patients (37,1%) primigravida and 115 patients (62,8%) were multipara.

Table 2 – Induction of Labor in Dr. Soetomo General Hospital in 2018

Variable	Cases	%
Induction Methods		
Misoprostol	144	78,6
Oxytocin Induction	26	14,2
Misoprostol + Oxytocin Induction	5	2,73
Transcervical Cathether	2	1,09
Transcervical Cathether + Misoprostol	4	2,18
Laminaria	2	1,09
Misoprostol Administration Method		
Orally	18	12,50
Vaginally	126	87,50
Intial Pelvic Score Before Induction		
PS 2	107	58,46
PS 3	53	28,96
PS 4	6	3,27
PS 5	17	9,28

The major induced labor was conducted with misoprostol (78.6%) followed by oxytocin induction (14,2%). Most of the administration of misoprostol to the patient were by vaginally (87,5%, and the most pelvic scores were 2 (58.46%) before underwent induced labor.

Table 3 – Disease Characteristic of Induction of Labor



The major disease that indicate to the patient need termination were severe preeclampsia (20,2%), followed by premature rupture of membrane (PROM) (16,93%).

Table 4 – Induction of Labor Outcome

Variable	Cases	%
Mode of Delivery		
Spontaneous/ vaginally Labor	132	72,28
Forceps Extraction	23	12,50
Caesarean Section	28	15,22
Complications during Labor Induction		
Fetal distress / Abnormality of NST	25	92,5
Failure to progress	2	7,4
Perinatal Outcome		
<500 gr	21	11
500 - 2000 gr	56	15
2000 - 2500 gr	28	31
> 2500 gr	78	43
APGAR Score		
0	49	26,77
<4	30	16,39
4-6	24	13,11
>6	80	43,71

Vaginal delivery was the preferred mode of delivery after the induction of labor with 132 patients (72,28%). Complications found during induction of labor are abnormality of NST and fetal distress (92,5%) and only two patient have to failure to progress. The labor induction failure followed with the caesarean operation were 27 patients (14,7%) and one patient (0,54%) with hysterotomy. From the perinatal outcome there were 78 babies (43%) with the weight over 2500 g, 28 babies (31%) were over 2000 g, and the other was below 2000 g. The most of the baby with APGAR score >6 (43,71%).

DISCUSSION

We have identified that most pregnant women with an indication of the induction of labor were at a productive age (17 – 34 years old), and most of them were multigravida. Some patients with advanced maternal age are over 35 years old and may increase multiple adverse effects for both mother and baby. It may increase of obstetric complications, including placental abruption, placenta praevia, malpresentation, low birthweight. It also increases preexisting maternal medical conditions, including hypertension, obesity, and diabetes, increasing maternal age as do pregnancy-related maternal complications such as pre-eclampsia and gestational diabetes (14). The most common the age of gestation was below 37 weeks, this condition caused by a few of the severe preeclampsia cases that indicated the women terminated the pregnancy soon. In non-severe preeclampsia, it can provide expectant management until 37 weeks of gestational age (10).

Our study demonstrated that misoprostol administration was the main medical treatment used in labor induction at preterm and term birth. This result was in line with Dr. Soetomo Hospital's labor protocol. The application of misoprostol 50 ug vaginally has wider in cervical ripening and labor-induction than orally. However, this procedure required close monitoring of the patients for the abnormal contractions (12). Another study has shown that the time to delivery was shorter

in those women who were receiving vaginal misoprostol than oral administration. More women in the oral group required oxytocin augmentation of labor. The hyperstimulation incidence was similar between the groups, but there was an increased incidence of tachysystole in the vaginal group. There was no difference between the groups due to the mode of delivery or neonatal outcome (13).

Preterm cases were the most cases of gestational age, and it happened because of the second most of the cases were indicated by severe preeclampsia and preterm premature rupture of membrane (PPROM) (10). In other study compared to expectant management, a strategy of labor induction was associated with fewer perinatal mortality. There were four perinatal deaths in the labor induction group than 25 perinatal mortality in the expectant management group. There were also lower cesarean rates without increasing rates of operative vaginal births, and there were fewer NICU admissions with a policy of induction (10). There are improvements perinatal outcomes in the induction of labor from 37 weeks of gestation without increasing the cesarean section rate (11).

CONCLUSION

Our results showed that misoprostol vaginally is the primary medicine used for labor induction in dr. Soetomo General Hospital. The induced cases have mainly achieved spontaneous/ vaginally birth, and most of them reached over six points on the APGAR score. Our results indicated that inducing labor in indicated pregnancy is a relatively standard and safe procedure to terminate the pregnancy and conduct a spontaneous/ vaginally birth. However, further intense study is required to assess the risk factors in conducting labor induction.

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ORIGINAL ARTICLE

PRE CLINIC GRADE AND CLINIC PERIODS EFFECT ON PROGRESS TEST OF UNISMA MEDICAL PROFESSION STUDENTS

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ABSTRACT

Introduction. Pre clinic grade point is often seen as predictor of good performance in professional education whose short term goal is to pass national examination which command progress test to evaluate the preparation. Purpose. To know the effect of pre clinic grade point and clinical study periods in progress test result of medical profession students.

Methods. 135 students of medical profession programme completed computer based progress test of 200 national standardized questions in 200 minutes using siPENA software. Progress test result then analysed based on how long they have been studied and their pre clinic grade point using ANOVA – Tukey HSD and Pearson correlation in SPSS for Windows ver 19

Results. Although students with pre clinic grade 2,50-2,74 have lower progress test result, but it's not statistically significant (p>0,05). The same happen in clinic study periods with the longer the students in their clinical rotation, the better their result (p>0,05). The trends which showing better result in higher pre clinic grade point and time they spend in clinical rotation agrees with previous studies.

Conclusion. Pre clinic grade point and clinic study periods has little to no effect on progress test result of medical profession students in UNISMA.

Medical and Health Science Journal.

INTRODUCTION

Faculty of Medicine aims to educate future doctors. In Indonesia, this education consist of two phases, which are medical bachelor programme for pre clinic study and medical profession programme for clinical training. Exit exam for medical education in Indonesia is national competency examination (*Uji Kompetensi Mahasiswa Program studi Profesi Dokter* / UKMPPD) which is taken in the end of medical profession programme in the form of computer based test and Objective Structured Clinical Examination (OSCE). In medical bachelor programme, studies are designed in problem based learning, which are arranged based on system organ, while in medical profession programme which is hospital based, the training is arranged in departemental clinical rotation. Pre clinic study problem based learning strategies including tutorial, lecture, practicum in laboratory, and clinical skill training. Assessment in pre clinic period such as written assignment, multiple choice question from tutorial and lecture material, practicum response test, and OSCE comprised score of block courses. Combined score of block courses and general basic courses such as religion, citizenship and enterpreneurship from all semesters formed cummulative grade point (indeks prestasi kumulatif/IPK). Only students with sufficient pre clinic grade could enter medical profession programme.

Clinical training strategies including apprenticeship in day clinic, emergency room,

ward, and operation room, night shift, morning reports, bed side teaching, clinical tutorial, journal reading, literature review and case presentation. Assessment as day to day performance in managing the case and the patients observed by clinician as clinical trainer, and formal assessment in the end of rotation in the form of written assessment, skill test and case test. Progress test is an assignment which consist of all subjects, in level of understanding and competencies expected for graduate medical doctor. This test is taken through out medical education to evaluate the growth of knowledge in medical student.[1] Prior academic performance was said to be the best predictor of subsequent academic performance,[2] thus medical profession students with good pre clinic grade point supposed to have good performance in academic assessment in their clinical training periods. Progress test for medical profession students in the form of computer based test could be seen as one academic assessment in clinical training periods that supposed to show that correlation.[1] Further, performance in progress test taken in the clinical training periods supposed to predict their likelihood to pass national examination computer based test.

Clinical training in teaching hospital aim to transfer basic clinical skills and giving students the foundation for clinical practice. The further their study in clinical rotation, the deeper and more practical their understanding should be. In this deduction, it is expected that the longer the students went into their clinical rotation, the better their progress test result. This study which evaluate the effect of pre clinic grade point and clinic rotation periods to progress test result is aimed to verify those presumption.

METHODS

In the beginning of semester, all medical profession student was gathered in Faculty of Medicine UNISMA to undergo progress test. As one way to prepare the student for computer based test national examination, this progress test was also using computer based test. The test was designed by Medical Education Unit Faculty of Medicine UNISMA. The questions were comprised from regional national examination try outs question distributed by Association of Indonesian Medical Faculty region V.

The process of developing the question set was as follow. First, every medical faculty must have one item bank administrator (IBA). IBA from all medical faculty then were trained in how to make a good test question and how to organize it. Next, in their own medical faculty, IBA trained lecturers and clinician to make test questions based on their expertise and specialities. Regional administrator then assigns IBA in each medical faculty to collect questions. The assignment is divided according to organ system and study discipline, each medical faculty assigned to different organ system or study discipline. Then Association of Indonesian Medical Faculty region V conducted a review meeting attended by expert and specialist representative from all medical faculty. Regional administrator organised the preparation of the review meeting so that specialists / experts from all fields are present. In review meeting, questions were examined by experts in matching fields in their congruence with the topic / field requested, vignette quality, options correctness, and other standards as guided by National Committee of National Examination. Regional administrator will collect corrected and accepted questions, then submit it to National Committee of National Examination according their request. Question that were exempted then distributed to all medical faculty to be used as try out test questions. Faculty of Medicine UNISMA also use this set of questions for progress test. Therefore this progress test questions quality is as closely as possible with national examination.

Students of medical profession programme Faculty of Medicine UNISMA were 135 while the capacity of the computer laboratorium was only 70 personal computer, so the test was conducted in three separated sessions. In order to prevent cheating and guessing, Medical Education Unit prepare three sets of test

questions. The software used in administrating and delivering the test was siPENA software developed by National Committee of National Examination and distributed by Association of Indonesian Medical Faculty region V. Item analysis provided by the software shows that all three sets of test have similar reliability, difficulty and discrimination index.

The mark was calculated based on total number of correct answers. There is no penalty for wrong answers. These marks then was analyzed on its association with the students grade (Indeks Prestasi Kumulatif / IPK) when graduate from pre clinic programme and how long the students has been in their clinical rotations. The students grades were grouped into 2,50 – 2,74 , 2,75 – 2,99, and more than 3,00 while the periods of clinical rotations were grouped into 6 months, 12 months, 18 months and 24 months.

The requirement for entrance to medical profession programme Faculty of Medicine UNISMA are graduated from medical bachelor programme Faculty of Medicine UNISMA with grade point of minimal 2,50 in 14 semesters or less. So the lowest group was set in 2,50, while because about 50-60% bachelor graduate have grade point of 3,00 or more so the highest group were set in 3,00.

Medical profession programme Faculty of Medicine UNISMA consist of 40 credit semester, which is taken in 109 weeks. Internal medicine, Surgery, OBGYN, Pediatric and Public Health are for ten weeks; ENT, Ophthalmology, Neurology, Radiology, Psychiatry, Physiatry, Forensic and Pharmacy are for five weeks and Anesthesiology and Dentistry for three weeks. First set of clinical rotation usually consist of Internal medicine, Surgery, Neurology or Pharmacy. The group of 6 months comes from this set of clinical rotation. After finishing those laboratories, come OBGYN, Paediatric, ENT and Ophthalmology. The group of 12 months come from this stage. The rest laboratories are randomly assigned with Physiatry and Public Health are in the very end of rotation. The group of 18 and 24 months come from this remaining rotation.

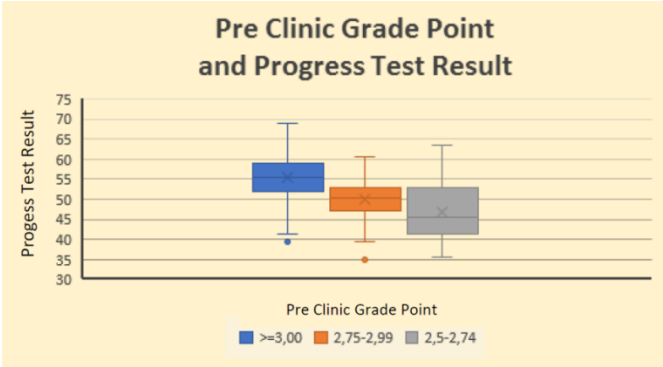
The data then underwent analyze of distribution and homogenity. After the data was declared of normal distribution and homogen, it was assigned to ANOVA and continued with Tukey HSD and Pearson correlation to evaluate significant difference and association between progress test result with pre clinic grade point and periods of clinical rotation.

RESULTS

From 135 medical profession students, only one person passed the cut off mark of national examination computer based test which is 66 or 68 mark. The overall mean score is 52,19. Mean score according to pre clinic grade point is shown in Table 1 and Graphic 1.

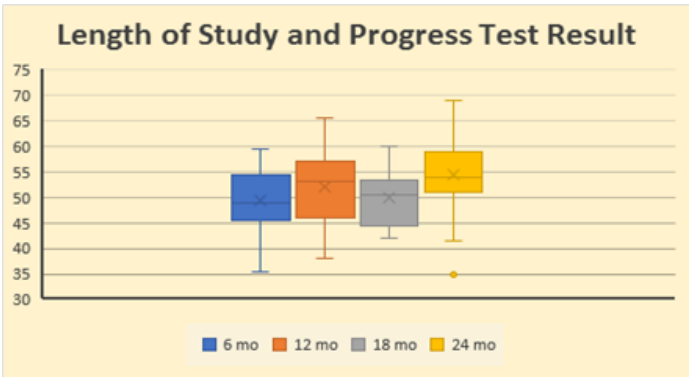
Table 1. Pre Clinic Grade Point and Progress Test Result

Pre Clinic Grade Point	N	Mean Progress Test Score
>=3,00	66	55,33 ± 5,71
2,75-2,99	48	50,16 ± 4,88
2,5-2,74	21	46,98 ± 7,85



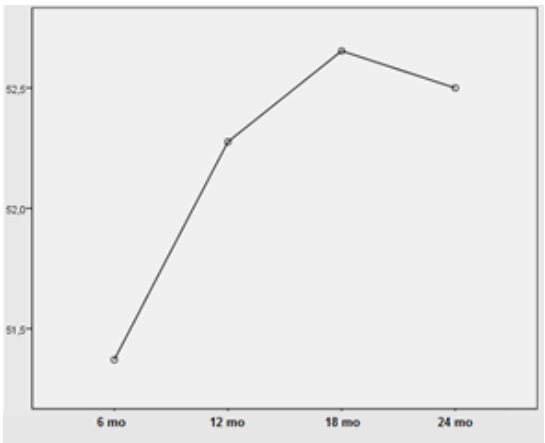
Graphic 1. Pre Clinic Grade Point and Progress Test Result

Statistic analysis using ANOVA followed by Tukey HSD showed no significant difference of progress test results from each group of pre clinic grade point with p value in range from 0,8 to 0,1. Pearson correlation even showed negative correlation with r= -0,007 which means the better the pre clinic grade point the worse progress test result, though in very low significance of p=0,934.



Graphic 2. Clinical Study Periods (as length of study) and Progress Test Result

Graphic 2 and Graphic 3 showed progress test result according to length of clinical study periods / clinical rotation. There are 31 students in 6 months group, with mean score 49,41 ± 6,1; 38 students in 12 months group, with mean score 52,06 ± 7,1; 13 students in 18 months group, with mean score 49,88 ± 5,71 and 53 students in 24 months group with mean score 54,47 ± 6,09.



Graphic 3. Clinical Study Periods and Progress Test Result

Though the graphic of mean score showing trend of better result in longer study period, statistic analysis using ANOVA followed by Tukey HSD showed no significant difference with p value in range from 0,8 to 1,0 while Pearson correlation showed positive correlation with r=0,059 with low significancy in p=0,495.

DISCUSSION

This study found that there are no significant difference in progress test results from different pre clinic grade point and that there is no correlation between pre clinic grade point and progress test results. This finding contradict other studies that found that prior academic performance is the best predictor of subsequent academic performance.2-5.

This contradiction could means that there are other factors influencing academic performance other than previous academic performance. There are non-cognitive factors like personality and learning styles, and demographic factors such as sex and ethnicity that were not evaluated in this study. Study by Shawwa *et al*[6]in Saudi Arabia found trends that students with better academic performance reported that they enjoy studying, prefer to study alone in silence and with no interruptions, and studied for longer hours during the weekend. They also tens to have particular style in studying like highlighting and skimming or reading before attempting to memorize the material, even to favor a certain posture or body position while studying. This is supported by study in Malaysia [7] which found that favoring particular place for reading have significant effects on the students' performance, although this study also found that demographic factors like gender or marital status do not have significant effect in academic performance. In order to increase the likelihood of medical profession students to pass national examination, futher research in the other factors is important.

This study also found no significant difference between students who just enter the clinical rotation with students who have been in the rotation for quite long time or almost finished it. This result is in concord with McManus *et al*[8,9]that found that success in the final examination was not related to a student's clinical experiences. Again, that study stated that learning styles is important.

Learning in hospital environment is different from pre clinic period. In pre clinic the lessons is structured with fixed schedule while in hospital its mostly of self-directed learning. Students need some adjustment to this change so they can be an effective hospital learners.[10]This study result give an impression that the students lack of ability in learning from clinical training, therefore, training of learning to learn in a hospital is needed. Study by Carrr *et al*[4] stated that junior doctors sometimes feel not sufficiently prepared in time management, aspects of prescribing and complex practical procedures.

McManus *et al* [8,9] found that strategic or deep learning style is related with success in examination. Deep learning process include identify general principles, integrate material across couses, and relate ideas to evidence. This learning style is motivated by interest in subject, vocational relevance and personal understanding. Strategic style is motivated to achieve high grades, to compete with other and to be succesful so in process this style use techniques that achieve highest grades resulting in patchy and variable understanding. To equip students with 'survival skills" as self-directed hospital learners, understanding and training of this two kinds of learning style is important so they can graduate from syllabus-boundness surface learning style they might be develop in pre clinic.

CONCLUSION

Taken this study result into consideration, Faculty of Medicine UNISMA needs to intensify national examination preparation programme for students who have finished all their clinical rotation. Before entering this program students need to be evaluated in factors contributing to

their academic performance so the program organizer and peer mentors could develop specific approach to address problems and increase the effectiveness of the program. Furthermore, this result should be communicated to clinician in teaching hospitals and there should be a coordinated effort in implementing quest of national examination to clinical training.

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ORIGINAL ARTICLE

THE EFFECT OF TOMATE JUICE ON TRIGLISERIDA LEVELS OF MALE WHITE RATS INDUCED BY ALLOXAN

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ABSTRACT

Background: Tomato juice is believed to affect triglyceride levels in the blood because it contains lycopene. This study aims to determine the effect of tomato juice (*Solanum lycopersicum*) on blood triglyceride levels in the wistar strain of male *Rattus norvegicus* induced by alloxan**.**

Methods: 24 were divided into 3 groups, (1) Group K (-) experimental animals without treatment, (2) Group K (+) experimental animals induced by alloxan 150 mg /kg BW (3) Treatment group K (P) animals tried alloxan induced 150 mg / kg and got 1.75 ml / head of tomato juice. **Results:** There was a significant difference in mean triglyceride levels between groups K (-) and group K (+). This indicates that the induction of alloxan increases blood triglyceride levels. There were significant differences in the mean triglyceride levels between the K (+) and K (P) groups because tomato juice contained lycopene which could reduce triglyceride synthesis.

Conclusions: Tomato juice (*Solanum lycopersicum*) reduced wistar strain male Rattus novergicus triglyceride levels induced by alloxan.

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INTRODUCTION

Diabetes Mellitus is a chronic disease characterized by an increase in blood sugar levels (hyperglycemia) in the blood as a result of a disruption in the metabolic system in the body[1]. From several epidemiological studies in Indonesia conducted by diabetes centers, around the 1980s,the prevalence of diabetes mellitus at the age of 15 years and over is 1.5-2.3% with a lower prevalence in rural areas than in urban areas [2]

Hyperglycemia is a condition of high blood sugar (glucose) levels in the blood. The underlying thing is insulin deficiency, relative or absolute. Hyperglycemia itself is caused by decreased insulin secretion. In patients with uncontrolled diabetes mellitus, it is often accompanied by disorders of lipid metabolism which have an impact on the occurrence of dyslipidemia [3].

Dyslipidemia is defined as a lipid metabolism disorder characterized by an increase or decrease in the lipid fraction in plasma. The main lipid fraction abnormalities are an increase in total cholesterol, LDL cholesterol, triglycerides, and an increased risk of coronary heart disease[4].

Triglycerides are esters of glycerol with fatty acids. Triglycerides are a form of lipids in the body that serve as a source of energy. When the body needs energy, the lipase enzyme in fat cells will break down triglycerides into fatty acids and glycerol and release them into the blood vessels. Food regulation has an effective effect on reducing triglyceride levels in the blood. The US National Health and Nutrition Examination Survey found the influence of carotenoid-rich foods on triglyceride levels in the blood in people with diabetes. One of the foods that has been linked to a decrease in blood triglyceride levels is tomatoes [5].

Tomato (*Solanum lycopersicum*) is a plant that is well known by Indonesian people. However, its use is limited to as a salad and an additional ingredient in cooking. Tomato processing increases the bioavailability and increases the absorption of the active compounds contained therein. One of the compounds in tomatoes that functions to reduce triglycerides is lycopene. Because lycopene is an antioxidant to catch free radicals in the body. ([4;6])

Alloxan is a compound used to induce damage to the pancreas through increased formation of Species Oxygen Radicals (ROS), resulting in diabetes mellitus. Alloxan induction results in lipolysis and triggers hypertriglyceridemia. Alloxan can be given intravenously, intraperitoneally, or subcutaneously in animal experiments. Alloxan induction of 120-150 mg / kgBW can lead to diabetes mellitus in experimental animals [7,]

METHODS

This research is an experimental study post test only control group design. Twenty four male Wistar rats were divided into 3 groups, (1) Group K (-) experimental animals without treatment, (2) Group K (+), the experimental animal was induced by 150 mg / kg BW of alloxan intraperitoneal (3) The treatment group K (P) animals were induced by 150 mg / kg BW of alloxan intrraperitoneal and 3 days after induction, tomato juice was given 1.75 ml /mouseintragastricfor 14 days.

Alloxan induction

Alloxan monohydrate injection witha dose of 23.22 mg which is dissolved intoNaCL 0.9% intraperitoneally. Solutionalloxan monohydrate is injected only oncethen waited for 3 days forreach a hyperglikemia state

Tomato Juice Making

Tomatoes weighing 200 grams, washed, cut into small pieces, blended for about 5 minutes and filtered using a filter until 100 ml of tomato juice is obtained and weighed to 97.4 grams, so that 1 gram of tomato juice is equal to 1.027 ml.

Measure Triglyceride Levels

The method of checking triglycerides is the colorimetric enzymatic method of GPO-PAP (Glycerol Peroxidase Phosphate Acid), triglycerides will be enzymatically hydrolyzed to glycerol and free acids with special lipases will form a color complex that can be measured using a spectophotometer. [9]

RESULTS

In this study, the results showed that the induction of an increase in the mean blood glucose level of the K (+) group was 401.5 mg / dl compared to the K (-) group of experimental animals without treatment of 195.7 mg / dl. This indicates that there has been a decrease in insulin secretion which results in hyperglycemia.

Measurement of triglyceride levels can be seen in table 1

Table 1. The results of the examination of triglyceride levels

NO	Triglyceride level (mg/dl)		
	K(-)	K(+)	K(P)
1	39	86	66
2	60	73	68
3	39	91	59
4	32	74	21
5	56	62	36
6	23	75	40
7	39	77	58
8	48	53	26
mean	42	73,88	46,75

Note:
K (-) : Group of experimental animals without treatment
K (+): Alloxan induced experimental animal group
K (P): Group of experimental animals induced by alloxan and receiving tomato juice (Solanum lycopersicum)

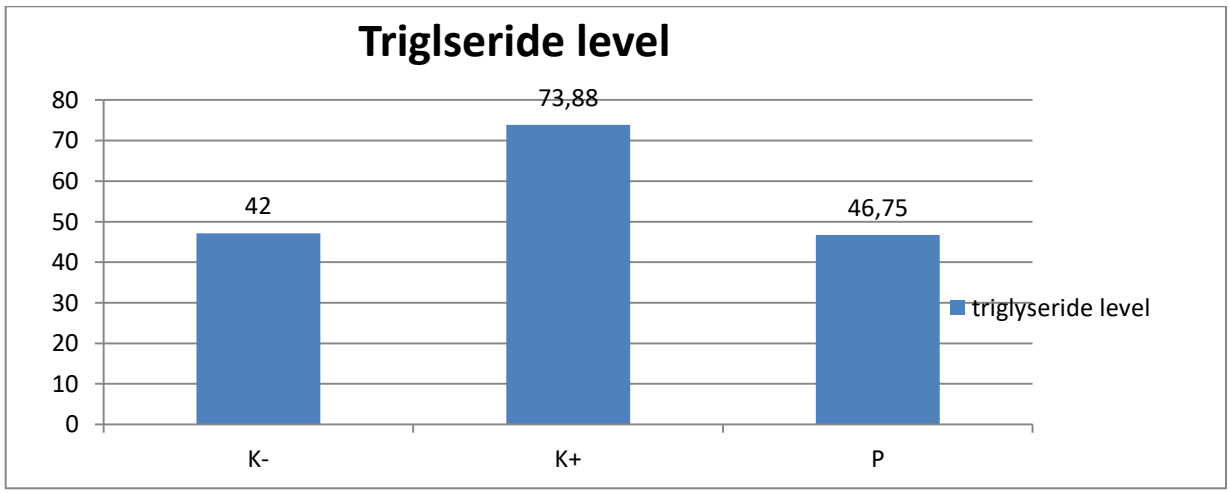

Figure 1. Average Triglyceride Levels of experimental animals

Note:
K (-) : Group of experimental animals without treatment
K (+): Alloxan induced experimental animal group
K (P): Group of experimental animals induced by alloxan and receiving tomato juice (*Solanum lycopersicum*)

From these data, it can be seen that there was an increase in the mean serum triglyceride levels in the experimental animal group which was induced by alloxan, when compared to experimental animals without treatment. A decrease in the mean serum triglyceride levels occurred in the experimental animal group which was induced by alloxan and tomato juice (Solanum lycopersicum), when compared to the experimental animal group which was induced by alloxan.

Furthermore, the analysis of normality test data was carried out and continued with the homogeneity test which showed that the triglyceride levels between groups were normal and homogeneous. Next, the test was carried out to determine whether there were differences between groups using the One-Way Anova test.

And the ANOVA test results showed a significant difference and was followed by the Poshoc test.

Table 2 The Results of Post Hoc Test with LSD Test

Group	Group	p value
K(-)	K(+)	0,001
	K(P)	0,52
K(+)	K(P)	0,001

Based on Table 2 it was found that there was a significant difference in triglyceride levels between the experimental animal group without K (-) treatment and the experimental animal group induced by alloxan with K (+) and there was a significant difference in triglyceride levels between the experimental animal group induced by alloxan K (+) and experimental animal group induced by alloxan and tomato juice K (P) (*Solanum lycopersicum*). There was no significant difference in triglyceride levels in the experimental animal group without K (-) treatment with the experimental animal groupinduced by alloxan and tomato juice K (P) *(Solanum lycopersicum*)**.**

DISCUSSION

Alloxan induction will increasing lipid profile, in this study, reseacher only focused on triglyseride level because it is easier for changes to occur with changes in diet.In this study the alloxan-induced group showed an increase in serum triglyceride levels in experimental animals. This can be seen in the results of data analysis which show that there is a significant difference in triglycerides (p = 0.00) between the experimental animal group without K (-) treatment (42 mg / dL) and the experimental animal group induced by alloxan K (+) (73.88 mg / dL).

Alloxan induction causes an increase in ROS resulting in damage to pancreatic β cells, so that insulin production will decrease and hyperglycemia occurs, this condition triggers lipolysis so that fatty acids in the blood increase. Lipolysis increases the formation of free fatty acids. Free fatty acids will enter the fat tissue or muscle cells by penetrating the endothelium and then re-oxidizing or being converted back into triglycerides [10]. This situation causes VLDL, LDL and triglycerides in the blood to increase (11).

From the results of this study, it was concluded that there was a significant difference between the mean triglyceride levels in the experimental animal group induced by alloxan K (+) with a level of 73.88 mg / dL and the experimental animal group induced by alloxan and tomato juice K (P) with a level of 46 , 75 mg / dL

This study used tomato juice (*Solanum lycopersicum*) because tomato juice (*Solanum lycopersicum*) is known to play a role in reducing triglyceride levels in the blood. Tomato (*Solanum lycopersicum*) is a type of vegetable that contains various kinds of antioxidants, including beta-carotene, vitamins C and E, anthocyanins and lycopene. Lycopene as a potential antioxidant can reduce oxidative stress by providing defense against free radicals and can also inhibit the increase in ROS so that it can prevent hypertriglyceridemia (11).

Giving tomato juice (*Solanum lycopersicum*) which contains lycopene which is a group of carotenoids such as beta-carotene which is responsible for the red color of tomatoes. In the body, lycopene can protect against diseases such as prostate cancer as well as several other types of cancer and coronary heart disease. The ability of lycopene in absorbing single oxygen is twice as good as beta carotene and ten times better than alpha-tocopherol [6, 11]

Tomatoes contain an oxidized fatty acid called 3-oxo-ODA which is an isomer of 9-oxo-oda. 13-oxo-oda is a strong agonist for Peroxisome Proliferator Activated Receptor Alpha (PPARα). PPARα serves as a major regulator for fatty acid oxidation. 13-oxo-oda will activate PPARα causing increased fatty acid oxidation. The increase in fatty acid oxidation will cause a decrease in triglyceride levels in the blood. The activation of PPARα will also lead to an increase in triglyceride levels [12]. In addition, PPARα functions as a regulator of energy balance (lipid

metabolism), especially as a regulator of fatty acid oxidation [13].

Tomatoes that are processed in the form of juice increase their bioavailability, so that they are easier to digest and absorb the active compounds. Fresh tomatoes contain 9-oxo-ODA, processing tomatoes into tomato juice converts 9-oxo-ODA to 13-oxo-ODA. 9-oxo-ODA which is a 13-oxo-ODA isomer, but 13-oxo-ODA is a more potent PPARα agonist than 9-oxo-ODA. PPARα is a member of the receptor family that functions as a regulator of the balance of energy (fat) metabolism. The ligands can be fatty acids or their derivatives, and 13-oxo-ODA. The bond between the ligand and PPARα can activate PPARα and result in a decrease in the concentration of triglycerides in plasma and in tissues [12], so it can be concluded that triglyceride levels in the blood can decrease due to the presence of 9-oxo-ODA found in tomatoes. [12;13, 14.]

The activated PPARα will increase the oxidation of fatty acids in the tissue, so that the fatty acids will be oxidized, this will cause a decrease in the accumulation of triglycerides in the tissue. The activated PPARα will increase the expression of the lipoprotein lipase (LPL) gene so that the lipoproteins that undergo lipolysis will ncrease [12, 15]

From the results of the above research, it can be concluded that giving tomato juice (Solanum lycopersicum) can significantly reduce triglyceride levels in male white rats (*Rattus norvegicus)* Wistar strain induced by alloxan.

CONCLUSION

Alloxan induction can increase serum triglyceride levels of male white rats (Rattus Norvegicus) and administration of tomato juice (Solanum lycopersicum) can reduce serum triglyceride levels of male white rats (Rattus novergicus) wistar strain induced by alloxan.

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REVIEW ARTICLE

THE ROLE OF TEA TREE OIL AS A SKIN ANTIMICROBIAL : A LITERATURE STUDY

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ABSTRACT

Backgroud: Skin disease due to microorganism infection are still widely found in community. The infections can be caused by bacteria, viruses, fungi, and parasite. Tea tree oil often used as a herbal medicine in the treatment of skin diseases due to microorganisms. This literature study is conducted to review the role of tea tree oil as an antimicrobial in skin infections.

Methods: Fifteen indexed journals published from 2015 to 2020 about tea tree oil and skin infections, were included. From 15 journals, 9 journals discuss antibacterial activity of tea tree oil, 2 journals discuss antiviral activity, 9 journals discuss antifungal activity, and 1 journal discusses antiparasitic activity. All journals state that tea tree oil has an antimicrobial effect on microorganisms that cause skin infections.

Results: From 9 journals, it was found that *A. baumanni*, *P. aeruginosa*, and *C. acnes* were the most sensitive bacteria to tea tree oil in terms of MIC and *S. epidermidis* was the most sensitive bacteria, seen from their inhibition zone. Eight journals state variations with significant differences in the activity of tea tree oil as an anti-fungal. Tea tree oil has stronger antibacterial activity than antifungal activity. It also has antiviral activity against HSV and antiparasitic on *S. scabiei*.

Conclusion: The conclusion of this study is that tea tree oil has antimicrobial activity against microorganisms that cause skin disease, including bacteria, viruses, fungi, and parasite.

Medical and Health Science Journal

INTRODUCTION

Skin is the largest organ in the human body with a surface area of 2 m^2. Skin has 2 main functional layers, epidermis and dermis, and underneath there is hypodermis or subcutis layer. As the outermost layer of the human body, the most important function of the skin is as a mechanical barrier for first defense. The skin is home to commensal microorganisms that will play a role in preventing invasion from foreign pathogens. When the barrier is damaged by trauma or when the balance between commensal microorganisms and pathogens is disturbed, skin disease or even systemic disease may occur. The entry of pathogens that penetrate the skin will trigger an immunological reaction from the body.

Microorganisms that enter through the skin are associated with the pathophysiology of dermatological infectious diseases. Wound infections are generally caused by the microorganisms *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli*. *Staphylococcus aureus* itself is commonly found in atopic dermatitis. Another example is the fungus *Malassezia* which causes many skin conditions pityriasis versicolor, seborrheic dermatitis, atopic dermatitis, and psoriasis (McLoone, Warnock & Fyfe, 2016). Apart from bacteria and fungi, viruses can also cause skin infections such as molluscum contagiosum which is caused by the *Molluscum contagiosum virus* (MCV) from the family *Poxviridae*.[1]

Globally, skin problems and diseases are common, and because of their visibility, often result in severe distress and stigma for sufferers. Therefore, many dermatological therapies have been developed, both herbal, conventional (chemical) and technological therapies. One of the many herbal therapies used for skin infections is tea tree oil *(Melaleuca* oil*)*. The content of tea tree oil is a mixture of components such as monoterpenes, sesquiterpenes and alcohol that contribute to various activities (analgesic, antiviral, antibacterial, antifungal, antiparasitic, anti-inflammatory, antioxidant, and anticancer). Tea tree oil has a tendency to be very minimal resistant and can overcome the development of resistance to conventional drugs in skin infections caused by microorganisms.[2]

Tea tree oil is an essential oil obtained by steam distillation of the native Australian plant *Melaleuca alternifolia*. Tea tree oil has been used for centuries by Australians as medicine, especially for wound care in 1920.[3] Long-term use of herbal therapy tea tree oil has a lower incidence of side effects, irritation or allergic reactions when compared to conventional therapy. Tea tree oil in topical use will have the added advantage of being cost effective and easy to use.[4] Seeing the potential and advantages of tea tree oil therapy, the development of this therapy needs to be improved in both the cultivation and pharmacology sectors. Therefore, the authors intend to review the role of tea tree oil as an antimicrobial in skin infections.

METHODS

The research design used is descriptive research. The method used is literature study to review the role of tea tree oil as skin antimicrobial. Database searched was Google Scholar. Search terms used were ‘tea tree oil as antibacteria, tea tree oil as antivirus, tea tree oil as antifungi, tea tree oil as antiparasit, role of tea tree oil as antimicroba, tea tree oil as antimicroba in vitro’. Limitations included ‘published between 2015-2020’ and ‘indexed by Scimago or SINTA (Science and Technology Index)’. This research was conducted in Surabaya from May to September 2020. This research get approval from the Ethics Commission for Health Research, Faculty of Medicine, Hang Tuah University.

RESULT

The results of the study are taken from 15 international journals indexed by Scimago about the role of tea tree oil as a skin antimicrobial. Nine journals discuss the activity of tea tree oil against bacteria, two journals discuss the activity of tea tree oil against virus, eight journals discuss the activity of tea tree oil against fungi, and one journal discuss the activity of tea tree oil against parasite.

Antibacterial activity

Research in the journal states the antimicrobial effect seen from the minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC), imaging through electron microscopy, and the zone of inhibition. The bacteria studied in the journal include *Staphylococcus aureus, Staphylococcus epidermidis, Cutibacterium acnes, Pseudomonas aeruginosa, Bacillus subtilis, Acinetobacter baumannii, Streptococcus pyogenes, Klebsiella pneumoniae,* and various other gram-positive and negative bacteria. The bacteria were cultured on Mueller-Hinton agar and given tea tree oil with different concentrations. The method used is the liquid microdilution method. After that, the bacteria will be observed for MIC, microscopic image, and zone of inhibition to determine the antimicrobial effect of tea tree oil.

Table 1 MIC of *S. aureus* and *P. aeruginosa* by 10 types of tea tree oil products [5]

Product	*S. aureus*	*P. aeruginosa*
Tea tree oil 1	2.5	2
Tea tree oil 2	0.5	0.25
Tea tree oil 3	1	2
Tea tree oil 4	0.5	0.5
Tea tree oil 5	0.75	1.5
Tea tree oil 6	0.5	0.5
Tea tree oil 7	2.5	2
Tea tree oil 8	2	2
Tea tree oil 9	0.5	0.25
Tea tree oil 10	0.75	1

Table 2 The number of *P. aeruginosa* that are inhibited by tea tree oil [6]

Tea tree oil	0.03%	0.06%	0.125%	0.25%	0.5%	1%	2%
Inhibited bacteria	0	0	0	4	2	7	7

Table 3 MIC and MBC of tea tree oil and rosemary oil against acne-causing bacteria [7]

Bacteria	Tea tree oil		Rosemary oil	
	MIC	MBC	MIC	MBC
S. aureus	0.78	0.78	1.56	1.56
S. epidermidis	0.78	0.78	1.56	1.56
C. acnes	0.39	0.39	0.39	0.39

Table 4 MIC of essential oil against bacteria [8]

Bacteria	**Basil**	**Oregano**	**Tea tree**	**Thyme**	**Chamomile**
A. baumanni	0.5-1.25	0.25-0.37	0.12-0.25	0.25-.0.5	>4
K. pneumoniae	1.5-3	1	0.5-0.75	0.5-1.5	>4
P. aeruginosa	>4	2-4	1-1.5	4	>4

Table 5 MIC of essential oil against *S. epidermidis* and *P. acnes* [9]

Essential Oil	***S. epidermidis***	***P. acnes***
Oregano	0.67	0.34
Thyme	1.3	0.65
Lemongrass	1.22	1.22
Tea tree	1.27	1.28
Lavender	2.52	2.52
Mentha	5.28	2.6
Chamomile	6.22	3.18

Ziółkowska-Klinkosz et al. conducted a study on 193 anaerobic bacteria which were given tea tree oil and the result was that anaerobic bacteria were more sensitive than gram negative. [10]

Li et al conducted a study that showed normal cell growth in control media and bacterial growth treated with tea tree oil were viewed using a microscope. The results for normal cell growth showed normal characteristics of cocci bacteria such as cell walls and cell

membranes that were attached to the peptidoglycan layer and normal cytoplasmic membrane. In addition, the cytoplasm appears to have a homogeneous electron density. Meanwhile, the bacteria that were given tea tree oil showed a clear morphological change in which the density of the cytoplasm became heterogeneous and some of them were seen leaving the cell. The separate distance between the cytoplasmic membrane and the cell wall is also seen. [11]

Table 6 Zone of inhibition of tea tree oil against bacteria (in mm)

	S. aureus	***S. epidermidis***	***C. acnes***	***P. acnes***	***S. pyogenes***
Esmael et al [7]	15.5	21.02	20.85		
Taleb et al [9]		9 – 15		9 – 18	
Ramadan et al [12]	19.2 ± 0.44	21.7 ± 0.58			19.2 ± 0.19

Antiviral activity

The viruses tested in this study were herpes simplex viruses (HSV) 1 and 2. The method used was to use vero cells that were infected with HSV and given tea tree oil. Tea tree oil's antiviral activity can be seen from its PFU (plaque-forming unit) and viral titer. Brun showed the results of his research where after being exposed to tea tree oil, the PFU of the HSV 1 was reduced compared to before.[5]

Table 7 HSV titers before and after being given tea tree oil [12]

	Pre-test	*Post-test*	Reduction
HSV 1	7.5	6.32	15.6%
HSV 2	7.66	6.11	20.23%

Antifungal activity

Eight journals discussed the activity of tea tree oil as an antifungal. All of them stated that tea tree oil acts as an antifungal in terms of MIC, MFC (minimum fungicidal inhibition), confocal features, and also the zone of inhibition. The fungi studied from 8 journals were *Candida sp., Aspergillus niger, and Trichophyton mentagrophytes*. Before being exposed to tea tree oil, the fungus is cultured in dextrose agar. The method used is the same as for bacteria, namely with liquid micro-dilution.

Table 8 MIC *C. glabrata* on 10 types of tea tree oil products [5]

Product	MIC of *C. glabrata*
Tea tree oil 1	2.5
Tea tree oil 2	1.5
Tea tree oil 3	2.5
Tea tree oil 4	1
Tea tree oil 5	2
Tea tree oil 6	0.75
Tea tree oil 7	2.5
Tea tree oil 8	2.5
Tea tree oil 9	1
Tea tree oil 10	1.5

Table 9 MIC and MFC *C. krusei* against tea tree oil and MPP [13]

	10^3 cfu/mL	10^6 cfu/mL
Tea tree oil		
MIC	0.5	1
MFC	0.5	1
MPP		
MIC	0.25	1
MFC	0.5	1

The research conducted by Francisconi showed a confocal picture of *Candida albicans* before and after being given tea tree oil. The results showed that many of the fungi that had been given tea tree oil died.[14]

Table 10 Zone of inhibition of tea tree oil against *Candida albicans* and *Trichophyton mentagrophytes*

	Candida albicans	*Trichophyton mentagrophytes*
Narang et al (1g) [15]	±38 mm	
Ramadan et al (25µg dissolved in 0.1% dimethyl sulfoxide) [12]	20.3 ± 0.44 mm	21.1 ± 0.44 mm
Patturaja and Geetha et al [16]		
250 µg/mL	14 mm	
500 µg/mL	20 mm	
1000 µg/mL	37 mm	

Antiparasitic activity

Fang et al. conducted research on S. scabiei which was given 10 types of essential oils (lavender, bitter orange, geranium¸ tea tree, clove, eucalyptus, manuka, cade, Japanese cedar, and palmarosa). This research was conducted using 2 methods, namely contact bioassays and fumigation bioassays. With the contact bioassays method, essential oils were diluted with paraffin to obtain a concentration of 1.5, 10%, then *S.scabiei* was viewed by stereomicroscope in 10, 20, 30, 40, 50, 60, 90, 120, 150, 180 minutes after exposure. tea tree oil. The result is that clove oil is the most effective essential oil where with 1% clove oil all *S.scabiei* dies in 20 minutes. Meanwhile, with tea tree oil, all *S.scabiei* died after 90 minutes of exposure to 5% tea tree oil and 30 minutes with 10% tea tree oil. The bioassays fumigation method was carried out with 100 µL of pure essential oil dripped on filter paper and then *S.scabiei* was inspected by stereomicroscope for the first 5 minutes, then every 5 minutes for 1 hour. The result is that tea tree oil is the most effective essential oil as an antiprotozoa followed by clove oil and eucalyptus oil. [17]

DISCUSSION

Based on 15 journals, it can be concluded that tea tree oil has antimicrobial activity in skin infections, both antibacterial, anti-fungal, antiviral, and also antiparasitic activities. The level of effectiveness of tea tree oil is different for

each type of microbe seen from MIC, MBC, MFC, virus titer number, zone of inhibition, and survival time. Each type of bacteria has a different sensitivity to tea tree oil. Seven of the nine journals comparing the MICs of bacteria exposed to tea tree oil revealed a variation of the MIC of 0.12% to 2.5%. The most sensitive bacteria are *A. baumanni* with an MIC of 0.12%[8], followed by *P. aeruginosa* with an MIC of 0.25% [5,6], *C acnes* with an MIC of 0.39% [7], *S. aureus* with an MIC of 0.5% [5], and *S. epidermidis* with an MIC of 0.78% (Esmael et al. , 2020). Of the 193 anaerobic bacteria that were exposed to tea tree oil, gram-positive anaerobic bacteria are more sensitive than gram-negative ones [10]. Judging from the microscopic image, the bacteria exposed to tea tree oil showed clear morphological changes such as cytoplasmic density changing to heterogeneous and some visible out of the cell, as well as visible distances between the cytoplasmic membrane and the cell wall.[11] Three journals that looked at the zone of inhibition as a parameter of tea tree oil activity stated that *S. epidermidis* has the most extensive inhibition zone, namely 15 - 21.7 mm compared to other bacteria with the same tea tree oil concentration. [7,9,12]

Two journals discussing the antiviral activity of tea tree oil against HSV stated that tea tree oil can inhibit and kill the growth of the virus which is seen from the PFU and its titer virus. [5,12] HSV 2 was found to be more sensitive to HSV 1 seen from the decrease in viral titer before and after exposure to tea tree oil with a decrease of 15.6% for HSV 1 and 20.23% for HSV 2. [12]

Five of the eight journals compared the fungal MIC to look at the antifungal activity of tea tree oil. The five journals states that the variation in MIC was quite significant, namely from 0.06% to 8.96% for *Candida sp*. When compared with bacterial MIC, tea tree oil activity is more effective as an antibacterial than antifungal.[5] In addition, other essential oils that are more effective for *Candida* were also found, namely MPP (mentha of pancalieri) oil. [13] The confocal image also shows the presence of antifungal activity of tea tree oil where a red color is seen which indicates microbial death.[14] Three of the eight journals that observed their zone of inhibition stated that there was anti-fungal activity of tea tree oil with different areas depending on the concentration of tea tree oil given. [12,15,16]

The journal that discusses the antiparasitic activity of tea tree oil against *S.scabiei* states that its effectiveness is seen from the survival time of *S.scabiei*. With different methods, the results found are different, namely that clove oil was more sensitive than tea tree oil with the contact bioassays method, while with the fumigation bioassays method, it was found that tea tree oil was the most sensitive followed by clove oil. [17]

CONCLUSION

Tea tree oil is an essential oil that can be used as a treatment for skin infections caused by microorganisms. The antimicrobial activity of tea tree oil is supported by its composition, namely terpinen-4-ol, γ-terpinen, 1,8-cineol, α-terpinen, α-terpineol, p-cymen, and α-pinen which are lipophilic. Tea tree oil that enters the cells of microorganisms will result in inhibition of metabolism and cell death of microorganisms. The death of microorganisms can help the healing process of wound infections caused by microorganisms. Based on the results of the discussion of 15 journals that examined the effects of tea tree oil on microorganisms in vitro, it was concluded that tea tree oil has antimicrobial activity against microorganisms that cause skin infections. Nine journals stated antibacterial activity in terms of MIC (minimum inhibitory concentration), MBC (minimum bactericidal concentration), microscopic image, and zone of inhibition. From the nine journals, it was found that the most sensitive bacteria were A. baumanii and P. aeruginosa. Two journals stated antiviral activity against HSV 1 and HSV 2 in terms of PFU (plaque-forming unit) and viral titer where it was found that HSV 2 was more sensitive to tea tree oil. Eight journals stated antifungal activity in terms of MIC, MFC (minimum fungicidal inhibition), confocal features, and zone of inhibition. The eight journals stated significant variations and differences in the anti-fungal activity of tea tree oil against candida sp. One

journal stated antiparasitic activity against S. scaibei in terms of survival time.

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REVIWE ARTICLE

COMPARISON OF TRIPLE DRUG THERAPY VERSUS DOUBLE DRUG THERAPY FOR LYMPHATIC FILARIASIS : A SYSTEMATIC REVIEW

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ABSTRACT

Backgroud: Lymphatic filariasis is a parasitic infection caused by nematodes such as filaria Wuchereria bancrofti, Brugia malayi, and Brugia timori. These parasites can be transmitted through mosquito bites such as several species of mosquitoes, particularly Anopheles, Aedes, Culex, and Mansonia with geographical variations in the dominant vector identity. The main strategy used consists of community-wide mass drug administration (MDA) for the entire population at risk to stop disease transmission and prevent infectious morbidity. WHO recommends the use of annual medication in combination with the triple drug ivermectin therapy. Objective: To compare DEC and albendazole (IDA) versus the two drugs albendazole and diethycarbamazine or albendazole and ivermectin therapy.

Methods: The literature search was carried out independently by the researcher using the Sciencedirect, Pubmed, and Cochrane online databases without limiting the type of study or the year of publication. The keywords used in this study were combined with the Boolean operator, namely "AND" namely ((((Lymphatic filariasis) AND (albendazole)) AND (diethylcarbamazine)) AND (ivermectin)) AND (compare).

Results: where triple drug therapy was significantly better in reducing and clearing microfilariae and worm nests in patients with lymphatic filariasis compared to two drug therapy alone. However, side effects occur more frequently in the combination of three therapies. The average side effects were low, such as headaches, joint pain, fatigue, and nausea.

Conclusion: although it has relatively low side effects that occur in three drug combinations rather than two drug combination therapy, triple therapy combination therapy is more effective than two drug therapy in treating lymphatic filariasis disease.

Medical and Health Science Journal

PRELIMINARY

Lymphatic filariasis is a parasitic infection caused by nematodes such as filaria Wuchereria bancrofti, Brugia malayi, and Brugia timori. Wuchereria bancrofti is responsible for more than 90% of infections that occur in tropical Asia, Africa, the Pacific islands, and in parts of the Caribbean and South America(1)(2). These parasites can be transmitted through mosquito bites such as several species of mosquitoes, particularly Anopheles, Aedes, Culex, and Mansonia with geographical variations in the dominant vector identity. Long-term infections can cause lymphatic system damage, characterized by severe swelling of the limbs (lymphedema) and then elephantiasis or scrotal lymphedema (hydrocele)(3). Lymphatic filariasis in addition to causing lymphedema (elephantiasis) and hydrocele, this disease also causes renal pathology that manifests as chyluria, and acute dermato lymphangio adenitis which causes regular fever(4). The World Health Organization (WHO) recommends mass treatment of entire populations once a year for years. The main strategy used consists of community-wide mass drug administration (MDA) to all populations at risk to stop disease transmission and prevent infectious morbidity(5). Treatment is a combination of two drugs of albendazole and a microfilarisidal drug (antifilaria), either diethyl carbamazine (DEC) or ivermectin. Albendazole is recommended for patients when DEC or ivermectin cannot be used(6)(7). An annual, single-dose, two-drug regimen (albendazole plus diethylcarbamazine (DEC) or albendazole plus ivermectin) for at least five years (according to the reproductive age of adult worms), covering at least 65% of the total population at risk to prevent transmission(8)(9). Recently, for specific settings, WHO has recommended the use of annual treatment with the triple therapy ivermectin, DEC and albendazole (IDA) combined with the dual therapy of albendazole and diethycarbamazine or albendazole and ivermectin(10)(11). The aim of this study was to compare the therapeutic efficacy of three drug therapy versus two therapeutic measures in treating lymphatic filariasis.

TRANSMISSION

Filariasis is transmitted by female mosquitoes from several genera, including Culex, Anopheles, Mansonia, and Aedes(12). The cycle of transmission begins when an infected female mosquito bites and deposits lymphatic filariasis larvae on the skin (Fig. 1).

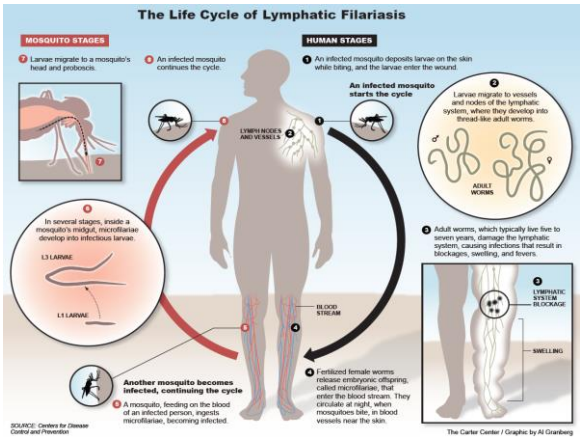

Figure 1. Life circle Lymphatic filariasis(13)

The larvae enter the bite wound and travel to the lymphatic vessels. Larvae develop for about 12 to 15 days in mosquitoes to become third stage infective larvae. The larvae enter the bite wound and travel to the lymphatic vessels. For 6 to 12 months, they become adult male and female worms in the lymph nodes, where male and female worms mate. The female worm then produces an early stage larva, called microfilariae (mf). During the 7 year life cycle, an adult female can release up to 10,000 offspring embryos (microfilariae) per day. Microfilariae (Mf) is carried by the natural lymph flow and introduced into the blood. When the human host is awake, Mf can survive permanently in the larger blood vessels. During sleep, however, they travel or migrate to the surface of the vessels, allowing them to be digested by biting mosquitoes at night. In mosquitoes, Mf undergoes several stages of molting and development. The larvae are ready to be transmitted from the carrier mosquito to humans in 10 to 12 days. Transmission in a community is influenced by several factors, namely the prevalence or number of infected people, the density of Mf in the blood of infected people, the density of carrier mosquitoes in endemic areas, characteristics that affect the growth and development of larvae and the

frequency of human contact with infected mosquitoes. Repeated mosquito bites over several months can cause lymphatic filariasis, thus indigenous people or long-term visitors living in endemic areas are at greatest risk(1)(14).

PATHOPHYSIOLOGY

In the human body, lymphatic vessels secrete circulating fluids and large molecules, such as proteins, from the extracellular spaces in almost every tissue of the body(8)(3). The lymph system is important for maintaining the correct extracellular fluid volume and clearing pathogens that have crossed the skin barrier and entered the extravascular compartment. The antigens, pathogens and invaders that ingest macrophages are transported afferently to the lymph nodes to undergo the process and uptake of additive immunity(15). After cleaning and filtering, the lymph fluid is returned to the blood vessel space. As a component of the adaptive immune system, T lymphocytes are programmed to recognize, respond to, and remember foreign antigens. The presence of a cell surface molecule known as CD4 or CD8 differentiates T lymphocytes. CD4 T lymphocytes, also called helper (Th) T cells, are productive cytokine producers(8). Cytokines are hormonal messengers in the immune system and are responsible for cell-mediated immune and allergic responses, so they are often classified as either pro-inflammatory (Th1 response) or anti-inflammatory (Th2 response). In patients with lymphatic filariasis, lymphatic vessel damage is mediated by a response to the presence of adult worms and the products released by these worms. Compounds secreted or secreted by live worms act on endothelial cells, causing lymph tissue, gradual loss of contractility of lymphatic vessels, unidirectional valve damage, and lymphangiectasis (pathological dilation of lymph vessels). Regardless of the treatment, lymph system damage can be permanent(16). Histologically, live Mf and adult worms rarely elicit an immune response. However, dead or dying Mf and adult worms are highly antigenic. Although the mechanism is not fully understood, the lymphatic filariasis antigen guarantees species survival by modulating the host immune system (Fig. 2) to support the anti-inflammatory response (Th2)(17). This response can be achieved by reducing the proinflammatory (Th1) response(17). As a result of weakening the immune system, the response to opportunistic pathogens and vaccines is severely reduced, such as tetanus toxoid, which can cause the disease to worsen, namely chronic lymphedema(18). Children born to infected mothers are more susceptible to contracting filarial infection(19)(20). In women treated with several cycles of antifilarial drugs before pregnancy, the incidence of children contracting lymphatic filariasis is reduced to less than 1%(21).). There is a hypothesis that placental antigen transfer modulates the infant's immune system, supporting the TH-2 response(17)(21).). Individual responses to the presence of adult worms and microfilariae vary as some develop clinical symptoms and others do not. The susceptibility, parasite load, and degree of cluster pathological changes in the family, suggest genetic polymorphisms play a role in lymph tissue remodeling, severity of lymphatic dysfunction, and degree of immune modulation(22).

EPIDEMIOLOGY

Classified as a tropical disease by the World Health Organization (WHO), this incurable condition affects more than 120 million people worldwide(8). Endemic disease in 73 countries, 1.1 billion people are at risk of being exposed to and contracting infectious diseases in tropical and sub-tropical regions of Asia, Africa, the western Pacific, and parts of South America and the Caribbean(2,4,23,24). In 1997, the World Health Assembly initiated a program aimed at the global elimination of lymphatic filariasis as a public health problem and by 2020 the world was clear of lymphatic filariasis based on the resolution WHA50(8)(25). The GPEFL is one of the fastest growing global public health programs in history. During the first decade, they focused on launching the Program, which included preparing guidelines based on available information, initiating programs in each WHO region where the disease is endemic and scaling up the program as quickly as possible(25)(26). Researchers have found that lymphatic filaria is associated with dermatitis, lymphedema, and elephantiasis on the limbs or

genitalia, which adversely affects personal and social life and limits work activities. By the end of 2011, 53 of 73 endemic countries had implemented mass drug administration, 12 of which had entered the surveillance stage. During 2000 to 2011, more than 3.9 billion doses of the drug were delivered to a cumulative target population of 952 million people(27). In 2011 World Health Organization (WHO) report confirms that it affects more than 120 million people living in 72 countries worldwide, and 39 African countries bear more than a third of the global burden of lymphatic filariasis(9)(28). Nigeria is the second endemic country in the world and also the country with the largest population at risk of lymphatic filariasis infection in the African continent (9)(4). A survey from the Federal Ministry of Health estimated that 20 million people in Nigeria are undergoing treatment for lymphatic filariasis. It states that this figure only represents about 20% of the population at risk. In addition, the Federal Ministry of Health's Nigerian Lymphatic Filarasis Elimination Program, with the assistance of the Carter Center, initiated a collaboration towards elimination of lymphatic filariasis in 2015 (29)(7)(9). In some communities as much as 5% of women can develop swelling of the limbs, and 50% of men can develop swelling of the genitals (hydrocele)(29)(30). The clinical severity and progression of the disease can lead to chronic health complications and disability, which may be accompanied by mental health problems and social stigma, while decreased productivity causes economic losses of nearly USD 1.3 billion per year(31). With several recent advances in diagnosis, pharmaceutical treatment options, and the establishment of the Global Program for the Elimination of Lymphatic Filariasis (GPEFL), WHO member countries were given a strategic plan consisting of 2 objectives, namely stopping the transmission and spread of lymphatic filariasis through mass drug administration (MDA). and alleviating suffering for those with chronic conditions associated with lymphatic filariasis(10)(32).

METHOD

Literature research is used as a reference in published articles which are carried out as an effort to enrich the following literature review. A review of published articles up to 9 October 2020 was involved in this literature review. The literature search was carried out independently by researchers using the Sciencedirect, Pubmed, and Cochrane online databases without limiting the type of study or the year of publication. The keywords used in this study were combined with the Boolean operator, namely "AND" namely ((((Lymphatic filariasis) AND (albendazole)) AND (diethylcarbamazine)) AND (ivermectin)) AND (compare). It is important to convey that researchers are trying to obtain good quality research evidence to support this literature review, namely a study using a randomized design to see the comparison between the combination of three drugs, albendazole, diethylcarbamazine, invermectin with two therapeutic drugs. Only studies published in English were included in the final review. All articles that met the inclusion criteria, even though they were published more than 10 years since this systematic review were carried out, were still used in the analysis to obtain a comprehensive picture. The data extracted from each research article includes: 1) the identity of the article (name of journal, name of researcher, and year of research), 2) country setting for the study, 3) sample size, 4) type of intervention given, 5) methodology and 6) study outcome. The inclusion criteria for research articles were articles containing: 1) lymphatic filariasis experienced in human subjects; 2) cases of lymphatic filariasis accompanied by therapeutic regimens; 3) original sources only; 4) contains a comparison of triple drug combination therapy as lymphatic filariasis therapy with a combination of two therapeutic drugs. The first step of a systematic review is to apply title / abstract filtering. The aim of this step is to remove all publications that do not discuss the comparison of triple therapeutic drug combinations with two therapeutic drugs in lymphatic filariasis. Search queries for conducting systematic reviews are shown in Table 1. In total 389 articles were

identified from the search and underwent a complete review (Figure 2).

Table 1. Search queries in conducting systematic reviews

Database	*Search queries*	Temuan
Crochane	((((Lymphatic filariasis) AND (albendazole)) AND (diethylcarbamazine)) AND (ivermectin)) AND (compare)	27
SienceDirect	((((Lymphatic filariasis) AND (albendazole)) AND (diethylcarbamazine)) AND (ivermectin)) AND (compare)	359
PubMed	((((Lymphatic filariasis) AND (albendazole)) AND (diethylcarbamazine)) AND (ivermectin)) AND (compare)	3

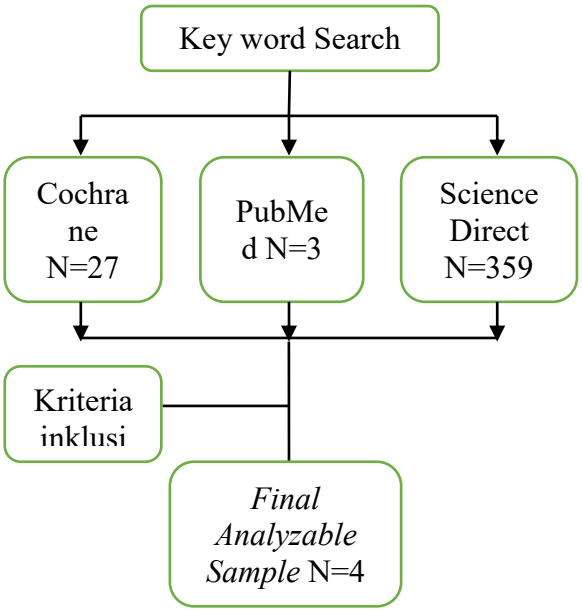

Figure 2. Identify data from article searches

RESULTS

The number of identified article search results was 389 articles. From these articles, 4 articles were used in the final study. The articles included in the final study came from several different countries. The article contains the results of a study using a combination of three drugs, namely albendazole (ALB), diethylcarbamazine (DEC), invermectin (IVM) compared to a combination of two drug therapies, namely albendazole (ALB) and ivermectin (IVM) or albendazole (ALB) and diethylcarbamazipe (DEC) for lymphatic filariasis therapy shown in comparison to the effectiveness of these treatment regimens. Thomsen's study (2016)(33) showed that a single dose of the triple combination ALB + DEC + IVM drug therapy resulted in almost total elimination of microfilariae at 36 hours and 7 days after treatment, and none of the patients experienced microfilaremia 12 months after treatment. Whereas the combination of the two single-dose therapies ALB + DEC resulted in a less specific decrease in microfilariae levels at 36 hours and 7 days, and 10 of the 11 patients continued to have mifillaremia at the 12 month time point. Twelve patients agreed to have blood drawn as additional blood samples (incidentally, 6 in each treatment group) and then examined for microfilaria 2 years after treatment. A total of 6

people who received 3 single drug treatment remained microfilariae at 2 years obtained p value = 0.047, compared with patients who received 2 drug therapy alone. ALB + DEC + IVM also resulted in a greater reduction in filarial antigen levels compared to DEC + ALB at 12 months. DEC + ALB + IVM also resulted in a greater reduction in filarial antigen levels compared to DEC + ALB at 12 months. However, this study also stated that patients treated with the three-drug regimen received more side effects than patients who received only two drug therapies, when the side effects of both objective and subjective groups were combined (9 of 12 (75%) in the group. 3 drugs and 7 of 12 (58%) in the 2 drug group). Side effects were mild to moderate in severity, started 8 hours after treatment, peaked at between 12 and 48 hours, and resolved 7 days later, except in 1 patient who had right inguinal tenderness on day 7. In King's study (2018)(34) used a sample of 182 patients, 172 (95%) evaluated at 12 months, 165 (91%) at 24 months, and 158 (87%) at 36 months after trial initiation. The triple drug regimen cleared micro filaremia in 55 patients (96%) at 12 months, at 52 (96%) at 24 months, and in 55 (96%)

Author	Publication Year	Method	Country	Sample	Intervention	Outcome
Thomsen et al(33)	2016	*Randomized*	Papua New Guinea	53 subject	Patients were stratified by sex and randomly assigned to 1 of the 2 treatment groups: DEC 6 mg / kg + ALB 400 mg or DEC 6 mg / kg + IVM 200 μg / kg + ALB 400 mg	Triple drug therapy (DEC + IVM + ALB) is safer and more effective than DEC + ALB for filariasis and has the potential to accelerate the elimination of lymphatic filariasis
King et al(34)	2018	*Randomized control trial*	Papua New Guinea	182 subject	Patients were randomized in a 1: 1: 1 ratio to a two-drug regimen of 6 mg diethylcarbamazine (Sanofi) per kilogram of body weight plus 400 mg of albendazole (GlaxoSmith-Kline) given once at the start of the trial, a two-drug regimen of 6 mg diethylcarbamazine per kilogram plus 400 mg of albendazole given at trial initiation and at 12 and 24 months, or a three-drug regimen of 200 μg ivermectin (Stromectol, Merck) per kilogram plus 6 mg diethylcarbamazine per kilogram plus 400 mg albendazole given once at trial initiation	These results suggest that a single dose regimen of three-drug ivermectin plus diethylcarbamazine plus albendazole is more effective at clearing microfilaria W. bancrofti from the blood than a single dose regimen of two-drug diethyl carbamazine with albendazole, which is the standard regimen used for mass drug administration for lymphatic filariasis elimination in outside sub-Saharan Africa. The frequency and severity of side effects after treatment with ivermectin plus dietylcarbamazine plus albendazole tends to be lower than for 2-drug therapy.

Bjerum et al(35)	2019	*Randomized, single blind*	Côte d'Ivoire	189 subject	Eligible individuals were randomized then divided into 2 groups reported in this study as follows: group 1 was given an IVM dose of 200 µg / kg (Merck & Co.) plus ALB 400 mg (GlaxoSmithKline) and group 2 was given IVM 200 µg / kg plus. DEC 6 mg / kg (Sanofi SA) plus ALB 400 mg	This study confirms that single-dose treatment with IDA IDA (IVM + DEC + ALB) is well tolerated and more effective against W. bancrofti larvae and adults than IA (IVM + ALB) and is comparable to 2 dose cycles of IA (IVM + ALB). . A greater overall cumulative reduction in MF within the first 2 years with a single dose of IDA (IVM + DEC + ALB) compared to 2 doses of IA (IVM + ALB) indicates better IDA effectiveness.
Dubray et al(36)	2020	*Cluster-randomized*	Haiti	5.998 (3.004 patients from five districts received IDA and 2,994 patients from five other districts received DA)	Each site was randomly assigned to receive an IDA regimen consisting of a single dose of IVM (200 µg / kg) + DEC (6 mg / kg) + ALB (400 mg) (5 regional sites) or an DA regimen consisting of a single dose of DEC (6 mg / kg) + ALB (400 mg) (5 areas)	The Haitian study reported that IDA was well tolerated in the lymphatic filariasis endemic community. The proportion of patients with side effects was significantly lower in people taking the IDA regimen than in people taking the DA regimen. IDA was well tolerated by study patients and was more effective at clearing Mf than DA.

at 36 months after trial initiation. In contrast, a single dose of the two drug regimen cleared microfilaremia in 18 patients (32%) at 12 months, at 31 (56%) at 24 months, and in 43 (83%) at 36 months. The three-drug regimen resulted in significantly greater microfilaria clearance at 36 months than the single-dose two-drug regimen (P = 0.02). The two-drug regimen given once a year for 3 years cleared microfilaremia in 20 patients (34%) at 12 months, at 42 (75%) at 24 months, and in 51 (98%) at 36 months. In patients receiving the three-drug regimen, microfilaria clearance at 36 months was better than the two-drug regimen given once a year for 3 years, with a difference of 2 percentage points (90% CI, - 10 to 6) (one-tailed P value for noninferiority, 0.004). In Bjerum's (2019) study(35) compared the combination therapy of Ivermectin, Diethyl carbamazine, Albendazole (IDA) with a combination of Ivermectin and Albendazole (IA) therapy. The IDA clearance rates at 6 and 12 months were significantly greater than those of IA (83% and 61% improvement, respectively) and showed greater microfilaria clearance at 24 months. IDA reduced mean individual Mf levels by more than 99% at 6 months, 98.9% at 12 months, and 93.2% at 24 months. Overall, there was an 81% greater reduction in microfilarial levels at 12 months compared to IA (incidence rate ratio [IRR], .19; 95% confidence interval [(CI), .12-.33; P <.0001). Cumulative microfilarial load (Mf) after administering a single dose of IDA for 24 months averaged 7.2 Mf / mL (783/109; total Mf at 6, 12, and 24 months divided by the total number of individuals examined at the same time points) versus 27.4 Mf / mL (3431/125) during the same period after 2 doses of IA, representing a 3.8-fold reduction in Mf levels with a single dose of IDA. IDA treatment disabled all worm nests detected in 74%, 81%, 79%, and 79% of patients at 6, 12, 24, and 36 months, respectively. Whereas IA treatment disabled all detected worm nests which accounted for 18%, 36%, 44%, and 40% of patients at 6, 12, 24, and 36 months respectively. Side effects that occur 24 hours after treatment. Of the patients in the IDA and IA groups 47% and 40% had side effects after treatment, respectively. No serious or severe side effects were observed. The frequency of mild and subjective (mild) side effects was similar between the 2 therapy groups, namely headache, joint pain, fatigue, and nausea being the most common symptoms. Saping effects (moderet) occurred in 5 patients (12%) after IDA and in 1 patient (2%) after IA (p value = 0.07). The patient's chance of having a (moderate) side effect increased by 23% for each incremental increase of the total 100 Mf / mL (odds ratio, 1.23; 95% CI, 1.09-1.43; P = 0.04) but all the effects of saping resolve within 2 to 3 days of initial therapy. Dubray's (2020) randomized study(36) in Haiti showed that significantly more participants who were Mf positive at baseline became Mf negative after IDA administration (Invermectin, Diethylcarbamazine, Albendazole) (94.4%, 34/36) than after DA administration (Diethylcarbamazine and Albendazole) (75.9%, 44/58) (P = 0.02). It was reported that two participants who were Mf positive as samples for IDA therapy had Mf counts of 3050 Mf / mL and 1383 Mf / mL. For the therapeutic safety study, this study demonstrated that 96.0% (5761/5998) of treated patients underwent a one-time examination during the 7-day follow-up period (2,917 IDA therapy and 2,844 DA therapy). Overall, 14.1% (812/5761) of patients assessed as having a treatment side effect reported at least one side effect during the week following treatment. The intracluster correlation coefficient for side effects is low (0.02). It is known that more patients who received DA (17.3%, 491/ 2,844) reported side effects compared to patients who received IDA (11.0%, 321/2917) (Table 3). The side effects reported were mostly mild, 88.7% (436/491) of all side effects in the DA group and 93.4%, (300/321) compared to all side effects in the IDA group. It was reported that more women reported side effects of therapy than men. Side effects that occurred more frequently occurred after treatment in positive micro filariasis patients, the comparison of side effects in people with microfilaremia had a low percentage difference,

namely on IDA treatment (34.1%,14/41) and on DA treatment (39.4%,26/66). For people with micro filaremia, the pre-treatment Mf count was significantly higher in people who experienced side effects after treatment compared to people without side effects (geometric mean: 20.98 Mf / mL vs. 8.81 Mf / mL, P = 0.002). The multivariable logistic regression analysis showed that after controlling for age, sex and infection status, the risk of experiencing side effects was significantly lower in patients receiving IDA compared to patients receiving DA.

CONCLUSION

The triple therapy combination is more effective than the two drug therapy in treating lymphatic filariasis. The therapeutic effectiveness can be seen in the final research article where triple drug therapy is significant in reducing and clearing microfilariae and worm nests in patients with lymphatic filariasis compared to two-drug therapy alone. There were fewer side effects from triple drug therapy than with two drug therapies. However, some studies say that the side effects are more in the combination of three therapies. The rate of side effects is low and can disappear two to three days after giving therapy. Some cases of side effects can rise to a moderate level but the percentage is small and no serious side effects have been reported after the administration of the three drug combination. Monitoring and supervision is needed in dealing with side effects that can be caused so as not to disturb the patient's comfort in continuing therapy.

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ORIGINAL ARTICLE

THE EFFECT OF HIGH DOSE VITAMIN C (ASCORBIC ACID) ON PROINFLAMMATORY CYTOKINES IN COVID-19

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ABSTRACT

Background: COVID-19 is a new pandemic that has claimed many lives in many countries. This pandemic was caused by the SARSCoV2. Until now, there is no specific antiviral drug or vaccine against Covid-19 for potential therapy in humans. This virus can cause cytokine storms which can worsen symptoms in sufferers due to an imbalance between increased oxidant production and available antioxidants. Vitamin C is an important antioxidant that protects the body from various bad effects of free radicals. At high concentrations vitamin C plays an important role in immunomodulation. This study was conducted to determine the effect of high doses of vitamin C on levels of pro-inflammatory cytokines in Covid-19.

Method: This research type is literature study. The population in this study were journals about Covid-19, vitamin C, antioxidants and free radicals, inflammatory reactions due to viral infections with samples taken from indexed journals published from 2015 to 2020. There are also clinical trials of high doses of vitamin C against inflammation in Covid-19 from these journals.

Results: The results of the study in a clinical trial conducted on 54 patients enrolled in 3 hospitals given a 1: 1 ratio for high-dose intravenous vitamin C (HDIVC) or placebo administration. The HDIVC group received 12 g of vitamin C / 50 ml every 12 hours for 7 days at a rate of 12 ml / hour, and the placebo group received bacteriostatic water for injection in the same way. HDIVC administration showed a reduction in inflammatory markers compared to placebo.

Conclusion: The conclusion of this study shows that high doses of vitamin C play a role in reducing levels of proinflammatory cytokines.

Medical and Health Science Journal

INTRODUCTION

COVID-19, an infectious disease caused by SARSCoV2, emerged in December 2019 and has spread rapidly, with cases now confirmed in several countries. Infected patients show higher leukocyte counts, abnormal respiratory findings, and elevated plasma levels of pro-inflammatory cytokines. The main pathogenesis of COVID-19 infection as a virus that attacks the respiratory system is severe pneumonia, viral load (RNAaemia) in serum, combined with the incidence of ground-glass opacities, and acute heart injury. Some severe cases treated in intensive care units show high levels of pro-inflammatory cytokines that promote an increase in reactive oxygen species causing extensive damage to the cellular lining of small vessels (capillaries). Oxidative stress in organisms infected with virus provokes free radical oxidation which increases disease severity.[1]

An important finding in COVID-19 patients is very high inflammatory parameters, including CRP (C-Reactive Protein) and proinflammatory cytokines IL-6 (Interleukin-6), TNFα (Tumor necrosis factor alfa), IL-8 (Interleukin-8). Cytokine storms are very common in patients with severe COVID-19. Cytokine storm refers to the excessive, uncontrolled release of pro-inflammatory cytokines.[2]

The antioxidant content of immune cells plays an important role in protecting them against oxidative damage and maintaining their proper function. In addition, in immune cells, antioxidants maintain the integrity and function of membrane lipids, cellular proteins and nucleic acids, and control signal transduction of gene expression. It has been shown that without sufficient antioxidants, ROS (Reactive Oxygen Species) produced by phagocytic immune cells can damage itself.[3]

Non-enzymatic antioxidants such as vitamin C provide great protection against oxidative stress by neutralizing or binding to reactive species or by breaking chain reactions.[4] Under normal conditions, the antioxidant system of the lungs protects its cells from oxidative agents through complex and coordinated system interactions. The antioxidant power of vitamin C is related to its electron transport properties such as transferring unpaired ROS electrons to itself. According to research by Bezerra et al. 2006 showed that vitamin C decreased the lung inflammatory response by inhibiting the release of TNF-α and NF-κB (Nuclear Factor Kappa-B). The histopathological evidence of the vitamin C group suggests that there is a severe reduction in neutrophil infiltration[5]

Currently, there is no specific antiviral drug or vaccine against COVID-19 for potential therapy in humans. For this reason, various kinds of efforts for a person to avoid the SARS-CoV-2 virus one of which is by increasing immunity. Efforts to increase immunity have been tried in various ways, ranging from eating herbs to consuming multivitamins, one of which is vitamin C as an antioxidant vitamin that does not yet know its effective function and properties to fight a virus. Vitamin C that is produced and marketed has a variety of different dosage sizes, but the effectiveness of vitamin C doses in increasing people's immunity is still unknown. Antioxidant defense mechanisms, such as vitamins C protect tissues against oxidants. For this reason, little is known about the use of vitamin C based on an effective dose to prevent or help relieve inflammation, especially inflammation COVID-19 and a study needs to be done. Therefore, the authors intend to conduct a study in the form of a literature study on the antioxidant effects of high doses of vitamin C on reducing the pro-inflammatory process in COVID-19.

METHODS

The research design used is descriptive research. The facts and circumstances that the researchers wanted to describe in this study were the effect of giving high doses of vitamin C (ascorbic acid) on pro-inflammatory cytokines in COVID-19. The method used was literature study. The topic to be analyzed in this study is the effect of giving high doses of vitamin C (ascorbic acid) on pro-inflammatory cytokines in COVID-19. Population is all or a set of objects under study. The population in this study were articles about COVID-19, vitamin C (ascorbic acid), antioxidants and free radicals, inflammatory reactions due to viral infections. The sample in this study was taken from articles published by international journals indexed by Scimago and Google scholar from 2015 to 2020. This research was conducted in Surabaya from May to September 2020. This research obtained approval from the Health Research Ethics Commission, Faculty of Medicine, Hang Tuah University.

RESULTS

The result of this study are based on clinical trials conducted by (J. Zhang et al., 2020) on 54 patients registered in 3 hospitals, namely Leishenshan Hospital (38 patients), Zhongnan Hospital of Wuhan University (10 patients), and Taihe University Hospital Hubei (6 patients). Of the 54 patients included in this

analysis, 48 (88.9%) received the full 7 day treatment course and 6 (11.1%) received only 5 or 6 days of treatment due to death (2) or discharge from the ICU (4). Patients were randomized to receive vitamin C or placebo within 48 hours of admission to the ICU. To accurately control the infusion rate and not affect fluid management in severe patients, researchers administered vitamin C or placebo via a pump-controlled central venous catheterization. The study group in this trial was 1) HDIVC (High Dose Intra Venous Vitamin C) 24 g of vitamin C per day. The patient was infused with 12 g of vitamin C diluted in 50 ml of bacteriostatic water every 12 hours at a rate of 12 ml / hour with an infusion pump for 7 days. 2) Placebo: 50 ml of bacteriostatic water infused every 12 hours at the same rate.[6]

Table 1 Laboratory findings about proinflammatory marker in a Trial of HDIVC in patients with Covid-19.[6]

Variable	Day	Vitamin C (n =26)	Placebo (n=28)
IL-6 (pg/ml)	1	22.56 [8.87-85.54]	54.73 [12.34-145.47]
	3	113.10 [21.80-288.73]	37.24 [5.59-85.28]
	7	19.42 [10.59-29.16]	158.00 [15.29-259.60]
CRP (mg/L)	1	39.86 [3.91-86.85]	56.84 [40.19-100.20]
	3	43.52 [3.41-65.72]	66.34 [29.76-107.39]
	7	29.47 [10.95-110.93]	30.20 [2.3-131.70]

DISCUSSION

The results of clinical trials show that high doses of vitamin C have a role in the process of reducing pro-inflammatory cytokines and other inflammatory markers such as CRP. Vitamin C is a water-soluble nutrient that the human body cannot synthesize on its own. Vitamin C acts as an anti-oxidant that scavenges reactive oxygen species (ROS), thereby protecting biomolecules such as proteins, lipids, and nucleotides from oxidative damage and dysfunction. Vitamin C accumulates in leukocytes, in concentrations 50-100 times higher than in plasma. During infection, the vitamin C present in leukocytes is used up quickly. Disruption of the balance between antioxidant defenses and oxidant formation can alter several signaling pathways involving the pro-inflammatory transcription factor, NF-κB. Increased oxidant levels lead to activation of NF-κB, triggering a signaling cascade, with the end result of further production of oxidative species and inflammatory mediators. NF-κB is involved in inflammatory response, pathogenesis of certain diseases and viral infections. Inhibition of NF-κB can be a mode of therapy against viral infections. Vitamin C is also known to increase anti-inflammatory cytokines (IL-10). Clinical studies have shown that 1 g / day of vitamin C increases secretion of IL-10 by peripheral mononuclear cells. IL-10 works as a negative feedback mechanism with IL-6 and controls inflammation, important in COVID-19.[7]

At high concentrations vitamin C plays an important role in immunomodulation. Vitamin C can inhibit the activation of NFkB, which is a major proinflammatory transcription factor, and plays an important role in overall immunity, including genetic regulation of chemokines,

cytokines, adhesion molecules, inflammatory mediators and inhibitors of apoptosis. Vitamin C can inhibit the production of IL-6 and TNF-α. Vitamin C can reduce the GM-CSF signaling response which functions as a regulator of cytokine redox signal transduction in the body's defense cells and has a possible role in controlling the inflammatory response. In addition, high doses of vitamin C can regulate the proliferation and function of T cells, B cells, and natural killer (NK) cells. This can help inhibit the development of cytokine storms and increase host immunity.[8]

Preclinical research on early sepsis reveals that vitamin C prevents sepsis-induced cytokine spikes that activate and sequester neutrophils in the lungs, thereby damaging the alveolar capillaries. Vitamin C enhances clearance of alveolar fluid by preventing the accumulation of activated neutrophils in the alveolar spaces, limiting damage to alveolar epithelial drains. Additionally, vitamin C prevents the formation of neutrophil extracellular traps, a biological event in activated neutrophils that increases vascular injury.[9]

CONCLUSION

From the results of literary studies, it can be concluded that at high concentrations vitamin C plays an important role in immunomodulation. Vitamin C can inhibit the activation of NFkB, which is a major proinflammatory transcription factor, and plays an important role in overall immunity, including genetic regulation of chemokines, cytokines, adhesion molecules, inflammatory mediators and inhibitors of apoptosis. Vitamin C can inhibit the production of IL-6 and TNF-α. Vitamin C can reduce the GM-CSF signaling response which functions as a regulator of cytokine redox signal transduction in the body's defense cells and has a possible role in controlling the inflammatory response. In addition, high doses of vitamin C can regulate the proliferation and function of T cells, B cells, and natural killer (NK) cells. This can help inhibit the development of cytokine storms and increase host immunity. Vitamin C is also known to increase anti-inflammatory cytokines (IL-10). With this ability, vitamin C plays an important role in reducing cytokine storms in Covid-19 by reducing levels of pro-inflammatory cytokines.

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ORIGINAL ARTICLE

THE EFFECT OF GIVING HONEY ON THE PROCESS OF WOUND HEALING IN BURNED PATIENTS

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ABSTRACT

Backgroud: Burns are one of the most dangerous injuries and the main cause of disability to death. Burns can be interpreted as one of the serious problems in society and are recorded to cause around 265,000 deaths each year. Honey can maintain the wound condition to keep it moist and in high viscosity to prevent infection.

Method: This study was conducted to determine the effect of honey on the wound healing process in burn patients. This study uses a literature review method. The population in this study is a journal with a background in the health sector with 10 international journals on burns with the qualifications of 9 SCIMAGO indexed journals and 1 SINTA indexed journal published from 2015 to 2020.

Results: Burns that treated in the form of pure honey can generate good results and heal in an average of 20 days. The healing process will be better, if the wound given a mixture of other ingredients which also have a low acidity such as garlic, chitosan and beeswax and olive oil. Honey has antimicrobial properties and a low pH level. The microbe most sensitive to honey is Staphylococcus aureus.

Conclusion: The conclusion from this study, honey can be used as an alternative treatment for burns.

Medical and Health Science Journal.

INTRODUCTION

Burns are defined by the World Health Organization (WHO) as tissue injuries to the skin caused by heat, radiation, electric shock, radioactive materials and contact with hazardous chemicals. Skin damage caused by ultraviolet (UV) rays and disturbances in the respiratory system caused by inhaling too much smoke can also be categorized as burns. Burns are one of the most dangerous injuries and the leading cause of limb disability and death. According to the World Health Organization (WHO), burns can be interpreted globally as one of the serious problems. Fire cases that have been recorded in the world occur around 265,000 deaths each year. The number of deaths due to burns is something that needs to be considered in every country. Millions of burn victims who survived the disabilities in their bodies were rejected from their neighborhoods[1].

Topical antibiotics that can treat wounds in humans and animals are very important to find[2] ,but to prevent antibiotic resistance, alternative medicine can be used to heal burns[3]. A long history explains that honey is an ingredient that can treat wounds. Since ancient times, honey has been used for its nutritional and therapeutic effects. Honey can be used as a sweetener and flavor in a dish. Honey is very easy to find almost all over the world. Carbohydrates are the most important nutrients in honey because they are present in the form of glucose, fructose and monosaccharides. Honey contains nutrients that can act as anti-inflammatory, antioxidant and anti- bacterial agents so it is good for the healing process of wounds on the skin. In scientific literature, the function of honey has been to prevent coughing, increase fertility and wound healing because it has

antioxidant and antibacterial properties[4]

Healing burns using honey still has to go through a further research process, therefore, the authors want to know the effect of honey on the wound healing process in burn patients[4]. With the incident in antibiotics, the use of honey can be needed again to handle medical treatment[5]. Seeing the many benefits of honey, therapy using honey needs to be developed, therefore the authors intend to examine the effect of honey on the healing process of burns.

METHODS

The research design used is descriptive research. This research will explain the effect of using honey topically for the treatment and healing process of burns. The method used is literature study. The population in this study were articles about burns, wound healing processes and honey. The journals used as references come from research with backgrounds in the health sector, especially skin medicine, nutrition, pharmacology, biology and beauty. The research sample is articles that have been published by national and international journals from 2015 to 2020 at least 10 articles that explain the process of healing burns using honey.

This research was conducted in Surabaya from April to Oktober 2020. This research get approval from the Ethics Commission for Health Research, Faculty of Medicine, Hang Tuah University.

RESULT

Samples in this study were taken from 10 international journals with the qualifications of 9 SCIMAGO indexed journals and 1 SINTA indexed journal about the role of honey in the healing process of burns.

Healing time

Jeffery et al., Stated that the average healing time using honey was 18.16 days[6]. Moustafa and Atiba's research showed that the burns treated with honey on day 24 were more closed[7]. According to Ait Abderrahim et al., The wound healing time using honey is about 25-27 days[8]. Hendy and Lister argue that treatment using honey takes 7 days[9]. According to Duncan et al., ALH can provide a healing time of 3 to 14 days[10], whereas according to Subrahmanyam all wounds treated with honey heal within 10 days[11].

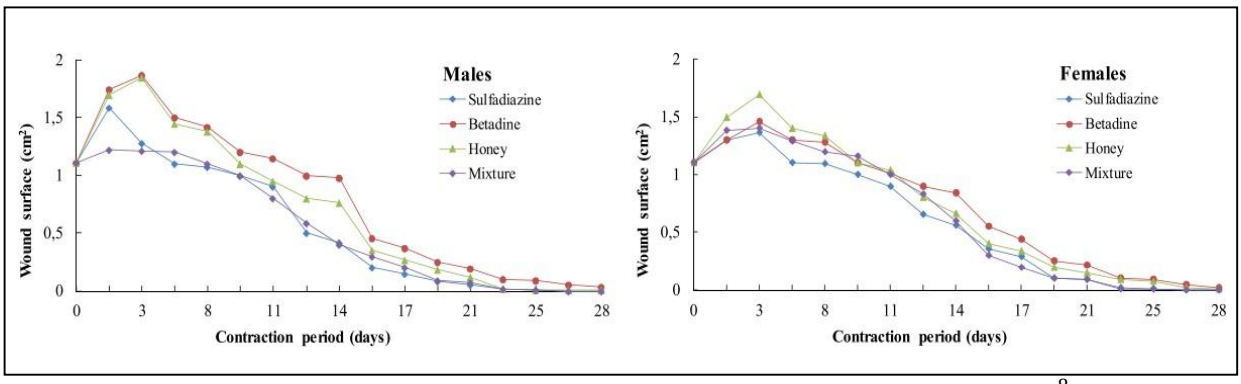

Figure 1 The green line shows the burn healing time using pure honey[8]

Wound Results

Duncan et al., Reviewed facial burns, Figure 1 is a photo of 2 patients who were successfully treated with ALH honey. This process takes about 3 to 14 days[10].

Jeffery et al. Observed 3 cases of burns treated with revamil honey gauze and revamil gel. The three wounds took 14-26 days to heal completely as shown in figure 2[6]. Smaropoulos and Cremers also observed 2 cases of burns that produced good scars within 7-18 days[5].

Ait Abderrahim et al., Conducted an experiment and the burns improved within 26 days[8]. In addition, Moustafa and Atiba's research and Hendy and Lister's research obtained satisfactory results in the honey

group, this can be seen from the smaller burns diameter[7.9].

Histologically, honey has also been shown to increase angiogenesis, this is supported by 2 literature. El-Kased et al., Observed that the layer of skin affected by burns and then given honey, on the 9th day the honey-treated skin showed few new blood capillaries and fibroblastic cell proliferation[12]. Furthermore, according to Schencke et al., The pure honey group experienced neoformation of blood vessels in all dermal scar tissue as shown in Figure 4[13].

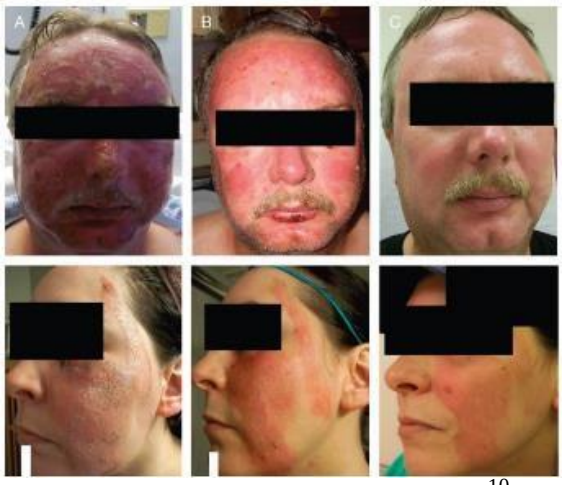

Figure 2 The result of healing using ALH[10]

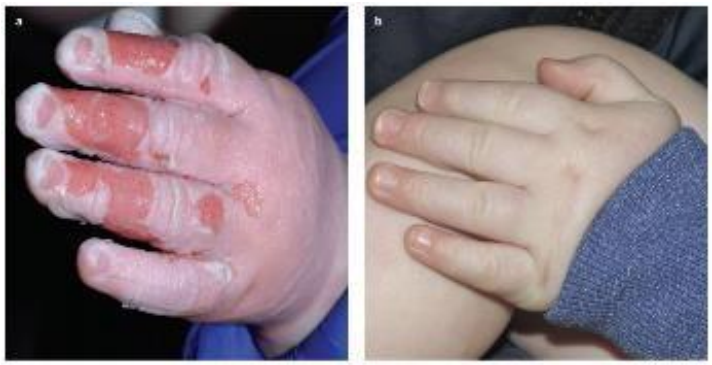

Figure 3 Giving revamil honey gauze to blister burns[6].

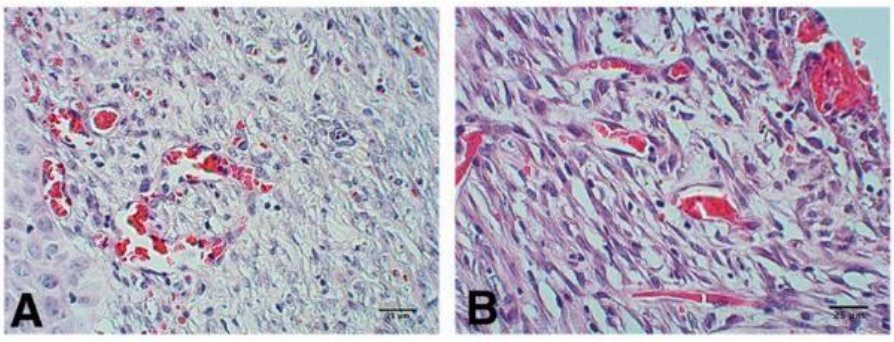

Figure 4 Angiogenesis in honey treated skin [13]

Degree of pain and patient satisfaction

Jeffery et al., Using revamil honey gel and revamil honey gauze, from all the cases he observed, the use was very easy even though there was a little exudate but still gave satisfactory results[6]. Smaropoulos and Cremers also described 2 cases of burns that were observed to be easy to use and painless in all patients[5]. According to the Subrahmanyam study comparing honey and vaseline treated with honey, 90% experienced zero pain or only mild pain, while the group treated with vaseline gauze 88% experienced zero or mild pain[11].

Antimicrobial properties

Duncan et al, who stated that the bacteria contained in burns were Staphylococcus aureus and P aeruginosa, besides that, according to him, there was no abnormal bacterial growth in all burn cultures in patients who were given honey[10]. Just like Subrahmanyam, the research results were taken on day 7 in both honey and vaseline groups and the results did not show any growth of any organisms[11]. According to Firdose et al., Honey has antimicrobial properties because it has a low pH and contains H2O2 or peroxide acid as shown in Figure 5[14] . According to Ait Abderrahim et al., S. Aureus which is a gram-positive bacteria is more sensitive to honey when compared to gram- negative bacteria. such as E. coli and P. aeruginosa, whereas C. albicans was more resistant to honey[8]

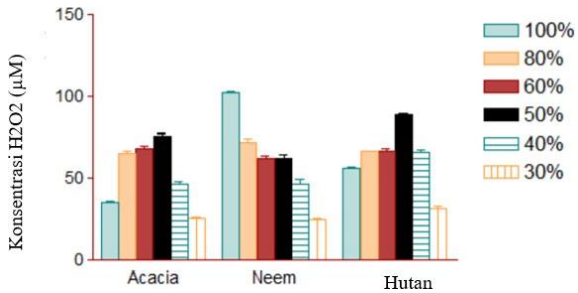

Figure 5. H2O2 levels in acacia honey, neem and forest honey[14].

Strain	MIC
	Madu euphorbia
S. aureus	6
E. coli	9
P. auruginosa	8
C. albicans	22

Figure 6. The minimum inhibition of euphorbia honey on 4 microbes[8]

Cost of treatment

According to Duncan et al., patients used between 1 to 4 tubes of product and the average cost of treatment was $ 26.15, with a range of $ 11.44 to $ 45.76 or IDR 170,000 to IDR 680,000[10]

DISCUSSION

Honey can be an alternative treatment because it is easier to obtain in the village. The effectiveness of honey as a treatment for burns depends on the type of honey used, the time of administration and the degree of severity of the wound[9]

Honey works in the wound healing process with the presence of hydrogen peroxide which can activate macrophages to release VEGF which stimulates fibroblast proliferation and angiogenesis in wounds. Honey is able to stimulate B lymphocytes and T lymphocytes, and activate neutrophil phagocytosis in cells. Honey also stimulates monocytes (MM6 cells) to secrete cytokines, tumor necrosis factor-a (TNF-a), interleukin-1 (IL-1) and IL-6, which activate the immune response to infection. TNF-a secretion can be induced by protein glycosylation. Furthermore, honey is able to degrade collagen IV through stimulation of matrix metalloproteinase 9 (MMP-9), a protease enzyme that plays a role in the release of keratinocyte cells from the basement membrane, thus allowing keratinocyte migration for re-epithelialization. Honey is able to induce cytokine production by leukocytes so that it will stimulate cell growth [15].

The healing time for burns using honey therapy varies from 3 to 36 days with an average of 20 days. Honey as an autolytic debridement agent is considered effective in wounds containing ≥40% damaged tissue. Honey creates a moist wound environment, thereby stimulating wound healing[6]

Honey gives satisfactory results for the healing of second degree partial burns because there is no abnormal bacterial growth, favorable patient satisfaction scores, lack of side effects and reasonable treatment costs support the use of honey as an effective, safe and economical form of treatment for burns[10]

CONCLUSION

Honey is beneficial for health, especially skin because it has a low pH, contains H2O2, has antioxidant properties and has a lot of ingredients, so honey can affect the healing process of burns. Honey can be used as an alternative for the treatment of burns because it can stimulate the proliferation of fibroblasts and angiogenesis, the healing time for burns with honey is 3 to 36 days, the results of wound healing are good, honey is easy to apply, causes mild pain and is easy to get, honey has antimicrobial properties, the bacteria most sensitive to honey is Staphylococcus aureus. The cost of treating using ALH honey is IDR 170,000 to IDR 680,000. It is not yet known the costs involved in treating other types of honey.

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