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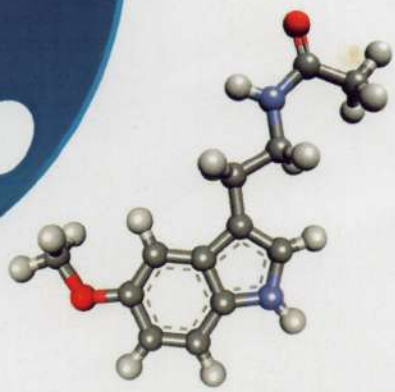

# The effects of *Phaleria macrocarpa* (Scheff.) Boerl extract on malondialdehyde level in preeclampsia-induced HUVEC culture

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Preeclampsia is a major cause of both maternal and perinatal morbidity and mortality The pathopysiology of preeclampsia remain unclear but early placental dysfunction followed by oxidative stress, increased lipid peroxidation, and reduced antioxidants play an important role. Malondialdehyde a final product of lipid peroxidation, commonly used as the oxidative stress marker Prevention and treatment of oxidative stress in preeclampsia using antioxidant including melatonin, beta-caroten, vitamin C or E has been developed but none is yet recommended. Thus the efforts are continuing to find an effective antioxidant in preeeclampsia. Melatonin seems to be promising since it has a great capacity to scavenge radicals and reduce oxidative damage. *Phaleria macrocarpa* a medicinal plant has long been used traditionally and known has high antioxidant capacity by in vitro and in vivo studies. HUVEC culture is an in vitro model widely used to study the preeclampsia pathogenesis. This study aims to determine the effects of *Phaleria macrocarpa* extract on MDA level in preeclampsia-induced HUVEC culture. Our results showed the *Phaleria macrocarpa*'s extract reduce MDA level siginifcantly at concentration of 0.977 µg/mL in preeclampsiainduced HUVEC culture and at 15.625 µg/mL reduce MDA level to control normal level. Thus, *Phaleria macrocarpa*'s extract might be used to overcome oxidative stress in preeclampsia, further clinical studies are encouraged.

**Keywords:** *Phaleria macrocarpa*, preeclampsia, oxidative stress, HUVEC, MDA.

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erratum written 0,977 µg/mL, should be 3,906 µg/mL

# The Effects of *Phaleria macrocarpa* (Scheff.) Boerl Extract on Malondialdehyde (MDA) Level in Preeclampsia-Induced Human Umbilical Vein Endothelial Cell (HUVEC) Culture

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**Abstract.** Preeclampsia is a major cause in both maternal and perinatal mortality and morbidity. The pathophysiology of preeclampsia remain unclear but early placental dysfunction followed by oxidative stress, increased lipid peroxidation, and reduced antioxidants play an important role. Malondialdehyde is the final product of lipid peroxidation, commonly used as the oxidative stress marker. Prevention and treatment of oxidative stress in preeclampsia using antioxidant including melatonon, beta-caroten, vitamin C or E has been developed but none is yet recommended. Thus the efforts are continuing to find an effective antioxidant in preeclampsia. Melatonin seems to be promising since it has great capacity to scavenge radicals and reduce oxidative damage. *Phaleria macrocarpa* a medicinal plant has long been used traditionally and known has high antioxidant capacity by in vitro and in vivo studies. HUVEC culture is an in vitro model widely used to study the preeclampsia pathogenesis. This study aims to determine the effects of *Phaleria macrocarpa* extract on MDA level in preeclampsia-induced HUVEC culture. Our results showed the *Phaleria macrocarpa*'s extract reduce MDA level significantly at concentration of 0.977µg/mL in preeclampsia-induced HUVEC culture and at 15.625µg/mL reduce MDA level to control normal level. Thus, *Phaleria macrocarpa*'s extract might be used as agent to overcome oxidative stress in preeclampsia, further clinical studies are encouraged.

**Keywords :** Phaleria macrocarpa, preeclampsia, oxidative stress, HUVEC, MDA

## 1. Introduction

Preeclampsia is one of the leading causes of maternal morbidity and mortality worldwide. It is estimated that maternal deaths worldwide are around 500,000 annually and about 10% - 15% are due to preeclampsia and eclampsia [1]. In 2006 WHO reported that 16% of maternal deaths in developed countries due to hypertension in pregnancy, higher than due to bleeding of 13%, abortion of 8% and sepsis of 2% [2].

Preeclampsia and eclampsia also adversely affect the fetus and the neonates. It is estimated that 15% of preterm births due to preeclampsia, where labor has to be performed to prevent the progression of preeclampsia [3].

Although there have been many studies but the etiopathogenesis of preeclampsia is still not fully elucidated but it is believed to be a multifactors. Therefore preeclampsia remains a 'disease of theories'. The difficulties increase because the syndrome of preeclampsia usually occurs in the third trimester when the underlying disorder has occurred in the early stages of placentation, thus difficult to understand its progression [4].

Endothelial dysfunction plays an important role in the pathophysiology of preeclampsia. Endothelial dysfunction is defined as an altered state of endothelial cell differentiation in response to sublethal injury or cytokine stimulation [5]. Under normal circumstances, endothelial cells maintain vascular integrity, regulating blood pressure, preventing intravascular coagulation, and regulating vascular smooth muscle tone by producing various substances including nitric oxide (NO), endothelin, prostacyclin and thromboxane [6,7]. Rodgers et al. [8] suggests that endothelial dysfunction occurs due to cytotoxic factors in the circulation. Impaired utero-placental perfusion in PE causes hypoxia, ischemia, placental oxidative stress, so the placenta produces free radicals such as superoxide anions ($O_2^-$) and $H_2O_2$, trophoblast debris, pro-inflammatory cytokines, and antiangiogenic factors which are thought to cause vascular endothelial dysfunction and causing excessive maternal inflammatory responses. Systemic maternal vascular endothelial dysfunction is the underlying cause of clinical manifestations in preeclampsia [9].

Oxidative stress is considered as a mediator of endothelial dysfunction in preeclampsia [6]. Pregnancy itself is a state of oxidative stress along with mitochondrial activity and increased production of Reactive oxygen species (ROS) but is offset by increased antioxidants production. Increased oxidative stress and lipid peroxides and reduced antioxidants play a role in the pathophysiology of preeclampsia [10-12]. Wang [13] found there is elevated levels of lipid peroxide in preeclampsia placental tissue compared to normal pregnancy placental tissue.

Malondialdehyde (MDA) is the final product of lipid peroxidation, thus it is used as one of the oxidative stress marker. Madazli et al. [14] found that MDA levels in preeclampsia placental and plasma were significantly higher than normal pregnancies (6.06±0.94 nmol/ml vs 4.49±0.71 nmol/ml) and (10.18±1.32 nmol/gr wet weight vs 6.72±1.27 nmol/gr wet weight). Whereas superoxide dismutase (SOD) levels decreased significantly in preeclampsia placental and plasma than normal pregnancies (23,51±2,27 U/ml vs 26,57±1,44 U/ml) and ( 40,83±9,62 U/gr wet weight vs 50,43±16,87 U/gr wet weight).

Zuspan [15] suggested that PE treatment will only be successful and rational if based on understanding the disease pathophysiology. In an attempt to determine the pathophysiology of a disease, in vitro model research is considered the best and most effective way [15]. HUVEC (Human Umbilical Vein Endothelial Cell) cell line culture and trophoblast cell line is an in vitro model widely used to study the pathogenesis of preeclampsia.

The preventions of preeclampsia consist of primary, secondary, and tertiary prevention. Primary prevention aims to prevent the onset of disease by avoiding pregnancy with contraception because the pathogenesis of preeclampsia remains unclear. Secondary prevention aims to inhibit the disease progression before the onset of clinical manifestations. Tertiary prevention aims to prevent the complications of a disease, in preeclampsia, the complications such as seizures, HELLP syndrome, and IUGR, which tertiary prevention can be interpreted as treatment Tertiary prevention includes

regular antenatal examination, appropriate referral, anti-hypertensive administration, anti-convulsant administration, and appropriate timing of delivery [17].

The use of traditional medicines in Indonesia is part of a culture that has been going on since long time ago. Act No. 381 of 2007 on national traditional drug policy regulates the development of traditional medicines in order to obtain good quality, safe, and scientifically tested traditional medicine [18].

Herbs or medicinal plants have been used traditionally as alternative medicine since ancient times. *Phaleria macrocarpa* (Scheff.) Boerl also known as Mahkota dewa belongs to the *Thymelaceae* family, that originated from Papua province, is very popular in Indonesia used in the treatment of various diseases such as cancer, hemorrhoids, diabetes mellitus, allergies, liver disease, heart disease, kidney disease, hypertension, migraine, skin diseases and others [19-21]. *Phaleria macrocarpa* (Scheff.) Boerl is widely used as an antioxidant because of alkaloids, saponins, flavonoids and polyphenols properties. The phenol and flavonoid compounds in the extract of *Phaleria macrocarpa* have antioxidant and anti-inflammatory activity [21-22].

To date there has been no research on the effect of the Phaleria macrocarpa's extract on the levels of TNF-α in preeclampsia-induced Human Umbilical Vein Endothelial Cell (HUVEC). The aim of this study is to determine the tffects of *Phaleria macrocarpa* (Scheff.) Boerl Extract on Tumor Necrosis Factor – Alpha (TNF- α) Level In preeclampsia-induced Human Umbilical Vein Endothelial Cell (HUVEC).

## 2. Materials and Method

Serum samples used were obtained from women at >20 - 42 weeks of gestational age, which were diagnosed preeclampsia and normal pregnancy at Dr. Hasan Sadikin General Hospital. Research subjects have fulfilled inclusion and exclusion criteria.

### *2.1. Cell culture*

HUVEC cell line was obtained from American Type Collection Culture with ATCC CRL-1730 code number. HUVEC cell line was growth into tissue culture flask (25 $cm^2$) containing RPMI 1640 media, 20% (v/v) FBS qualified (fetal bovine serum) supplementation, 10% endothelial supplement, 1% Penicillin G - Streptomycin solution stabilized, and 1% antimycotic Fungizone Amphotericin B and 1% gentamicin. The cells were then incubated at $37^OC$ and 5% $CO_2$ (v/v). Culture medium is replaced every 2 - 3 days. Then cells are passaged every seven days until reach 80-90% confluence.Phaleria macrocarpa's extract.

### *2.2. Phaleria macrocarpa's Extract*

*Phaleria macrocarpa* (Scheff.) Boerl was obtained from the Research Institute for Industrial Plants at Manoko, Lembang, West Java, Indonesia. The plant species was identified by the laboratory of Plant Taxonomy staff at Herbarium Bogoriense, Bogor, Indonesia.

### *2.3. Measurement of MDA Level*

As many as $6x10^5$ cells/mL induced with normal and preeclampsia serum, were placed into 60-well plate, then incubated at $37^OC$ and 5% $CO_2$ (v/v). Each well then was washed with $37^OC$ PBS 3-4 times. Furthermore, various concentrations of Phaleria macrocarpa's extract (0,977; 1,953; 3,906; 7,813; 15,625; 31,25; 62,5; 125; and 250 µg/mL) were added into each well, then incubated for 24 and 72 hours $37^OC$ and 5% $CO_2$ (v/v). Each well then was washed with $37^OC$ once for five minutes. Transfer the cells into centrifugation tube using 1.5 mL pipette. Centrifuged at 1.500 rpm for 10 minutes at 4°C. Use the supernatant as a sample for the ELISA method measurement, then the rest of the sample can be stored at -80 °C.

*2.4. Data Analysis*

Data distribution was analyzed with Shapiro-Wilk normality test. Data was analyzed with repeated ANOVA (analysis of variance) test and followed by Bonferroni test as post hoc comparison test.

## 3. Results

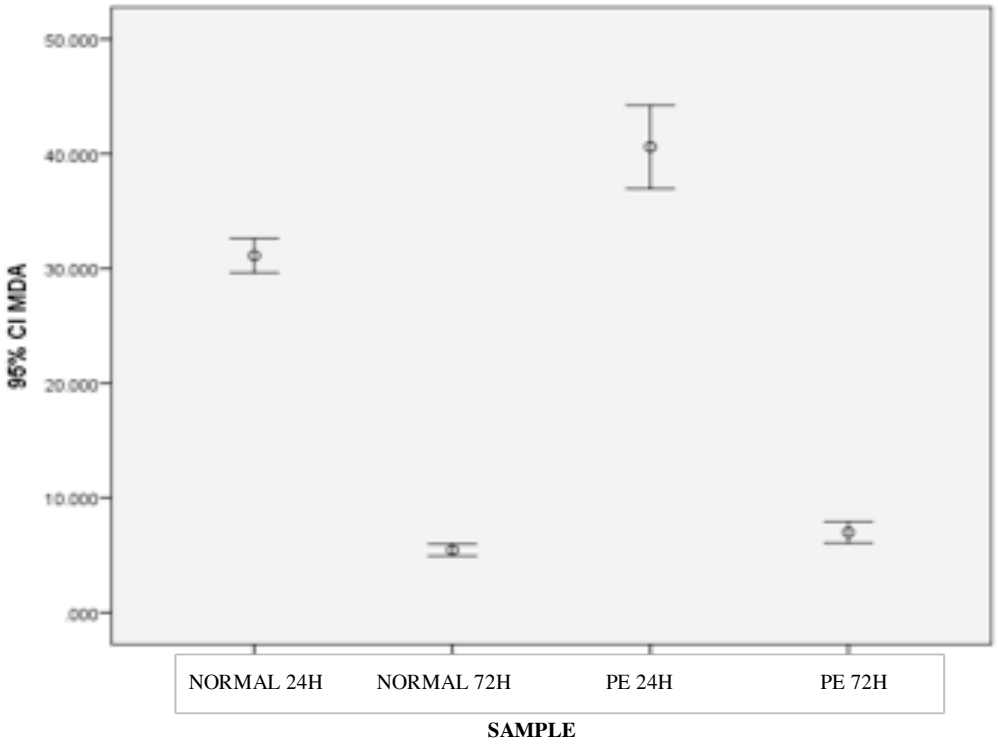


Figure 1. MDA levels in normal and preeclampsia-induced HUVEC based on incubation time.

As shown in figure 1 MDA levels in preeclampsia HUVEC culture model is higher than normal pregnancy HUVEC culture model. The MDA levels at 72 hours incubation time was lower than the 24 hours incubation time in both normal and preeclampsia models.

Variables tested in this study were normally distributed both in normal and preeclampsia model treated with *Phaleria macrocarpa*'s extract in various concentrations incubated for 24 and 72 hours.

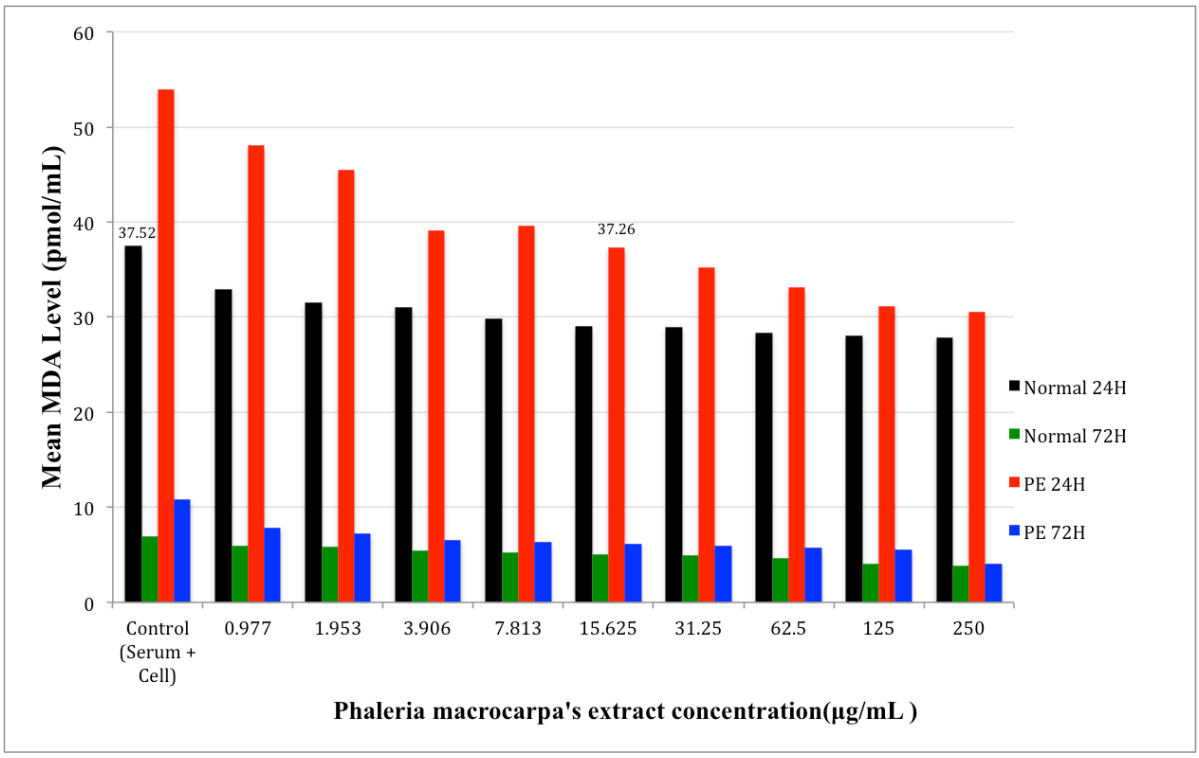


Figure 2. MDA levels in normal and preeclampsia HUVEC culture model based on Phaleria macrocarpa's extract concentration

Figure 2 shows *Phaleria macrocarpa*'s extract at concentration 15.625 µg/mL reduce MDA level in preeclampsia model to be almost equal as normal pregnancy model level.

Table 1. MDA levels (pmol/mL) mean comparison before and after various concentrations of *Phaleria macrocarpa*'s extract treatment at 24 hours and 72 hours incubation time in normal and preeclampsia HUVEC culture model.

| *Phaleria macrocarpa*'s extract concentration (µg/mL) | Mean ± SD | P value |
|---|---|---|
| Control | 27.293 ± 20.740 | |
| 0.977 | 23.700 ± 18.870 | 0.017 |
| 1.953 | 22.510 ± 17.890 | 0.002 |
| 3.906 | 20.530 ± 15.823 | 0.000 |
| 7.813 | 20.245 ± 15.900 | 0.000 |
| 15.625 | 19.370 ± 15.050 | 0.000 |
| 31.25 | 18. 760 ± 14.474 | 0.000 |
| 62.5 | 17.944 ± 13.791 | 0.000 |
| 125 | 17.180 ± 13.311 | 0.000 |
| 250 | 16.600 ± 13.550 | 0.000 |

Table 1 shows MDA level decreased in preeclampsia and normal serum-induced HUVEC ATCC CRL 1730 following increased *Phaleria macrocarpa*'s extract concentration. MDA level significantly decreased after exposure of *Phaleria macrocarpa*'s extract on concentration 0.977 µg/mL. ($p<0,05$).

Table 2. MDA (pmol/mL) levels mean comparison between preeclampsia and normal serum-induced HUVEC culture model treated with *Phaleria macrocarpa*'s extract in various concentrations incubated for 24 and 72 hours.

| *Phaleria macrocarpa*'s extract concentration (µg/mL) | 24 H INCUBATION TIME | | | 72 H INCUBATION TIME | | |
|---|---|---|---|---|---|---|
| | NP[a] (Mean ± SD) | PE[b] (Mean ± SD) | P value | NP[a] (Mean ± SD) | PE[b] (Mean ± SD) | P value |
| 0.977 | 32.951 ± 0.068 | 48.063 ± 0.003 | 0.002 | 5.947 ± 0.002 | 7.824 ± 0.001 | 0.000 |
| 1.953 | 31.488 ± 0.564 | 45.483 ± 0.672 | 0.003 | 5.847 ± 0.007 | 7.219 ± 0.001 | 0.002 |
| 3.906 | 31.033 ± 0.062 | 39.064 ± 0.008 | 0.003 | 5.450 ± 0.001 | 6.563 ± 0.003 | 0.001 |
| 7.813 | 29.882 ± 0.013 | 39.545 ± 0.001 | 0.001 | 5.232 ± 0.001 | 6.323 ± 0.003 | 0.002 |
| 15.625 | 29.004 ± 0.003 | 37.260 ± 0.353 | 0.002 | 5.083 ± 0.008 | 6.126 ± 0.001 | 0.003 |
| 31.25 | 28.987 ± 0.006 | 35.237 ± 0.007 | 0.000 | 4.901 ± 0.006 | 5.913 ± 0.003 | 0.004 |
| 62.5 | 28.360 ± 0.494 | 33.095 ± 0.008 | 0.046 | 4.611 ± 0.077 | 5.710 ± 0.002 | 0.032 |
| 125 | 28.010 ± 0 | 31.135 ± 0 | 0.000 | 4.069 ± 0.004 | 5.508 ± 0.001 | 0.002 |
| 250 | 27.889 ± 0.018 | 30.566 ± 0.006 | 0.004 | 3.891 ± 0.002 | 4.012 ± 0.001 | 0.177 |

[a] Normal Pregnancy
[b] Preeclampsia

Table 2. shows significant MDA levels mean difference in preeclampsia and normal serum-induced HUVEC culture model treated with *Phaleria macrocarpa*'s extract in various concentrations incubated for 24 and 72 hours.

## 4. Discussion

This were the first study to evaluate the effects of *Phaleria macrocarpa* (Scheff.) Boerl extract on Malondialdehyde (MDA) level in Preeclampsia-Induced Human Umbilical Vein Endothelial Cell (HUVEC). Preeclampsia and eclampsia have been known since ancient times but their pathophysiology is still not clearly understood. Abnormal trophoblast invasion and placental perfusion disorders are thought to be the underlying cause of preeclampsia.

There is compelling evidence that endothelial dysfunction plays a role in the pathophysiology of preeclampsia. A consistent finding is the presence of glomerular endotheliosis in more than 70% of primiparous preeclampsia patients and this glomerular endotheliosis will disappear after delivery [8].

To date, invitro research using HUVEC has been done a lot recently. Previous invitro research on HUVEC cultures by treating with anti-inflammatory and antioxidant compounds such as curcumin and Papua ant nest (*Myrmecodia pendens*) decrease oxidative stress and inflammation characterized by decreased levels of MDA, and TNF-α. These studies conclude that the Papuan ant nests and curcumin have a therapeutic effect on preeclampsia [23-24].

Oxidative stress is considered as a mediator of endothelial dysfunction in preeclampsia. Increased oxidative stress and lipid peroxides and reduced antioxidants play a role in the pathophysiology of

preeclampsia [10-12]. Malondialdehyde (MDA) is the final product of lipid peroxidation, thus it is used as one of the oxidative stress marker.

In this study results showed level of MDA levels in preeclampsia HUVEC culture model was higher than normal pregnancy HUVEC culture model. MDA level also decreased in preeclampsia and normal serum-induced HUVEC ATCC CRL 1730 following increased *Phaleria macrocarpa*'s extract concentration. MDA level significantly decreased after exposure of *Phaleria macrocarpa*'s extract on concentration 0.977 μg/mL. *Phaleria macrocarpa*'s extract at concentration 15.625 μg/mL reduce MDA level in preeclampsia model to be almost equal as normal pregnancy model level, thus this concentration is both clinically and statistically siginificant. Result of *Phaleria macrocarpa*'s extract on MDA levels shows siginifcant mean difference in preeclampsia and normal serum-induced HUVEC culture model treated with *Phaleria macrocarpa*'s extract in various concentrations incubated for 24 and 72 hours.

The result of present study suggests that *Phaleria macrocarpa*'s extract contains antioxidant activity which is phenol and flavonoid compounds. It was also described that MDA level decreased in preeclampsia and normal serum-induced HUVEC ATCC CRL 1730 following increased *Phaleria macrocarpa*'s extract concentration. Thus, *Phaleria macrocarpa*'s extract might be used as antioxidant in preeclampsia. Since the decreased the level of MDA in preeclampsia-induced HUVEC ATCC CRL 1730 culture, further clinical studies regarding the use of *Phaleria macrocarpa*'s extract in treatment are encouraged.

## 5. Conclusion

The *Phaleria macrocarpa*'s extract reduce MDA level siginifcantly at concentration of 0.977 μg/mL in preeclampsia-induced HUVEC ATCC CRL 1730 culture. The *Phaleria macrocarpa*'s extract at concentration 62.5 μg/mL reduce MDA level to control normal level.

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