Pimpinella Treatment on Reducing Apoptosis of Kidney Cells Following UVB Radiation in Rats

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ABSTRACT

Introduction: Pimpinella alpina Molk (PM) is a botanical antioxidant was able to inhibit apoptosis in various cells. Apoptosis is a leading cause of tubular atrophy and therefore chronic kidney disease. However, the effect of PM on reducing apoptosis in kidney cells remains unclear. Objective: aim of this study to elucidate the effect of PM on reducing apoptosis in kidney cells. Methods: In the post test only control group design, 35 male rats were grouped into 7 comprise: NC-G, samples were neither exposure to UVB nor PM treatment; NG-7 and NG-15, all samples were only exposure to UVB irradiation for 7 days; P10-7, P15-7, P10-15, P15-15 groups, samples were exposure to UVB for 7 days and treated with PM for 7 and 15 days respectively. Bax and Caspase3 expression were assessed by rt-PCR and IHC staining method. Results: Statistical analysis showed that RNA-Bax and RNA-caspase3, Bax and caspase3 protein expression in P15-7, P10-15 and P15-15 were lower significantly compared to those of NG-7, p<0.05, and no significant difference compared to those of NC-G, p > 0.05. Conclusion: PM treatment with 100 and 150 mg/day for seven and fifteen days were able to decrease Bax and Caspase3 expression in kidney cells following UVB irradiation. Even, the decreased in Bax and caspase3 expression were comparable to normal.

Key words: Pimpinella alpina Molk, Kidney Cells, Apoptosis, Bax, Caspase3.

INTRODUCTION

The Ultraviolet B of sunlight (295 to 320 nm) is the most powerful and major contributor to damaging skin such as sunburn, inflammation, photo aging, and photocarcinogenesis.6,7 The cellular mechanism of skin damages which is induced by UVB has been established. There are growing evidences that UVB can induce reactive oxygen species (ROS), DNA fragmentation, and apoptosis of keratosit skin cells. The prominence ROS which is generated by skin following UVB irradiation is oxygen superoxide (O2) and hydrogen peroxide (H2O2) resulted from mitochondrial oxidative phosphorylation.3 Subsequently, H2O2 is promptly distributed in systemic blood stream and immediately reduced to OH− by the reaction of Fenton or Heber-Weis.8 Radical hydroxyl (OH−) is the most dangerous and devastating ROS due to its velocity to react against protein, nucleic acid, lipid membrane, and other molecules of cell which in turn induce DNA fragmentation and apoptosis. In addition to OH−, O2− also constitutes a second dangerous ROS owing to its capability to stimulate ferritin, lactoferin, and transferrin to release Fe and produce OH− via Fenton reaction.9 Consequently, DNA fragmentation, apoptosis, and cell losses triggered by UVB may be experienced by a variety of deeper organ including kidney.7 Numerous evidences point out that daily intake of flavonoids from plants is able to inhibit apoptosis in various cells including liver, penis, and prostate.9,10

Pimpinella alpina Molk (PM), is a botanical antioxidant and phytoandrogen containing flavonoids and stigmasterol that has conventionally been used to increase vitality and rejuvenation tonic for adult and old male in Indonesia.9 Several studies pointed out that PM treatment in rats have been proven able to ameliorate oxidative stress and impede apoptosis in liver, prostate, penile cells.10,11 The oxidative stress improvement was characterized by increased in glutathione peroxidase (GPx) and decreased in xanthine oxidase (XO), whereas inhibiting various tissues apoptosis marked by decreased in RNA Bax and caspase3, and increase in Bcl-2.12,13 However, the effect of PM on reducing apoptosis in kidney cells remain unclear.

According to the comprehensive meta-analysis on chronic kidney disease (CKD), the incidence of CKD worldwide is ranging from 11%-13%.7 Aside from as an accelerator of cardiovascular risk, CKD also cause decrease in renal function and to be a predictor of hospitalization,14 cognitive dysfunction,15 and poor quality of life.16 CKD is characterized by the existing protein within urine (proteinuria) and or reducing glomerular filtration rate (GFR).17 Accordingly, the degree of kidney damage originated from CKD can be determined using protein (albumin) to creatinine ratio and may be estimated from creatinine concentration.18 Pathogenesis of CKD is determined by glomerular pathology namely tubular atrophy, constituting the important hallmark of CKD.19 Tubular atrophy can be defined as the vanishing of any single tubular epithelial cells or whole epithelial cells of tubules and often in conjunction with interstitial fibrosis.7 To date, there are numerous evidences obtained from mice model that programmed cell death is a leading reason of tubular atrophy. An
Apoptosis occurs following UVB irradiation is exerted by dependent caspase models comprise intrinsic and extrinsic pathways. In the intrinsic apoptosis, process is initiated by alteration of mitochondrial potential membrane following acquire apoptotic stimuli. Subsequently, mitochondria lose their membrane integrity and induce releasing of cytochrome c which in turn stimulates procaspase9 and caspase3 produce DNA disintegration and cell death. Alternatively, in the extrinsic apoptosis, process is induced by the activation of FAS/CD95, by which initiator caspase9 is activated following formation CD95 death inducing signaling complex (DISC) which activates caspase3 as an initiator caspase. The activated caspase3 directly activate caspase3 or indirectly cleave Bid (Bcl2 interacting domain) into truncated Bid (tBid). Subsequently, tBid move to mitochondria and induce cytochrome c release and therefore activates caspase9 and caspase3 as executioner caspase.

Considering, PM has antioxidant properties, therefore using PM to protect kidney cells from ROS attack is a rational choice. Objective of this study is to elucidate the PM effect on reducing apoptosis in kidney cells following UVB radiation.

METHODS

In the posttest only control group design, 35 male rats of Sprague Dawley (SD) strain, 6 months aged, and 250-300 gram Body Weight (BW), were grouped into 7 comprising: Normal control group (NC-G), Negative control group (NC-G), Negative control group (NG-7) and NG-15, and PM treatment group consisting of four groups: PM10-7, PM15-7, P10-15, and P15-15. In NG-G, rats were neither exposure to UVB nor PM treatment. In both NG-7 and NG-15, rats were only exposure to UVB for 7 days, however, in NG-15 the 7 days left was utilized to restore damaging cell caused by the prior UVB irradiation. In PM treatment group all samples were exposure to UVB for 7 days and treated with PM100 and 150 mg doses per day for 7 (P10-7 & P15-8) and 15 days (P10-15 & P15-15) orally. All rats were preserved in adaptation for one week with environmental temperature (20°-24°C), stable wetness (55-60%), and restricted photoperiod (12 h daylight and 12 h shady) properties before starting treatment. All samples in each group obtain standard nutritional (Ain 93) and water adlibitum during the study. Kidney organ sample from rats were taken and RNA Bax and Caspase3 was isolated and measured by rt-PCR. Moreover, expression of Bax and caspase3 was also identified with immunohistochemical (IHC) stain method. Measurement of kidney apoptosis was performed at Gajah Mada University laboratory Yogyakarta. The study has been run following agreed by the Ethical Commission of Sultan Agung Islamic University.

RESULTS

Following PM treatment for 7 and 15 days, RNA Bax and caspase3 was isolated from kidney cell and protein expression of Bax and caspase3 in kidney cells were identified with rt-PCR and IHC staining method respectively at day 8 and 16. The results of the rt-PCR and IHC measurement are summarized in Table 1.
The result of the present study pointed out that the highest expression of RNA-Bax was in NG-7, followed by NG-15, P10-7, P15-7, P10-15, NC-G, and the lowest was in P15-15. Meanwhile, the highest RNA caspase3 expression was in NG-7, followed by NC-G, NG-15, P10-7, P15-7, P10-15, and the lowest was in P15-15. Likewise, by measurement of IHC stained method on Bax and Caspase3 expression showed the highest was in NG-7, followed by NG-15, P10-7, P15-7, NC-G, and the lowest was in P10-15 and P15-15. Moreover, the highest expression of Caspase3 protein was in NG-7, followed by NC-G, NG-15, P10-7, P15-7, P10-15, and the lowest was in P15-15. Anova analysis demonstrated that RNA Bax and caspase3 measured by rt-PCR and protein expression of Bax and Caspase3 assessed by IHC amongst group were significant different, $p < 0.05$. In order to recognize the difference expression of Bax and caspase3 between two group will be described below.

### RNA BAX expression

By Post Hoc LSD statistical analysis, RNA Bax expression in NG-7 was higher compared to that of NC-G, $p < 0.05$. Expression of RNA Bax in P10-7, P15-7, P10-15, and P15-15 was significantly lower compared to that of NG-7 and NG-15, $p < 0.05$ respectively. Meanwhile, RNA Bax expression in NG-15 was significantly lower compared to that of NG-7, $p < 0.05$. Moreover, RNA Bax expression in P15-15 was lower significantly compared to that of P10-15, P15-7, P10-7, $p < 0.05$. However, when compared to NC-G, the difference of RNA Bax in P15-15 was not significant, $p > 0.05$ (Figure 1).

### RNA Caspase3 expression

The result of statistical analysis showed that RNA caspase3 in NG-7 was significantly higher compared to that of NG-G, $p < 0.05$. Expression of RNA caspase3 in P10-7, P15-7, P10-15, and P15-15 was significantly lower compared to that of NG-7, P15-7, $p < 0.05$. However, RNA expression in NG-15 was significantly higher than that of NG-7, $p < 0.05$ respectively. RNA caspase3 expression in NG-15 was significantly lower than that of NG-7, $p < 0.05$. Moreover, appearance of RNA caspase3 in P15-15 was significant lower equated to that of P10-15, P15-7, P10-7, and NC-G, $p < 0.05$ (Figure 1).

### Expression of Bax protein

Statistical analysis using Post Hoc LSD on protein expression of Bax pointed out that in NG-7 and NG-15 was significantly higher than that of NC-G, $p < 0.05$. In P15-7, P10-15, and P15-15 Bax expression was significantly lower than that of NG-7 and NG-15, $p < 0.05$. However, Bax appearance in NG-7 and NG-15 had no significant difference, $p > 0.05$. Moreover, in P15-7, P10-15, and P15-15 Bax protein expression had no significantly difference when compared to that of NC-G, $p > 0.05$ (Figures 2 and 3).

### Expression of Caspase3 protein

The result of Post Hoc statistical analysis demonstrated that expression of caspase3 protein in NG-7 was higher than that of NC-G, $p < 0.05$. However, when compared to NG-15, the difference expression of caspase3 protein in Nor-G did not exist, $p > 0.05$. Caspase3 protein in NG-15 was significantly lower than that of NG-7, $p < 0.05$. Furthermore, caspase3 protein in P10-7, P15-7, P10-15, and P15-15 was significantly lower than that of NG-7, $p < 0.05$, whereas compared to that of NG-15 the significant difference did not exist, $p > 0.05$. Caspase3 in P150-15, P10-15, and P15-7 was not significantly higher than that of NC-G, $p > 0.05$ (Figures 2 and 3).

### DISCUSSION

In the present study pointed out that UVB irradiation during ten minutes per day for seven days works appropriately induce apoptosis in kidney cells, albeit UVB irradiation was done on skin. It was characterized by the increase in protein expression of Bax and caspase3 in negative control group compared to that of normal group. As hypothesized previously, UVB irradiation was capable of increasing H$_2$O$_2$ level, by which ROS production particularly OH• can be stimulated following circulated in systemic blood stream. It is also supported by another study was published by Shahzad M et al. demonstrated that H$_2$O$_2$ was able to induce nephrotoxicity, oxidative stress, apoptosis, and reduced cell survival. These oxidative stress and apoptosis were facilitated by enhancing protein pro-apoptosis Bax and down-regulated anti-apoptosis such as Bcl-xL. The result of the present study was also strengthened by the past study that UVB irradiation was capable of inducing apoptosis in liver cells interceded by ROS particularly O$_2^-$ and OH•. O$_2^-$ and OH• free radicals are resulted from Fenton reaction of circulated in systemic blood stream. It is also supported by another study was published by Chang and colleague. Subsequently, H$_2$O$_2$ is converted to OH• via Fenton reaction triggered by enhancement of Fe concentration released from ferritin, lactoferrin, and transferrin induced by O$_2^-$ and OH•. Moreover, OH• instantaneously induced oxidative stress characterized by the increment level of MDA and 8-OHdG, in contrary the decrement of total antioxidant capacity (TAC) and Gpx activity and eventually DNA fragmentation and apoptosis.

**Table 1: Mean of Bax and Caspase3 Expression in Kidney following PM Treatment.**

| Variables | NC-G N=5 ±x±SD | NG-7 N=5 ±x±SD | NG-15 N=5 ±x±SD | Groups P10-7 N=5 ±x±SD | P15-7 N=5 ±x±SD | P10-15 N=5 ±x±SD | P15-15 N=5 ±x±SD | P (Anova) |
|-----------|----------------|----------------|----------------|--------------------------|----------------|----------------|----------------|----------|
| RNA Bax (µg) | 8.058 (0.478) | 27.336 (3.742) | 21.444 (1.060) | 14.004 (0.998) | 12.598 (1.482) | 10.814 (0.706) | 7.526 (1.423) | 0.000 |
| IHC Bax (%) | 0.800 (0.447) | 2.800 (0.447) | 2.400 (0.547) | 2.000 (0.707) | 0.800 (1.095) | 0.600 (0.547) | 0.600 (0.447) | 0.000 |
| RNA Caspase3 (µg) | 15.070 (2.351) | 22.802 (4.290) | 15.504 (2.959) | 11.692 (1.245) | 10.800 (0.615) | 10.382 (0.644) | 7.328 (0.453) | 0.000 |
| IHC Caspase3 (%) | 1.400 (0.894) | 2.800 (0.447) | 1.400 (0.547) | 1.200 (0.447) | 1.200 (1.095) | 0.800 (0.547) | 0.800 (0.836) | 0.001 |

Malondialdehyde (MDA). It was plausible, considering apoptosis be stimulated following circulated in systemic blood stream. It is also supported by another study was published by Shahzad M et al. demonstrated that H$_2$O$_2$ was able to induce nephrotoxicity, oxidative stress, apoptosis, and reduced cell survival. These oxidative stress and apoptosis were facilitated by enhancing protein pro-apoptosis Bax and down-regulated anti-apoptosis such as Bcl-xL. The result of the present study was also strengthened by the past study that UVB irradiation was capable of inducing apoptosis in liver cells interceded by ROS particularly O$_2^-$ and OH•. O$_2^-$ and OH• free radicals are resulted from Fenton reaction of circulated in systemic blood stream. Subsequently, H$_2$O$_2$ is converted to OH• via Fenton reaction triggered by enhancement of Fe concentration released from ferritin, lactoferrin, and transferrin induced by O$_2^-$ and OH•. Moreover, OH• instantaneously induced oxidative stress characterized by the increment level of MDA and 8-OHdG, in contrary the decrement of total antioxidant capacity (TAC) and Gpx activity and eventually DNA fragmentation and apoptosis. In the present study PM treatment with 150 mg/day for seven days and 100 mg and 150 mg/day for 15 days could ameliorate apoptosis in kidney cells characterized by down-regulated protein pro-apoptosis Bax and caspase3. The decrease in Bax and Caspase3 expression in the 100 and 150 mg dose per day, both for 7- and 15-days treatment were equivalent to normal. In the present study Bax and caspase3 expression is in line with the study was published by Widayati et al. demonstrated that treatment of PM with 100 and 150 mg dose/day was able to decrease Bax and Caspase3 expression in liver cells following exposure to UVB light. In this study also demonstrated that decrease in Bax and Caspase3 expression was preceded by improvement of stress oxidative characterized by increased in superoxydisedismutase (SOD), catalase (CAT), and glutathion peroxidase (GPx) activities, and decreased in xanthin oxidase (XO), 8-hydroxy-2-deoxyguanosine (8-OHdG) and Malondialdehyde (MDA). It was plausible, considering apoptosis induced by UVB radiation is heralded by rigorous oxidative stress.
Figure 1: Bax and Caspase3 Expressions following PM Treatment in each group, measured by rtPCR. Post Hoc analysis: *P < 0.05, **P > 0.05.

Figure 2: Bax and Caspase-3 Expression following Treatment in each group, measured by IHC stain methods.

Figure 3: Bax and Caspase3 Expressions following Treatment in each group, measured by IHC stain methods. *p<0.05; **P>0.05.
Improvement of Apoptosis in kidney cells was induced by UVB irradiation following treatment of PM may be mediated by stigmasterol and flavonoids contained in Pimpinella alpina Molk. Stigmasterol is an androgen derive from plant that have been proven capable of increasing testosterone concentration and inhibition of apoptosis in Sprague Dawley male's prostate and penile cells of rat model. It was plausible, since testosterone is anti-apoptosis owing to its capability to increase Bcl-2 and decrease caspase3 expression. Bcl-2 is an anti-apoptosis along with Bax as pro-apoptosis protein have critical role in cellular apoptosis regulation, particularly using intrinsic pathway mediated by alteration of mitochondrial permeability and therefore cytochrome c release. In this context following UVB radiation, ratio of Bax/Bcl-2 was increased and lead to apoptosis. Conversely, following PM treatment Bax/Bcl-2 ratio was decreased and lead to inhibition of apoptosis. In addition, flavonoids have been documented was able to reduce oxidative stress characterized by the enhancement of SOD, GPx, CAT activities, and decreased in activity of XO, concentration of MDA and 8-OHdG which in turn reduce apoptosis.

In the present study apoptosis was measured by rt-PCR and IHC stain method. Rt-PCR was used to identify RNA Bax and caspase3 expression isolated from kidney cells, meanwhile IHC was used to identify protein expression of Bax and caspase3 taken from kidney cells. In the present study expression of Bax and caspase3 was recognized by both rt-PCR and IHC methods have similar pattern, increased and decreased in Bax and caspase3 expression tend in parallel fashion (Figure 4). In addition, RNA Bax expression and protein expression of Bax have strong correlation \( r = 0.753; \ P < 0.05 \). Similarly, RNA caspase-3 expression and protein expression of caspase3 also have positive correlation \( r = 0.661; \ P < 0.05 \) (Figure 5). These results suggested that both rt-PCR and IHC staining method are appropriate to measure expression of Bax and caspase3 as marker of apoptosis cells. Finally, the result of the present study, treatment of PM particularly in 100 mg dose per day for 15 days and 150 mg dose per day for 7 and 15 days could improve apoptosis in kidney cells characterized by decrease in RNA and protein expression of Bax and caspase3. Moreover, the decrease in apoptosis marker as mentioned above was comparable to normal.

CONCLUSION

In summary, treatment of PM with 100 and 150 mg daily dose for seven and fifteen days could reduce Bax and Caspase3 protein expression in kidney cells following UVB radiation. Even the decrease in protein Bax and caspase3 was comparable to normal condition.

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CONFLICTS OF INTEREST

No conflict of interest to be declared related to data collection, statistical analysis, writing of the manuscript, and publish the results.

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Graphical Abstract
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