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Original Article

Influence of *Polygonum minus* Aqueous Extract on Monoamine Oxidase-A Transcriptional Activators KLF-11 and SIRT1 Levels in the Hippocampus of Stress-induced Depressed Mice

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ABSTRACT

Background: Monoamine oxidase-A (MAO-A) enzyme is responsible for the breakdown of monoamines (serotonin and norepinephrine). MAO-A is also a target to treat the depressive disorders. Kruppel-likefactor11(KLF11) and Sirtuin1(SIRT1) are the main transcriptional activators of MAO-A. *Polygonum minus* (*P. minus*) aqueous extract showed some neuroprotective properties in previous studies like improved memory and positive mood. The aim of current study was to evaluate the effects of *P. minus* aqueous effects on KLF11 and SIRT1 levels in hippocampus of stressed mice. **Materials and Methods:** Balb/c mice (22g-26g) were used in this study and *P. minus* aqueous extract was administered for 8 weeks with three different doses (*P. minus* 50mg, *P. minus* 100 mg and *P. minus* 200mg) in different groups. Amitriptyline 20 mg was used as positive control antidepressant. Chronic ultra-mild stress protocol was used for 6 weeks to induce the depression among mice groups except control group. **Results**: The results showed that all doses of *P. minus* reduce the KLF11 level significantly but only *P. minus* 200mg showed reduction in SIRT1 level in hippocampus of mice significantly. **Conclusion:** It is concluded that *P. minus* aqueous extract treatment showed a significant reverse in an elevated level of KLF11 and SIRT1 in hippocampus of stressed mice after treatment of 8 weeks.

Keywords: MAO-A, *P. minus*, KLF11, SIRT1, Stress, Mice.

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INTRODUCTION

Monoamine oxidase (MAO) is the enzyme responsible for monoamine breakdown. MAO inhibitors have also been proposed as antidepressants by inhibiting MAO-A.[1] Monoamine oxidases are enzymes that break down the monoamines' oxidation by cutting off their amine group with oxygen. Monoamine oxidase A and B have long been known as prospective therapeutic targets for depression and neurodegenerative diseases. Because of its role in serotonin and norepinephrine modulation, MAO-A is frequently associated with depression.[2] The MAOs are a flavin-containing amine oxidoreductase protein family.[3] MAOs have a vital role in the inactivation of monoamine neurotransmitters and the breakdown of monoamines present in food. They have been connected to various mental and neurological diseases, some of which can be treated with monoamine oxidase inhibitors (MAOIs), which prevent MAOs from performing their functions.[4]

Kruppel-likefactor11 (KLF11) is a cytostatic protein member of the Specificity protein 1/Kruppel like factor (Sp1/KLF) transcription factor family. It acts as a transcriptional activator for MAO-A.[5] KLF11 increases the brain's MAO-A expression by attaching on binding sites and play an important role in stress-related depressive disorders.[6] KLF11 protein expression usually significantly increases in the hippocampus, so no significant changes in KLF11 expression were detected in the striatum and hypothalamus in the previous research that suggested that KLF11 protein expression is selectively affected by chronic stress.[7] It is observed in a previous study KLF11 became suppressed in hypermethylation and upregulated in hypomethylation.[8] A researcher discovered that continuous stress exposure induces glucocorticoids in blood and activates the KLF11/MAO-A pathway in the rat brain, which results in increased MAO-A mRNA and enzymatic activity. An overexpressing of KLF11 increases MAO-A mRNA levels and enzymatic activity.[6]

Sirtuin 1, a silent mating type information regulation 2 homolog 1 (SIRT1) is a protein that belongs to the Sirtuin family and some previous studies suggested that SIRT1 protein could affect monoamine transmitter levels in the brain by activating MAO-A transcription. therefore, dysregulation of SIRT1 is also involved in depression.[9-10] KLF11 directly regulates MAO-A gene transcription, but SIRT1 indirectly regulates MAO-A gene transcription. Flavonoids from a herbal extract can alter the KLF 11 and SIRT1 level in the brain mostly, they can downregulate them; in that case, MAO-A expression will be decreased.[11] An important thing related to SIRT1 is that it has been reported to deacetylate and may activate the NHLH2 (Nescient Helix-Loop-Helix 2), a transcription factor of the MAOA gene.[9] Sirt1 showed more binding in the prefrontal cortex and decreased in the hypothalamus. Sirt1 regulation of MAO-A expression can be mediated through NHLH2 that have a binding site on the methylated regions of the MAO-A promoter.[12]

Polygonum minus Huds, synonymous with *Pericardia minor,* is from the family Polygonaceae and is commonly referred to as Kesum or laksa leaf in Malaysia. This herb is associated with antioxidant activities and has many beneficial effects.[13] The leaves of this herb have been reported to

be high in an antioxidant flavonoid named Quercetin-3-glucuronide and Quercitrin (Quercetin 3-rhamnoside). Quercetin 3-glucuronide is a flavanol glucuronide, a phenolic substance also known as Miquelianin.[14] The bioactive profile of *Polygonum minus* leaf part shows that quercetin-3-glucuronide is an abundant bioactive flavonoid in its aqueous leaf extract.[15]

This study investigated the effects of *Polygonum minus* leaf extract on transcriptional factors of MAO-A like KLF-11 and SIRT1 in stress-induced depressed mice.

MATERIALS AND METHODS

BioKesum® supplement, A water-soluble commercially available *Polygonum minus* aqueous extract containing flavonoids from its leaf part (standardized as quercetin-3-glucuronide 0.45% and 0.15% quercitrin) was obtained by Biotropics Malaysia Berhad. Amitriptyline (Apotex Inc. Canada).

Animals and Experimental Protocol

Ault male balb/c mice (22–26g) were purchased from the Animal Research and Service Centre, Kelantan Campus, Universiti Sains Malaysia. A chronic ultra- mild stress technique was adopted to induce stress on animals. The normal control group was without any Chronic ultra- mild stress (CUMS) remaining groups were influenced by Chronic ultra- mild stress (CUMS). Chronic ultra-mild stress remained for 6 weeks. Treatment remained for 8weeks. Table 1 is expressing the number of groups and their protocols individually.

Ethical Approval

All experimental procedures were carried out after getting the approval from USM Institutional Animal Care and Use Committee (USM IACUC) of Universiti Sains Malaysia (No of Animal Ethical Approval: USM/IACUC/2020/ (123) (1075). and USM/IACUC/2021/ (127) (1129).

Chronic Ultra Mild Stress Protocol

Two different stressors were given on daily basis; first stress was applied in the morning and the second stress in the evening, as followed by the latest research.[16] As shown in Figure 1.

Measurement of KLF 11 and SIRT1 from hippocampus

The concentrations of KLF 11 and SIRT 1 were measured from the hippocampus by Elisa Kits (Qayee Bio-Technology Co., Ltd Unit 201-229 Shanghai, China) at 450nm by using a microplate reader and all protocol was followed absolutely as provided by the manufacturer.

Table 1: Experimental Groups and Protocols.

Groups	Treatment
Group 1	Control group (Without CUMS) treated with distilled water only
Group 2	(CUMS group, a negative Control) Chronic ultra- mild stress (CUMS) treated with 6 weeks of CUMS and distilled water for 8 weeks
Group 3	CUMS+ Amitriptyline 20mg, a Positive Control
Group 4	CUMS+ *P. minus* treated group with 50mg/kg
Group 5	CUMS+ *P. minus* treated group with 100mg/kg
Group 6	CUMS+ *P. minus* treated group with 200mg/kg

Chronic Ultra Mild Stress Protocol			
Crowded housing	6 hours	Cage tilt	8 hours
Restricted access to Food and water	8 hours	Continuous light	Over the night
Forced swimming	20min	Tail pinch	2 minutes for each
Restraint stress	2 hours	Foreign object in Cage	Over the night
Cage tilt	8 hours	Continuous light	Over the night
Restricted access to food	8hours	Crowded Housing	6 hours
Forced swimming	20min	Wet bedding	Over the night

Figure 1: Chronic Ultra Mild Stress Protocol.

Statistical Analysis

Statistical analysis was performed using SPSS version 26 statistical software (IBM, New York, NY, USA). Data were analyzed by one-way ANOVA followed by post-hoc comparisons between all groups by using Tukey test. Differences in mean values with $p < 0.05$ were considered as a level of significance in all tests. Means were calculated with standard error means (SEM).

RESULTS

Effects of *P. minus* extract supplement on Kruppel like factor11 (KLF-11) Level

KLF11 protein level was measured from the hippocampus of the brain. Results are sketched in Figure 2, results showed a significant increased level in KLF11 protein in CUMS group as compared to control group, whereas CUMS+ Amitriptyline 20mg and CUMS+ *P. minus* 50mg treated group reversed the KLF11 level by $p < 0.05$ significance. Maximum dose administration groups (CUMS+ *P. minus* 100 mg and *P. minus* 200mg) reversed the KLF11 significantly. Maximum dose groups retained the KLF11 in the hippocampus more than the positive control.

Effects of *P. minus* extract supplement on Sirtuin 1 (SIRT1) Level

As shown in Figure 3, the Stress group (CUMS) showed a significant increase in SIRT1 level as compared to the control group, Only CUMS+ *P. minus* 200mg group reversed significantly. remaining all groups did

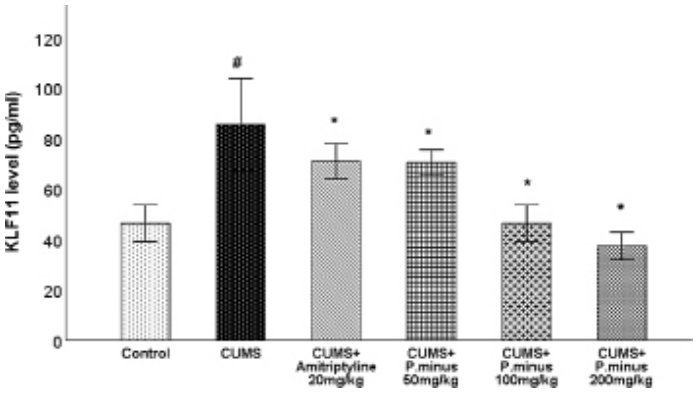

Figure 2: Effects of *P. minus* aqueous extract on Kruppel like factor11(KLF11) level(pg/ml) in CUMS induced depressive mice. Values were expressed in ± SEM (n=8).
($p < 0.05$), vs. Control group; * ($p < 0.05$), vs. CUMS group.

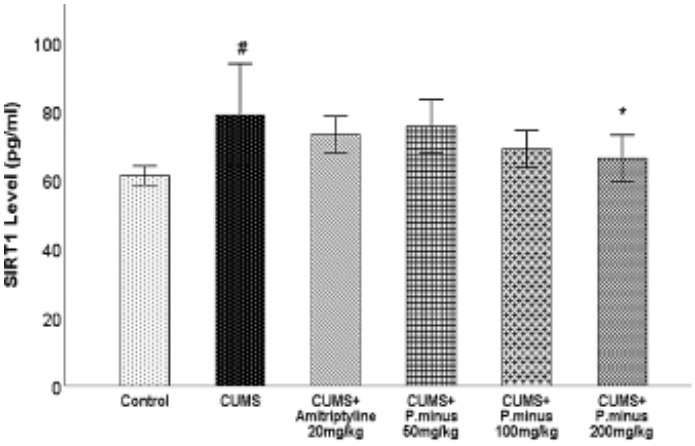

Figure 3: Effects of *P. minus* aqueous extract on Sirtuin 1(SIRT1) level(pg/ml) in CUMS induced depressive mice. Values were expressed in ± SEM (n=8). # ($p < 0.05$), vs. Control group; * ($p < 0.05$), vs. CUMS group.

not show any significant decrease as compared to CUMS treated group, even positive control group also showed non-significant decrease in comparison of negative control (CUMS) group.

DISCUSSION

KLF11-MAO-A and SIRT1-MAO-A pathways have advanced connections in new depression studies. KLF11 and SIRT1 are the main transcription key activator of MAO-A.[11] KLF11 is directly involved in MAO-A gene activation whereas, SIRT1 is indirectly involved in the activation of the MAO-A gene may be through NHLH2 (Nescient Helix-Loop-Helix 2) as shown in Figure 2.[12] Downregulation of SIRT1 in the brain has some effect on CUMS-induced depression-like behaviors such as anorexia, anhedonia and hopelessness. Another side the increased expression of SIRT1 may cause severe depressive-like symptoms. The abnormal expression of SIRT1 may affect the indirect transcriptional regulation mechanism for MAO-A, and acetylation of signalling protein may affect the neuroplasticity. In ultimate results, it contributes to MDD.[17] SIRT1 in the brain regulates mood and behavior by deacetylating the NHLH2 transcription factor that activates MAO-A transcription. SIRT1 is related to anxiety and other psychiatric illnesses. These data indicate the clear part of SIRT1 in modulating the behavior and mood, which can lead towards the development of brain-permeable SIRT1 drugs for neurodegenerative and psychiatric diseases.[9] A recent study showed that KLF11 and SIRT1 are the main transcriptional up-regulators and activators of MAO-A. KLF11 directly activate the MAO-A gene transcription while SIRT1 indirectly activate it. They also concluded that flavonoids from herbal extract could alter the KLF 11 and SIRT1 level in the brain. Mostly, they could downregulate them, and MAO-A expression was decreased.[11]

Chronic ultra-mild stress can significantly increase the KLF11 protein level (Figure 3), same results were observed by another study in which KLF11 was increased under influence of chronic stress.[18] Stress can increase these two factors which further enhance the MAO-A gene transcription and lead to degradation of monoamines abnormally, some researchers also suggested that herbal extracts that contain flavonoids have more chance to interfere with the KLF11-MAO-A and SIRT1-MAO-A molecular pathways.[11] In the current study, KLF 11 and SIRT1 proteins were examined for further digging out the reason behind MAO-A inhibition. *P. minus* effects on KLF11-MAO-A and SIRT1-MAO-A pathway showed that it may reverse the KLF 11 protein level after treatment of 8 weeks significantly with all doses but in the case of SIRT1 only *P. minus* 200 mg treatment showed a significant decrease. Aqueous extract of this plant showed significant beneficial effects on memory and cognitive functions with 100mg/kg dose in mice.[19] Because of its therapeutic significance, this species has been the subject of several investigations. The identification of the biomolecules produced by *P. minus* and their chemical characteristics has been investigated. *P. minus* has been demonstrated to have an excellent antioxidant activity in previous research, which might be owing to its high flavonoid and phenolic component content.[20]

Previous studies also suggested that chronic stress exposure can increase the KLF11. SIRT1 level in mice brain, their findings showed that might be these increased levels are due to increased corticosterone level in the blood.[17-18] In current findings, it was also observed that corticosterone level was increased in stressed mice but reversed by *P.minus* treatment significantly with 100mg and 200mg dosed treatment so it could be another reason for the decrease in KLF11 and SIRT1 but still in the depression diagnosis it is unclear, still unknown that corticosterone is a first responsible factor of depression causing by decreasing the brain volume or an abnormality in MAO-A gene leads depression first.[21]

Increased level of KLF11 can increase the MAO-A level which further decreases the monoamines like serotonin and norepinephrine, which can further lead a severe depression. Our treatment groups including *P. minus* 100mg and *P. minus* 200 mg dose groups significantly reversed the KLF11 protein level in comparison to the stress group. While *P. minus* 50 mg and Amitriptyline 20 mg treated groups showed an increase by $p < 0.05$ level of significance.

In the case of SIRT1, as shown in Figure 4, the stress group showed a significant increase in SIRT1, but it was only reversed by *P. minus* 200mg treated group significantly. Another study showed that chronic stress can increase the SIRT1 level in the mice brain significantly.[17]

P. minus aqueous extracts revealed more antioxidant activity than other common herbs such as Ulam raja, selom, pegaga, and curry leaves, with antioxidant activity equal to the synthetic antioxidant butylhydroxytoluene (BHT).[22] *P. minus* is acknowledged as a promising source of natural antioxidants.[23] Q3G is an effective anti-oxidative metabolite of quercetin.[24] It has been shown that it can go from the small intestine to the brain,[25] which shows its importance for the central nervous system. quercetin-3-glucuronide medication significantly improved Alzheimer's impairments in the hippocampal formation, basal synaptic transmission and long-term potentiation.[26] This component may involve

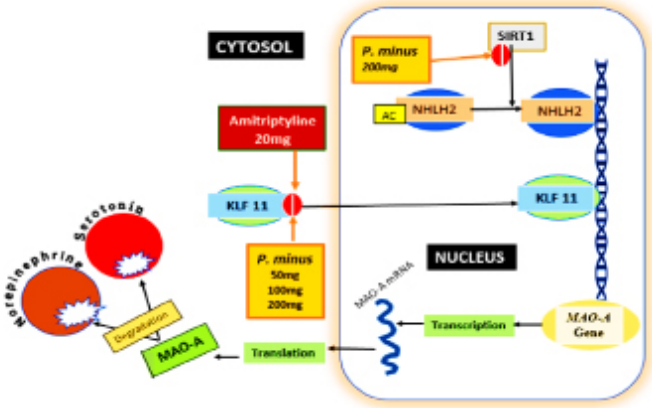

Figure 4: Effects of *P. minus* aqueous extract on MAO-A enzyme and KLF11-MAO- A and SIRT1-MAO-A molecular signalling pathways.

in MAO-A inhibition by reducing the formation of hydrogen peroxide when MAO-A interacts with serotonin.[27]

Quercitrin (Quercetin 3-rhamnoside) is the second most abundant constituent of *Polygonum minus* aqueous leaf extract.[15] Quercitrin is a glycoside formed by the flavonoid quercetin and the deoxy sugar rhamnose.[28] It is an antioxidant flavonoid, derived from quercetin.[29] Quercitrin has several pharmacological activities, including, anti-inflammatory, antimicrobial and hypolipidemic effects.[30]

Our findings also showed that amitriptyline may have involvement only in the KLF11-MAO-A pathway rather than the SIRT1-MAO-A pathway. As amitriptyline is a tricyclic anti-depressant but has some MAO-A inhibitory effect as well, this study is showing that its MAO-A inhibitory activity was might be due to KLF11-MAO-A pathway interruption.

Current findings suggest that *P. minus* aqueous extract has reducing effect in the KLF11 level more than SIRT1 level. All of the *P. minus* treated groups showed a significant decrease in KLF11 protein level in hippocampus of mice, whereas only maximum dose *P. minus* 200mg treated group showed significant decrease in SIRT1 level. This study is showing the results regarding effects of *P. minus* aqueous extract on KLF11 and SIRT 1 level first time, before it there was no specific study found regarding this extract, but previously done research work showed that a flavonoid extract had reversed the stress-induced increase in KLF11 and SIRT1 level significantly.[11]

KLF11 is formed in response to neuronal stress, which transcriptionally activates MAO-A which increase the MAO-mRNA. SIRT1 deacetylates the brain-specific helix-loop-helix transcription factor NHLH2 on lysine 49 to increase its activation. Inhibition of all of these two proteins will reduce the transcription of the MAO-A gene and decrease the amount of MAO-A mRNA It lowers the translation process of MAO-A enzyme production. Decreased enzyme activity will lower the degradation of monoamines and increase the serotonin and norepinephrine levels in the brain for effective neurotransmission.[9]

CONCLUSION

It is concluded that *P. minus* aqueous extract showed a significant decrease in an elevated level of MAO-A transcriptional factors KLF11and SIRT1 in hippocampus of stress induced depressive mice. KLF11 was reversed significantly with all doses of *P. minus* extract whereas SIRT1 was reversed with *P. minus* 200mg dose only.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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