ISSN: 3033-3504

Journal of Clinical Medicine and Regenerative Medicine

SCIENTIFIC Research and Community

Research Article

Open Access

The Benefit of Melinjo Peel (Gnetum Gnemon) Ethanol Extract to Prevent Hepatocytes from Damage in Hyperuricemia Rat Model - Induced High Fructose

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ABSTRACT

Introduction: Hyperuricemia can induce a dysfunctional exchange of sodium and calcium in mitochondria which will lead to the production of reactive oxygen species (ROS). ROS plays a role in aging, DNA damage, oxidation, production of inflammatory cytokines, and cell apoptosis. Uric acid metabolism is catalyzed by xanthine oxidase (XO) to produce hydrogen peroxide (H_2O_2) which can form scar tissue in the liver. Alt1 and Hgf expression plays a role in reflecting hepatic cell from damage and repair.

Method: It was a true experimental study with post-test only control group design using stored biological material of 32 samples, divided into four groups, K0: the control group without treatment; P1: intervention group of 86% fructose and 0.5% CMC; P2: intervention group of 86% fructose and allopurinol; P3: intervention group of 86% fructose and ethanol extract of melinjo peel. Alt1 and Hgf expression determination using real-time PCR (rt-PCR) with Livask method $2^{-\Delta Ct}$.

Result: Alt1 expression in hyperuricemia model rats after 10 days of treatment with ethanol extract of melinjo peel was lower than the control group (p=0.001), CMC (p=0.001), and allopurinol (p=0.059). Hgf expression tends to have the same cycling threshold in all groups (p=0.065). There was no correlation between Alt1 expression and Hgf after 10 days of treatment (r=-0.08; p=0.661).

Conclusion: The ethanol extract of melinjo peel has the potential to be a hepato-protector in the hyperuricemia model rat by reducing Alt1 expression better than the other treatment groups.

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Received: December 28, 2024; **Accepted:** January 02, 2025, **Published:** January 13, 2025

Keyword: Melinjo Peel Ethanol Extract, Alt1, HGF, Hyperuricemia, Rat

Introduction

The Global Burden of Disease (GBD) estimates that 1-2% of the world's population is affected by hyperuricemia. The 2015-2016 National Health & Nutrition Examination Survey (NHANES) reported that the prevalence of gout in adults in the United States was 9.2 million people (3.9%), with the proportion of adult males at 5.9 million people (5.2%) and adult females at 3.3 million people (2.7%) [1]. Population-based data on the prevalence of hyperuricemia from 24 countries indicate that hyperuricemia is relatively more common in the Asian region, with the highest percentage in Taiwan at 52%, followed by China and the Philippines at 25% and Indonesia at 18%. Of the 21% of the population who experienced hyperuricemia, 3.9% of patients experienced complications such as metabolic syndrome, diabetes mellitus, nephrolithiasis and even chronic renal failure [2].

Risk factors such as age, gender, elevated blood pressure, body mass index (BMI), dyslipidemia, alcohol consumption, excessive consumption of meat and seafood can trigger an increase in uric acid [3,4]. Fructose intake can induce the pathogenesis of hyperuricemia [5]. In addition, the endogenous mechanism of uric acid formation also occurs continuously from the metabolism of nuclear 2-ribonucleic acid, which is then converted into hypoxanthine, xanthine and uric acid by the heparin-produced enzyme xanthine oxidase (XO) [6].

Xanthine oxidase enzymes play an important role in the synthesis of uric acid and are very active in the liver, intestine and kidneys. Xanthine Oxidase produces hydrogen peroxide (H2O2) which can cause scar tissue formation in the liver structure [7]. Uric acid stimulates increased reactive oxygen species (ROS) metabolism and activation of nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase), which produces superoxide radicals and NOX4 subunits [8]. These molecules can reduce the mitochondrial membrane potential in hepatocytes and induce lipid accumulation and liver fibrosis [9-11]. Damage to hepatocytes

can lead to an increase in the enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Studies using uric acid or high fructose diet induced hyperuricemia in rats have shown high levels of ALT and AST [12].

One of the effective drugs to treat hyperuricemia is allopurinol. However, allopurinol has a number of side effects, including rash, nausea and vomiting, and at high doses can cause liver damage [13]. Therefore, other alternatives derived from natural materials are needed as an option in the treatment of hyperuricemia that can prevent the risk of liver damage.

Melinjo is a type of tree fruit that grows in tropical areas, including Indonesia. Melinjo fruit or seeds are used by the community as a side dish or vegetable [14]. However, other functions of melinjo are not widely used, and often the skin of melinjo is neglected and becomes household waste. Melinjo peel contains compounds that can inhibit the action of the XO enzyme, including flavonoids. Ethanol extract of melinjo peel can reduce uric acid levels in hyperuricemia model rats [15-17]. This peel is also anti-inflammatory effect [18]. Flavonoids can also inhibit oxidative reactions and reduce inflammation [19,20]. However, the protective effect of melinjo peel ethanol extract on hepatocyte damage in hyperuricemia as seen by the expression of Alt1 and Hgf has never been studied before, so further research needs to be done to analyze the effect of melinjo peel ethanol extract (*Gnetum gnemon*) on the expression of Alt1 and Hgf in rat hyperuricemia model liver.

Material and Method

Stored Biological Material

This study was a true experimental study using a stored biological material with a post-test only control group design. The stored biological material is RNA isolates from liver of white male Wistar hyperuricemia rat model. Thirty-two samples that were stored in the freezer at -800C used in this study. RNA isolates that were used meet the criteria of the International Agency for Research on Cancer (IARC, 2017), which an RNA concentration at least 40 µg/m with an A260/280 ratio value of 1.8-2.2.

Realtime PCR (rt-PCR)

The working solution (20 µl) was prepared as follows: KAPA SYBR RT mix 10 µl + primer forward 1 µl + primer reserve 1 µl + NF water as 6 µl and cDNA 2 µl. Alt 1 gene Forward: 5' TGT GCC TCC TGG AAG AGA CT 3' Reserve: 5' TGT TGC GTC AGA GAC TGT CC 3'. Hgf gene Forward: 5' GAA TGC ATG ACC TGC AAC GG 3' Reserve: 5' TGT CGG GAT ATC TTT CCG GC 3'. GAPDH gene Forward: 5' CCA TCA CCA TCT TCC AGG AG 3' Reserve: 5' CCT GCT TCA CCA CCT TCT TG 3'. Expression measurements were performed using the Rotor gene for 45 cycles.

Statistical Analysis

Normality of Ct Alt1 and Ct Hgf data was analyzed by Saphiro-Wilk test. To know the different of Alt1 expression between control group and hyperucemia model was analyzed by mann-whitney u test and kruskal-wallis to analyze the comparison of Alt1 expression among groups. Hgf Expression different between groups was analyzed by independent t - test and one way anova to analyze the comparison of Hgf expression between control and other groups (CMC, melinjo peel and allopurinol groups). Correlation between Alt1 gene and Hgf gene expression after 10 days of treatment were analyzed with Spearman correlation, $p<0.05$.

Results

The quality of stored biological material was assessed by examining the concentration and purity of RNA extraction using a nanodrop device, and the average RNA concentration was 4538.7+1117.9 g/mL with RNA purity of 2.05+0.04.

Table1 above shown a significant difference (p=0.001) in the mean ΔCt Alt1 of each group. The highest mean cycling threshold was obtained in group P3 (7.49+0.58). Based on the average cycling threshold, it can be seen that group P3 has a lower Alt1 expression compared to the other groups.

Table 1: Mean Difference in Cycling Threshold of Alt1 Gene on Control Group, CMC, Allopurinol, and Extract Ethanol of Melinjo Peel

Groups	Mean+SD (ΔCt)	p value[a]	p value[b]
K	-1,45+3,50	0,081	0,001
P1	-1,03+0,52	0,440	
P2	2,45+4,93	0,049	
P3	7,49+0,58	0,006	

K: normal rat; P1: hiperuremia model with CMC 0,5%; P2: hiperuricemia model with allopurinol; P3: hiperuricemia model with extract ethanol melinjo peel; [a] *Shapiro-Wilk*; [b]*Kruskal-Wallis*

Based on figure 1 Alt1 gene expression on hyperuricemia rat model which is give allopurinol 0.09 fold change lower than untreat hyperuricemia and extract melinjo peel 0.003 fold change lower. However extract ethanol melinjo peel 0.03 fold change on Alt1 expression lower than allopurinol.

Alt1 Gene Expression

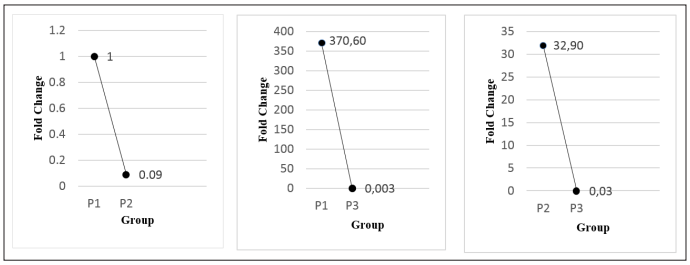

Figure 1: Alt1 Gene Expression Difference Among Control Group, Allopurinol and Extract Ethanol Melinjo Peel.

Table 2 above shows a non-significant difference (p=0.065) in the mean ΔCt of each group. The highest mean cycling threshold was obtained in group P1 (14.18±1.90). Based on the average cycling threshold, it can be seen that group P1 has a lower Hgf expression compared to the other groups.

Table 2: Mean Difference in Cycling Threshold of HGF Gene on Control Group, CMC, Allopurinol, and Extract Ethanol of Melinjo Peel

Groups	Mean+SD (ΔCt)	p value[a]	p value[b]
K	-1,45+3,50	0,081	0,001
P1	-1,03+0,52	0,440	
P2	2,45+4,93	0,049	
P3	7,49+0,58	0,006	

K: normal rat; P1: hiperuremia model with CMC 0,5%; P2: hiperuricemia model with allopurinol; P3: hiperuricemia model with extract ethanol melinjo peel; [a]Shapiro-Wilk; [b]One Way ANOVA

Based on figure 2 Hgf gene expression on Hyperuricemia rat model which is give allopurinol 4 fold change higher than untreat hyperuricemia and extract melinjo peel 2.8 fold change higher. However extract ethanol melinjo peel 0.71 fold change on Hgf expression lower than allopurinol.

HGF Gene Expression

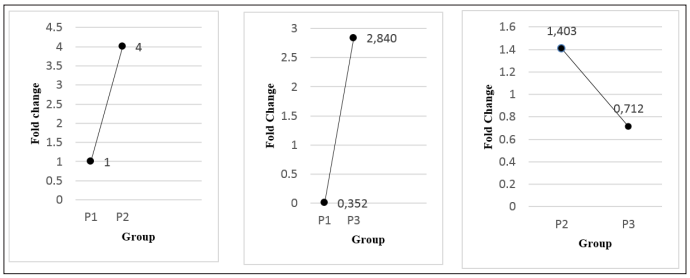

Figure 2:
P1: Hiperuremia Model with CMC 0,5%
P2: Hiperuricemia Model with Allopurinol
P3: Hiperuricemia Model with Extract Ethanol Melinjo Peel

Table 3 shown that the correlation between Alt1 expression and Hgf after 10 days of treatment is very weak negative (r=-0.08) and not significant (p=0.661).

Table 3: The Correlation Between Alt1 Gene Expression and HGF Gene After 10 Days of Treatment

Groups	Mean+SD (ΔCt)	Mean+SD (ΔCt Hgf)	r[a]	*p value*[b]
K	-1,45+3,50	13,71+1,28	-0,08	0,661
P1	-1,03+0,52	14,18+1,90		
P2	2,45+4,93	12,18+1,65		
P3	7,49+0,58	12,67+1,28		

K: normal rat; P1: hiperuremia model with CMC 0,5%P2: hiperuricemia model with allopurinol P3: hiperuricemia model with extract ethanol melinjo peel Coeficien correlation , Spearman

Discussion

In this study, hyperuricemia was induced by feeding fructose for 10 days. Dietary fructose can cause metabolic syndrome, one of which is hyperuricemia [21]. Fructose-induced Wistar rats had elevated uric acid levels after 7- 14 days of treatment [22]. Wistar rats induced with 86% fructose for 10 days increased uric acid levels [17]. Fructose is one of the three main monosaccharides consumed by humans, along with glucose and galactose. Free fructose is absorbed directly from the intestinal lumen and transported into the circulation mainly by GLUT5 and GLUT2. Fructose can cause a short-term increase in uric acid level and a high fructose diet can also cause inflammation and lipid accumulation in hepatocytes [23]. Uric acid directly activates the hepatic NLRP3 inflammasome pathway and Bax apoptosis and induces an increase in ROS levels in hepatocytes [24].

Alt1 expression is expressed by endothelial cells, Kupffer cells and hepatocytes as one of the genes expressed when liver cells are damaged, so it may reflect the state of the cells [25]. Serum uric acid plays a role in hepatic lipid accumulation through the formation of ROS mediated by uric acid and pro-inflammatory cytokines, leading to increased expression of thioredoxin (TXN). TXN-interacting protein (TXNIP), which then interacts with NLRP3, activates inflammation in liver cells and leads to the release of IL-1β and IL-18. The ROS-TXNIP pathway of inflammatory signalling induces deregulation of lipid metabolism-related gene expression and lipid accumulation. Uric acid induces disturbances in hepatic lipid metabolism and is closely associated with liver injury. Patients with hyperuricemia have twice the risk of elevated ALT and AST levels compared with normal uric acid levels [26]. This is consistent with the results of the study showing that mice with hyper-uricemia conditions have higher Alt1 expression.

This study shown that Alt1 expression in hyper-uricemia model rats after treatment with melinjo peel ethanol extract is lower than the control group and CMC 0.5%. Melinjo peel extract can reduce uric acid levels in hyperuricemia model rats and reduce hepatic XDH gene expression [17]. The efficacy of melinjo peel and leaf extracts can reduce uric acid levels in Wistar strain male rats induced by melinjo seeds because melinjo peel contains flavonoids with very strong antioxidant activity, so it can reduce uric acid levels by inhibiting the work of the enzyme xanthine oxidase, which has the potential as anti-hyperuricemia [27,28]. By inhibiting the formation of XO, the formation of ROS is inhibited [29]. Flavonoids may also improve free fatty acid-induced NASH [30].

Ethanol extract of melinjo peel has the same ability as allopurinol in reducing Alt1 expression in the hepatic wistar rat hyperuricemia model, it is proven by the results of the study which shown that the group given ethanol extract of melinjo peel has a lower Alt1 expression value compared to the allopurinol. Hyperuricemia model mice given melinjo peel ethanol extract and allopurinol have a high cycling threshold of Il-1β expression, indicating that both reduce Il-1β expression [18]. Flavonoids effectively reduce IL-1β levels by reducing oxidative stress and inactivation of inflammation [31].

Hepatic cells that experience loss of mass, volume, or physiological and biochemical functions due to various circumstances, Hgf binds to its specific receptor c-Met and transmits signals into the cell, triggering intrinsic kinases in affecting cell proliferation, growth and survival [32]. The results of this study showed that Hgf expression after administration of melinjo peel ethanol extract tended to be higher compared to the control group and 0.5% CMC and lower compared to the allopurinol group. Mice induced with uric acid for 14 days showed lower hepatocyte growth factor (Hgf) mRNA expression compared to the group given allopurinol for 7 days [33].

In this study, the expression levels of Alt1 and Hgf were found to be very weakly negatively correlated, indicating that low Alt1 expression correlates with high Hgf expression or vice versa. This shows that cells have the ability to repair themselves in order to achieve homeostasis. After injury, some tissues have the additional capacity to increase the rate of cell turnover, the formation of new cells to repair the damage through regeneration. One of the genes to be expressed is Hgf. MET (Hgf receptor) and epidermal growth factor receptor are activated within 30 minutes. The expression of more than 100 genes in hepatocytes increases within 1 hour after liver cell damage, and complete cell regeneration occurs within 7-10 days after Hgf expression [34].
The results showed that Hgf expression levels tended to have the same cell cycle threshold. These results are supported by the

theory that approximately 1-2% of hepatocytes enter the cell cycle, while the rest are at rest (G0). Hepatic cells have a unique cell regeneration mechanism that is different from other cells, i.e. under homeostatic conditions the liver has a low cell turnover rate and cells survive for weeks to months without dividing. In contrast, after injury, the liver can produce large numbers of new cells [35]. The melinjo peel extract group had lower Alt1 expression levels and higher Hgf expression levels compared to the 0.5% CMC (placebo) group. Hgf can reduce the levels of macrophages and CYP2E1, resulting in a reduced inflammatory response [36]. Flavonoids in ethanol extract can also modulate Alt1 expression and Hgf-mediated anti-fibrotic effects [37].

Ethanol extract of melinjo peel has hepatoprotective effects with its ability to suppress Alt1 expression through a mechanism as an antioxidant that can inhibit ROS [38]. Flavonoids can improve hepatic antioxidant function by increasing the levels of superoxide dismutase, glutathione S-transferase and glutathione peroxidase, improving insulin sensitivity and inhibiting hepatic stellate cell activation by regulating the activities of enzymes such as heme oxygenase-1, cytochrome P450 and telomerase, and reducing inflammation [39]. Giving ethanol extract of melinjo peel to hyperuricemia model rats for 10 days has low malondialdehyde (MDA) levels [18].

Conclusion

Alt1 expression was lower in the melinjo peel ethanol extract group than in the control, CMC and allopurinol groups. Hgf expression was higher in the melinjo peel ethanol extract and allopurinol groups than in the control and CMC groups. There was no correlation between Alt1 and Hgf expression after 10 days of treatment.

Ethical Approval

This study has been approved by ethical health research from Universitas Sumatera Utara No.0281/KEPH-MIPA/2023

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