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Administration of Corosolic Acid Decreased MDA, HMG-CoA, Through Increased Leptin And GLP-1 Levels in Obese Male Rats

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ABSTRACT
Obesity is a condition where excessive fat is accumulated, which poses a health risk. Several treatments for obesity have been carried out, ranging from lifestyle adjustments to medication to surgery. Corrosolic Acid (CA) is a natural compound that has the potential to act as an obesity agent through many mechanisms, including through reactive oxygen species (ROS). This study aims to prove that CA can reduce MDA levels and HMG-CoA reductase levels and increase leptin levels and GLP-1 levels in male Wistar rats with obesity. Wistar obese rats were orally treated with CA compound induction at a dose of 10 mg/Kg BW. MDA, HMG-CoA reductase, leptin and GLP-1 levels were examined using serum and plasma from mice in both groups of mice before and after treatment, using the ELISA method. CA to the treatment group can reduce the body weight of rat MDA levels significantly at $p<0.0001$, HMG-CoA reductase levels significantly at $p<0.0001$ and increase leptin and GLP-1 levels significantly at $p<0.0001$. CA's mechanism for treating obesity is through the ROS mechanism because CA has antioxidant levels that can capture free radicals in the body.CA has been proven to be an alternative drug in treating obesity by reducing body weight, MDA, and HMG-CoA levels and increasing leptin and GLP-1 levels in obese Wistar rats.

Introduction

Obesity is a condition of excessive fat accumulation that risks health. Currently, obesity has become a worldwide pandemic, followed by various complications including Diabetes Mellitus (DM). Obesity with this complication can result in premature aging. Premature aging is the premature aging of body cells so as to accelerate death. Various

safe clinical approaches are urgently needed to treat obesity and prevent complications. Anti-Aging Medicine is an effort that can be done to prevent or inhibit the condition.

Obesity can be confirmed individually using body mass index (BMI). If BMI is at 25-29.9 it is said to be level 1 obesity, while if the index is above 30 then it is said to be level 2 obesity (Asia Pacific 2000) Obesity is suffered by various groups and is not limited by age. In recent years, obesity has become a global problem, where the case has an impact of death by 4 million cases each year. Not only in developed countries, obesity cases are also found in developing countries. There is a 30% increased risk of obesity in children in developing countries (WHO, 2023)

Body Mass Index (BMI) is an indicator in determining obesity. Mejia-Crus et al. (2018) in his research states that there is a close relationship between BMI and oxidative stress, namely the greater the BMI, the higher the oxidative stress in obese patients (Mejia-Cruz et al., 2018). Oxidative stress is a condition of imbalance between pro-oxidants and anti-oxidants in which antioxidant enzymes such as SOD, are significantly decreased.

A meta-analysis cohort study of more than 300,000 people concluded that obesity can increase the risk of diseases such as DM by four and a half times, hypertension two and a half times, and coronary heart disease three times. Riskesdas (2018) stated that in Indonesia there was an increase in obesity cases in productive age (aged 35-54 years), namely an increase of 10.5% in 2007, by 14.8% in 2013, to 21.8% in 2018. This will increase the percentage of premature aging and death (Kementerian Kesehatan Republik Indonesia, 2019).

There are several treatments for obesity such as lifestyle management, drug administration, and surgery. Lifestyle rearrangement is done by combining food diet with exercise. Administration of anti-obesity drugs is carried out if the BMI reaches more than 30. The operation is performed when the BMI reaches more than 40. However, surgery must be followed by a healthy lifestyle that is suitable for maximum fat loss (Bischoff et al. 2020).

In addition, several safe clinical approaches are needed to treat obesity and prevent complications. Anti-aging medicine is one of the efforts that can be done to prevent or inhibit the condition. Anti-aging medicine is a treatment that aims to optimize the body to stay fit and organs function optimally so that biological age is not in line with chronological age. Related to aging, the reaction mechanism that plays a role in this case is one of them is free radicals. Free radicals (reactive oxygen species) or better known as ROS are compound reactions that damage cell components that play an important role in maintaining the cell. The accumulation of cell damage due to ROS that occurs continuously will cause aging in these organisms (Pangkahila, 2017).

Obesity is caused by many factors, both intrinsic and extrinsic factors. The causes of obesity include an unbalanced lifestyle, genetic and hormonal. Obesity caused by hormones is the result of hormonal disorders such as hypothyroidism, growth hormone deficiency, and Cushing's disease (Wilding, 2020). Sex hormones, such as testosterone and estrogen, can regulate body fat distribution, interact with adipose (leptin) signals, facilitate visceral fat mobilization, and subcutaneous fat deposition. Decreased levels of serum testosterone and sex hormone binding globulin (SHBG) are associated with leptin levels and body weight. While Leptin can affect gonadotropin sensitivity in the hypothalamus (Qu and Donnelly, 2020).

Some of the examination parameters in the study of obesity are related to fats / lipids and enzymes involved in the body. The usual test parameters include

malondialdehyde (MDA), HMG-CoA reductase enzymes, leptin, GLP-1, insulin and others.

Malondialdehyde (MDA) is the end product of lipid peroxidation and is commonly used as a biomarker to assess oxidative stress. In the process of lipid peroxidation, in addition to MDA, other free radicals with a short half-life are formed, which complicates laboratory research (Hardiany and Paramita, 2019). MDA levels can be measured by spectrophotometric methods, namely thiobarbituric acid reactive agent tests (Aguilar et al., 2022)), and currently MDA levels can be measured with ELISA kits based on competitive ELISA principles.

Cholesterol synthesis in the liver can be reduced by inhibition of the enzyme HMG-CoA reductase, so that there can be an increase in the number of Low Density Lipoprotein (LDL) receptors. Yunarto et al. (2019) states that LDL can enter the liver and then be excreted into bile, so that LDL levels in plasma decrease (Yunarto et al., 2019).

Leptin is a hormone that acts through Lepr-b receptors on neurons for control of eating and energy expenditure. Leptin bound by neural receptors in the hypothalamus will decrease the action of neuropeptide Y and increase α-MSH (Alpha melanocyte stimulating hormone), thereby decreasing appetite and decreasing thermogenesis (Obradovic et al., 2021).

Leptin requires Proopiomelanocortin-containing (POMC) as a precursor to α-MSH activity. Leptin suppresses glucagon production allowing hyperinsulinemia to occur, triggering a program of lipogenesis regulated by SREBP1c. Leptin also activates Adenosine Monophosphate Protein Kinase (AMPK) which can lower palmitoyl-COA levels, and inhibit the control of serine palmitoyl transferase (SPT) from de nove ceramide synthesis. This will reduce beta cell apoptosis and insulin resistance (Petersen et al., 2018). Li et al. (2020) revealed in his research there is a correlation between leptin and insulin, so that an increase in leptin also affects insulin and blood glucose levels (Li et al., 2020).

Insulin is an endocrine peptide hormone that binds to plasma membrane receptors in target cells. Insulin resistance is a decrease in the response of target cells / organs to physiological insulin capabilities so that at normal insulin levels, target tissues cannot respond to glucose resulting in suppression of endogenous glucose production, lipolysis inhibition, cellular glucose uptake, and glycogen synthesis. It is also associated with increased expression of lipoprotein lipase enzymes, lipase sensitive hormones, Peroxisome Proliferator-actived receptor-γ (PPARy), and increased production of free faty acid from the portal vein to the liver and other tissues (Petersen et al., 2018).

Research (Wang, et al., 2023) in his research states that low levels of GLP-1 in the body are associated with an increased risk of type 2 diabetes (Lastyaat al. 2014). Low GLP-1 levels correlate with insulin resistance and increased appetite. GLP-1 is called one of the breakthroughs in the world of medicine. Decreased GLP-1 levels can be mediated by GLP-1 receptor agonists, for which the FDA has approved both injection and oral treatment.(Wang, et al., 2023)

Pentacyclic triterpenes and their derivatives are anti-diabetic compounds that have recently been widely studied. Corosolic acid and oleanolic acid are triterpene pentasicyclic groups that have shown dose-dependent inhibitory activity of glucosidase and amylase. Further studies revealed that the anti-diabetic effect of oleanolic acid is through inhibition of pancreatic amylase and lipase activity in individuals with impaired glucose levels. Corosolic acid shows antidiabetic effects in humans by reducing plasma glucose levels (Silverio, 2022).

Corosolic acid (CA) is a bioactive compound found in several plants including, Lagerstroemia speciosa plants or known as banaba leaves, Gymnema sylvestre which is native to India, Africa and Australia has benefits in regulating blood sugar through GLUT4 translocation (Di Fabio et al., 2014). Corosolic acid can improve insulin sensitivity and glucose absorption, as well as decrease abnormal fat metabolism after exposure for 2 weeks or more. Fat accumulation and abnormal fat metabolism is one of the hallmarks of obesity caused by type 2 diabetes. Corosolic acid is able to target the proliferated peroxisome receptor (PPAR) responsible for metabolizing fat. The pathways targeted by corosolic acid are oxidative stress and anti-inflammatory pathways (Alkholifi et al., 2023).

Research Methods

This study is a true experimental study using randomized pre and post test control group design (Figure 1) (Pococks, 2008), to compare the effect of therapy using CA and placebo in male rats (Rattus norvegicus) Wistar obese strain aged 10-11 months against MDA, HMG-KoA Reductase, Leptin and GLP-.

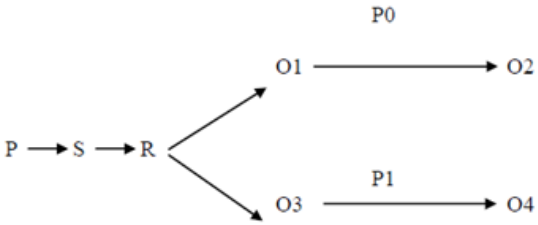

Figure 1 Research Design

Information:

P = Population
S = Sample
R = Random
P0 = Treatment in control group (No CA)
P1 = Treatment in the treatment group with CA administration at a dose of 10 mg / kg body weight
O1 = Observation of body weight, MDA and HMG Ko-A, Leptin, GLP-1 in the control group (pretest)
O2 = Observation of MDA and HMG body weight Ko-A, Leptin, GLP-1 in the control group (post-test)
O3 = Observation of body weight, MDA and HMG Co-A, Leptin, GLP-1 in the treatment group (pretest)
O4 = Observation of body weight, MDA and HMG Co-A, Leptin, GLP-1 in the treatment group (post-test).

CA trial research on rats was carried out at the Pharmacology Laboratory Unit of FK Udayana University and ELISA examination was carried out at the Biomedical Laboratory Unit, Udayana University. Research time starts in May 2023.

Results and Discussions

Experimental research with pre-test-post-test control group design, using 20 obese male wistar ratsaged 10-11 months, body weight in accordance with the criteria of LOI obesity index value> 0.3, healthy and able to eat / drink normally. Rats were divided into 2 (two) groups, namely the control group (P0), the group that was not given CA and the treatment group (P1), the group that was given CA at a dose of 10 mg / kg body weight.

Corosolic acid (CA) in question is CA derived from standardized supplement capsules banaba extract from Piping Rock. CA levels in the capsule were previously determined by testing the High Performance Liquid Chromatography (HPLC) method, with CA levels of 7.29 mg / g. The results of CA level analysis in the capsule are listed in Appendix 5.

The research was carried out at the Integrated Biomedical Laboratory Unit of FK Udayana University and the examination of CA composition was carried out at the Analytical Chemistry Laboratory Unit, Udayana University. Research time starts in April 2023.

Uji Normalitas Data

Body weight data, malondialdehyde (MDA) levels, HMG CoA reductase enzymes, leptin, and GLP-1 were tested for normality using the Shapiro-Wilk test. The results are presented in Table 1- 2.

Table 1 Normality Test Results of Body Weight, MDA Levels, HMG CoA Reductase, Leptin, and GLP-1

Subject Group	n	p	Information
Weight P0 pre	10	0,233	Normal
Weight P1 pre	10	0,004	Abnormal
MDA P0 pre	10	0,301	Normal
MDA P1 pre	10	0,026	Abnormal
HMG CoA P0 pre	10	0,288	Normal
HMG CoA P1 pre	10	0,033	Abnormal
Leptin P0 pre	10	0,002	Abnormal
Leptin P1 pre	10	0,471	Normal
GLP-1 P0 pre	10	0,458	Normal
GLP-1 P1 pre	10	0,138	Normal

Tabel 2 Hasil Uji Normalitas Data Berat Badan, Kadar MDA, Enzim HMG CoA Reduktase, Leptin, dan GLP-1

Subject Group	n	p	Information
Weight P0 pre	10	0,017	Ubnormal
Weight P1 pre	10	0,298	Normal
MDA P0 post	10	0,159	Normal
MDA P1 post	10	0,003	Ubnormal
HMG CoA P0 post	10	0,962	Normal
HMG CoA P1 post	10	0,670	Normal
Leptin P0 post	10	0,150	Normal
Leptin P1 post	10	0,520	Normal
GLP-1 P0 post	10	0,414	Normal
GLP-1 P1 post	10	0,686	Normal

Based on Table 1 and Table 2, it was found that there were several groups of data that were not normally distributed, namely weight P1 pre levels MDA P1 pre, HMG CoA P1 pre, Leptin P0 pre, MDA P1 post, and weight P0 post Furthermore, data transformation was carried out using logarithmic functions, and the results of data transformation remained not normally distributed. The results of the overall data analysis are listed in Appendix 6.

Data homogeneity test

Data on body weight, MDA levels, HMG CoA Reductase Enzyme, leptin, and GLP-1 were tested for homogeneity using Levene's test. The results show that MDA post and GLP-1 post content data are not homogeneous ($p<0.05$), while the other variables are homogeneous ($p>0.05$), and are presented in Table 3 below.

Table 3 Homogeneity of Body Weight, MDA Levels, HMG CoA Reductase Enzymes, Leptin, and GLP-1

Subject Group	n	p	Information
Pre weight Post weight	0,81	0,381	Homogen
Pre weight Post weight	0,01	0,925	Homogen
MDA pre	0,47	0,503	Homogen
MDA post	20,01	0,001	Inhomogeneous
HMGR pre	1,26	0,276	Homogen
HMGR post	3,73	0,069	Homogen
Leptin pre	1,84	0,192	Homogen
Leptin post	0,24	0,628	homogen
GLP-1 pre	0,71	0,410	Homogen
GLP-1 post	5,53	0,030	Inhomogeneous

The Effect of Corosolic Acid (CA) on Rats' Body Weight

Analysis of the effect of treatment was tested based on the average body weight between groups before and after treatment in the form of CA at a dose of 10 mg / kg body weight. The results of the meaningfulness analysis with the Mann-Whitney test are presented in Table 5.4.

Table 4 Differences in Average Body Weight Between Groups Before and After CA Administration at a Dose of 10 mg / kg Body Weight

Variable	Group	Before the Conduct Rerata±SD	After the Behaviour Rerata±SD	p
Weight	P0	261,10±9,40	263,70±9,08	0,574***
	P1	303,10±15,88	268,30±10,01	0,005***
	p	<0,001**	0,285**	

Description: * T-independent test; ** Mann-Whitney test; ***Wilcoxon test

Table 4 shows, that before treatment the average body weight of the treatment group (P0) was 261.10±9.40 and the average of the treatment group (P1) was 303.10±15.88. Meaningfulness analysis with a t-independent test shows that the p value < 0.001. This means that the average body weight in both groups before treatment was significantly different ($p<0.05$). After treatment, the average body weight of the treatment group (P0) was 263.70±9.08 and the average weight of the treatment group (P1) was 268.30±10.01. Meaningfulness analysis with a t-independent test shows that the p value = 0.238. This showed that after treatment, the average body weight was not significantly different ($p > 0.05$).

Influence of Corosolic Acid (CA) Grant on Malondialdehyde Rate (MDA)

Analysis of the effect of treatment was tested based on the average MDA levels between groups before and after treatment in the form of CA at a dose of 10 mg / kg body weight. The results of the meaningfulness analysis with the Mann-Whitney test are presented in Table 5 below.

Table 5 Differences in Average MDA Levels between Groups Before and After CA Administration at a dose of 10 mg/kg body weight

Variable	Group	Before the Conduct Rerata±SD	After the Behaviour Rerata±SD	p
MDA	P0	3,61±0,22	2,71±0,07	0,005***
	P1	3,64±0,21	0,49±0,01	0,005***
	p	0,791**	<0,001**	

Description: * T-independent test; ** Mann-Whitney test; ***Wilcoxon test

Table 5 shows that before treatment the mean MDA of the treatment group (P0) was 3.61±0.22 and the mean of the treatment group (P1) was 3.64±0.21. Meaningfulness analysis with a t-independent test shows that p value = 0.791. This means that the mean MDA in the two groups before treatment was not different (p>0.05). After treatment, the mean MDA of the treatment group (P0) was 2.71±0.07 and the average of the treatment group (P1) was 0.49±0.01. Significance analysis with a t-independent test showed that the value of p<0.001. This showed that after treatment, the average MDA levels were significantly different (p<0.05).

The Effect of Corosolic Acid (CA) on Reducing HMG CoA Reductase Enzyme Levels

Analysis of the effect of treatment was tested based on the average levels of HMG CoA reductase between groups before and after treatment in the form of CA at a dose of 10 mg / kg body weight. The results of the significance analysis with the t-independent test and the Mann-Whitney test are presented in Table 6 below.

Table 6 Differences in Average HMG CoA Reductase Levels Between Groups Before and After CA Administration at a Dose of 10 mg/kg body weight

Variable	Group	Before the Conduct Rerata±SD	After the Behaviour Rerata±SD	p
HMG CoA Reduktase	P0	7,52±0,77	8,79±0,24	0,007***
	P1	6,62±1,05	2,02±0,13	0,005***
	p	0,019**	<0,001*	

Description: * T-independent test; ** Mann-Whitney test; ***Wilcoxon test

Table 6 shows that before the treatment the average levels of the enzyme HMG CoA reductase of the treatment group (P0) were 7.52±0.77 and the average of the treatment group (P1) was 6.62±1.05. Meaningfulness analysis with a t-independent test showed that the p value = 0.019. This means that the average levels of the enzyme HMG CoA reductase in both groups before treatment were different (p < 0.05). After treatment, the mean MDA of the treatment group (P0) was 8.79±0.24 and the average of the treatment group (P1) was 2.02±0.13. Meaningfulness analysis with a t-independent test showed that the value of p<0.001. This showed that after the treatment, the average levels of the enzyme HMG CoA reductase were significantly different (p < 0.05).

The Effect of Corosolic Acid (CA) on Leptin Levels

Analysis of the effect of treatment was tested based on the average leptin levels between groups before and after treatment in the form of CA at a dose of 10 mg / kg body weight. The results of the meaningfulness analysis with the t-independent test and the Mann-Whitney test are presented in Table 7 below.

Table 7 Differences in Average Leptin Levels between Groups Before and After CA Administration at a dose of 10 mg / kg body weight.

Variable	Group	Before the Conduct Rerata±SD	After the Behaviour Rerata±SD	p
Leptin	P0	2,76±0,35	1,55±0,17	0,005***
	P1	2,54±0,18	3,94±0,22	0,005***
	p	0,123**	<0,001*	

Description: * T-independent test; ** Mann-Whitney test; ***Wilcoxon test

Table 7 shows that before treatment the average leptin levels of the treatment group (P0) were 2.76±0.35 and the mean of the treatment group (P1) was 2.54±0.18. Meaningfulness analysis with a t-independent test showed that the p value = 0.123. This means that the average leptin levels in the two groups before treatment were not different ($p > 0.05$). After treatment, the average leptin levels of the treatment group (P0) were 1.55±0.17 and the average of the treatment group (P1) was 3.94±0.22. Significance analysis with a t-independent test showed that the value of $p<0.001$. This showed that after treatment, the average leptin levels were significantly different ($p<0.05$).

The Effect of Corosolic Acid (CA) on Glucagon Like Peptide-1 (GLP-1) Levels

Analysis of the effect of treatment was tested based on the average GLP-1 levels between groups before and after treatment in the form of CA at a dose of 10 mg / kg body weight. The results of the meaningfulness analysis with the t-independent test are presented in Table 8 below.

Table 8 Differences in Average Glucagon Like Peptide-1 (GLP-1) Levels between Groups Before and After CA Administration at a Dose of 10 mg / kg body weight.

Variable	Group	Before the Conduct Rerata±SD	After the Behaviour Rerata±SD	p
GLP-1	P0	248,11±15,62	155,97±12,05	0,005***
	P1	248,66±18,13	338,45±23,55	0,005***
	p*	0,943*	<0,001*	

Description: * T-independent test; ** Mann-Whitney test; ***Wilcoxon test

Table 8 above, shows that before treatment the average GLP-1 levels of the treatment group (P0) were 248.11±15.62 and the average treatment group (P1) was 248.66±18.13. Meaningfulness analysis with a t-independent test showed that the p value = 0.943. This means that the average GLP-1 levels in the two groups before treatment were not different ($p>0.05$). After treatment, the average GLP-1 level of the treatment group (P0) was 155.97±12.05 and the average level of the treatment group (P1) was 338.45±23.55. Significance analysis with a t-independent test showed that the p< value was 0.001. This showed that after treatment the average GLP-1 levels were significantly different ($p<0.05$).

Corosolic Acid (CA) Can Lose Weight in Obese Rats

Corosolic acid is an active compound found in the plant Lagerstroemia speciosa Banaba which is proven to have several bioactivities, one of which is as an antioxidant.

CA is found in many weight-loss supplements known as ursolic 2-alpha-hydroxy acids. Recent research has reported that CA plays an important role in antioxidant effects through ROS reduction and acts as an antioxidant in the body (Li et al. 2016; Peng et al. 2021; Guo et al. 2016)**.**

In this study it was proven that CA administered in obese wistar rats could lose weight in rats although it was not significantly different at $p > 0.05$. However, when compared to obese control (P0) mice, the rats' body weight increased no differently (Table 5.4). A compound or plant extract can reduce weight in obese rats because of several different possible mechanisms of action, including reducing appetite, increasing metabolism, inhibiting fat absorption, increasing fat burning, reducing fat deposits, reducing glucose and cholesterol levels and increasing physical activity and reducing stress.

In a study reported Ramadhan 2018, Jasminum sambac (L) ethanol extract can reduce body weight in obese rats at a dose of 100mg / Kg body weight and can reduce fat levels at a dose of 300 mg / Kg body weight. In his research it was also mentioned that weight loss in rats was caused by loss of appetite due to reduced calorie intake (Ramadan, 2017). Berawi and Asvita (2016) in their research, reported that Dutch eggplant extract at a dose of 200-300 mg / Kg body weight decreased blood glucose levels, blood LDL cholesterol levels and rat body weight induced by a high-fat diet (Berawi &; Asvita, 2016). Rahmanisa and Wulandari (2016) also report that green tea can reduce weight and body fat accumulation by increasing energy expenditure and fat oxidation (Rahmanisa &; Wulandari, 2016). Candra and Pangkahila (2017) in their research reported that alpha lipoic acid can reduce body weight and subcutaneous and visceral fat levels of wistar rats followed by physical exercise. In his research, alpha lipoic acid also works by increasing glucose and lipid metabolism in cells (Chandra et al., 2017).

Recently, in a Purnama review article (2022), several herbal plant extracts were shown to be effective in regulating various cell signal cascades such as AMPK, PPARγ, PPARα, and C/EBP transcription factors or lipogenic proteins such as SREBP-1c, ACC, FAS, PL and LPL (Dewa Julio Angga Purnama, 2023).

Meanwhile, in this study CA is thought to be able to lose weight in rats because of the strong antioxidant effect. This is supported by research reported by Zhao et.al 2020, that CA is proven to have powerful antioxidants by capturing free radicals, reducing oxidative damage and reducing damage caused by oxidative stress. In his study also reported another effect of CA, which has anticancer effects related to the development of hepatocellular carcinoma (HCC) cell proliferation associated with NAFLD (Zhao et al., 2020). In addition, CA can reduce the body weight of obese mice and lower fasting blood glucose levels. This is supported by the reports of Cannarella et.al 2023 and Hibi et al. 2022 that CA can improve glucose tolerance in healthy and hyperglycemic individuals, administration of CA 1mg/day for 2 weeks can improve postprandial glucose and insulin sensitivity (Cannarella et al. 2023; Hibi et al. 2022).

Corosolic Acid (CA) can Reduce Malondialdehyde (MDA) Levels in Obese Wistar Rats

Malondialdehyde (MDA) is a byproduct of lipid peroxidation, which is a process that occurs when free radicals attack lipids in cell membranes. MDA is a biomarker of oxidative stress and can be used to assess the degree of oxidative damage in the body. Subjects who were obese showed increased systemic oxidative stress, which increased when obesity was associated with abdominal adiposity. Serum malondialdehyde (MDA) concentrations increase with increasing BMI levels, which is statistically significant in

class I and class II obese subjects compared to normal-weight subjects (Widiastuti et al., 2022) MDA is a highly reactive three-carbon diaaldehyde produced as a byproduct of polyunsaturated fatty acid peroxidation and arachidonic acid metabolism (Pahimi et al., 2022).

The highest levels of MDA were found in obese mice in the pre- and post-treatment P0 groups. This showed that the control group had high free radicals in the body of mice compared to the group of obese treated mice. Table 5 shows a very significant difference in MDA levels ($p<0.0001$) in the post P0 group against the post P1 group, proving that CA has a high antioxidant effect and can protect cells from oxidative damage. Free radicals in the body will react with surrounding cell molecules to obtain electron pairs so that they become more stable. But molecules in the cell body that capture electrons will turn into new, reactive free radicals. This process will take place continuously in the body and if not stopped can cause losses such as DNA or cell damage, inflammation, aging, cancer and other degenerative diseases. In this case, the role of antioxidants is very important to neutralize the impact of continued damage due to free radicals.

Based on recent research conducted by Li et.al, 2022, states that CA has an antioxidant effect by reducing ROS levels in the body. In his study, a decrease in ROS levels was investigated in rats induced by metabolic syndrome by being fed a high-fat and high-sugar diet to see the effects of endothelial dysfunction and erectile function in metabolic syndrome mice (Li et al. 2022). This metabolic syndrome is associated with a pathological condition characterized by abdominal obesity, insulin resistance, high blood pressure and high total cholesterol. So this is very supportive of this research topic.

Other supporting evidence, corosolic acid can lower MDA levels due to its antioxidative, and anti-inflammatory properties were reported by Yamada et.al 2008, Cannarella et.al 2023, Zhang et al. 2022, and Aljarba et al. 2021, corosolic acid has antioxidant properties and can reduce oxidative stress, which can contribute to a decrease in MDA levels. A study in rats with diabetic nephropathy found that treatment with Lagerstroemia speciosa extract, which contains corosolic acid, reduced MDA levels and increased glutathione peroxidase and superoxide dismutase levels, which showed antioxidant effects (Aljarba et al., 2021; Yamada et al., 2008; Zhang et al., 2022). Another study found that corosolic acid therapy significantly increased endogenous antioxidant levels and decreased lipid peroxidation compared to the diabetes control group and the diabetic isoproterenol group (Cannarella et al., 2023).

Corosolic Acid (CA) can Lower HMGCR Levels in Obese Wistar Rats

Corosolic acid (CA) is a natural compound found in various kinds of plants, one of which is in banaba leaves (Lagerstroemia speciosa). CA has been widely studied for its health benefits, including its effect on HMG-CoA reductase, which is an important enzyme in cholesterol synthesis. In cases of obesity, HMG-CoA reductase increases significantly so that cholesterol synthesis is not controlled. Giving CA to obese mice was shown to significantly reduce HMG-CoA reductase levels (Table 6). In this study, HMG-CoA reductase levels in P0 post group obese mice increased compared to HMG-CoA reductase levels in P1 post group obese mice. Significant differences in $p<0.0001$ were strongly seen in the treatment group with a 3x reduction in HMG-CoA reductase levels.

The results of this study are supported by several previous studies that state that CA can reduce HMG-CoA reductase levels. Li et al. 2022, in his research stated that CA found in hawthorn (functional food and Chinese medicinal herbs) can reduce HMG-CoA reductase levels in the prevention and treatment of atherosclerosis, where this inhibition can cause a decrease in cholesterol synthesis (Li et al. 2022).

CA can reduce HMG-CoA reductase levels through several mechanisms, including inhibition of HMG-CoA reductase, antidyslipidemia and antidiabetic properties, inhibition of glomerular mesangial cell proliferation, and AMPK activation. CA has been shown to have antidyslipidemic and antidiabetic effects, improving glucose absorption and utilization. This effect can indirectly impact HMG-CoA reductase activity, as dyslipidemia and diabetes are often associated with increased cholesterol synthesis. CA has been shown to inhibit glomerular mesangial cell growth and protect against diabetes-related kidney damage (Li et al. 2016). Although this is not directly related to HMG-CoA reductase, it does suggest that corosolic acid may have beneficial effects on metabolic disorders associated with increased cholesterol synthesis. In addition, CA has been shown to inhibit adipose tissue inflammation and improve insulin resistance through AMPK activation in mice fed a high-fat diet (Liu et al. 2021). It may also contribute to decreased activity of HMG-CoA reductase and cholesterol synthesis.

Corosolic Acid (CA) can Increase Leptin Levels in Obese Wistar Rats

Leptin is a hormone produced by adipose tissue that plays a role in regulating appetite and metabolism. Obesity is influenced by the hormone leptin, and overweight people generally have higher body fat mass and more adipose tissue, thus leading to the release of large amounts of leptin. However, in obese people, leptin resistance occurs due to a lack of leptin receptors, and serum leptin concentrations increase, so leptin cannot exert its effect on the hypothalamus (Legiran, 2018; Sumadewi, 2017).

Leptin and insulin are two hormones that play an important role in regulating glucose homeostasis and energy balance in the body. Both hormones act centrally, regulating food intake and glucose metabolism. Leptin and insulin regulate each other directly, where leptin inhibits insulin, while insulin stimulates leptin synthesis and secretion. Leptin decreases insulin synthesis and secretion by pancreatic beta cells and increases insulin extraction in the liver, thereby reducing insulin delivery. This so-called adipoinsular axis is part of leptin-mediated inhibitory feedback on insulin secretion to decrease adipogenesis. Leptin also enhances immune responses and regulates inflammation, coagulation, fibrinolysis, and platelet aggregation. Studies have shown that high leptin levels are associated with increased BMI and insulin resistance (Kumar et al., 2020).

In certain cases, obesity can occur due to leptin resistance which causes low leptin levels. The effect of leptin levels in obese people apart from leptin resistance is overweight and increased fat mass. In this study, the group of obese rats in the P0 group had leptin levels quite low compared to the leptin levels of the P1 group of obese mice. Pre- and post-treatment P1 group leptin levels increased significantly at $p<0.0001$ (Table 5.7). This can prove that CA can raise leptin levels in obese mice. In this case, it is likely that the mice experienced leptin resistance so that it increased appetite which led to weight gain. It may also be possible to develop insulin resistance. Insulin resistance is a condition in which the body's cells do not respond well to the hormone insulin, which functions to regulate blood sugar levels by allowing glucose to enter the body's cells. When insulin resistance develops, there will be an increase in insulin in the blood, stimulating an increase in fat in fat cells, an increase in appetite, and changes in metabolism, especially in processing carbohydrates and fats so that it can trigger weight gain (Tamara Willner, 2023). This is supported by data on the body weight of mice in the control group who gained weight compared to the treatment group given CA. However, it needs to be further analyzed related to the cause of low leptin levels in obese mice influenced by insulin resistance.

Corosolic Acid (CA) can Increase GLP-1 Levels in Obese Wistar Rats

Glucagon-Like Peptide-1 (GLP-1) is a hormone produced by the cells of the small intestine and plays an important role in the regulation of blood sugar and appetite. This hormone has some influence on obesity, and its effects can vary depending on the context and role of GLP-1 in the body. One of the effects of GLP-1 on obesity is a reduction in appetite. GLP-1 stimulates satiety and may reduce appetite. This happens when GLP-1 interacts with GLP-1 receptors in the brain, which send signals to the body that it needs to eat enough. Therefore, drugs targeting GLP-1 or GLP-1 analogues are used in the treatment of obesity to help with weight loss by reducing food intake (Wang et al., 2023).

In this study, the P0 obese rat group had lower GLP-1 levels than the P1 obese rat group. In general, GLP-1 levels in obese and overweight patients are relatively lower than normal people. Stinson et al. 2021 also reported that in children and adolescents who are overweight and obese tend to be lower compared to those who have normal weight (Stinson et al., 2021). In addition, a decrease in GLP-1 levels or a decrease in GLP-1 function occurs in people who are obese even in people with normal glucose tolerance (Wang et al., 2023).

The administration of CA in the obese rat group had an effect on significantly increasing GLP-1 levels in the P1 group with $p<0.001$ (Table 5.8). This provides sufficient evidence that with CA administration, GLP-1 levels of obese mice increased compared to the group of obese P0 mice that experienced decreased GLP-1 levels. With increasing GLP-1 levels, GLP-1 function may increase, resulting in a decrease in appetite. A decrease in appetite may have occurred in obese mice in this trial, as shown by data on significant weight loss in mice in the CA treatment group compared to the control group.

In addition to reducing appetite, GLP-1 plays a role in regulating blood sugar levels by increasing insulin release and reducing the release of glucagon, a hormone that increases blood sugar levels. This makes GLP-1 an important target in the treatment of type 2 diabetes and obesity, as it helps control the high blood sugar often associated with obesity. Some findings from the study suggest that GLP-1 receptor agonists may help control blood sugar levels in type 2 diabetes and lose weight in obese patients by reducing food intake (Klen &; Dolžan, 2022; Müller et al., 2019; Nachawi et al., 2022). GLP-1 also has cardioprotective and neuroprotective effects, reduces inflammation and apoptosis, and is associated with learning and memory, reward behavior, and appetite (Müller et al., 2019). GLP-1 receptor agonists are also recommended as first- or second-line therapy in patients with cardiovascular disease, a high risk of cardiovascular disease, chronic kidney disease, or heart failure (Nachawi et al., 2022).

Thus, CA can increase GLP-1 levels in obese mice through several mechanisms, including a decrease in appetite because with the increasing levels of GLP-1 in obese mice, the desire to eat becomes more controlled, so that it can lose weight in mice. However, other mechanisms are very possible, so further analysis is needed regarding the CA mechanism against GLP-1.

Novelty

Throughout the author's search, the potential of CA has been widely reported to have a wide range of biological activities such as antidiabetic, anti-inflammatory, antihyperlipidemia, antihyperglycemia and antioxidants. However, knowing the relationship of the CA mechanism to obesity has not been fully done.

This study proves that CA can be used as an antiobesity agent whose mechanism is the same as pre-existing antiobesity drugs. CA has very high antioxidants, so in obese mice CA can lose weight through decreased appetite with increased levels of GLP-1 and

leptin associated with body weight. In addition, CA can also reduce MDA levels in obese mice, where obese mice have higher MDA levels than normal mice. CA can also decrease the activity of HMG-CoA reductase which acts on cholesterol synthesis. So that CA works through the ROS mechanism, where CA captures ROS which can reduce MDA levels, and cholesterol synthesis is likely to decrease, so that obesity rates decrease with marked weight loss.

Conclusion

This study can be concluded that giving CA can reduce the body weight of male rats (Rattus norvegicus) Wistar obese strain compared to the body weight of male rats (Rattus norvegicus) Wistar obese strain that are not given CA.

Giving CA can reduce levels Malondialdehyde (MDA) male rats (Rattus norvegicus) Wistar obese strain compared to Malondialdehyde levels (MDA) male rats (Rattus norvegicus) Wistar obese strain that are not given CA.

Giving CA can reduce levels of HMG-CoA Reductase in male rats (Rattus norvegicus) galur Wistar obese, compared to levels HMG-KoA Reductase of male rats (Rattus norvegicus) obese Wistar strains that CA does not give.

Giving CA can increase leptin levels of male rats (Rattus norvegicus) Wistar obese strains, compared to leptin levels of male rats (Rattus norvegicus) obese Wistar strains that CA does not give.

CA administration can increase GLP-1 levels in male rats (Rattus norvegicus) Wistar obese strains, compared to GLP-1 levels of male rats (Rattus norvegicus) obese Wistar strains that CA does not give.

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