

KAEMPFEROL GLYCOSIDES; A KEY FOR FATTY LIVER (NAFLD), OBESITY & INSULIN RESISTANCE: A REVIEW

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ABSTRACT

Kaempferol is one of the flavonoids commonly found in vegetables, fruits and traditional medicines. In nature almost all dietary flavonoids exist in their glycoside forms. Kaempferol glycosides are widely distributed in nature and show multiple bio activities, yet few reports have compared them. The present article relates to kaempferol glycosides for preventing and treating Fatty liver, Diabetes or Insulin resistance, Obesity, Hyperlipidemia etc from extracts of same isolated from various plant sources.

KEYWORDS:**I. INTRODUCTION**

The pervasiveness of non-alcoholic fatty liver disease (NAFLD), which is characterized by excessive fat deposition in the liver, insulin resistance, central obesity and other metabolic syndrome characteristics, has been quickly increasing and is at the forefront of worldwide concern.^[1] Excess liver fat is on the rise, owing to the rising prevalence of obesity.^[2] Several studies have pointed that NAFLD has been linked to insulin resistance, which results in a resistance to insulin's antilipolytic impact in the adipose tissue, resulting in an increase in free fatty acid.^[1,2]

Almost all dietary flavonoids are found in their glycoside forms in nature.^[3] Kaempferol is a flavonoid that can be found in a variety of foods, fruits, and traditional medicine. Kaempferol commonly forms glycosides with glucose, rhamnose, galactose, and rutinose, and glycosides can only be made by specific plant species that have specific enzymes and genetic information.^[4]

Flavonols are most typically found as glycosides in plants. Astragalin (kaempferol-3-O-glucoside) and kaempferitrin (kaempferol-3,7-dirhamnoside) are the two most major kaempferol glycosides. According to multiple studies, a high intake of foods rich in kaempferol glycosides may lower the risk of developing liver disorders, diabetes mellitus, obesity, oxidative stress, metabolic syndromes and several types of cancer.^[6]

II. KAEMPFEROL GLYCOSIDE**1. SOURCES**

Kaempferol and its derivatives are extracted from plant sources (*Glycine max* L. Merrill, *Justicia spicigera*, *Pteridium aquilinum*, *Acacia nilotica*, *Carthamus tinctorius* L, *Rosa rugosa* Thunb, *Moringa oleifera*, *Tilia americana* var. *Mexicana*, *Lycium barbarum*, *Diospyros kaki* L., *Camellia sinensis*, to mention a few), by using solvents (mainly methanol, ethanol, acetone and water) and various extraction methods (extraction assisted with ultrasound, microwaves, ultrasound and microwaves, and simple extraction) has been investigated in several works. These flavonoids (mostly kaempferol glycosides and kaempferitrin) have also been shown to have antidiabetic, hepatoprotective, antioxidant and anticancer properties.^[5]

2. EXTRACTION

The extraction of desired compounds from plants is critical, as it influences yields as well as a purity and quality of the extract. In general, there are three stages to the process: sample conditioning (homogenisation), first extraction, and pre-concentration/purification. The type of material will determine the homogenization procedure, storage, and drying conditions (leaves, flowers, stems, root or fruit). It is recommended that extraction be done with fresh material held at freezing temperatures (-80 °C) to avoid component deterioration. In practice, however, dry samples are favored because they are easier to handle and store. Furthermore, particle size, polarity and solvent pH, temperature and mechanical assistance help all effect extraction efficacy. Kaempferol is frequently extracted using large volume fractions of methanol or ethanol (60-80 percent). Pre-

main concentration's goal is to extract or isolate adequate amounts of the desired chemical. The pre-concentration method chosen will be determined by the available equipment for final analysis, which may need differing volumes and purity of the target material. Organic solvents (primarily ethanol, methanol and acetone) combined with water are commonly used to extract kaempferol and kaempferitrin; however, because of the increased pressure, it has been proposed that the

use of pressurised liquids and supercritical fluids is generally more effective than standard techniques.^[5]

3. ACTIVITIES

The use of kaempferol glycosides in diverse pharmacological effects are getting prominence. Investigators figured out various activities of Kaempferol Glycosides shown in table 1.

Table 1: Activities of Kaempferol glycosides.

SL NO.	KG ACTIVITIES	REFERENCES
1	Hepatoprotective ^[4]	Yanqing Zang et.al ^[15] , 2017
2	Antidiabetic ^[16]	Hua Li et.al ^[16] , 2015
3	Antiobesity ^[12]	Yanqing Zang et.al ^[17] , 2015
4	Antiinflammatory ^[17]	Giany O. De Melo et.al ^[18] , 2009
5	Antioxidant ^[18]	Hyun Ah Jung et.al ^[19] , 2009
6	Antitumour ^[19]	Kostas Dimas et.al ^[20] , 2002
7	Antibacterial ^[20]	R.E Shafek et.al ^[21] , 2012
8	Antiviral ^[21]	Silvia Schwarz et.al ^[22] , 2013
9	Gastroprotective ^[22]	Yrvinn Campos-Vidal et.al ^[23] , 2020
10	Neuroprotective ^[23]	Yueting Wu et.al ^[24] , 2016

1. FATTY LIVER(NAFLD)

The liver is the key metabolic organ, and it is responsible for maintaining glucose and lipid metabolism equilibrium. NAFLD (non-alcoholic fatty liver disease) is a prevalent liver disease that is closely linked to insulin resistance and type 2 diabetes. The prevalence of this disorder will only rise as the number of people who are overweight or obese rises. The mechanism behind the

development of NAFLD are unknown, however they are thought to entail a combination of elevated FFAs and probably impaired lipid oxidation in the liver due to insulin resistance. Dietary fat may play a significant role in the development of NAFLD, and hepatic steatosis caused by excessive dietary fat consumption may contribute to the hepatic insulin resistance seen in this condition.^[9]

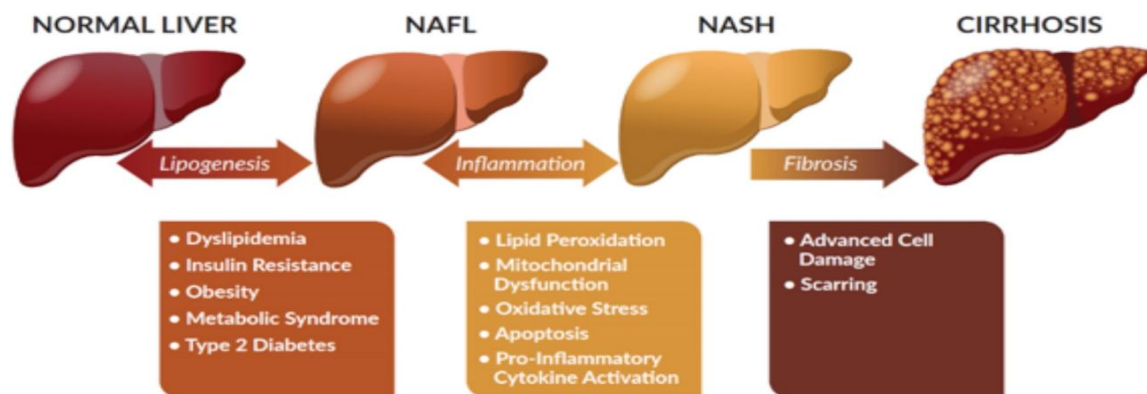


Figure 1: Spectrum of NAFLD.^[15]

Aberrant lipid metabolism, production of reactive oxygen species, increased hepatic lipid peroxidation, activated Stellate cells, and abnormal cytokine production patterns are all possible processes in the pathophysiology of NAFL and NASH, all of which contribute to liver cell injury and fibrosis. According to the “multi-hit” theory, the first “hit” is the accumulation of extra fat in the hepatic parenchyma. This process has been connected to insulin resistance, which is seen in patients with NAFL and NASH on a regular basis. The

second “hit” is oxidative stress which is caused by an imbalance between pro-oxidant processes in the liver, which can be caused by microsomal CYP2E1, mitochondrial release of reactive oxygen species (ROS), H₂O₂ release from peroxisomal fatty acid oxidation, and cytokines released from activated inflammatory cells. Preoxidation of membrane lipids causes the generation of malondialdehyde and 4-hydroxynonenol, which causes the production of proinflammatory cytokines, activation

of stellate cells, and fibrogenesis, as well as direct hepatocyte injury.^[6]

Hepatoprotective effects of kaempferol 3-O-rutinoside (K-3-R) and kaempferol 3-O-glucoside (K-3-G) (figure 2), two kaempferol glycosides isolated from *Carthamus tinctorius L.*, were investigated using a mode of hepatotoxicity induced by carbon tetrachloride (CCL₄) in mice. Male mice were fed orally K-3-R and K-3-G at doses of 200 mg/kg and 400 mg/kg for 7 days receiving CCL₄ intraperitoneally. K-3-R and K-3-G therapy raised

total protein (TP) levels while preventing the CCL₄-induced elevations in serum aspartate aminotransferase (AST), serum alkaline phosphatase (ALP), and hepatic malondialdehyde (MDA) levels. In comparison to CCL₄-treated mice, mice treated with K-3-R and K-3-G had considerably recovered glutathione (GSH) levels and normal catalase (CAT) and superoxide dismutase (SOD) activities. Histopathological study revealed that K-3-R and K-3-G reduced CCL₄-induced liver histological changes. These findings show that K-3-R and K-3-G can help to protect the liver from oxidative damage.^[10]

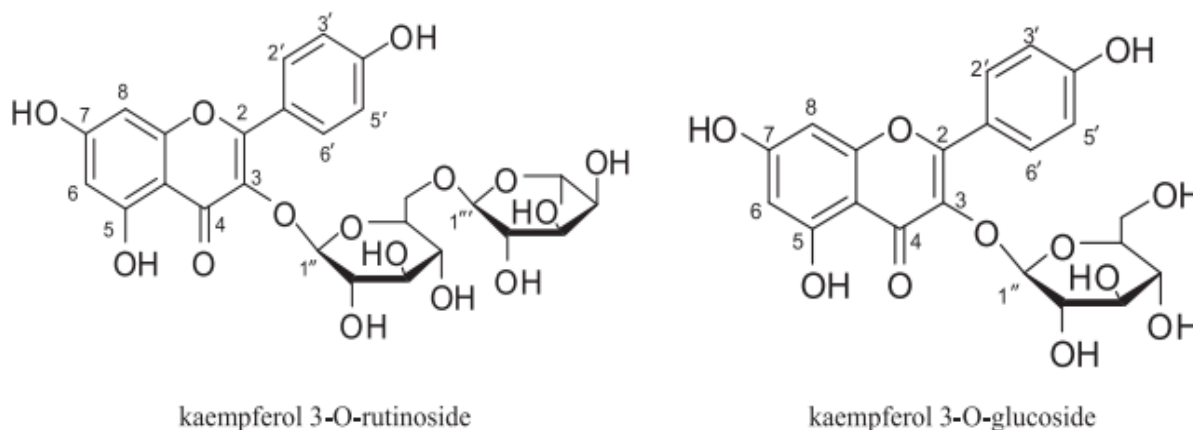


Figure 2: Chemical structure of kaempferol 3-O-rutinoside and kaempferol 3-O-glucoside.

In a study, researchers looked at the antioxidant and hepatoprotective effects of kaempferol 3-O-β-D-(2,6-di-O-α-L-rhamnopyranosyl) galactopyronoside (KG) isolated from unripe soybean leaves in CCL₄-induced hepatotoxicity in mice. The mice were grouped into three, control, CCL₄ (CCL₄ injected), and the KG (CCL₄ injected with KG administration). Serum and liver indicators of hepatic damage were examined. In mice pretreated with KG, serum ALT, AST activity, hepatic glutathione, superoxide dismutase, catalase, and glutathione peroxidase activities were all normalised. Furthermore, pretreatment with KG improved the levels of liver thiobarbituric acid reactive compounds, showing that KG can help to prevent liver injury, possibly due to its antioxidant characteristics. Unripe soy leaves could be employed as functional food components, according to the study.^[4]

TGs have a role in the formation of lipid reserves in the liver and have been linked to disorders including metabolic syndrome and type 2 diabetes. In comparison to the HF group, dietary KG caused a significant reduction in serum and hepatic triglyceride levels. The KG group had a higher serum HDL-Chol level and a lower serum LDL-Chol level. Dietary KG improves lipid buildup, according to the study. Chang et al. showed that dietary kaempferol has beneficial effect on serum and hepatic lipid levels in rats^[24], and Yu et al. found that supplementing rats with kaempferol glycosides reduce serum TG levels considerably.^[12]

2. INSULIN RESISTANCE

Insulin, a peptide released by β-cells in the pancreatic islets of Langerhans, is the hormone responsible for maintaining homeostasis by lowering blood glucose levels. Insulin secretion impairment and insulin resistance are both intrinsically linked to the development of diabetes mellitus (DM), a condition that is growing more prevalent worldwide. Persistent hyperglycemia is defined as chronic hyperglycemia induced by a decrease in insulin availability (type 1 DM) or a decrease in insulin sensitivity (type 2 DM), which is typically associated with obesity (type 2 DM). Regardless of the underlying aetiology of the condition, both kinds of diabetes are treated with an emphasis on blood glucose management. Exogenous insulin is used to lower blood glucose levels; sulfonylurea, dipeptidylpeptidase-4 inhibitor, glucagon-like peptide-1 analogue are used to improve insulin production; and peroxisomal proliferator-activated receptor (PPAR) is used to combat insulin resistance. Some chemical substances found in nature, particularly flavonoids and their glycosides, have been shown to improve glucose absorption. Although most flavonoids are PPAR agonists that increase insulin activity, kaempferol 3-O-neohesperidoside (fig.3) isolated from *Cyathea phalerata* Mart. was shown to have insulin like action and hence might be used as a “insulin mimetic”.^[14] The flavonoid structure of kaempferol 3-O-neohesperidoside is identical to one previously identified as a PPAR agonist flavanoid. The insulin-mimetic effect of kaempferol 3-O-neohesperidoside flavonoid is, however, unique.^[11]

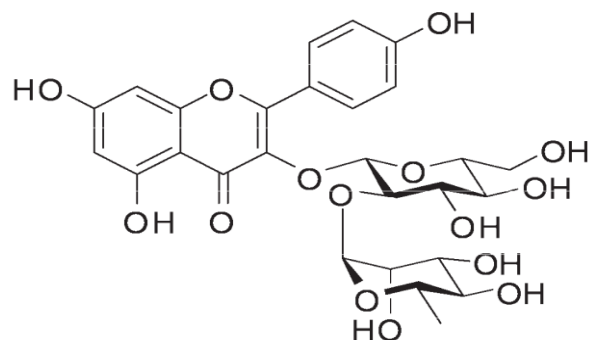


Figure 3: kaempferol 3-O-neohesperidoside.

In genetically type 2 diabetic mice, the anti-diabetic effects of a kaempferol glycoside (KG) rich fraction and kaempferol, an aglycone of KG, were investigated. The level of haemoglobin A1c was reduced by feeding KG and kaempferol (K), respectively. Feeding K and KG lowered the area under the curve (AUC) in the oral glucose tolerance test (OGTT). When KG and K were fed to mice, the level of liver triglycerides and the activity of fatty acid synthase were both lower than in control mice. These findings imply that KG and K may be beneficial in the treatment of diabetes. The primary

flavonoids in KG were discovered as kaempferol 3-O- β -D-glucopyranosyl (1->2)-O-[α -L-rhamnopyranosyl (1->6)]- β -D-galactopyranoside, kaempferol 3-O- β -D-glucopyranosyl(1->2)-O-[α -L-rhamnopyranosyl(1->6)]- β -D-glucopyranoside, kaempferol 3-O- β -D-(2-O- β -D-glucopyranosyl) galactopyranoside and kaempferol 3-O- β -D-(2,6-di-O- α -L-rhamnopyranosyl) galactopyranoside, (figure 4) implying that these compounds or some of them may be involved in diabetes mitigation.^[7]

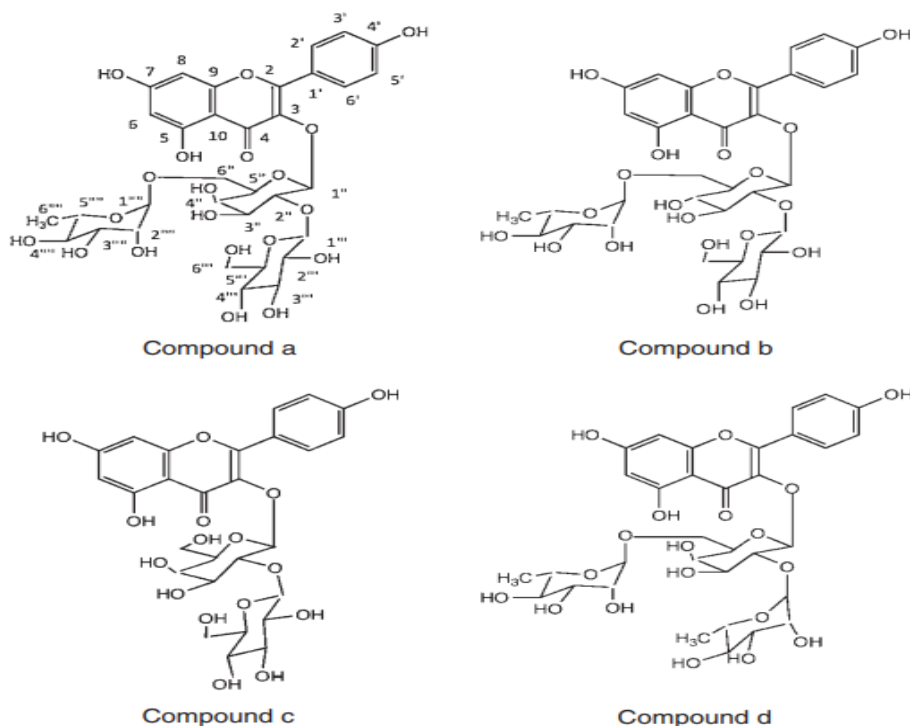


Figure 4: Chemical Structures of Compounds a, b, c, and d.

Compound-a:kaempferol3-O- β -D-glucopyranosyl(1->2)-O-[α -L-rhamnopyranosyl(1->6)]- β -D-galactopyranoside; **compound-b:**kaempferol 3-O- β -D-glucopyranosyl(1->2)-O-[α -L-rhamnopyranosyl(1->6)]- β -D-glucopyranoside; **compound-c:**kaempferol3-O- β -D-(2-O- β -D-glucopyranosyl)galactopyranoside; **compound-d:** kaempferol 3-O- β -D-(2,6-di-O- α -L-rhamnopyranosyl)galactopyranoside.

3. OBESITY

Obesity is a complicated disorder caused by a combination of genetic, nutritional, lifestyle, and environmental factors. Obesity and overweight are on the rise all across the world. Obesity is caused by up-

regulation of appetite or down-regulation of calorie use by regulating cellular activities, physical activity and other factors (figure 4). As a result of this dysregulation, an excess of adipocytes form, which increases cytokine release, resulting, in vascular complications.

Hyperlipidemia, cardiovascular abnormalities and atherosclerosis are all linked to these issues. Obesity in combined with atherosclerosis leads to serious pathological disorders as colon cancer, gallstones, liver

and gut ailments, and so on. As a result, managing obesity is critical for preventing and reversing chronic comorbidities.^[8]

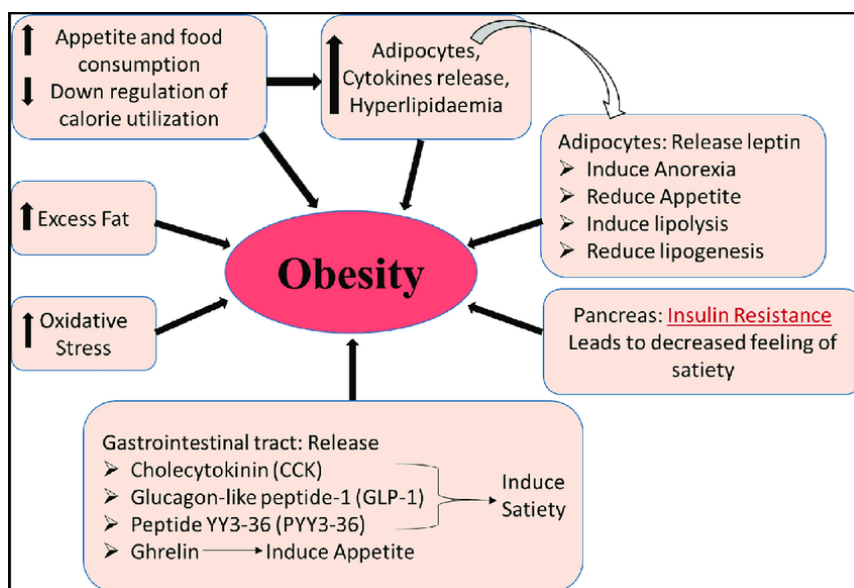


Figure 5: The diagrammatic representation of basic pathogenesis of obesity.^[8]

Leptin is a hormone that indicates the state of the body’s energy storage, and when the energy stores expand, leptin stimulates satiety and energy expenditure by acting on the central nervous system. Human obesity, on the other hand, is frequently accompanied by a weak central response to leptin action, resulting in leptin resistance and compensatory hyperleptinaemia. In a research study, serum leptin levels in the HF group were considerably higher than those in the CON group (Table.2), implying

that an HF diet causes leptin resistance as previously described. The decreased serum leptin level in the HFKG group compared to the HF group implies that KG ingestion improves leptin resistance. The most abundant hormone generated by adipose tissue, adiponectin, including high molecular weight (HMW) adiponectin, has been reported to be a better predictor of metabolic abnormalities and insulin resistance associated with obesity.^[12]

Table 2: Effects of dietary kaempferol glycosides on the serum, liver, faeces lipids, and serum leptin, insulin and TNF-α levels.^[13]

Dietary group	CON	HF	HFKG
Serum			
TC (mg dl ⁻¹)	106 ± 3	116 ± 7	102 ± 3*
TG (mg dl ⁻¹)	50.8 ± 3.5 ^b	62.4 ± 3.3 ^a	45.6 ± 1.1 ^b
HDL (mg dl ⁻¹)	91.0 ± 9.0	68.9 ± 8.0	79.1 ± 14.2
LDL (mg dl ⁻¹)	43.1 ± 7.5	49.7 ± 6.6	37.0 ± 8.2
Adiponectin (µg ml ⁻¹)	1.96 ± 0.07	1.77 ± 0.07	1.86 ± 0.05
HMW adiponectin (µg ml ⁻¹)	0.31 ± 0.07	0.17 ± 0.00	0.22 ± 0.05
Leptin (ng ml ⁻¹)	13.4 ± 4.6 ^b	81 ± 26.8 ^a	25.1 ± 8.5 ^b
TNF-α (pg ml ⁻¹)	181 ± 7	252 ± 49	169 ± 10*
Liver			
TC (mg per g of liver)	2.71 ± 0.24	2.48 ± 0.20	2.72 ± 0.18
TG (mg per g of liver)	38.3 ± 1.0 ^{ab*}	45.7 ± 2.5 ^a	35.6 ± 2.8 ^b
Faeces			
Total Lipid (mg per 3 days of faeces)	50.5 ± 2.1 ^b	65.2 ± 4.8 ^a	73.6 ± 3.3 ^a
T-Chol (mg per 3 days of faeces)	5.92 ± 0.31	5.11 ± 0.59	5.97 ± 0.7
TG (mg per 3 days of faeces)	1.30 ± 0.19 ^b	3.98 ± 0.63 ^a	3.38 ± 0.63 ^a
Total bile acid (mg per 3 days of faeces)	0.89 ± 0.07 ^b	1.75 ± 0.21 ^a	1.56 ± 0.18 ^a

Each value is the mean ± SEM. n = 3–7 for each group. Values without a common letter differ significantly (p < 0.05), *compare with HF group (0.05 < p < 0.1).

SREBP-1c and PPAR- γ are important regulators of the hepatic lipid metabolism. Several enzymes involved in liver fatty-acid production and glucose transport, gluconeogenesis, and lipolysis are stimulated by these regulators. Increased PPAR- γ and SREBP-1c expression is closely linked to fatty liver disease in obese people. The HFKG group had lower PPAR- γ and SREBP-1c expressions (Figure 6), which we believe is connected to the decrease in hepatic TG levels, but it could also be associated to the prevention of adipose tissue growth and

body weight gain. In HFD-induced animal models, adenosine monophosphate-activated protein kinase (AMPK) is found to inactivate PPAR- γ and SREBP-1c transcription and reduce hepatic steatosis. Kaempferol significantly activated hepatic AMPK in mice in a recent study, and AMPK is suggested to be a potential therapeutic target in the treatment of diabetes and obesity. The anti-obese and anti-diabetic actions of KG are probably to be mediated by SREBP-1c and PPAR- γ regulation via AMPK activation.^[12,13]

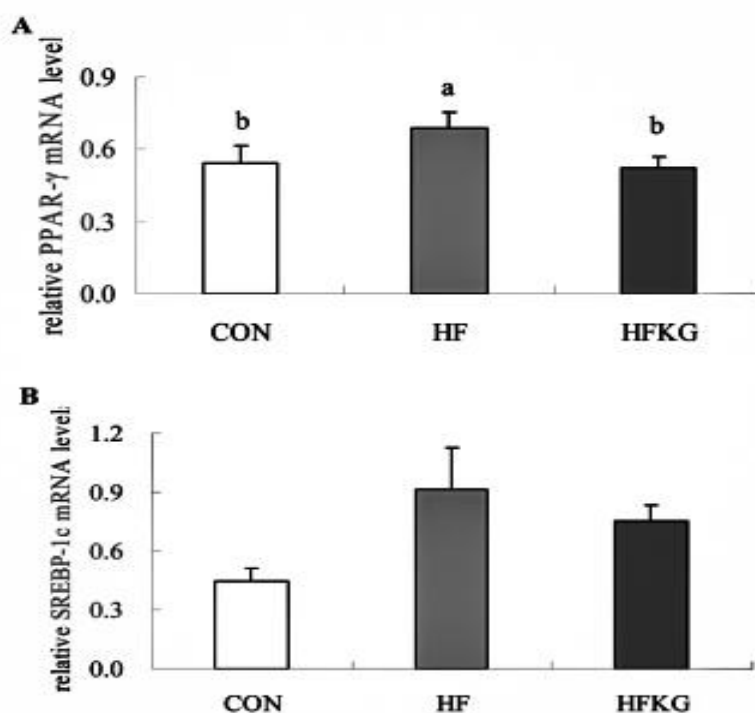


Figure 6: Effects of dietary kaempferol glycosides on the hepatic PPAR- γ and SREBP1 expression^[13]. (A) PPAR- γ expression; (B) SREBP1 expression. Each value is mean \pm SEM. n = 6–7 for each group. Values without a common letter differ significantly ($p < 0.05$).

Thus, dietary KG (kaempferol glycosides) can help with obesity by lowering adipose tissue and cholesterol levels, as well as having positive effects on diabetes by improving insulin and leptin resistance in mice.^[12]

ACAT (Acyl-CoA:cholesterol acyltransferase) is a key enzyme in the esterification of cholesterol. ACAT, in particular, converts cholesterol to its ester form, allowing cholesterol to accumulate in cells. ACAT-1 and ACAT-2 are the two isoenzymes of human ACAT. ACAT-1 (50 kDa) is found in the adult liver, adrenal gland, macrophage and kidney, while human ACAT-2 (46 kDa) is found in the small intestines. ACAT inhibitors can block cholesterol absorption from food and cholesteryl ester accumulation in vascular endothelial cells, making it a potential target material for the prevention and treatment of hypercholesterolemia, obesity cholesterol gallstones or atherosclerosis. Tae-Sook Jeong et al. conducted an experiment with kaempferol glycosides extract, which demonstrated an excellent inhibitory

effect on human ACAT-1 and ACAT-2, indicating that they might be utilised to successfully prevent or treat hyperlipidemia, obesity, and cholesteryl ester buildup.^[14]

CONCLUSION

The use of kaempferol glycosides in diverse pharmacological effects is gaining attention. It can be used to prevent and treat fatty liver, diabetes, metabolic syndrome, obesity, and hyperlipidemia by inhibiting the increase of high-fat diet-induced body fat, inhibiting the activities of Acyl-CoA:cholesterol acyltransferase (ACAT), inhibiting the increase of cholesterol and triglycerides in plasma and liver, by SREBP-1c and PPAR-regulation through AMPK activation, and by improvement of insulin and leptin resistance. Further research should concentrate on isolating and identifying active molecules, as well as a detailed study of kaempferol glycosides and their activities.

ABBREVIATIONS

TNF- α : Tumor necrosis factor
 ACAT: Acyl-CoA:cholesterol acyltransferase
 PPAR- γ : Proliferator-activated receptor
 SREBP-1: Sterol regulatory element-binding protein
 AMPK: Adenosine monophosphate-activated protein kinase
 HbA1c: Hemoglobin A1
 KGs: Kaempferol glycosides
 HFKG: High Fat Kaempferol Glycosides
 TC: Total cholesterol
 TG: Triglyceride
 HFD: High Fat Diet

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