Original Article

JHSMR Journal of Health Science and Medical Research

The Modulatory Effects of Pinocembrin from the Nigerian Propolis on IL-6, IL-1β, and Adipokines in Rats with Chronic Glucose and Fructose Administration

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Received 15 January 2025 ● Accepted 17 February 2025 ● Published online 10 June 2025

Abstract:

Objective: The study investigated the effects of pinocembrin on cytokines and the adipokines associated with metabolic disturbances that arise from prolonged sugar intake.

Material and Methods: Twenty-four male Wistar rats were divided into 4 groups: control, glucose/fructose administration, glucose/fructose administration plus pinocembrin treatment, and glucose/fructose administration plus metformin treatment. The control group was administered distilled water orally, while the glucose/fructose group received an oral sugar solution comprising 30% glucose and 20% fructose. The pinocembrin and metformin treatment groups were given the same sugar solution, but received either pinocembrin or metformin as an additional component, respectively. Administration continued for 8 weeks, after which blood samples were collected for biochemical analysis.

Results: Chronic administration of glucose and fructose led to the dysregulation of adipokines and inflammatory markers, hyperinsulinemia and hyperglycaemia. However, treatment with pinocembrin significantly mitigated these metabolic and inflammatory alterations.

Conclusion: The findings suggest that the prophylactic use of pinocembrin from the Nigerian propolis has the potential to modulate glucose and lipid metabolism, as well as inflammatory pathways, thereby preventing sugar-induced metabolic disturbances.

Keywords: adipokines, cytokines, fructose, glucose, Nigerian propolis, pinocembrin

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J Health Sci Med Res
doi: 10.31584/jhsmr.20251219
www.jhsmr.org

Introduction

Chronic consumption of glucose and fructose is consistently linked to the onset of metabolic disorders, including insulin resistance[1], inflammation[2], and dyslipidemia[3]. These metabolic alterations are often accompanied by the dysregulation of cytokines like interleukin-6 (IL-6)[4] and interleukin-1β (IL-1β)[5], as well as the disrupted homeostasis of adipokines, such as leptin[6] and adiponectin[7], which are signalling proteins secreted by adipose tissue[8]. Discovering the compounds capable of modulating these inflammatory and metabolic pathways could offer a promising therapeutic approach for mitigating the adverse health consequences associated with excessive or prolonged sugar consumption.

Propolis, a resin-like material collected by honey bees, has been documented to display a variety of beneficial biological properties, including anti-inflammatory[9], antioxidant[10], and metabolic regulatory properties[11], including the propolis of Nigerian origin[12]. Pinocembrin, a flavanone found in propolis, has demonstrated promising therapeutic potential in several disease conditions[13,14]. However, the effects of pinocembrin on metabolic disturbances induced by chronic exposure to glucose and fructose have not been extensively investigated.

This study investigated the regulatory effects of pinocembrin, isolated from Nigerian propolis, on inflammatory cytokines (IL-6 and IL-1β) and adipokines (leptin and adiponectin) in a rat model of chronic glucose and fructose administration.

Material and Methods

Experimental design

The experiment was conducted using twenty-four male Wistar rats obtained from the Ahmadu Bello University animal facilities. The rats were acclimated for 7 days before the start of the study. They were contained in an environment with a normal day/night cycle, unvarying ambient temperature, and unrestricted access to standard rat feed and water. Rats were arbitrarily separated into 4 groups, with each group consisting of 6 rats: control group, a glucose/fructose administration group, a glucose/fructose administration plus pinocembrin treatment group, and a glucose/fructose administration plus metformin treatment group. The study was approved by the Ahmadu Bello University committee on the use of animals for research.

Oral administration with glucose and fructose

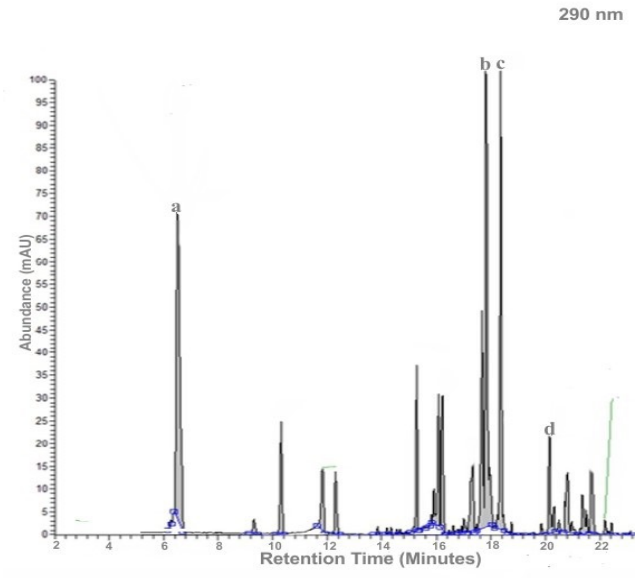
The control group received a normal diet and the oral administration of distilled water as a vehicle. The glucose/fructose group was provided an aqueous sugar solution containing 30% glucose and 20% fructose as their drinking water for 8 weeks. The glucose/fructose plus pinocembrin treatment group was given the same glucose/fructose sugar solution, in addition to the daily oral administration of pinocembrin isolated from the Nigerian propolis at a dose of 50 milligrams per kilogram body weight. The glucose/fructose plus metformin treatment group received the same glucose/fructose solution, along with the daily oral administration of metformin (50 mg/kg) as a positive control. Their drinking water, containing the solutes, was constantly replenished.

Sample collection and analysis

At the end of the 8-week study period, the rats were humanely sacrificed, and blood samples were taken for biochemical analysis. Plasma levels of IL-6, IL-1β, leptin, adiponectin, and insulin were measured using ELISA kits from Sigma-Aldrich, Burlington, Massachusetts, USA. Plasma glucose was also measured using the On Call Plus glucometer by Acon Labs Inc., USA.

High-performance liquid chromatography (HPLC) isolation of pinocembrin

Pinocembrin, the active compound of interest, was isolated from the Nigerian propolis using high-performance liquid chromatography; see Figure 1. The propolis sample was first extracted with ethanol, and the resulting extract was then subjected to HPLC separation. A C18 reversed-phase column was used, with a mobile phase comprising a gradient mixture of water and acetonitrile. The elution of pinocembrin at a retention time of 17.8 minutes (Table 1) was monitored by ultraviolet detection at 290 nm.



Pinocembrin is the peak marked "b". Properties of the marked compounds are shown in Table 1

Figure 1 Chromatogram HPLC of the Nigerian propolis used for this study

Table 1 Properties of some of the compounds separated from the Nigerian propolis

	Peak	Retention time (min)	Height (mAU)	Area	Class	Molecular formula
a	Gallic acid	6.5	71.12	53154	Phenolic acid	$C_7H_6O_5$
b	Pinocembrin	17.8	99.96	109036	Flavonoid	$C_{15}H_{12}O_4$
c	Chrysin	18.5	99.94	86500	Flavonoid	$C_{15}H_{10}O_4$
d	Piperine	20.3	23.08	30007	Alkaloid	$C_{17}H_{19}NO_3$

mAU=milli Absorbance Unit

Statistical analysis

Statistical analyses were conducted using GraphPad Prism version 8.0. All data are presented as the mean±scanning electron microscope. One-way ANOVA, followed by Tukey's post-hoc test, was utilized to evaluate the differences among the experimental groups. A p-value less than 0.05 was set as the threshold for statistical significance.

Results

Effects of pinocembrin on plasma glucose and insulin levels

Chronic administration of glucose and fructose resulted in a substantial increase in plasma glucose levels compared to the control group. Interestingly, administration of either pinocembrin or metformin significantly mitigated

the hyperglycaemic effects induced by the high sugar administration, as seen in Figure 2a. The glucose/fructose administration group also displayed a significant elevation in plasma insulin levels, as demonstrated by the increased homeostatic model assessment of the insulin resistance index (HOMA-IR) in the administration group (Figure 2b), indicating the development of insulin resistance in these animals. Compared to the glucose/fructose administration group, treatment with pinocembrin or metformin significantly helped to prevent the elevation of insulin levels.

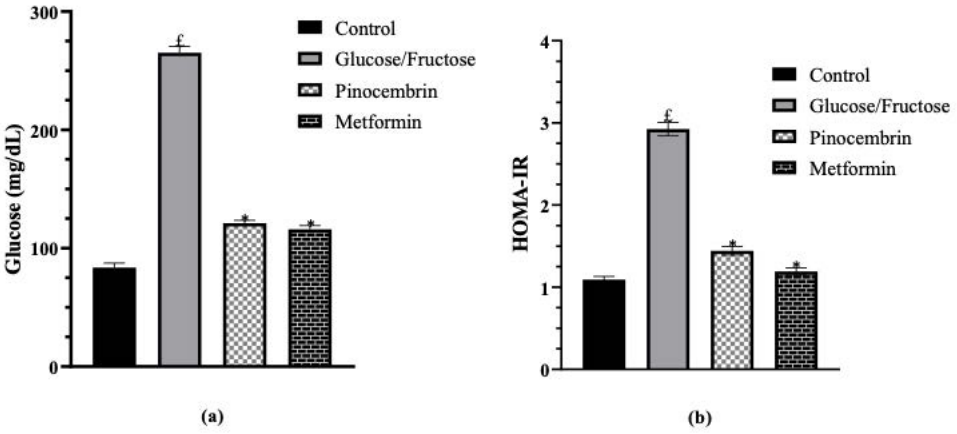
HOMA-IR=(fasting plasma glucose(mg/dL)×fasting insulin (μU/mL))/405

Effects of pinocembrin on inflammatory cytokines

In Figure 3 and 4, the glucose/fructose administration group exhibited significantly elevated plasma levels of the inflammatory cytokines IL-6 and IL-1β, respectively, compared with the control group. However, treatment with pinocembrin isolated from the Nigerian propolis was able to significantly prevent these increases in IL-6 and IL-1β when compared to the glucose/fructose administration group. The positive control group receiving metformin also demonstrated a reduction in the plasma levels of these inflammatory markers.

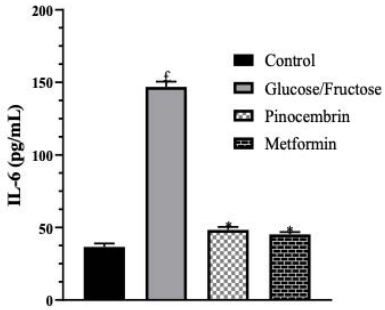
Effects of pinocembrin on adipokines

In the glucose/fructose administration group, plasma leptin was markedly elevated (Figure 5) while the adiponectin level was substantially decreased (Figure 6). Pinocembrin administration significantly mitigated the increase in leptin and significantly prevented the decrease in adiponectin levels when compared to the glucose/fructose administration group. Metformin treatment also exhibited some modulatory effect on these adipokines.



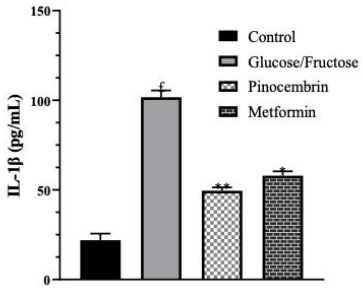
All data are presented as the mean±SEM. One-way ANOVA, followed by Tukey's post-hoc test, was utilized to evaluate the differences among the experimental groups. A p-value<0.05 was set as the threshold for statistical significance. £; a p-value<0.01 compared with the control group. *p-value<0.01 compared with the glucose/fructose group

Figure 2 Pinocembrin prevents the hyperglycaemic effects induced by high sugar administration



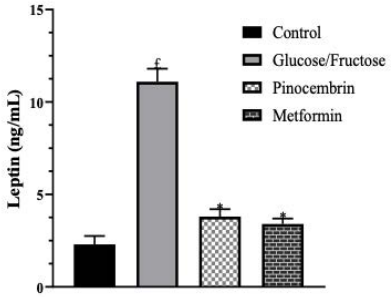
All data are presented as the mean±SEM. One-way ANOVA, followed by Tukey's post-hoc test, was utilized to evaluate the differences among the experimental groups. A p-value<0.05 was set as the threshold for statistical significance. £; a p-value<0.01 compared with the control group. *p-value<0.01 compared with the glucose/fructose group

Figure 3 Treatment with pinocembrin effectively prevents an increase in IL 6



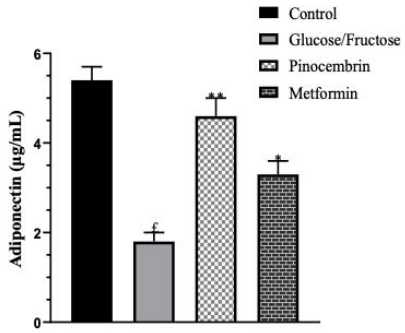
All data are presented as the mean±SEM. One-way ANOVA, followed by Tukey's post-hoc test, was utilized to evaluate the differences among the experimental groups. A p-value<0.05 was set as the threshold for statistical significance. £; p-value<0.01 compared with the control group. *p-value<0.05 compared to the glucose/fructose group, **p-value<0.01 compared with the glucose/fructose group

Figure 4 Treatment with pinocembrin markedly prevents an increase in IL-1β



All data are presented as the mean±SEM. One-way ANOVA, followed by Tukey's post-hoc test, was utilized to evaluate the differences among the experimental groups. A p-value<0.05 was set as the threshold for statistical significance. £; p-value<0.01 compared with the control group. *p-value<0.01 compared with the glucose/fructose group

Figure 5 Pinocembrin mitigates leptin levels



All data are presented as the mean±SEM. One-way ANOVA, followed by Tukey's post-hoc test, was utilized to evaluate the differences among the experimental groups. A p-value<0.05 was set as the threshold for statistical significance. £; a p-value<0.01 compared to the control group. *p-value<0.05 compared with the glucose/fructose group, **p-value<0.01 compared with the glucose/fructose group

Figure 6 Pinocembrin prevents drops in adiponectin levels

Discussion

The findings from the present study demonstrate that pinocembrin, a flavanone isolated from the Nigerian propolis, was able to modulate several key metabolic and inflammatory parameters in a rat model of chronic glucose and fructose administration. This high sugar administration mimicked the metabolic disturbances observed in humans consuming high fructose diets, leading to hyperglycaemia, insulin resistance, and a pro-inflammatory state.

Treatment with pinocembrin was able to effectively mitigate the hyperglycaemic effects and prevent the development of resistance to insulin in these rats. Previous research has reported the ability of pinocembrin to mitigate hyperglycaemic conditions[15]. The modulation of glucose and insulin levels further lends credence to the use of pinocembrin in this study, as it suggests that this natural compound from the Nigerian propolis has therapeutic potential in managing carbohydrate metabolism dysregulation.

Importantly, pinocembrin was shown to significantly attenuate the increases in the cytokines IL-6 and IL-1β that were induced by the glucose/fructose administration. These cytokines have been implicated in the genesis of metabolic disorders and associated comorbidities[16]. Their chronic elevation in response to high sugar intake can add to the genesis of insulin resistance[5,17], dyslipidaemia[18], and other cardiometabolic abnormalities[19]. This anti-inflammatory activity of pinocembrin is consistent with previous reports on the biological properties of this flavanone-flavonoid[20,21]. By modulating these cytokines, pinocembrin may help prevent the metabolic consequences associated with chronic sugar intake.

Interestingly, pinocembrin also exhibited modulatory effects on the adipokines leptin and adiponectin. Leptin is an important hormone produced by adipose tissue that plays an essential role in modulating energy balance, appetite, and metabolism[22]. Similarly, adiponectin is an adipokine secreted by adipose tissue that is a key regulator in energy metabolism and insulin sensitivity[23,24]. Pinocembrin was able to mitigate the increase in leptin and prevent the reduction in adiponectin levels observed in the glucose/fructose administration group. These findings suggest that pinocembrin helps to improve adipose tissue function and the balance of adipokines, thereby contributing to the overall amelioration of the metabolic disturbances induced by chronic high sugar consumption.

Conclusion

The findings demonstrate that pinocembrin, a flavanone compound isolated from the Nigerian propolis, was able to effectively regulate glucose and insulin levels, suppress pro-inflammatory cytokines, and modulate key adipokines in a rat model of chronic high sugar intake. These results suggest that pinocembrin may have therapeutic potential in preventing cardiometabolic disorders associated with diet-induced metabolic disruptions. Further investigation is necessary in order to elucidate the precise mechanisms of action and assess the clinical applicability of this natural compound, especially as a prophylactic.

Conflict of interest

No conflict of interest declared.

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