

## **EFFECT OF ALOIN ADDED TO METFORMIN ON RENAL FOAM CELLS IN AN AGED, OBESE MOUSE MODEL OF TYPE 2 DIABETES MELLITUS**

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### **Abstract**

*Background: Type 2 Diabetes Mellitus (T2DM) is associated with chronic hyperglycemia, obesity, dyslipidemia, and oxidative stress, which contribute to renal lipid accumulation, inflammation, and foam-cell formation. Aloin, a bioactive compound from Aloe vera, has antioxidant and anti-inflammatory properties and may enhance the renoprotective effects of metformin. Objective: To evaluate the effect of adding aloin to metformin on renal foam-cell occurrence and renal histopathological changes in an aged, obese mouse model of T2DM. Methods: A laboratory experimental study with a post-test-only control-group design was conducted using 32 aged, obese male mice with T2DM. Mice were randomly assigned to receive metformin (250 mg/kg body weight/day) or metformin plus aloin (750 µg/kg body weight/day) for 28 days. Kidney tissues were examined using hematoxylin and eosin staining, and differences in renal foam-cell occurrence were analyzed using the chi-square test. Results: Renal foam cells were observed in 68.8% of mice receiving metformin and 18.8% of those receiving metformin plus aloin, representing a significant reduction ( $p = 0.004$ ). The combination therapy also showed better-preserved glomerular and tubular architecture and fewer inflammatory cell infiltrates. Conclusion: The addition of aloin to metformin was associated with a significantly lower occurrence of renal foam cells and better-preserved renal histological architecture. These findings suggest that aloin may serve as a potential adjunct to metformin for attenuating diabetes-associated renal histopathological changes.*

**Keywords:** aloin; metformin; type 2 diabetes mellitus; renal foam cells; kidney histopathology

### **INTRODUCTION**

Type 2 Diabetes Mellitus (T2DM) is one of the most prevalent chronic metabolic disorders worldwide and remains a major public health concern due to its increasing incidence and long-term complications. The growing prevalence of obesity, population ageing, sedentary lifestyles, and unhealthy dietary patterns has substantially contributed to the global rise in T2DM. According to the International Diabetes Federation, more than 530 million adults are currently living with diabetes, and this number is expected to continue increasing over the coming decades. Despite advances in glucose-lowering therapies, T2DM remains a leading cause of cardiovascular disease, Chronic Kidney Disease (CKD), blindness, and lower-limb amputation, resulting in considerable morbidity, mortality, and healthcare costs worldwide. (Dianna, 2021) (American Diabetes Association, 2024) (Tuttle et al, 2022).

Diabetic Kidney Disease (DKD) is among the most common microvascular complications of T2DM and represents the leading cause of CKD and end-stage kidney disease globally. Approximately one-third of individuals with T2DM develop renal impairment during the course of their disease. Traditionally, the development

of DKD has been attributed to persistent hyperglycemia, glomerular hyperfiltration, activation of the renin–angiotensin–aldosterone system, oxidative stress, and chronic inflammation. However, recent evidence indicates that DKD is a multifactorial disorder involving complex interactions among metabolic dysregulation, lipid abnormalities, inflammatory responses, and structural remodelling of renal tissue. These mechanisms contribute not only to glomerular injury but also to tubular damage, interstitial fibrosis, and progressive deterioration of renal architecture. (American Diabetes Association,2024)(Rooney,2017)(Kidney,2024).

Obesity, a major risk factor for T2DM, further accelerates the progression of DKD through mechanisms beyond impaired glucose metabolism. Chronic insulin resistance, elevated circulating free fatty acids, and dyslipidemia promote excessive lipid influx into renal tissue while impairing fatty acid oxidation and intracellular cholesterol homeostasis. Consequently, ectopic lipid accumulation develops within podocytes, mesangial cells, tubular epithelial cells, and infiltrating macrophages, a phenomenon known as renal lipotoxicity. Increasing evidence indicates that renal lipid dysregulation plays an important role in diabetic kidney injury by promoting mitochondrial dysfunction, oxidative stress, inflammatory signalling, apoptosis, and extracellular matrix deposition. These findings suggest that abnormal lipid metabolism is an active contributor to DKD progression rather than merely a secondary consequence of diabetes.(Merscher,2023)

One of the characteristic histopathological consequences of renal lipotoxicity is the formation of foam cells, which are lipid-laden macrophages generated through excessive uptake of modified lipoproteins, particularly oxidized low-density lipoprotein. Although foam cells are classically associated with atherosclerosis, recent studies have demonstrated similar pathological processes within diabetic kidneys. Renal foam cells contribute to sustained inflammatory responses through the release of pro-inflammatory cytokines, chemokines, and reactive oxygen species, thereby promoting macrophage recruitment, tubular injury, extracellular matrix accumulation, and interstitial fibrosis. Their presence reflects persistent renal lipid dysregulation and chronic inflammation, suggesting that foam-cell formation may serve as a histopathological indicator of lipid-associated renal injury in DKD.(Merscher,2023) (Forbes,2013).

Current management of T2DM emphasizes comprehensive metabolic control to delay diabetic complications. Metformin remains the recommended first-line pharmacological therapy because of its efficacy, favourable safety profile, and cardiovascular benefits. In addition to reducing hepatic glucose production and improving insulin sensitivity, metformin has been reported to exert anti-inflammatory and antioxidant effects through modulation of cellular energy metabolism. Nevertheless, diabetic kidney disease frequently progresses despite adequate glycemic control, indicating that persistent dyslipidemia, lipotoxicity, oxidative stress, and inflammation are not completely addressed by glucose-lowering therapy alone. These observations highlight the need for adjunctive therapeutic strategies capable of targeting additional pathogenic mechanisms involved in diabetic kidney injury (American Diabetes Association,2024) (Rooney,2017) (Kidney,2024).

Natural bioactive compounds have increasingly attracted attention as complementary therapies for metabolic diseases because of their diverse pharmacological activities. Aloin, an anthraquinone glycoside isolated from Aloe

vera, has been reported to possess antioxidant, anti-inflammatory, and lipid-modulating properties in experimental studies. Although its precise molecular mechanisms remain incompletely understood, available evidence suggests that aloidin may attenuate oxidative stress, suppress inflammatory responses, and improve lipid metabolism. These biological activities provide a plausible rationale for combining aloidin with metformin to target pathological mechanisms beyond glycemic control, particularly those associated with renal lipid dysregulation and foam-cell formation (Opazo-Rios et al,2020) (Han Yi zhen et al.,2024)(Y.Wang et al,2024) (Forbes,2013).

Despite growing interest in aloidin, evidence regarding its use as an adjunct to metformin in diabetic kidney disease remains limited. Most previous studies have focused on biochemical or molecular outcomes, whereas histopathological evidence regarding renal foam-cell formation is still scarce. Moreover, few investigations have evaluated combination therapy in aged, obese diabetic animal models that more closely resemble the metabolic characteristics commonly observed in patients with T2DM. Addressing this knowledge gap may improve understanding of whether adjunctive therapy targeting renal lipid dysregulation can attenuate diabetes-associated renal injury.

Therefore, this study aimed to evaluate the effect of adding aloidin to metformin on renal foam-cell occurrence and renal histopathological changes in an aged, obese mouse model of type 2 diabetes mellitus. We hypothesized that the addition of aloidin to metformin would be associated with a lower occurrence of renal foam cells and better-preserved renal histological architecture compared with metformin alone.

## METHODS

This laboratory experimental study employed a post-test-only control-group design to evaluate the effect of adding aloidin to metformin on renal foam-cell occurrence and renal histopathological changes in an aged, obese mouse model of Type 2 Diabetes Mellitus (T2DM). Thirty-two healthy male white mice (*Mus musculus*), aged 18 weeks and weighing 30–40 g, were included in the study. Sample size was determined using the Federer formula, resulting in 16 animals per group. Mice with random blood glucose levels  $\geq 176$  mg/dL were eligible for inclusion.

Obesity was induced by feeding the animals a high-fat diet until the target body weight (30–40 g) was achieved. Type 2 diabetes mellitus was induced by intraperitoneal administration of streptozotocin (STZ) three days before baseline blood glucose measurement at a dose of 2 mg per mouse. Random blood glucose levels were measured on days 0, 14, and 28. An aged mouse model was established by ultraviolet (UV) irradiation for nine consecutive days.

Following confirmation of diabetes, the animals were randomly allocated into two groups ( $n = 16$  each): the positive control group, which received metformin (250 mg/kg body weight/day), and the treatment group, which received metformin (250 mg/kg body weight/day) combined with aloidin (750  $\mu$ g/kg body weight/day). Both treatments were administered orally twice daily for 28 consecutive days, with aloidin given 30 minutes after metformin administration.

At the end of the treatment period, all animals were euthanized by cervical dislocation, and both kidneys were harvested for histopathological examination. Kidney tissues were fixed, processed using standard paraffin-embedding techniques, sectioned, and stained with Hematoxylin and Eosin (H&E). Histopathological

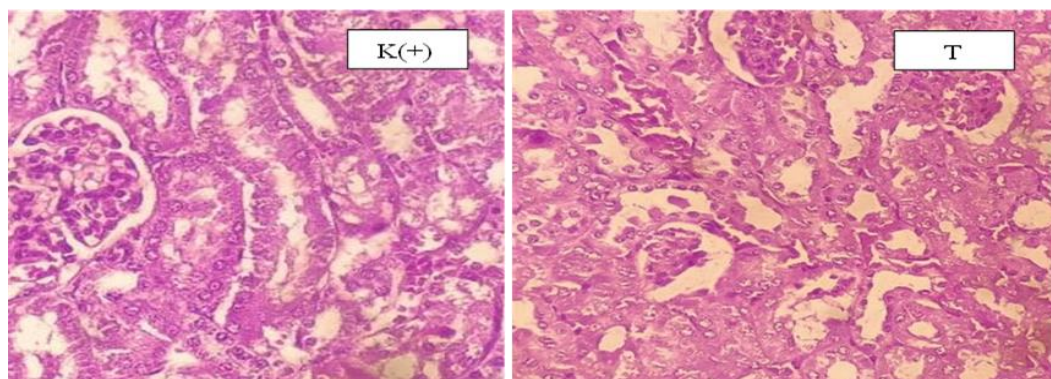
evaluation was performed under light microscopy at 100× and 400× magnifications. The primary outcome was the presence or absence of renal foam cells. Renal histopathological features, including glomerular architecture, tubular morphology, and inflammatory cell infiltration, were also evaluated descriptively and compared between the positive control and treatment groups.

## RESULTS

**Table 1. Distribution and Comparison of Renal Foam Cell Presence Between Groups**

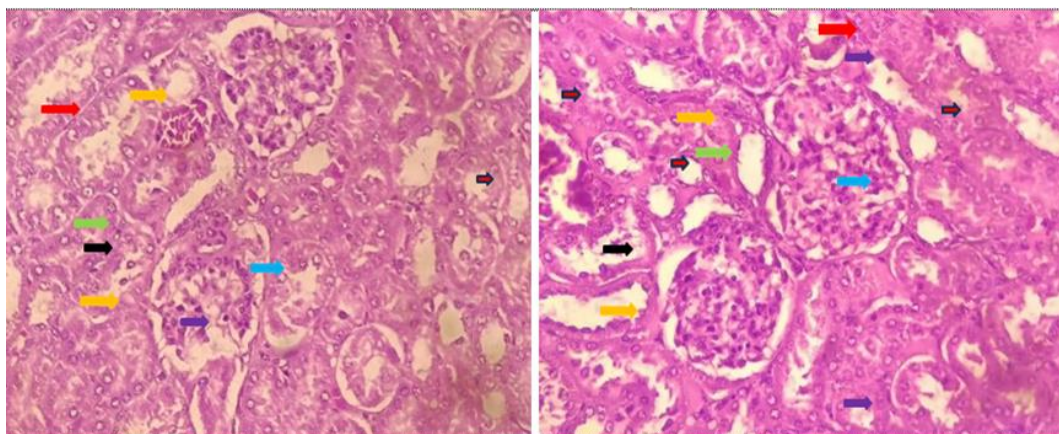
| Group       | Foam Cells (+), n (%) | Foam Cells (-), n (%) | Total, n | <i>p</i> -value |
|-------------|-----------------------|-----------------------|----------|-----------------|
| Treatment   | 3 (18.8)              | 13 (81.2)             | 16       | 0.004           |
| Control (+) | 11 (68.8)             | 5 (31.2)              | 16       |                 |
| Total       | 14 (43.8)             | 18 (56.2)             | 32       |                 |

As shown in Table 1, renal foam cells were identified in 3 of 16 mice (18.8%) in the treatment group (metformin plus aloin) and 11 of 16 mice (68.8%) in the positive control group (metformin alone). Conversely, the absence of renal foam cells was observed in 81.2% of the treatment group compared with 31.2% of the positive control group. Chi-square analysis demonstrated a statistically significant difference in renal foam-cell occurrence between the two groups ( $p = 0.004$ ). These findings indicate that mice receiving the combination of aloin and metformin had a significantly lower frequency of renal foam cells than those receiving metformin alone.



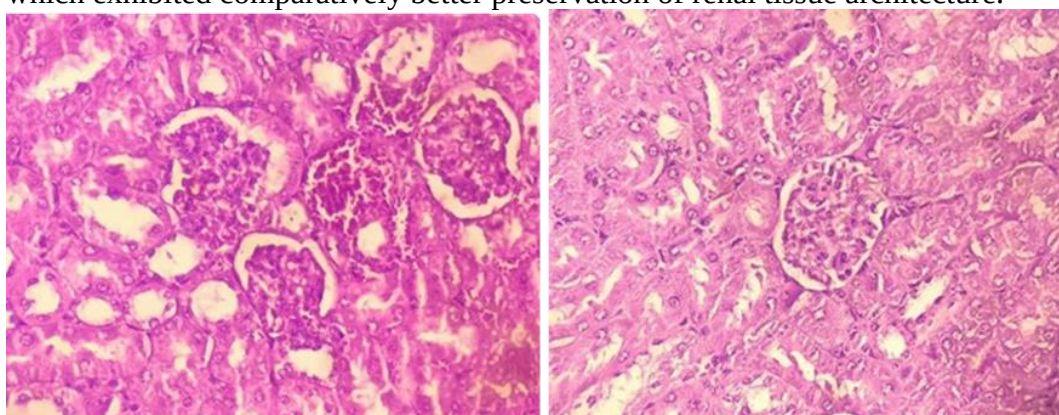
**Fig 1. Comparison of Kidney Histology Images in Control (+) and Treatment Groups**

Representative hematoxylin and eosin-stained kidney sections are presented in Figure 1. Compared with the positive control group, the treatment group showed better-preserved renal histological architecture, with relatively intact glomeruli and renal tubules and fewer apparent structural abnormalities.



**Fig 2. Histological Images of The Kidney from Positive Control Group (→ = hemorrhage, → = foam cells, → = inflammatory cells, → = cloudy swelling, → = necrosis, → = glomerular and bowman's capsule adhesion, → = inflammation)**

Figure 2 illustrates representative renal histopathological findings in both groups. The positive control group demonstrated more prominent histological alterations, including glomerular and tubular changes accompanied by inflammatory cell infiltration and foam-cell formation. In contrast, these histopathological alterations appeared less pronounced in the treatment group, which exhibited comparatively better preservation of renal tissue architecture.



**Fig 3. Histological Image of Kidney from the Treatment Group**

Figure 3 demonstrates the overall renal histopathological appearance following treatment. Kidney sections from mice receiving metformin plus aloin exhibited comparatively better-preserved glomerular and tubular structures than those from the positive control group, in which histological alterations appeared more extensive.

## DISCUSSION

As shown in Table 1, renal foam cells were identified in 18.8% of mice receiving metformin plus aloin compared with 68.8% of mice receiving metformin alone, and the difference between groups was statistically significant ( $p = 0.004$ ). This finding indicates that the addition of aloin to metformin was associated with a substantially lower occurrence of renal foam cells in the aged, obese mouse model of Type 2 Diabetes Mellitus (T2DM). Because renal foam-cell formation is considered a histopathological manifestation of lipid accumulation and chronic

inflammation within the diabetic kidney, the reduced frequency observed in the combination-treatment group may suggest attenuation of diabetes-associated renal histopathological alterations (Rooney,2017) (Han et al.,2024) (Wang et al.,2024).

The finding presented in Table 1 is biologically plausible because renal foam-cell formation has recently been recognized as an important feature of Diabetic Kidney Disease (DKD). Persistent hyperglycemia, obesity, insulin resistance, and dyslipidemia disrupt renal lipid homeostasis by promoting excessive lipid uptake while impairing lipid utilization and cholesterol efflux. Consequently, lipid-laden macrophages accumulate within the renal interstitium and gradually differentiate into foam cells, which contribute to chronic inflammation, oxidative stress, extracellular matrix remodelling, and progressive glomerular and tubulointerstitial injury. These processes accelerate the progression of DKD and are increasingly recognized as potential therapeutic targets (Han et al.,2024) (Wang et al.,2024) (Fang et al.,2024).

Metformin remains the recommended first-line pharmacological therapy for T2DM because of its well-established glucose-lowering efficacy and favourable cardiovascular and renal safety profile. However, current evidence indicates that DKD progression may persist despite adequate glycemic control, partly because metabolic disturbances such as renal lipotoxicity, oxidative stress, and chronic inflammation are not completely corrected by glucose-lowering therapy alone. In the present study, the significantly lower occurrence of renal foam cells in the metformin-plus-aloin group compared with the metformin-only group suggests that aloin may provide additional renoprotective effects when administered as an adjunct to metformin.

Although the molecular mechanisms were not investigated in this study, the present findings are consistent with previous experimental evidence demonstrating that aloin possesses antioxidant, anti-inflammatory, and lipid-regulating activities. These biological properties may complement the metabolic actions of metformin by reducing the renal microenvironment that favours lipid accumulation and foam-cell formation(Rios et al.,2020). Nevertheless, because oxidative stress biomarkers, inflammatory cytokines, renal lipid content, and macrophage-specific markers were not evaluated, the proposed mechanisms should be regarded as biologically plausible explanations rather than definitive conclusions.

Several limitations should be considered when interpreting these findings. The present study assessed only histopathological outcomes and did not include molecular or biochemical markers of lipid metabolism, oxidative stress, or inflammation. Therefore, the observed reduction in renal foam-cell occurrence cannot be directly attributed to specific signalling pathways. Future studies should incorporate analyses of renal lipid metabolism, oxidative stress biomarkers, inflammatory mediators, macrophage polarization, and renal function parameters to better elucidate the mechanisms underlying the potential renoprotective effects of aloin. Nevertheless, the significant reduction in renal foam-cell occurrence observed in Table 1 supports the potential role of aloin as an adjunct to metformin in attenuating diabetes-associated renal histopathological changes in an aged, obese mouse model of T2DM.

Figure 1 shows that kidney sections from mice treated with metformin plus aloin exhibited comparatively better-preserved renal histological architecture than those from mice receiving metformin alone. The combination-treatment group

demonstrated relatively intact glomerular and tubular structures with fewer apparent histopathological alterations, suggesting that the addition of aloin may contribute to maintaining renal structural integrity under diabetic conditions. This observation is consistent with the findings in Table 1, which demonstrated a significantly lower occurrence of renal foam cells in the metformin-plus-aloin group(Rooney,2017)(Han et al.,2024).

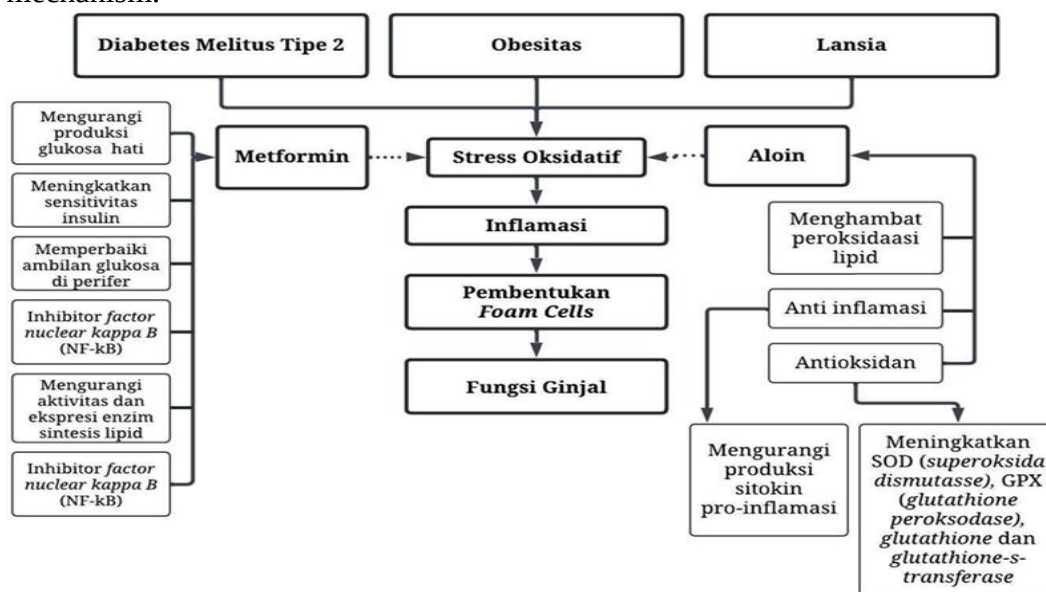
The improved renal morphology observed in Figure 1 is biologically plausible because diabetic kidney disease is characterized by chronic hyperglycemia, obesity, and dyslipidemia, which promote renal lipotoxicity, oxidative stress, and persistent inflammation, ultimately leading to progressive glomerular and tubular injury(Han et al.,2024) (Wang et al.,2024). Preservation of renal architecture is therefore considered an important indicator of reduced histopathological damage in experimental diabetic kidney disease.(Kidney,2024). Although the present study did not evaluate molecular pathways, previous studies have suggested that aloin possesses antioxidant and anti-inflammatory properties that may complement the metabolic effects of metformin.(Rios et al.,2020). Accordingly, the histological appearance shown in Figure 1 should be interpreted as supportive evidence of the potential renoprotective effect of aloin rather than confirmation of a specific biological mechanism.

Figure 2 demonstrates that renal histopathological alterations, including glomerular and tubular abnormalities accompanied by inflammatory cell infiltration and foam-cell formation, were less pronounced in mice treated with metformin plus aloin than in those receiving metformin alone. These observations are consistent with the findings in Table 1, which showed a significantly lower occurrence of renal foam cells in the combination-treatment group, suggesting that adjunctive aloin may help preserve renal tissue integrity under diabetic conditions(Sugahara et al.,2021)

The histopathological differences observed in Figure 2 are biologically plausible because diabetic kidney disease is characterized by persistent metabolic stress that promotes lipid accumulation, inflammatory cell recruitment, and progressive glomerular and tubular injury. Chronic inflammation and oxidative stress further amplify tissue damage, contributing to structural remodelling and disease progression.(Wang et al,2023). Although the present study did not investigate the underlying molecular pathways, previous experimental studies have shown that aloin possesses antioxidant and anti-inflammatory properties, which may contribute to limiting diabetes-associated renal injury(Rios et al.,2020). Therefore, the improved histological appearance observed in the combination-treatment group should be interpreted as being consistent with, rather than proving, the potential renoprotective effects of aloin.

Figure 3 provides higher-magnification histological evidence of renal foam-cell formation, demonstrating fewer foam cells in mice treated with metformin plus aloin than in those receiving metformin alone. This qualitative observation is consistent with the quantitative findings in Table 1, which showed a significantly lower occurrence of renal foam cells following adjunctive aloin treatment. Together, these findings suggest that the addition of aloin may be associated with reduced lipid accumulation and preservation of renal histological integrity in the diabetic kidney(Wang et al.,2025).

Foam-cell formation is increasingly recognized as an important histopathological feature of diabetic kidney disease because it reflects impaired renal lipid homeostasis and macrophage lipid overload. Excessive lipid deposition promotes macrophage activation, chronic inflammation, and progressive glomerular and tubulointerstitial injury, thereby accelerating diabetic kidney disease progression(Wang et al.,2024). Although the present study did not investigate the underlying molecular mechanisms, previous studies have suggested that natural compounds with antioxidant and anti-inflammatory activities may attenuate renal lipid accumulation and inflammatory injury(Charlton,2020). Therefore, the findings presented in Figure 3 should be interpreted as histopathological evidence supporting the potential renoprotective effect of aloin as an adjunct to metformin rather than confirmation of a specific molecular mechanism.



**Figure 4. Proposed Mechanism of Aloin as an Adjunct to Metformin in Attenuating Diabetes-Associated Renal Injury**

Figure 4 summarizes the proposed mechanism underlying the findings of the present study. In aged, obese mice with type 2 diabetes mellitus, chronic metabolic disturbances are believed to promote oxidative stress and inflammation, leading to foam-cell formation and subsequent renal injury. The lower occurrence of renal foam cells observed in the metformin-plus-aloin group suggests that the combination treatment may interfere with these pathological processes, thereby contributing to better preservation of renal histological integrity(Rooney et al.,2024)(Charlton et al.,2020)(Liu et al.,2022)(Sibony et al,2024).

Metformin is known to improve glucose homeostasis and has additional anti-inflammatory effects through modulation of pathways such as NF-κB and AMPK, whereas aloin has been reported to possess antioxidant, anti-inflammatory, and anti-lipid peroxidation properties in experimental studies(Sibony et al,2024) (Khalil et al.,2024) (Pereira et al.,2018). Nevertheless, these molecular pathways were not directly evaluated in the present study. Therefore, the mechanistic model presented in Figure 4 should be regarded as a hypothesis supported by previous evidence rather than direct experimental confirmation. Further studies

incorporating oxidative stress biomarkers, inflammatory mediators, and molecular analyses are warranted to validate the proposed mechanism.

## CONCLUSION

The addition of aloin to metformin was associated with a significantly lower occurrence of renal foam cells and comparatively better-preserved glomerular and tubular architecture in aged, obese mice with type 2 diabetes mellitus. These findings support the potential of aloin as an adjunct to metformin for attenuating diabetes-associated renal histopathological changes. However, further studies incorporating renal function, oxidative stress, inflammatory, and lipid-metabolism markers are required to confirm its renoprotective effects and underlying mechanisms.

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