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Effect of the aqueous extract of *Gossypium herbaceum* on lipid parameters and histopathological alterations in Wistar rats fed a high-fat diet

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ABSTRACT

Objective: To evaluate the effects of *Gossypium herbaceum* aqueous leaf extract on lipid parameters and hepatic and cardiac histopathological alterations in Wistar rats fed a high-fat diet. **Methods:** Experimental study with 25 female Wistar rats divided into five groups: control, high-fat diet, diet plus extract, diet plus exercise, and diet plus extract and exercise. The extract was administered orally (400 mg/kg). Serum biochemical analyses and histopathological evaluations were performed. **Results:** A reduction in triglycerides and total cholesterol levels was observed in groups treated with the extract, alone or combined with exercise. No significant changes were observed in HDL levels. Histopathological analysis showed reduced hepatic steatosis and inflammation, with no evidence of fibrosis or cardiac alterations. **Conclusion:** The results suggest that the aqueous extract of Gossypium herbaceum may exert a lipid-modulating effect and may indicate hepatoprotective potential, representing a possible experimental adjuvant strategy for dyslipidemia.

Keywords: *Gossypium herbaceum*, Dyslipidemia, Phytotherapy, Experimental model, High-fat diet.

INTRODUCTION

Cardiovascular diseases are the leading cause of mortality in Brazil and worldwide and are associated with multiple metabolic and behavioral risk factors (ANVISA, 2022). Among these factors, dyslipidemia stands out, characterized by alterations in serum cholesterol and triglyceride levels, and may be classified according to its origin as primary, with a genetic basis, or secondary, mainly related to inadequate lifestyle habits (KERBER SL, et al., 2010; BRAZILIAN SOCIETY OF CARDIOLOGY, 2017; BORBA CAM, et al., 2023).

In addition to constituting an important cardiovascular risk factor, dyslipidemia is also directly associated with the development of hepatic disorders, particularly Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), and is considered a multifactorial condition with a major impact on public health (OLIVEIRA AKM, et al., 2022).

The accumulation of lipids in the liver, resulting from metabolic imbalances, may progress to inflammatory processes and, in more advanced cases, to fibrosis and cirrhosis, reinforcing the importance of effective preventive and therapeutic strategies (CREGE DRXO, et al., 2016; PEREZ GS, 2014).

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The therapeutic management of dyslipidemia involves pharmacological and non-pharmacological approaches, with the choice depending on the individual cardiovascular risk. In patients at low or intermediate risk, lifestyle interventions, such as dietary changes and regular physical activity, are recommended as the first line of treatment and may be associated with the use of bioactive compounds, such as phytosterols (KERBER SL, et al., 2010; BRAZILIAN SOCIETY OF CARDIOLOGY, 2017).

In this context, there is growing interest in the use of phytotherapeutic compounds as alternatives or adjuvants in the management of dyslipidemias, especially in individuals with low to moderate cardiovascular risk or as a complement to traditional pharmacological therapies (OLIVEIRA AKM, et al., 2022).

Phytosterols have been widely recognized for their ability to reduce total cholesterol and low-density lipoprotein (LDL) levels, without significantly interfering with high-density lipoprotein (HDL) and triglyceride levels, being used both alone and as adjuvants to statin therapy (DEMONTY I, et al., 2009; GYLLING H, et al., 2014; CABRAL CE and KLEIN MRST, 2017).

These compounds may act on different metabolic pathways, including the modulation of intestinal lipid absorption and the regulation of hepatic metabolism (DEMONTY I, et al., 2009; GYLLING H, et al., 2014; CABRAL CE and KLEIN MRST, 2017).

The genus Gossypium, commonly known as cotton, contains several secondary metabolites with potential biological activity, including phytosterols, flavonoids, tannins, and phenolic compounds (LEÃO RBA, et al., 2007; PERERA WPRT, et al., 2021; AL-SNAI A, et al., 2019). Among these compounds, β-sitosterol has been identified as one of the main phytosterols associated with cholesterol-lowering effects, being reported in different parts of the plant, especially in the leaves (MARTINS SL, et al., 2004; LEÃO RBA, et al., 2007; BOTELHO FGC, et al., 2019).

Despite the traditional use of Gossypium herbaceum in different cultures through aqueous infusions of leaves, stems, and roots, scientific studies that systematically evaluated its efficacy and safety in the treatment of dyslipidemia were still limited (LIU G, et al., 1985; GADELHA ICN, et al., 2011; TONIOLLI R, et al., 2018).

Although the genus Gossypium is recognized for the presence of phytosterols and other bioactive metabolites, such as flavonoids and phenolic compounds, investigations evaluating, in an integrated manner, its systemic effects on biochemical parameters and histopathological alterations in experimental models are still limited (LEÃO RBA, et al., 2007; PERERA WPRT, et al., 2021; AL-SNAI A, et al., 2019).

This knowledge gap reinforced the need for experimental investigations that would allow understanding its metabolic effects and possible impacts on target organs, such as the liver and heart. Experimental models of dyslipidemia induced by a high-fat diet in Wistar rats have been widely used because they mimic metabolic disturbances observed in humans, allowing the integrated evaluation of biochemical and histopathological parameters (CREGE DRXO, et al., 2016; NINAHUAMAN MFML, et al., 2017). Thus, in vivo studies have become fundamental tools for the scientific validation of the use of herbal therapy traditionally employed.

In view of this context, the present study aimed to evaluate the effects of the aqueous extract of Gossypium herbaceum leaves on serum lipid profile and on hepatic and cardiac histopathological alterations in Wistar rats subjected to a high-fat diet, investigating both the isolated administration of the extract and its combined use with physical exercise.

METHODS

The present experimental study was approved by the Ethics Committee on Animal Use of Centro Universitário de Adamantina (CEUA/FAI), under protocol no. 22007. Twenty-five female Wistar rats (Rattus norvegicus), weighing between 300 and 400 g, were used and maintained under controlled conditions of temperature, relative humidity, and a 12-hour light/dark cycle, with free access to water and standard chow throughout the experimental period. Subsequently, the animals were randomly distributed into five experimental groups (n = 5), as described in **Table 1**.

Table 1 - Distribution of experimental groups and respective treatments.

Group	Experimental Condition
Group I (Control)	Standard diet
Group II (HFD)	High-fat diet
Group III (HFD + AE)	High-fat diet + oral administration of aqueous extract
Group IV (HFD + EX)	High-fat diet + physical exercise
Group V (HFD + AE + EX)	High-fat diet + oral administration of aqueous extract + physical exercise

Source: Borba CAM, et al., 2026.

The animals were initially subjected to a high-fat diet composed of Labina® feed, pork lard, and eggs, according to NINAHUAMAN MFML, et al. (2017), in the proportion of 860 g of feed, 140 g of pork lard, and 10 eggs (±50 g), with an approximate intake of 21 g/animal/day for 28 days, without significant weight gain.

Subsequently, a cafeteria diet was adopted for 13 weeks, rich in fats and carbohydrates, with chocolate offered ad libitum to promote weight gain and metabolic alterations (KAGIOS C, et al., 2025; GAMARANO GC, et al., 2023; LEITE CAVALCANTI JP, et al., 2025).

The final high-fat diet consisted of hydrogenated animal fat, eggs, and white chocolate, in a 2:1:1 proportion, associated with the standard chow diet throughout the experimental period, according to adaptations described by CREGE DRXO, et al. (2016) and PEREZ GS (2014).

The aqueous extract of *Gossypium herbaceum* was prepared to experimentally reproduce the traditional use of the plant, generally employed as an infusion, which justified the use of water as the extraction solvent. Although aqueous solvents show lower efficiency in the extraction of lipophilic compounds such as phytosterols, this approach more closely reflects its traditional use (SALGADO JM, et al., 2008).

The aqueous extract was administered by gavage at a dose of 400 mg/kg/day, according to the experimental groups. The choice of dose was based on literature data related to the biological activity of phytosterols and their potential lipid-lowering effect, considering the absence of specific standardization for *Gossypium herbaceum* (CABRAL CE and KLEIN MRST, 2017). This approach allowed the establishment of an initial parameter for the evaluation of possible biological effects.

The groups subjected to physical exercise underwent swimming sessions three times per week for 20 minutes, without additional load , in water maintained at approximately 32 °C and at sufficient depth to prevent the animals from touching the bottom, according to the protocol described by Cheik NC, et al. (2006).

The association with physical exercise was included in the experimental design due to its well-established role in the modulation of lipid metabolism and reduction of cardiovascular risk, allowing the evaluation of possible complementary effects between herbal intervention and physical activity (CHEIK NC, et al., 2006; SWIFT DL, et al., 2018).

The experimental period comprised the initial phase of metabolic induction by high-fat diet, followed by the maintenance phase of the diet associated with the proposed treatments, allowing an integrated evaluation of biochemical and histopathological parameters, according to models previously described in the literature (CREGE DRXO, et al., 2016; NINAHUAMAN MFML, et al., 2017).

After the experimental period, the animals were anesthetized and blood samples were collected by puncture of the inferior vena cava. The samples were centrifuged at 2500 rpm for five minutes to obtain serum. Total cholesterol, high-density lipoprotein (HDL), triglycerides, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels were measured using commercial kits. The results were expressed as mean ± standard error of the mean (SEM). Statistical analysis was performed using ANOVA followed by Tukey's test ($p < 0.05$), using Statistica® 7.0 software (VICINI L, et al., 2020).

Liver and heart samples were collected after euthanasia, fixed in 10% formalin for 48 hours, and processed using standard histological techniques. The sections were stained with Hematoxylin and Eosin (HE). In the liver, steatosis, inflammation, and fibrosis were evaluated (graded on a scale from 0 to 4).

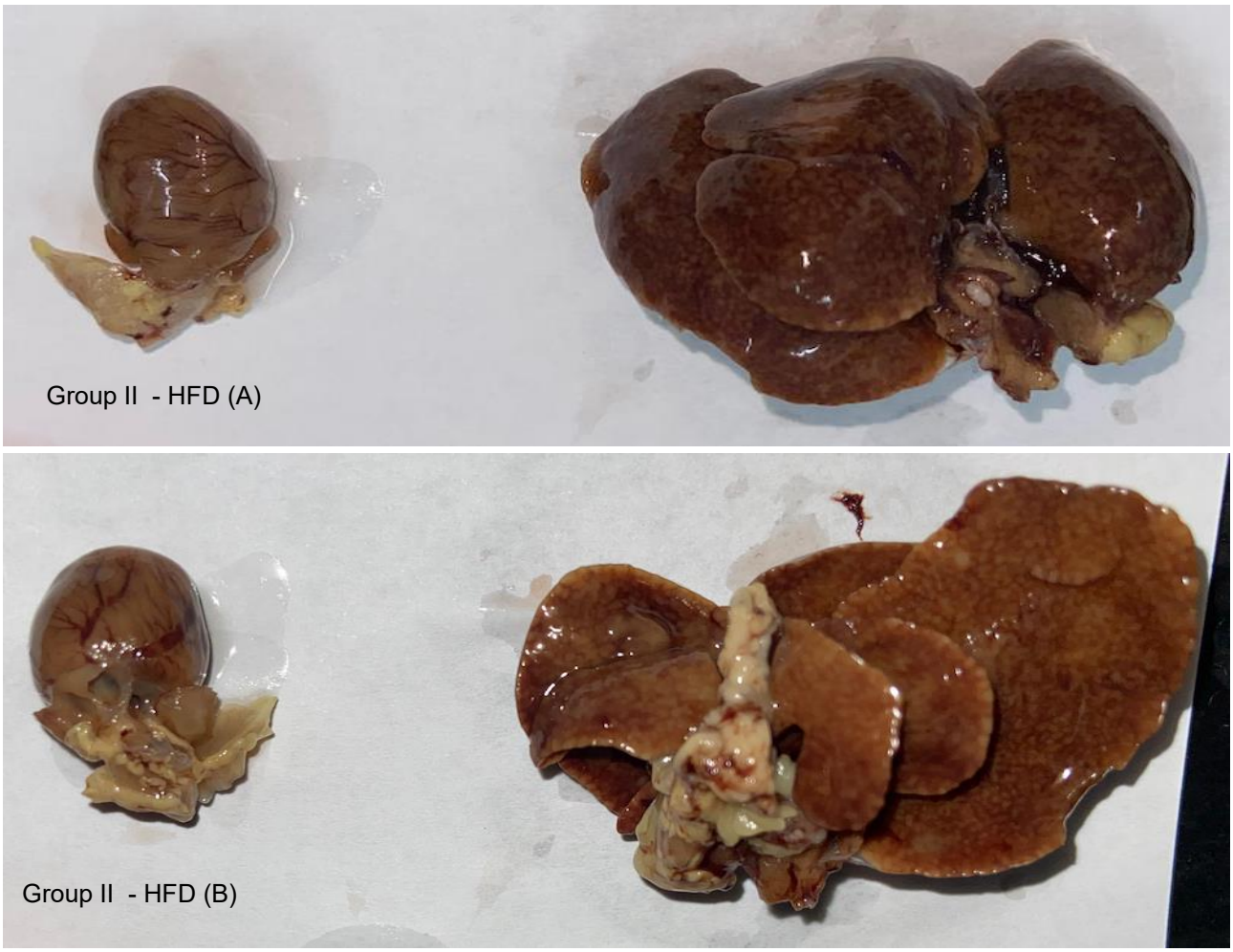
In the heart, inflammation and fibrosis were evaluated. Collagen detection was performed using Picrosirius Red staining, with analysis under polarized light (JUNQUEIRA LCU, et al., 1978; RIZZONI D, et al., 2006).

Three fields per slide were analyzed, totaling 15 fields per group. Collagen area was expressed as percentage values and analyzed using GraphPad Prism® software.

RESULTS

Macroscopic evaluation of the liver showed that most organs presented normal color, consistency, shape, and size. However, one liver belonging to the group subjected exclusively to the high-fat diet (Group II – HFD) showed multiple small circular whitish lesions distributed throughout the organ. This finding was not observed in the other experimental groups (**Figure 1**). Macroscopic evaluation of cardiac tissue revealed no structural or color alterations in any of the analyzed groups, with all samples consistent with normal morphology.

Figure 1 - Macroscopic evaluation of liver and heart from an animal in Group II (HFD – high-fat diet). Representative images of the same specimen obtained in different anatomical planes: frontal view (A) and dorsal view (B).



Source: Borba CAM, et al., 2026.

Histopathological analysis of the liver revealed qualitative differences among the groups regarding the presence of steatosis and inflammatory infiltrate. Animals subjected exclusively to the high-fat diet (Group II – HFD) showed greater lipid accumulation in hepatocytes, characterizing predominantly macrovesicular hepatic steatosis.

In the groups treated with the aqueous extract of *Gossypium herbaceum*, either alone or associated with physical exercise (Groups III and V), a lower occurrence of hepatic steatosis was observed compared to the HFDgroup. Animals subjected to the high-fat diet associated with physical exercise (Group IV) also showed a lower frequency of these histopathological alterations.

Regarding hepatic inflammatory infiltrate, a lower frequency of mononuclear inflammatory foci was observed in the groups treated with the aqueous extract, especially when associated with physical exercise.Statistical analysis showed no statistically significant differences among the groups ($p > 0.05$). No areas compatible with hepatic fibrosis were identified in any of the experimental groups.

In cardiac tissue, no relevant structural alterations were observed among the groups. Minimal inflammatory infiltrate was observed and showed no statistically significant difference ($p > 0.05$). Likewise, no statistically significant deposition of collagen fibers was observed (**Figure 2** and **Figure 3**).

Biochemical analysis revealed differences in lipid parameters among the experimental groups. Animals subjected exclusively to the high-fat diet (Group II – HFD) showed increased serum triglyceride and total cholesterol levels compared to the control group (**Figure 4**).

In the groups treated with the aqueous extract of *Gossypium herbaceum*, either alone (Group III) or associated with physical exercise (Group V), a trend toward reduced serum triglyceride and total cholesterol levels was observed compared to the HFD group. Similar results were observed in the group subjected to the high-fat diet associated with physical exercise (Group IV). High-density lipoprotein (HDL) levels showed no significant differences among the experimental groups.

Regarding hepatic enzymes, serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels showed no significant increases among the analyzed groups. Overall, comparative analysis among the experimental groups showed that animals subjected exclusively to the high-fat diet (Group II – HFD) presented more pronounced metabolic alterations, characterized by higher serum triglyceride and total cholesterol levels, in addition to a higher frequency of hepatic steatosis and inflammatory infiltrate, findings consistent with similar experimental models described in the literature (CREGE DRXO, et al., 2016; NINAHUAMAN MFML, et al., 2017).

In contrast, the groups treated with the aqueous extract of Gossypium herbaceum, either alone or associated with physical exercise (Groups III and V), showed a trend toward improvement in lipid parameters and a lower frequency of hepatic histopathological alterations compared to the HFD group. A similar result, although less pronounced, was also observed in the group subjected exclusively to physical exercise (Group IV), indicating a possible association between the interventions and qualitative improvements in the evaluated parameters.

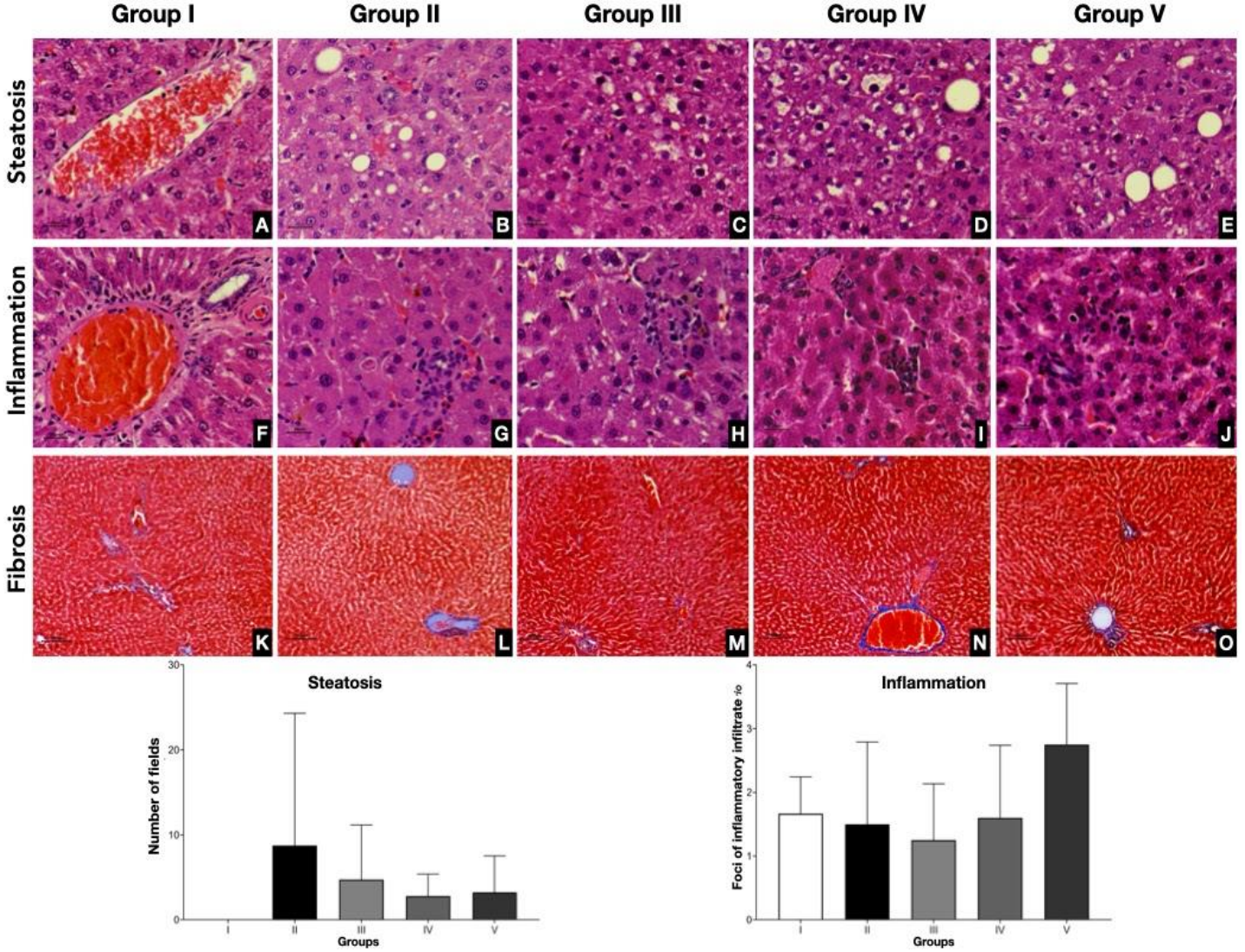
The absence of relevant cardiac alterations among the groups, associated with the maintenance of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels within normal ranges, suggests a favorable safety profile of the aqueous extract under the evaluated experimental conditions, with no evidence of detectable tissue toxicity during the studied period (GADELHA ICN, et al., 2011).

When integrating the main findings observed among the experimental groups, animals subjected exclusively to the high-fat diet (Group II – HFD) showed the worst metabolic profile and a higher frequency of hepatic alterations, characterized by increased total cholesterol and triglyceride levels, in addition to a greater occurrence of steatosis and inflammatory infiltrate.

In contrast, the groups treated with the aqueous extract of *Gossypium herbaceum*, either alone or associated with physical exercise (Groups III and V), showed a trend toward improvement in these parameters, with a more pronounced reduction in the group subjected to the combined intervention.

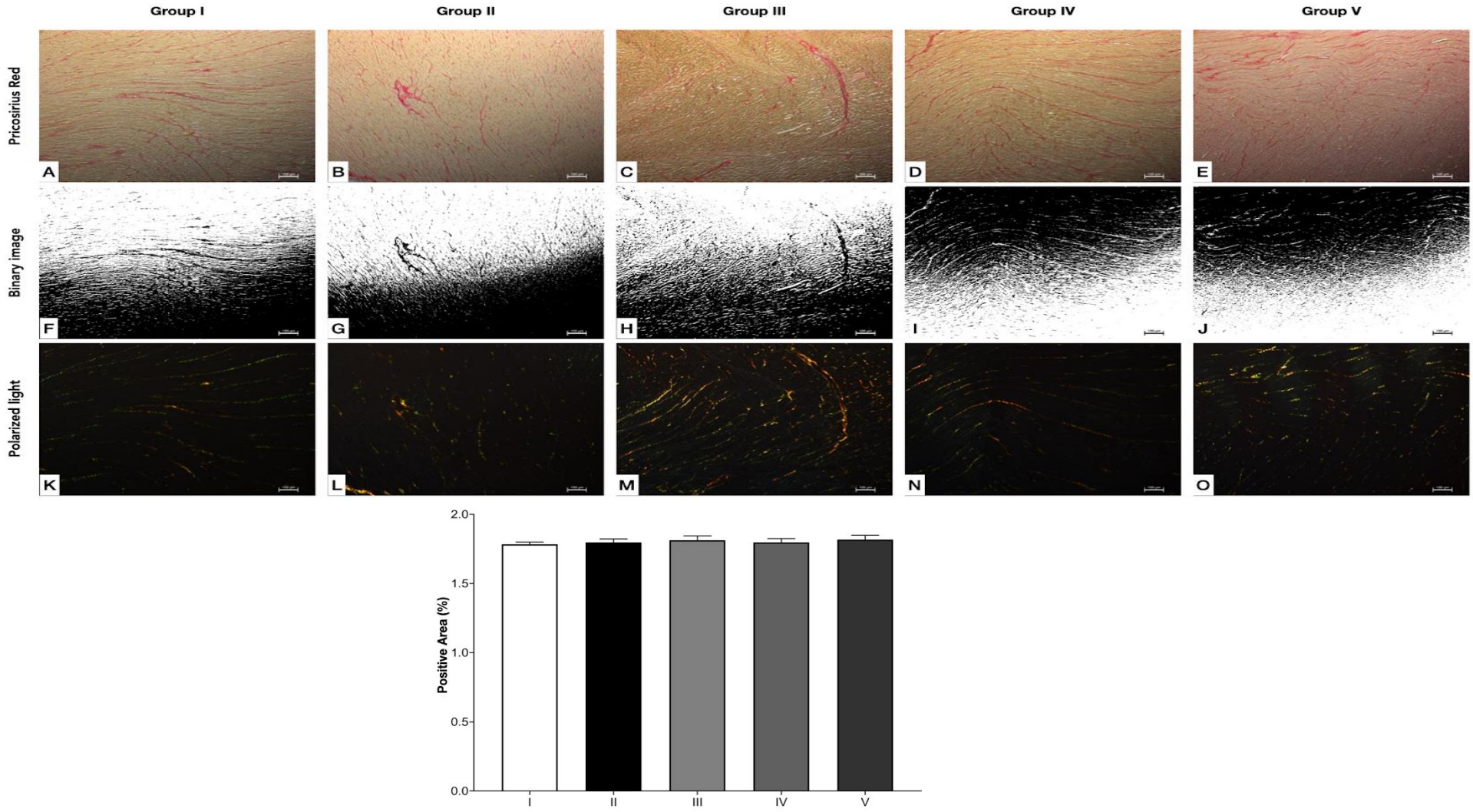
The physical exercise-only group (Group IV) also showed a favorable response, although less pronounced. No relevant alterations were observed in HDL levels, hepatic enzymes, or cardiac histology among the groups. A comparative synthesis of these results is presented in **Figure 5**.

Figure 2 - Quantification of steatosis, inflammatory infiltrate, and hepatic histological analysis.



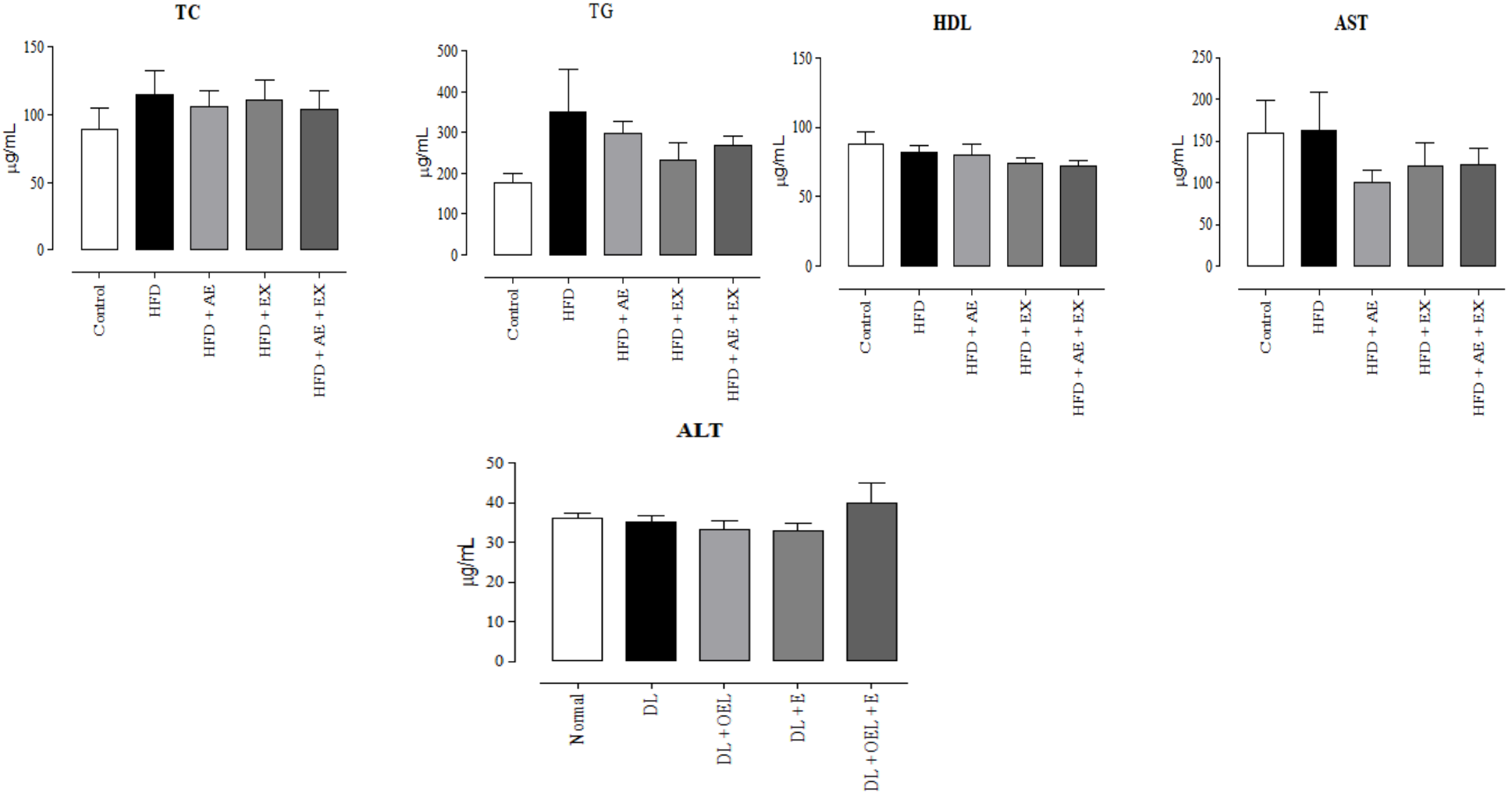
Source: Borba CAM, et al., 2026.

Figure 3 - Quantification of myocardial fibrosis by Picrosirius Red staining.



Source: Borba CAM, et al., 2026.

Figure 4 - Serum biochemical parameters: TC, TG, HDL, AST, and ALT.



Source: Borba CAM, et al., 2026.

Figure 5 - Comparative synthesis of the effects of high-fat diet, aqueous extract of *Gossypium herbaceum*, and physical exercise on the main biochemical and hepatic parameters in the experimental groups.

EXPERIMENTAL GROUPS	Group I CONTROL	Group II HFD	Group III HFD + AE	Group IV HFD + EX	Group V HFD + AE + EX
BIOCHEMICAL PARAMETERS					
Total Cholesterol (TC)	=	↑↑	↓↓	↓	↓↓
Triglycerides (TG)	=	↑↑	↓	↓↓	↓↓
HDL-Cholesterol (HDL)	=	=	=	=	=
Liver Enzymes (AST and ALT)	=	=	=	=	=
HISTOLOGICAL PARAMETERS					
Hepatic Steatosis	Absent	↑↑	↓↓	↓	↓↓
Hepatic Inflammatory Infiltrate	Absent	↑↑	↓↓	↓	↓↓↓
Hepatic Fibrosis	Absent	Absent	Absent	Absent	Absent
Cardiac Alterations (Histology and Fibrosis)	Absent / Preserved	Absent / Preserved	Absent / Preserved	Absent / Preserved	Absent / Preserved

LEGEND				
HFD - High-fat diet; AE - Aqueous extract of *Gossypium herbaceum*; EX - Physical exercise (swimming three times per week)				
= normal	↑↑ increased	↓ slightly decreased	↓↓ decreased	↓↓↓ markedly decreased

Source: Borba CAM, et al., 2026.

DISCUSSION

The use of experimental models of diet-induced dyslipidemia in Wistar rats is a widely employed strategy for investigating metabolic disturbances associated with the development of cardiovascular diseases, allowing the reproduction of conditions similar to those observed in humans, particularly increased serum lipid parameters and hepatic alterations resulting from excessive consumption of fats and carbohydrates (CREGE DRXO, et al., 2016; NINAHUAMAN MFML, et al., 2017).

In the present study, the initial induction through a conventional high-fat diet, composed of feed, pork lard, and eggs, did not promote significant weight gain, a result also described by NINAHUAMAN MFML, et al. (2017), demonstrating the variability of the metabolic response of rodents to lipid-rich diets. The subsequent adoption of a cafeteria diet proved effective in inducing excess weight and metabolic alterations compatible with secondary dyslipidemia. This dietary pattern, characterized by high levels of saturated fats and simple carbohydrates, promotes increased body weight, insulin resistance, and lipid abnormalities (KAGIOS C, et al., 2025; GAMARANO GC, et al., 2023; LEITE CAVALCANTI JP, et al., 2025). Thus, its use contributed to the establishment of an experimental model suitable for evaluating the effects of the aqueous extract of *Gossypium herbaceum*.

In addition to biochemical alterations, dyslipidemia models allow the evaluation of morphological alterations in target organs. The presence of hepatic steatosis and inflammatory infiltrate in animals subjected exclusively to the high-fat diet reinforces the adequacy of the adopted experimental model (CREGE DRXO, et al., 2016; PEREZ GS, 2014). The hepatic alterations observed in the group subjected exclusively to the high-fat diet confirm the impact of prolonged lipid consumption, frequently associated with hepatic fat accumulation and activation of inflammatory processes.

The lower degree of hepatic steatosis in the groups treated with the aqueous extract of *Gossypium herbaceum*, either alone or associated with physical exercise, indicates a possible modulatory effect on lipid accumulation in hepatocytes. This effect may be related to the presence of phytosterols, flavonoids, and phenolic compounds described in the genus *Gossypium*, metabolites with recognized antioxidant, anti-inflammatory, and lipid-lowering properties (MARTINS SL, et al., 2004; LEÃO RBA, et al., 2007; PERERA WPRT, et al., 2021). Although the aqueous extract may be less efficient in extracting lipophilic compounds, the observed response suggests that even reduced concentrations or the combined action of different metabolites may exert relevant biological effects (SALGADO JM, et al., 2008).

The reduction of hepatic inflammatory infiltrate observed in the treated groups, especially when associated with physical exercise, is consistent with evidence demonstrating the role of physical activity and dietary interventions in the modulation of systemic inflammation (CHEIK NC, et al., 2006; SWIFT DL, et al., 2018). The absence of hepatic fibrosis in all groups suggests that the experimental period was not sufficient for the development of more advanced chronic alterations, generally associated with prolonged exposure to harmful factors (PEREZ GS, 2014).

In cardiac tissue, the absence of relevant structural alterations and myocardial fibrosis indicates that the experimental model did not promote detectable morphological impairment during the evaluated period. This finding suggests that the experimental duration was sufficient to induce metabolic and hepatic alterations; however, it was possibly insufficient to trigger histologically detectable cardiac lesions, generally described in later stages of dyslipidemia (RIZZONI D, et al., 2006).

Serum biochemical parameters constitute important indicators of lipid metabolism modulation. The reduction in triglyceride and total cholesterol levels observed in the groups treated with the aqueous extract, either alone or associated with physical exercise, suggests a possible beneficial effect on the lipid profile. Phytosterols exert their effects mainly through the reduction of intestinal cholesterol absorption by competing with this compound during micelle formation, which contributes to reduced serum total cholesterol and triglyceride levels (DEMONTY I, et al., 2009; GYLLING H, et al., 2014; CABRAL CE and KLEIN MRST, 2017).

The absence of alterations in HDL levels is consistent with the literature, which demonstrates that phytosterols exert a predominant effect on total cholesterol and LDL, without significant impact on this

lipoprotein fraction (SALGADO JM, et al., 2008; CABRAL CE and KLEIN MRST, 2017). Additionally, maintenance of the overall lipid composition of the diet may have contributed to this result.

The maintenance of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels within normal ranges suggests the absence of detectable hepatotoxicity under the evaluated conditions, even considering the presence of potentially bioactive compounds in the plant, such as gossypol (GADELHA ICN, et al., 2011).

The integrated analysis of the experimental outcomes, summarized in **Figure 5**, indicates that the groups subjected to therapeutic interventions showed an overall more favorable response compared to the group exposed exclusively to the high-fat diet. The simultaneous improvement of lipid and hepatic parameters suggests that the aqueous extract of *Gossypium herbaceum*, particularly when associated with physical exercise, may contribute to the modulation of different components of experimental dyslipidemia.

Despite the observed results, some limitations should be considered. The exclusive use of the aqueous extract may have restricted the extraction of lipophilic compounds, such as phytosterols, reducing the magnitude of the effects. The absence of isolation and quantification of bioactive compounds limits the precise identification of those responsible for the observed findings. In addition, the experimental duration may not have been sufficient for the development of more advanced chronic alterations, such as hepatic and cardiac fibrosis. In addition, the small sample size (n = 5 per group) may have limited the statistical power to detect significant differences among treatments. Furthermore, as this was an experimental animal model, the findings should not be directly extrapolated to clinical conditions in humans and additional studies are needed to confirm the observed effects.

Therefore, future studies should explore different extraction methods, dose variations, and longer experimental periods, as well as detailed chromatographic analyses, to further elucidate the therapeutic potential and safety of the use of *Gossypium herbaceum* in dyslipidemia.

CONCLUSION

The results of this study suggest that the aqueous extract of Gossypium herbaceum leaves, administered either alone or in association with physical exercise, may exert a potential modulatory effect on serum triglyceride and total cholesterol levels in Wistar rats subjected to a high-fat diet, without significant alterations in HDL cholesterol levels. Histopathological analyses indicated a lower occurrence of hepatic steatosis and inflammation in the treated groups, with no evidence of hepatic or cardiac fibrosis and no signs of hepatotoxicity under the evaluated experimental conditions. Taken together, these findings suggest the potential of the aqueous extract of *Gossypium herbaceum* may indicate hepatoprotective potential and may be considered an experimental adjunctive strategy for the modulation of lipid metabolism, particularly when associated with physical exercise.

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