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ORIGINAL ARTICLE

Anti-Inflammatory and Cell Survival Effects of Harpagophytum Procumbens (Devil's Claw) on ARPE-19 Cells

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Abstract

Background: To evaluate the anti-inflammatory and cytoprotective effects of Harpagophytum procumbens on human adult retina pigment epithelium cells (ARPE-19) under oxidative stress conditions

Methods: ARPE-19 cells were cultured under standard conditions and divided into four groups including (I) control (untreated), (II) hydrogen peroxide (H_2O_2), (III) Harpagophytum procumbens, and (IV) H_2O_2 + Harpagophytum procumbens. ARPE-19 cells were exposed to hydrogen peroxide to induce oxidative damage. The effects of Harpagophytum procumbens extract were assessed by measuring tumor necrosis factor-alpha (TNF-α), vascular endothelial growth factor A (VEGF-A), 8-hydroxy-2'-deoxyguanosine (8-OHdG), poly (ADP-ribose) polymerase-1 (PARP-1), and apoptotic activity.

Results: Treatment with Harpagophytum procumbens significantly reduced pro-inflammatory (TNF-α), pro-angiogenic (VEGF-A), and oxidative DNA damage markers (8-OHdG, PARP-1), while also attenuating apoptosis in stressed ARPE-19 cells ($p<0.001$).

Conclusions: To our knowledge this study is the first to demonstrate the antioxidant, anti-inflammatory, anti-angiogenic, and anti-apoptotic effects of Harpagophytum procumbens on ARPE-19 cells, suggesting its potential as a complementary therapy for retinal diseases such as age-related macular degeneration (AMD), in which oxidative stress, inflammation, and neovascularization play key pathogenic roles.

Keywords: Harpagophytum, macular degeneration, cell culture techniques.

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INTRODUCTION

Harpagophytum procumbens or devil's claw, is a plant native to the arid and semi-arid regions of southern Africa. It is named for its distinctive, claw-like hooked fruits and grows well in sandy, poor soils. Its creeping stems and tuberous roots are rich in pharmacologically active compounds that underline its well-documented analgesic and anti-inflammatory properties. Traditionally, devil's claw has been used in African herbal medicine in treatment of musculoskeletal pain, arthritis, and digestive disorders (1-2). The anti-inflammatory effects of devil's claw have been investigated *in vitro, in vivo,* and in clinical settings. It is widely employed for the management of osteoarthritis and lower back pain, and its extracts are formulated into both herbal supplements and pharmaceutical products. In addition to its ethnobotanical importance, devil's claw is gaining attention for its potential application in chronic inflammatory diseases (1-5).

Age-related macular degeneration (AMD) is a progressive disease that affects the macular region of retina. It has two types: dry (atrophic) and wet (neovascular), both of which cause vision loss in the elderly population. Oxidative stress, chronic low-grade inflammation of the retina pigment epithelium (RPE), Bruch's membrane, and choroid, and genetic predisposition are key contributors to its pathogenesis (6-7). Treatment of atrophic AMD focuses on slowing progression through antioxidant supplementation, lifestyle modification, and emerging therapies such complement inhibitors, while neovascular AMD is managed mainly with intravitreal anti–vascular endothelial growth factor (anti-VEGF) injections to prevent choroidal neovascularization and vision loss. Combination and sustained-delivery therapies are being explored to reduce treatment burden and enhance long-term efficacy. Nevertheless, disease progression may still occur, and novel therapeutic agents are under investigation to achieve better visual outcomes (8-9).

Harpagophytum procumbens, a medicinal plant known for its potent anti-inflammatory activity, may help slow oxidative stress in retinal diseases. By downregulating pro-inflammatory mediators such as cytokines and prostaglandins, it can reduce inflammation-driven oxidative damage and restore cellular redox balance. This suppression of inflammatory signaling also limits the expression of angiogenic factors like vascular endothelial growth factor (VEGF), thereby decreasing pathological neovascularization. In addition, reducing inflammatory stimuli can suppress apoptotic cell death by modulating both intrinsic and extrinsic signaling pathways. Through these effects, Harpagophytum procumbens may serve as a complementary therapeutic agent for the management of AMD by protecting retinal cells and maintaining tissue homeostasis. In this study, the effects of Harpagophytum procumbens extract on TNF-α and VEGF-A levels as well as the oxidative stress response in ARPE-19 cells were investigated. In this context, the levels of tumor necrosis factor-alpha (TNF-α), vascular endothelial growth factor A (VEGF-A), 8-hydroxy-2′-deoxyguanosine (8-OHdG), poly (ADP-ribose) polymerase-1 (PARP-1) and apoptotic activity were assessed.

MATERIALS AND METHODS

Cell Culture and Experimental Protocol

The ARPE-19 human retinal pigment epithelial cell line (ATCC® CRL-2302™) was maintained in Dulbecco's Modified Eagle Medium/Ham's F-12 (DMEM/F-12; Sigma-Aldrich, USA) supplemented with 10% fetal bovine serum (FBS), 100 U/mL penicillin, and 100 μg/mL streptomycin. Cultures were incubated at 37 °C in a humidified environment containing 5% CO_2. Subculturing was carried out every 3–4 days by detaching cells with 0.25% trypsin-EDTA. Prior to experimental interventions, cells were seeded in flasks and grown to roughly 80% confluence. The ARPE-19 cells were treated with different concentrations of H2O2 (0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 and 1.0 in mM) for 4 h. To generate an oxidative stress model in ARPE-19 cells, the MTT assay was employed to evaluate proliferative capacity under exposure to hydrogen peroxide (H_2O_2), a prototypical reactive oxidant. The analysis demonstrated that H_2O_2 elicited a dose-dependent suppression of cell viability (R^2=0,9666). Notably, treatment with 0.5 mM H_2O_2 produced a marked decline in survival of ARPE-19 cells. Based on these findings, subsequent experimental procedures utilized 0.5 mM H_2O_2 as the standardized condition for induction of oxidative damage for 4h incubation. Experiments were performed in triplicate. The inhibition rate (%) was shown in Figure 1. Similarly, some evidence is available in the literature to Hydrogen peroxide-induced cellular stress models in ARPE cells (10).

The main bioactive constituent of Devil's claw, harpagoside, is a glycoside that shows reasonable aqueous

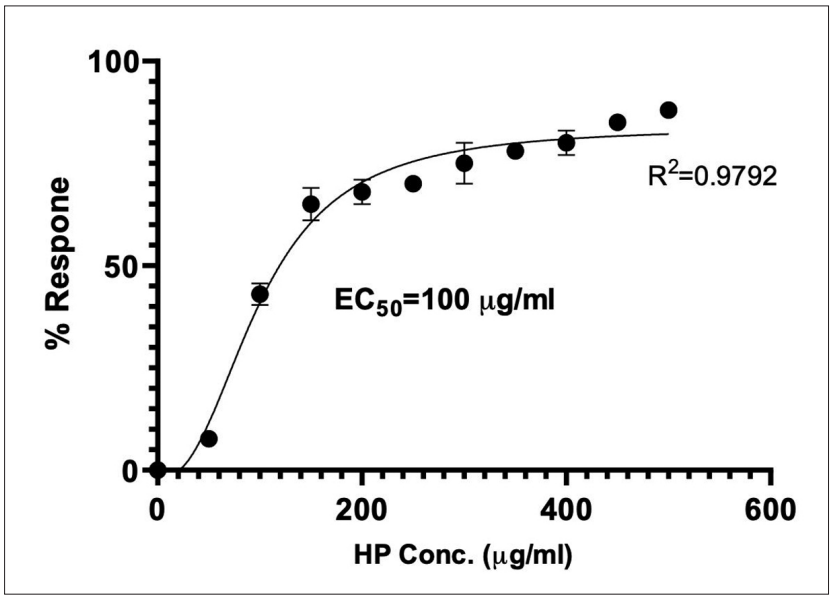

Figure 1: The inhibition rate (%) of H2O2 (0-1 mM) in ARPE-19 cells.

solubility. A ready to use Harpagophytum Procunmens (Dewil's Claw) extract (300 mg) containing capsules (1,200mg Equivalent of Devil's Claw Extract, from 300mg of 4:1 extract) obtained from Nutricost® (NTC.12.23, Universal Product Code: 810014673578) as a gift from a colleague was used in the study. Constituent of capsule containing HP extract were dissolved directly in growth medium of ARPE-19 cells sonicated with ultrasonic homogenizer (Bandelin HD2070, Germany). The cells were incubated with different concentrations of HP extract (ranging from 50 to 500 $\mu g/ml$) for 24 h. Detection of half maximal effective concentration 50 (EC50 = 100 $\mu g/ml$) value for HP was given below as Figure 2. The cells were incubated with HP extract (Final concentration 100 $\mu g/ml$) containing growth medium for 24 h.

Four distinct experimental sets were organized as follows:

- **Control Group:** Untreated cells maintained under standard conditions for 24 hours.

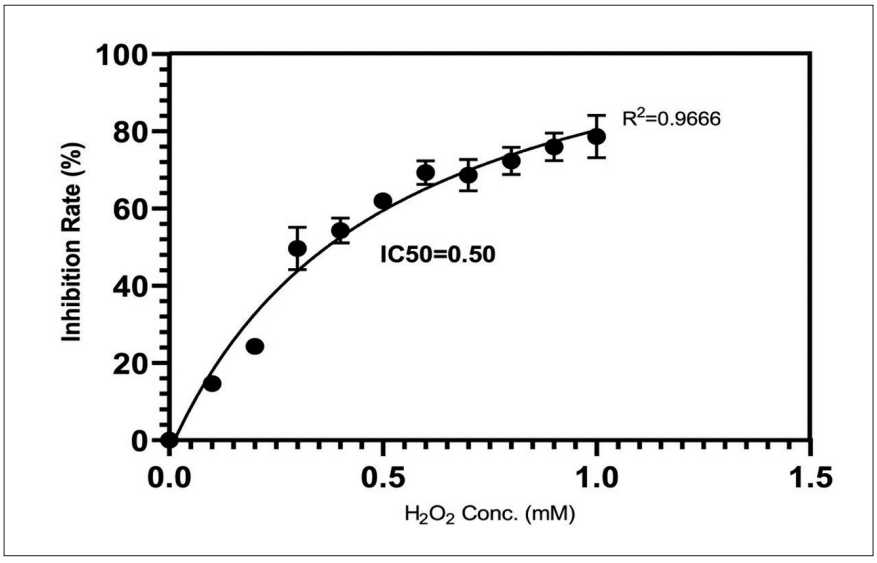

Figure 2: Detection of half maximal effective concentration 50 (EC50) value for HP.

- **Group 1 (H_2O_2):** Treated with 0.5 mM hydrogen peroxide for 4 hours.
- Group 2 (HP): Treated with Harpagophytum procumbens (100 μg/ml) for 24 hours.
- Group 3 (HP+ H_2O_2): Pre-treated with Harpagophytum procumbens (100 μg/ml) for 20 hours followed by H_2O_2 (0.5 mM) exposure for 4 hours.

Apoptosis and Biochemical Analysis

The APOPercentage™, a colorimetric apoptosis detection kit, dye-dependent method used to identify and quantify apoptotic cell death in cultured cells under in-vitro conditions were purchased from Biocolor Ltd. (UK). This method specifically labels cells undergoing apoptosis. During the apoptotic process, loss of membrane asymmetry enables the dye to associate with membrane phospholipids, particularly phosphatidylserine, resulting in intracellular dye accumulation. Apoptotic cells exhibit a red coloration that can be detected at 550 nm wavelength, which was measured using a microplate reader (Tecan Infinite M200 Pro, Austria). Results were expressed as fold change relative to the control group. Manufacturer's protocol was followed for apoptosis experiments. Apoptosis was quantified using the APOPercentage™ Assay (Biocolor Ltd., UK) according to the manufacturer's instructions. To determine the sensitivity of the assay, absorbance was measured at 550 nm against a range of H_2O_2 concentrations (0–10 mM) as a positive control. Further validation of the experimental model was deemed unnecessary, as the cytoprotective, anti-apoptotic, and anti-inflammatory properties of carvacrol against oxidative stress are already well-established in the literature (11).

In parallel, molecular markers of inflammation, angiogenesis, and DNA damage were assessed via biochemical analysis. The levels of TNF-α, VEGF-A, 8-OHdG, and PARP-1 were quantified using commercially available ELISA kits (BT Lab, China) following the manufacturer's specifications. The optical density for these markers was recorded at 450 nm using the TECAN Infinite Pro200 microplate reader. All experimental results, including both apoptotic activity and biochemical marker levels, were expressed as a fold change relative to the untreated control group to ensure standardized comparison across all experimental conditions.

Statistical Analysis

Statistical calculations were performed with GraphPad Prism v8.0 (GraphPad Software, USA). Values are expressed as mean ± standard deviation (SD). Intergroup differences were assessed using one-way analysis of variance (ANOVA), followed by Tukey's multiple comparison post hoc analysis. Statistical significance was defined at a threshold of $p < 0.05$.

RESULTS

The modulatory influence of Harpagophytum procumbens on TNF-α, VEGF-A, 8-OHdG, PARP-1, and apoptosis in ARPE-19 cells is summarized in Table 1.

Table 1. Mean Values of Biochemical Analysis of the Groups

Biochemical Analysis	**Group I Control**	**Group II H2O2** (Hydrogen peroxide)	**Group III HP** (Harpagophytum procumbens)	**Group IV H2O2+HP** (Hydrogen peroxide+ Harpagophytum procumbens)
TNF α	33.36±5.117	60.98±3.242	20.10±2.597	36.02±7.157
VEGF-A	48.34±4.161	69.07±1.683	31.31±1.476	52.83±5.314
8-OHdG	14.89±1.555	19.68±1.417	14.79±1.019	14.45±2.567
PARP-1	11.77±1.476	27.58±1.800	10.45±1.241	15.57±2.675
Apoptosis	100.0±0	171.3±11.18	86.13±3.336	105.8±3.156

TNF-α levels peaked in the H_2O_2 group, whereas the lowest concentrations were recorded in the HP group. Compared with the control, H_2O_2 exposure resulted in a highly significant increase ($p < 0.001$), while HP treatment markedly reduced TNF-α ($p < 0.001$). The HP + H_2O_2 group did not differ significantly from the control ($p > 0.05$) (Figure 3).

For VEGF-A, H_2O_2 exposure induced a significant elevation compared to control, whereas HP treatment led to a substantial reduction ($p < 0.001$ for both). No significant variation was detected between the HP + H_2O_2 group and the control ($p > 0.05$) (Figure 4).

Regarding oxidative DNA damage marker 8-OHdG, the H_2O_2 group demonstrated a sharp increase compared with control ($p < 0.001$). HP treatment significantly lowered 8-OHdG levels relative to the H_2O_2 group ($p < 0.001$). Differences among the control, HP, and HP + H_2O_2 groups were statistically insignificant ($p > 0.05$) (Figure 5).

PARP-1 expression was considerably higher in H_2O_2-treated cells compared to controls ($p < 0.001$). In contrast, HP administration significantly decreased PARP-1 levels relative to H_2O_2 treatment ($p < 0.001$) (Figure 6).

In the apoptosis assay, the control group value was normalized to 100%. The H_2O_2 group exhibited the highest apoptotic percentage, while the HP group showed the lowest. A significant rise in apoptosis was observed in H_2O_2-treated cells ($p < 0.001$), whereas HP treatment produced a notable reduction compared with controls ($p < 0.001$) (Figure 7).

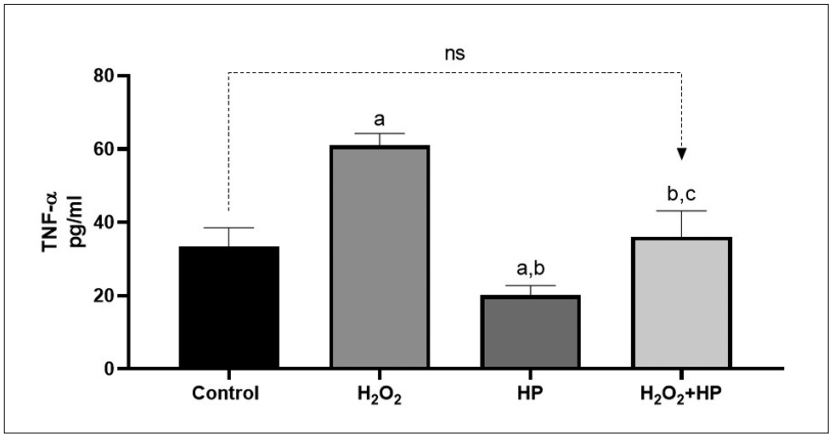

Figure 3: TNF-α values of the groups. H_2O_2 exposure significantly increased TNF-α expression, whereas HP treatment markedly reduced TNF-α ($p < 0.001$ for both). TNF-α levels in the HP + H_2O_2 group did not differ significantly from the control group ($p > 0.05$).ap<0.001 vs Control, bp<0.001 vs H2O2, cp<0.001 vs HP, ns: not significant.

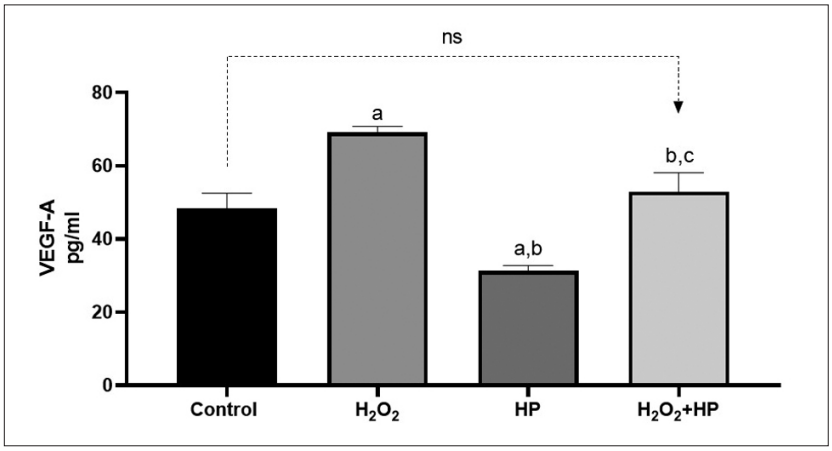

Figure 4: VEGF-A values of the groups. H_2O_2 exposure induced a significant elevation of VEGF-A compared to control, whereas HP treatment significantly reduced VEGF-A ($p < 0.001$ for both). There was no significant difference between the HP + H_2O_2 group and the control ($p > 0.05$). ap<0.001 vs Control, bp<0.001 vs H2O2, cp<0.001 vs HP, ns: not significant.

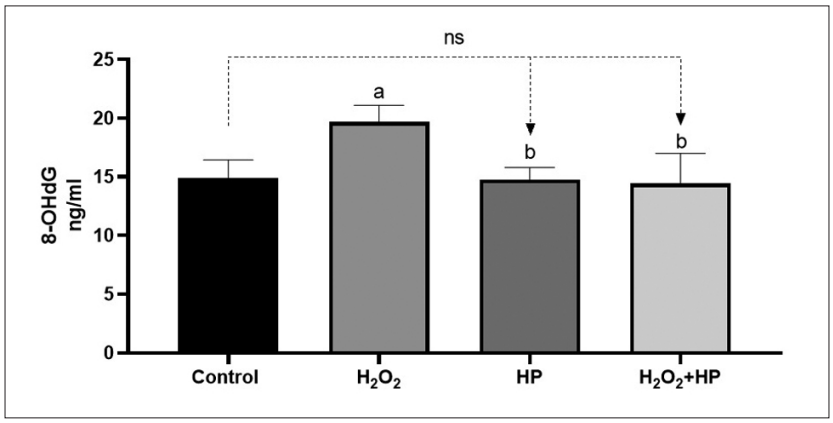

Figure 5: 8-OHdG values of the groups. H_2O_2 markedly increased 8-OHdG levels, while HP treatment significantly reduced the levels of H_2O_2 ($p < 0.001$ for both). No significant differences were observed among the control, HP, and HP + H_2O_2 groups ($p > 0.05$). ap<0.001 vs Control, bp<0.001 vs H2O2, ns: not significant.

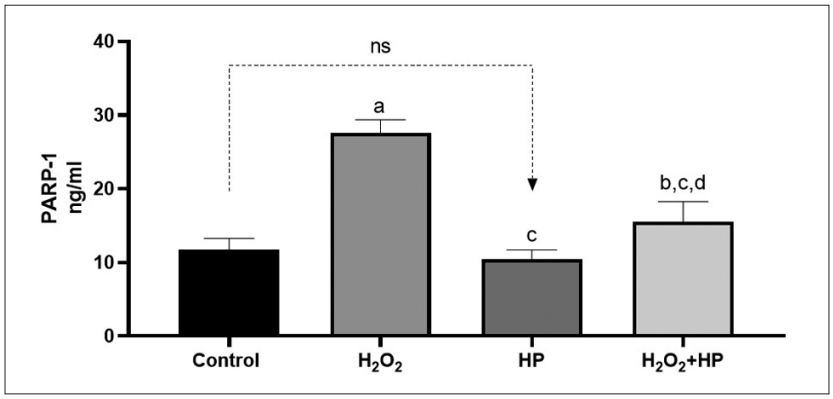

Figure 6: PARP-1 values of the groups. PARP-1 expression was significantly elevated by H_2O_2 and markedly reduced by HP treatment ($p < 0.001$ for both). ap<0.001 vs Control, bp<0.01 vs Control, cp<0.001 vs H2O2, dp<0.001 vs HP, ns: not significant.

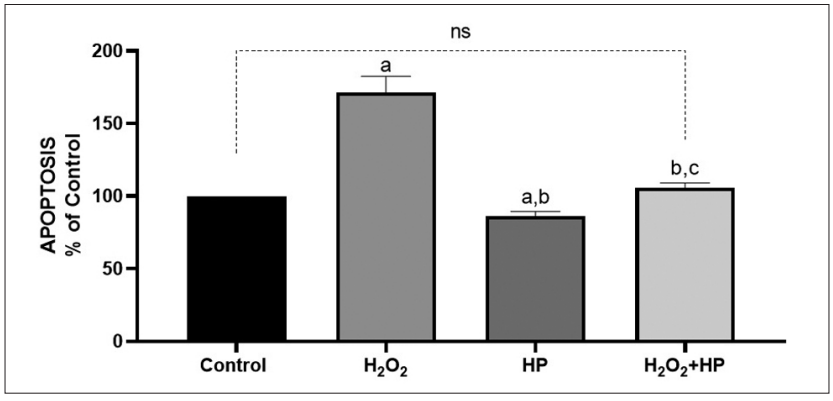

Figure 7: Apoptotic activity of the groups. Apoptosis was highest in the H_2O_2 group and lowest in the HP group. H_2O_2 significantly increased apoptosis, while HP treatment markedly reduced it ($p < 0.001$ for both). ap<0.001 vs Control, bp<0.001 vs H2O2, cp<0.001 vs HP, ns: not significant.

DISCUSSION

The results of this study demonstrate that Harpagophytum procumbens exhibits strong anti-inflammatory, anti-angiogenic, anti-apoptotic and DNA-protective effects in ARPE-19 cells subjected to oxidative stress. While our findings are based on *in vitro* data, they suggest that Harpagophytum procumbens may have therapeutic potential for retinal diseases in which chronic inflammation, oxidative imbalance and increased cell death play a role in the pathology, including AMD.

Harpagophytum procumbens is an African native plant traditionally used to treat pain and inflammation. The active compounds are Harpagoside (the main iridoid glycoside), Harpagide, Procumbide, Phenolic compounds (flavonoids, acteoside) and Beta-sitosterol and these compounds are primarily found in the secondary tubers (1-2). Its anti-inflammatory effects have been studied *in vivo* and *in vitro* settings (2,12-16). Harpagoside, a key bioactive compound in Harpagophytum procumbens exerts its anti-inflammatory effects through multiple mechanisms. It inhibits cyclooxygenase-2 (COX-2) and lipoxygenase (LOX) enzymes, thereby reducing the synthesis of pro-inflammatory mediators like prostaglandins and leukotrienes, like non-steroidal anti-inflammatory drugs (NSAIDs) but with potentially fewer side effects (16). Additionally, it suppresses the synthesis of main pro-inflammatory cytokines such as TNF-α, Interleukin-1 beta (IL-1β), Interleukin-6 (IL-6), which are central to chronic inflammation and autoimmune responses (2). In an *in vitro* study using human HepG2 hepatocarcinoma and RAW 264.7 murine macrophage cell lines, Harpagophytum procumbens extract was shown to inhibit nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), a key regulator of inflammatory expression, thereby contributing to its broader immunomodulatory potential. (17). Furthermore, its flavonoids and phenolic acids exhibit antioxidant properties by decreasing reactive oxygen species (ROS), and reducing oxidative stress commonly associated with inflammation (12).

Age-related macular degeneration is a chronic progressive disease of retina and is a leading cause of irreversible vision loss in the late decades of life, usually over 50 years. It is characterized by chronic inflammation, oxidative stress, and RPE cell degeneration. Oxidative stress is a major factor in the development of AMD, primarily through its impact on mitochondrial function, excessive production of ROS, and resulting DNA damage within RPE cells (7). The RPE is very sensitive to oxidative damage due to its constant disclose to light and oxygen, as well as its critical function in digesting photoreceptor outer segments. Nutrients such as specific vitamins and trace elements play vital roles in the eye's antioxidant defense system and have been increasingly linked to AMD progression (18). Therefore, the use of antioxidant-based interventions is being explored as a supportive approach in the prevention and treatment of AMD.

Tumor necrosis factor-alpha has been shown to have an important role in the pathogenesis of AMD, particularly by contributing to chronic inflammation, oxidative stress, and RPE cell dysfunction (18). In our study Harpagophytum procumbens treatment markedly reduced the levels of TNF-α. Elevated levels of TNF-α have been associated with increased apoptosis of RPE cells, disruption of the blood-retinal barrier, and enhanced expression of VEGF, thereby promoting both dry and neovascular forms of AMD (19-20). Consequently, therapeutic strategies aimed at reducing TNF-α levels have garnered interest for their potential to slow AMD progression. Although no TNF-α inhibitors are currently approved for treating AMD, several agents with anti-TNF-α activity such as infliximab, have been tested experimentally or off-label, with limited success and safety concerns (21-22). In contrast, natural compounds like curcumin and resveratrol are being actively explored as safer alternatives for modulating TNF-α–mediated inflammation in AMD (23-24). While resveratrol and curcumin possess potent antioxidant and anti-inflammatory properties, their poor bioavailability and rapid metabolism significantly limit their therapeutic efficacy *in vivo* (25-26). Although data on the bioavailability of Harpagophytum procumbens are limited, available studies indicate measurable absorption and detectable plasma levels in animal models (27). Harpagophytum procumbens may serve as a promising natural therapeutic agent for protecting retinal pigment epithelium cells through the attenuation of TNF-α–mediated inflammation, potentially offering clinical advantages with fewer adverse effects.

Vascular endothelial growth factor A plays a major role in the pathogenesis of neovascular AMD. In our oxidative stress model, H_2O_2 exposure significantly increased the levels of VEGF-A. Harpagophytum procumbens treatment resulted in a greater reduction in VEGF-A expression. Inflammation and neovascularization are close-

ly interconnected processes that play central roles in the pathogenesis of many retinal diseases, including AMD and diabetic retinopathy. Inflammatory mediators such as cytokines, chemokines, and prostaglandins promote endothelial cell activation and upregulate angiogenic factors like VEGF. Existing *in vitro* and *in vivo* researchs suggest anti-inflammatory and antioxidant effects of Harpagophytum procumbens, including reduced cytokine production and suppression of NF-κB or Activator Protein-1(AP 1) signaling, however, VEGF-A modulation has not been reported before (15,17). Resveratrol, a polyphenolic compound studied in the context of AMD, has been shown to reduce VEGF expression, likely through inhibition of the NF-κB signaling pathway (28). The reduction in VEGF-A expression observed with Harpagophytum procumbens treatment may suggest a capacity to modulate pathways involved in retinal or choroidal neovascularization.

Another noteworthy observation in this study is the impact of Harpagophytum procumbens on markers of oxidative DNA damage. The administration of Harpagophytum procumbens resulted in a significant reduction of 8-OHdG, a well-established biomarker for oxidative DNA lesions (29). Additionally, the activation of PARP-1, a DNA repair enzyme that becomes overactive in response to DNA strand breaks, was also markedly diminished (30). These findings suggest that Harpagophytum procumbens exerts a protective effect against DNA damage through antioxidative and possibly anti-inflammatory mechanisms. Apoptosis is a hallmark of progressive RPE degeneration in AMD, contributing to the gradual loss of visual function (31). In this study, oxidative stress induced by hydrogen peroxide led to a significant increase in apoptosis in ARPE-19 cells, a well-established *in vitro* model for human RPE. This response aligns with the pathophysiological mechanisms observed in dry AMD, where chronic oxidative damage promotes RPE cell death. Remarkably, treatment with Harpagophytum procumbens significantly attenuated apoptosis in these cells. This anti-apoptotic effect suggests that Harpagophytum procumbens may confer cytoprotective benefits, potentially through its antioxidant or anti-inflammatory constituents, thereby preserving RPE integrity under oxidative stress conditions.

While our findings underscore the therapeutic potential of Harpagophytum procumbens in protecting RPE cells from oxidative stress, several limitations should be acknowledged. The study was conducted using a monolayer ARPE-19 cell culture model subjected to an acute oxidative insult with hydrogen peroxide. Although this model is widely accepted for investigating early cellular responses in AMD research, it does not fully recapitulate the chronic, progressive, and multifactorial pathogenesis of macular degeneration *in vivo*. Moreover, critical pharmacokinetic parameters such as systemic absorption, metabolic stability, and retinal tissue bioavailability of Harpagophytum procumbens were not assessed and remain to be elucidated. Additional limitations include the exclusive use of a single cell line, the absence of *in vivo* validation, and the lack of standardization of the extract's bioactive components, all of which may influence reproducibility and translational potential. Although the apoptosis results provide evidence for differences in cell viability between groups, the fact that these levels were not validated by alternative techniques (e.g., Annexin V/PI, caspase activity) is also a limitation of this study. Despite these limitations, the use of a standardized oxidative stress induction protocol provides a reproducible and robust *in vitro* platform for evaluating potential therapeutic agents. Future investigations incorporating *in vivo* models, dose-response analyses, and comprehensive pharmacological profiling will be essential to validate these findings and to determine the translational potential of Harpagophytum procumbens in the management of retinal diseases.

In conclusion, Harpagophytum procumbens demonstrated significant anti-inflammatory, anti-angiogenic, anti-apoptotic and DNA-protective effects in ARPE-19 cells subjected to oxidative stress. To our knowledge this is the first study to report the effects of Harpagophytum procumbens on ARPE-19 cells. New treatment approaches in AMD aim to slow atrophy progression and reduce the need for frequent intravitreal injections by targeting inflammation, oxidative stress, and cell death. Through its combined protective actions, Harpagophytum procumbens may be a complementary agent in this context. By lowering inflammatory mediators, VEGF-A levels, and oxidative DNA damage, Harpagophytum procumbens may help preserve retinal pigment epithelium integrity and delay retinal degeneration. While these *in vitro* observations suggest a protective mechanism against retinal degeneration, further in vivo and clinical studies are strictly required to determine if these findings could eventually support AMD therapies or improve patient outcomes.

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Abbreviations List

ARPE-19: Adult Retinal Pigment Epithelium-19.
TNF-α: Tumor necrosis factor-alpha.
VEGF-A: Vascular endothelial growth factor A.
PARP-1: Poly (ADP-ribose) polymerase-1.
8-OHdG: 8-hydroxy-2′-deoxyguanosine.
AMD: Age related macular degeneration.
HP: Harpagophytum procumbens.
FBS: Fetal bovine serum.
DMEM/F-12: Dulbecco's Modified Eagle Medium/Ham's F-12.
NF-κB: Nuclear Factor kappa-light-chain-enhancer of activated B cells.
AP-1: Activator Protein-1.
COX-2: Cyclooxygenase-2.
LOX: Lipoxygenase.
NSAIDs: Non-Steroidal Anti-Inflammatory Drugs.
IL-1β : Interleukin-1 beta.
IL-6 : Interleukin-6.
RPE: Retina pigment epithelium.
ROS: Reactive oxygen species.

Ethical Approval Statement

The study was carried out on human adult retina pigment epithelium cells (ARPE-19). According to the institutional guidelines, the use of established cells does not require ethical approval.

Consent for Publication

Not applicable.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare no competing interests.

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Authors Contributions

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