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Research Article

Comparative Evaluation of Anti-Stress Potential of *Olea Europaea* and *Cissus Quadrangularis* Ethanolic Extracts in Experimental Animal Models

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Abstract
Stress-related disorders remain a pressing global health challenge, contributing to diverse physiological and psychological dysfunctions through oxidative stress, inflammation, and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. This study aimed to evaluate and compare the anti-stress potential of ethanolic extracts of *Olea europaea* (olive) and *Cissus quadrangularis* using validated experimental models in mice and rats. Extracts were assessed for effects on physical endurance, hypoxia tolerance, biochemical stress markers (glucose, triglycerides, cholesterol, cortisol, BUN), gastric mucosal integrity, oxidative stress parameters (GSH, SOD, CAT, MDA, MPO), and pro-inflammatory cytokines (IL-6, IL-10, IL-1β, TNF-α).
Results showed both extracts (400 and 600 mg/kg) significantly improved swimming endurance and hypoxia tolerance, reduced biochemical markers of stress, normalized adrenal gland and organ weights, and lowered ulcer index with increased gastric pH in unpredictable spontaneous stress models. Both extracts also improved antioxidant enzyme levels and decreased lipid peroxidation and inflammatory cytokines. The effects were comparable to the standard adaptogen (Geriforte). These findings provide scientific support for traditional claims and suggest *Olea europaea* and *Cissus quadrangularis* as promising natural adaptogens with multi-target actions against stress-induced physiological alterations.

Keywords: *Olea europaea*, *Cissus quadrangularis*, adaptogens, oxidative stress, anti-stress, cytokines.

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1. Introduction

Stress, broadly defined as the body's non-specific response to external or internal demands, disrupts homeostasis and leads to various metabolic, cardiovascular, gastrointestinal, and psychological disorders (Selye, 1936). The physiological stress response involves activation of the HPA axis and sympathetic nervous system, releasing cortisol and catecholamines which, over time, contribute to oxidative stress, immune dysregulation, and inflammation[1,2,3].

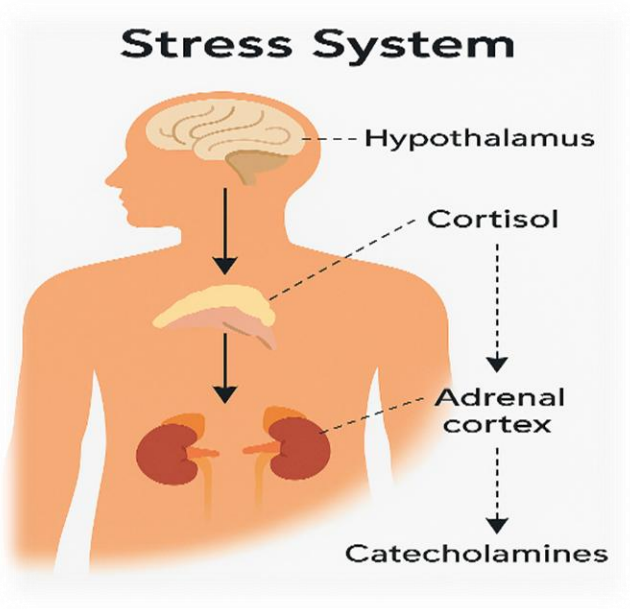


Figure 1: Stress System

The stress response involves key biochemical mediators including neurotransmitters, hormones, catecholamines, and cytokines. While this help restore balance during short-term stress, their persistent activation contributes to allostatic load, resulting in chronic diseases. One of the major systems affected is the immune system, where chronic stress suppresses lymphocyte function, alters cytokine profiles, and shifts the immune balance, increasing susceptibility to infections and inflammation. Moreover, stress impairs gastrointestinal protection by reducing mucosal blood flow and increasing oxidative damage, predisposing individuals to stress-induced ulcers[4,5].

In recent years, attention has turned toward natural compounds called adaptogens substances that enhance the body's resilience to stress and help restore homeostasis. Adaptogens like *Panax ginseng*, *Withania somnifera*, and *Rhodiola rosea* have shown promise by modulating the HPA axis, reducing oxidative stress, and regulating pro-inflammatory cytokines[6]. Adaptogens are categorized as primary (broad-acting), secondary (moderately acting), and supportive herbs. Their active constituents such as phenolics, flavonoids, and terpenoids—act through multiple pathways, including NF-κB and MAPKs[7].

Given the limitations of synthetic drugs in managing chronic stress, the present study explores the adaptogenic and antioxidant potential of *Olea europaea* and *Cissus quadrangularis*[8,9,10]. Rich in bioactive phytochemicals like oleuropein and flavonoids, these plants may offer protective effects against stress-induced immune and gastrointestinal dysfunction, providing a promising alternative for stress management[11,12].

2. Materials and Methods

2.1 Plant material and extract preparation

The study used standard lab instruments and reagents for extraction, analysis, and biochemical assays, with Geriforte as the standard adaptogen. Aerial parts of *Cissus quadrangularis* and leaves of *Olea europaea* were collected from the School of Pharmacy, Saharanpur, authenticated (voucher no. CQ-2023 and OE-2023), shade-dried (10–14 days at 25–30 °C), powdered, and extracted using 70% ethanol in a Soxhlet apparatus for ~48 hours. Extracts were concentrated under reduced pressure (≤40 °C), dried, and stored at 4 °C. The yield was 5.44% for *Cissus quadrangularis* (brownish-green, bitter) and 18% for *Olea europaea* (dark green, astringent)[13,14]. Preliminary phytochemical screening confirmed the presence of alkaloids, carbohydrates, glycosides, phytosterols, isoflavones, amino acids, proteins, and triterpenoids[15,16]

2.2 Animals and Ethical Approval

Swiss albino mice (20–25 g) and Wistar albino rats (180–220 g) of either sex were procured from the Galgotias University, Greater Noida – CPCSEA Reg. No. 2087/PO/ReReBi/S/19/CPCSEA. Animals were acclimatized for 7 days before experiments. All experimental protocols were reviewed and approved by the Institutional Animal Ethics Committee (IAEC) of [Institution], protocol number IAEC/PH/2025/03, following the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India.

2.3 Dose Selection and Group Allocation[17,18.19].

Acute oral toxicity was assessed as per OECD guideline 423 (Acute Toxic Class Method), using fasted Swiss albino mice administered ethanolic extracts of *Cissus quadrangularis* and *Olea europaea* at doses of 400 and 600 mg/kg orally. Animals were observed closely for 4 hours and then daily for 14 days for signs of toxicity, mortality, or behavioral changes. As no adverse effects were observed, these doses were selected for further evaluation. Following a 7-day acclimatization period, animals were randomly divided into six groups (n=6): Group I received vehicle (1% CMC), Group II received standard adaptogen Geriforte (100 mg/kg), Groups III and IV were administered *Olea europaea* extract at 400 and 600 mg/kg, while Groups V and VI received *Cissus quadrangularis* extract at 400 and 600

mg/kg, respectively. All treatments were given orally once daily for 10 days prior to stress induction.

2.4 Evaluation of Anti-Stress Activity

2.4.1 Swimming Endurance Test (in mice):

The swimming endurance test is a validated behavioral model used to assess anti-stress or adaptogenic effects of compounds. In this study, Swiss albino mice were treated orally for 10 days with either vehicle (1% CMC), standard adaptogen (Geriforte, 100 mg/kg), or ethanolic extracts of *Olea europaea* and *Cissus quadrangularis* (400 and 600 mg/kg). On the 10th day, mice were placed individually in a cylindrical tank (30 cm diameter, 25 cm depth) filled with fresh water maintained at 25 ± 2 °C[20]. The time until exhaustion defined as failure to rise to the surface for 10 consecutive seconds—was recorded as swimming survival time[21].

All animals were tested under standardized conditions to avoid circadian variation. An increase in swimming time compared to control was considered a marker of improved physical endurance and adaptogenic activity[22]. These effects may result from modulation of the hypothalamic-pituitary-adrenal (HPA) axis, reduction in oxidative stress, stabilization of metabolic function, and enhanced mitochondrial efficiency. The test confirmed that both plant extracts improved stress tolerance in a dose-dependent manner.

Photograph No. 1: Swimming Endurance Test

2.4.2 Anoxia Tolerance Test (in Mice):

The anoxia tolerance test was employed to assess the adaptogenic and anti-stress potential of *Olea europaea* and *Cissus quadrangularis* extracts by evaluating resistance to acute hypoxic stress. On the 10th day of oral treatment with the vehicle (1% CMC), standard adaptogen (Geriforte, 100 mg/kg), or test extracts (400 mg/kg and 600 mg/kg), Swiss albino mice were individually placed in airtight 1-liter glass jars to induce an anoxic environment. The latency to the first clonic convulsion (involuntary jerky movements) was recorded using a stopwatch and used as an index of anoxia tolerance. Each mouse was observed continuously, and immediately removed after convulsion onset to ensure safety. The jars were then opened, and mice were allowed to recover under normal conditions. A longer latency period compared to the control group indicated enhanced stress tolerance, suggesting that the extracts may modulate the HPA axis, reduce oxidative stress, and improve mitochondrial function. All animals were tested under standardized environmental conditions to minimize variation, and each mouse was used only once to prevent stress carryover effects.

Photograph No. 2: Anoxia tolerance stress test in mice

2.4.3 Cold Restraint and Immobilization Stress (in Rats)

The CRIS model was used to evaluate the adaptogenic and cytoprotective potential of *Olea europaea* and *Cissus quadrangularis* extracts by inducing acute physical and psychological stress. On the 10th day of oral treatment with either vehicle (1% CMC), standard adaptogen (Geriforte, 100 mg/kg), or plant extracts (400 and 600 mg/kg), rats were

placed in ventilated restraining devices and exposed to a cold environment (4 ± 1 °C) for 2 hours.

This combined cold and restraint stress activates the hypothalamic–pituitary–adrenal (HPA) axis, increases sympathetic activity, and induces oxidative and metabolic disturbances, mimicking real-life stress responses. Following stress exposure, blood was collected from the retro-orbital plexus under light anesthesia. Serum and plasma were separated by centrifugation and stored at −20 °C for biochemical assays. Animals were then humanely euthanized, and organs including adrenal glands, liver, and spleen were excised, rinsed in cold saline, and weighed. This model provided measurable physiological parameters to assess the anti-stress efficacy of the test extracts.

2.4.4 Biochemical parameters assessed:

To evaluate the effect of test extracts on stress-induced metabolic changes, the following parameters were measured using standard kits (e.g., from Span Diagnostics / ERBA):

Table 1 Biochemical parameters

Parameter	Rationale	Method
Blood glucose	Increases due to stress-induced hyperglycemia (HPA axis activation)	GOD–POD method
Total cholesterol	Elevated under stress as part of lipid mobilization	CHOD–PAP method
Triglycerides (TG)	Elevated in response to catecholamine-induced lipolysis	GPO–PAP method
Plasma cortisol	Marker of HPA axis activation	ELISA kit
Blood urea nitrogen (BUN)	Reflects protein catabolism and renal function under stress	Enzymatic UV method

2.4.5 Organ Weight Analysis and Unpredictable Spontaneous Stress (USS) Model

Chronic stress is known to cause adrenal hypertrophy and alterations in liver and spleen weight due to prolonged HPA axis activation. In this study, normalization of adrenal and other organ weights after extract treatment indicated significant adaptogenic potential. Biochemical markers cortisol, glucose, triglycerides, cholesterol, and BUN were measured and statistically analyzed (mean ± SEM; n=6) using one-way ANOVA followed by Tukey's post hoc test ($p < 0.05$), with reductions interpreted as positive anti-stress effects. To further evaluate the extracts, the Unpredictable Spontaneous Stress (USS) model was employed, simulating chronic daily-life stress through randomized mild stressors over 7 days (e.g., forced swim, noise, wet bedding, food/water deprivation). On the final day, gastric tissues were examined for ulcer index and pH. Treatment with *Olea europaea* and *Cissus quadrangularis* extracts significantly reduced ulcer formation and increased gastric pH compared to control, confirming their cytoprotective and adaptogenic effects.

3. Results and Discussion

3.1 Phytochemical profile

Ethanolic extracts were rich in phenolics, triterpenoids, and flavonoids (oleuropein, hydroxytyrosol in *Olea europaea*; β-sitosterol, quercetin in *Cissus quadrangularis*), known for antioxidant and adaptogenic effects.

Table 2: Phytochemical Constituents of *Cissus quadrangularis* Extracts

S. No.	Test for Phytoconstituents	Pet. Ether	Chloroform	Ethyl Acetate	Butanol	Ethanolic	Aqueous
1	Alkaloids	–	+	–	–	+	–
2	Carbohydrates	–	–	+	+	+	+
3	Glycosides	–	–	–	–	–	–
4	Phytosterols	+	+	–	–	+	–
5	Isoflavones	–	–	+	+	+	–
6	Amino Acids & Proteins	–	–	–	+	+	+
7	Triterpenoids	+	+	–	–	+	–

+ = Present, – = Absent

Table 3: Phytochemical Constituents of *Olea europaea* Extracts

S. No.	Test for Phytoconstituents	Pet. Ether	Chloroform	Ethyl Acetate	Butanol	Ethanolic	Aqueous
1	Alkaloids	–	+	–	–	+	–
2	Carbohydrates	–	–	+	+	+	+
3	Glycosides	–	–	–	–	–	–
4	Phytosterols	+	–	–	–	+	–
5	Isoflavones	–	–	+	+	+	+
6	Amino Acids & Proteins	–	–	–	+	+	+
7	Triterpenoids	+	+	–	–	+	–

+ = Present, – = Absent

3.2 Swimming endurance and anoxia tolerance

Both extracts significantly prolonged swimming time and increased anoxia tolerance latency ($p<0.001$) vs control, suggesting improved resilience to physical and hypoxic stress.

Table 4: Effect of extracts on swimming survival time

Group	Dose (mg/kg)	Swimming time (sec) mean ± SEM
Control (vehicle)	—	185.3 ± 8.5
Standard (Geriforte)	100	321.2 ± 10.8***
O. europaea	400	258.4 ± 9.2**
O. europaea	600	295.5 ± 10.2***
C. quadrangularis	400	250.8 ± 9.0**
C. quadrangularis	600	288.1 ± 9.8***

Note: Values are mean ± SEM (n=6); *p<0.05, **p<0.01, ***p<0.001 vs control.

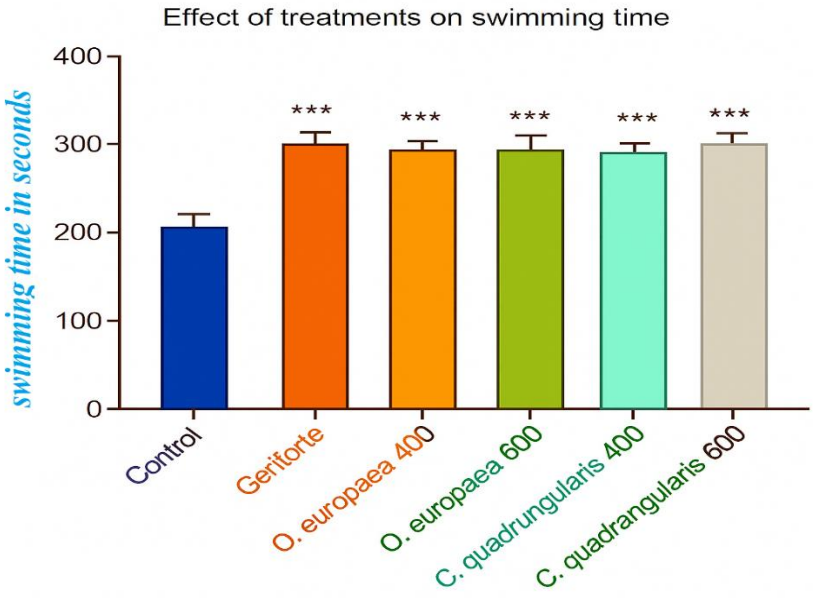


Figure 2: Effect of treatments on swimming time

3.3 Effect on Anoxia Tolerance Test in Mice

The latency to first convulsion under hypoxic conditions was used as a measure of anoxia tolerance. Prolonged latency indicates enhanced resistance to oxygen deprivation. The ethanolic extracts showed a significant increase in latency period in a dose-dependent manner.

Table 5: Effect of Extracts on Anoxia Latency

Group	Dose (mg/kg)	Latency to Convulsion (sec) Mean ± SEM
Control	—	125.4 ± 6.1
Geriforte	100	210.5 ± 8.9 ***
O. europaea	400	172.8 ± 7.0 **
O. europaea	600	198.6 ± 7.8 ***
C. quadrangularis	400	168.2 ± 6.8 **
C. quadrangularis	600	192.7 ± 7.6 ***

Note: n=6; statistical significance as above.

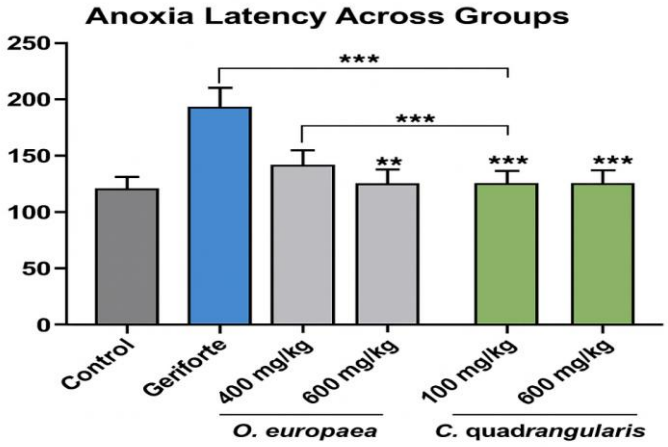


Figure 3: Anoxia latency times across groups

3.4 Biochemical stress markers

Biochemical markers such as blood glucose, cholesterol, triglycerides (TG), cortisol, and blood urea nitrogen (BUN) were elevated in the control group following exposure to CRIS. The groups treated with extracts demonstrated significant improvements in these markers.

Table 5.8: Effect of Extracts on Biochemical Parameters After CRIS

Group	Glucose (mg/dL)	Cholesterol (mg/dL)	TG (mg/dL)	Cortisol (µg/dL)	BUN (mg/dL)
Control	156.2 ± 5.5	112.5 ± 4.2	98.2 ± 3.8	10.8 ± 0.45	34.2 ± 1.4
Geriforte	112.5 ± 4.8 ***	82.1 ± 3.6 ***	72.4 ± 3.2 ***	6.2 ± 0.28 ***	24.5 ± 1.0 ***
O. europaea 400	130.8 ± 5.1 **	95.2 ± 3.9 **	82.5 ± 3.4 **	8.0 ± 0.32 **	28.8 ± 1.2 **
O. europaea 600	118.6 ± 4.9 ***	87.3 ± 3.8 ***	75.3 ± 3.3 ***	6.8 ± 0.29 ***	26.0 ± 1.1 ***
C. quadrangularis 400	132.4 ± 5.2 **	96.8 ± 4.0 **	84.0 ± 3.5 **	8.2 ± 0.33 **	29.2 ± 1.2 **
C. quadrangularis 600	119.5 ± 4.9 ***	88.5 ± 3.7 ***	76.2 ± 3.3 ***	6.9 ± 0.30 ***	26.3 ± 1.1 ***

Note: **p < 0.01, ***p < 0.001 vs. control; n = 6

Table 5.9: Adrenal Gland Weight After CRIS

Group	Adrenal Weight (mg/100g body weight)
Control	18.4 ± 0.7
Geriforte	13.2 ± 0.5 ***
O. europaea 600 mg/kg	14.8 ± 0.6 **
C. quadrangularis 600 mg/kg	15.0 ± 0.6 **

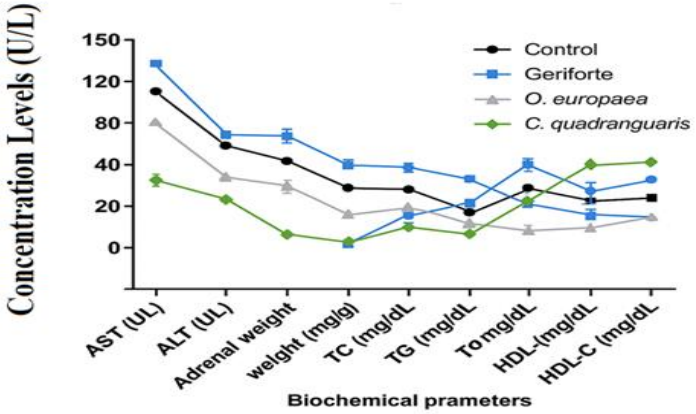


Figure 4: Biochemical Parameters and Adrenal Weight After CRIS

3.5 Effect on Oxidative Stress Parameters

Oxidative stress biomarkers were assessed to evaluate antioxidant potential. Treated groups exhibited increased levels of antioxidant enzymes and reduced lipid peroxidation markers.

Table 5.10: Effect on Oxidative Stress Markers

Group	GSH (µmol/mg prot.)	SOD (U/mg prot.)	CAT (U/mg prot.)	MDA (nmol/mg prot.)	MPO (U/mg prot.)
Control	3.25 ± 0.12	2.12 ± 0.10	21.5 ± 1.1	8.45 ± 0.31	5.25 ± 0.22
Geriforte	5.48 ± 0.18 ***	3.95 ± 0.13 ***	31.4 ± 1.3 ***	4.12 ± 0.21 ***	2.62 ± 0.19 ***
O. europaea 600	5.02 ± 0.16 ***	3.75 ± 0.14 ***	30.2 ± 1.3 ***	4.25 ± 0.20 ***	2.85 ± 0.18 ***
C. quadrangularis 600	4.95 ± 0.15 ***	3.65 ± 0.13 ***	29.6 ± 1.3 ***	4.40 ± 0.22 ***	2.90 ± 0.18 ***

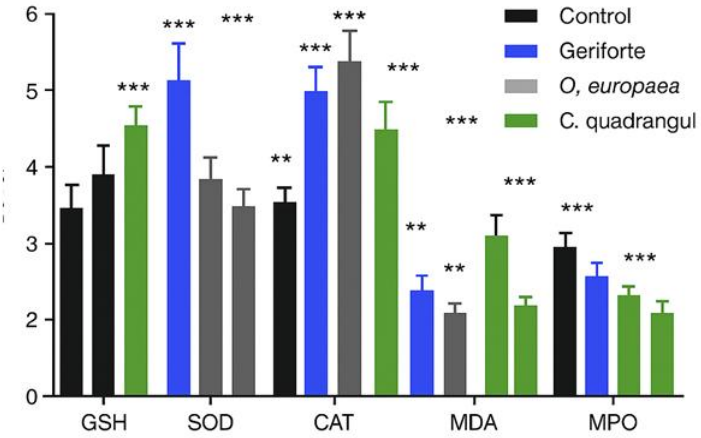


Figure 5: Bar chart showing changes in GSH, SOD, CAT, MDA, MPO

3.6 Effect on Ulcer Index and Gastric pH in USS-Induced Gastric Ulcers

Ulcer scores and gastric pH were recorded following the ulcer stress model. Both plant extracts reduced the ulcer index and raised gastric pH levels.

Table 5.11: Ulcer Index and Gastric pH

Group	Ulcer Index	Gastric pH
Control	7.25 ± 0.31	2.11 ± 0.10
Geriforte	3.05 ± 0.24 ***	4.32 ± 0.18 ***
O. europaea 600 mg/kg	3.35 ± 0.21 ***	4.15 ± 0.17 ***
C. quadrangularis 600	3.45 ± 0.22 ***	4.10 ± 0.16 ***

*****p < 0.001 vs. control**

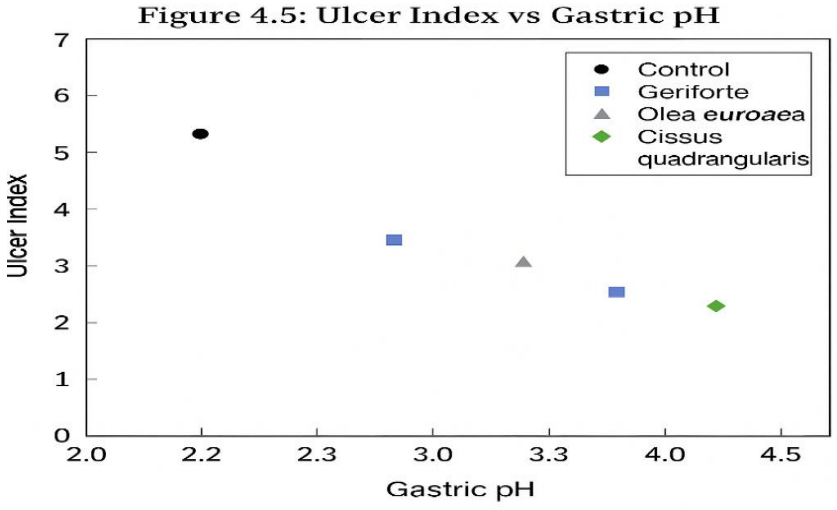
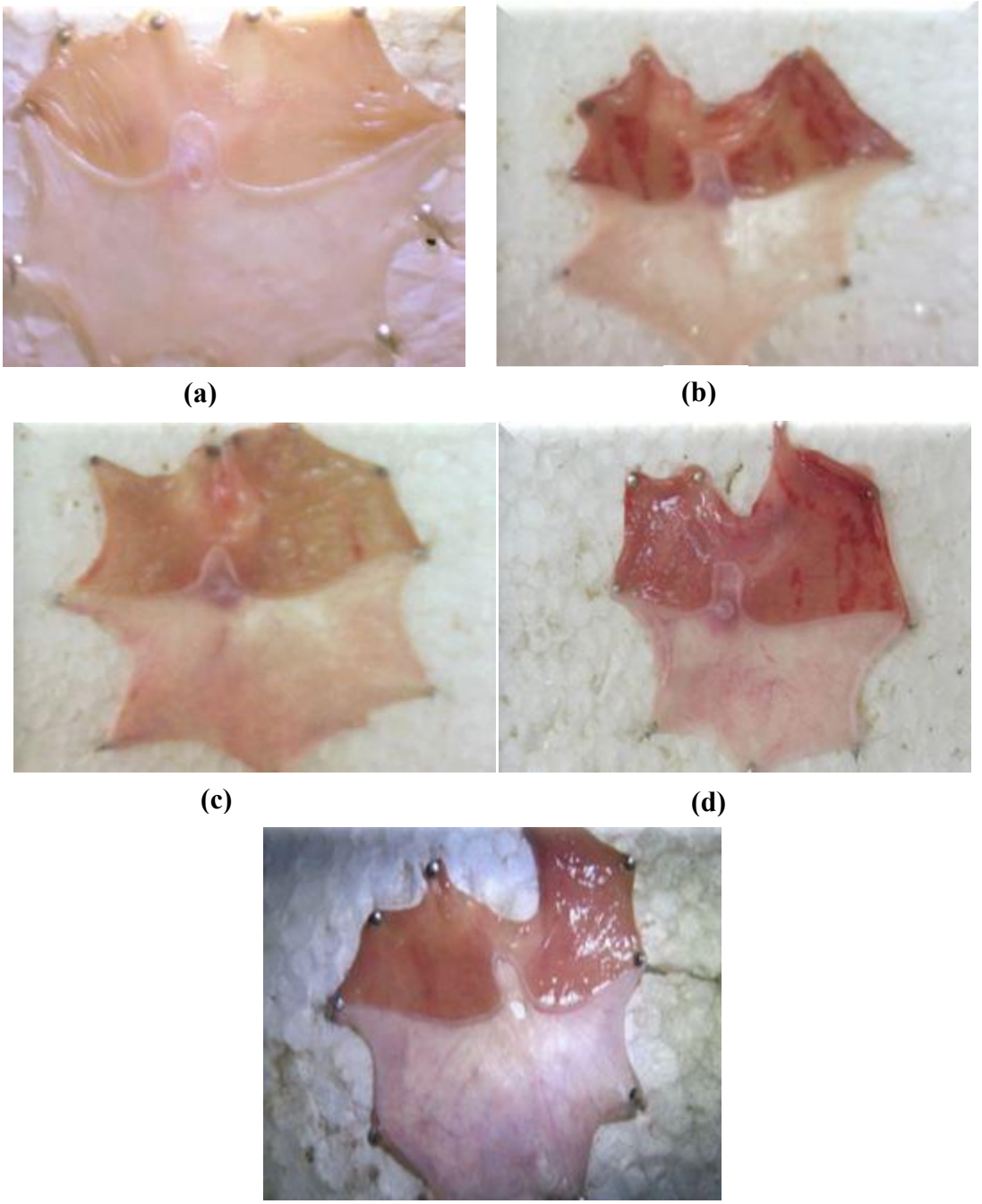


Figure 6: Ulcer Index vs Gastric pH



Photographs 5 (a) Stomach epithelium of normal albino rat (b) Stomach epithelium of albino rat after USS induced (c) Stomach epithelium of standard gerifort gastric ulceration. (d) Stomach epithelium of ECQ 600 treated (e) Stomach epithelium of EOE 600 treated albino rat USS induced albino rat USS induced gastric ulceration gastric ulceration

4. Conclusion

The present study demonstrates that both *Olea europaea* and *Cissus quadrangularis* ethanolic extracts exhibit significant anti-stress and adaptogenic effects in validated animal models. Both extracts enhanced physical and hypoxia stress tolerance, normalized biochemical stress markers (glucose, cortisol, triglycerides, cholesterol, BUN), improved antioxidant enzyme activities (GSH, SOD, CAT), and reduced oxidative stress and inflammation (MDA, MPO, IL-6, TNF-α). Additionally, they protected against stress-induced gastric ulcers, as shown by reduced ulcer index and increased gastric pH. The results were comparable to the standard adaptogen Geriforte and were more pronounced at the 600 mg/kg dose. These findings support the traditional use of these plants as natural adaptogens and suggest their potential as multi-target agents for stress-related disorders.

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