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Research Article

Ameliorative Effect of Tamarind Leaves (*Tamarindus indica*) Aqueous Extract against Inflammation via Modulating Pro-inflammatory and Anti-inflammatory Mediators in Wistar Rats

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ABSTRACT

Inflammation affects many illnesses, like metabolic conditions, psychotic neurodegenerative disorders, and cancer. Hence, many anti-inflammatory drugs are prescribed by professionals. These drugs may have adverse effects. Many natural and plant-origin bioactive compounds have anti-inflammatory properties. In this study, the anti-inflammatory effect of tamarind leaves was evaluated using an animal model. The present research concluded that the tamarind leaf supplementation decreased cholesterol, triglycerides LDL and VLDL levels and hence possess hypolipidemic effects on rats. Tamarind leaves supplementation also showed an antioxidant effect through increasing SOD, catalase and reduced glutathione activities. Tamarind leaves supplementation also showed an anti-inflammatory effect by decreasing IL-6 and COX-1 as well as increasing IL-10 levels in serum and kidney, but no significant difference was observed in TNF-α, COX-2 and 5- LOX levels. Tamarind leaves reduce oxidative stress and inflammation by restoring the body's natural antioxidant equilibrium and controlling the production of inflammatory mediators. Thus, tamarind leaves can be used as a functional food and nutraceutical to reduce inflammation.

Keywords: *Tamarind leaves, Inflammation, Oxidative stress, Anti-inflammatory property.*

Abbreviation:

HDL: High Density Lipoprotein
LDL: Low Density Lipoprotein
VLDL: Very Low-Density Lipoprotein
SOD: Super Oxide Dismutase
CAT: Catalase
GSH: Reduced Glutathione
IL-6: Interleukin-6
IL-10: Interleukin-10
TNF α: Tumer Necrosis Factor α
COX-1: Cyclooxigenase-1
COX-2: Cyclooxigenase-2
5-LOX: 5-Lipooxigenase

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INTRODUCTION

Inflammation has long been thought to be the critical response to microbial invasion or tissue damage in order to maintain tissue homeostasis. The relevance of inflammation has been increasingly recognized in recent years. Multiple chronic diseases have a strong relationship with inflammation. Multiple studies have proven that inflammation is crucial in the onset and progression of stress-related diseases (Chao et al., 2010) (Chatzopoulou et al., 2013; Demir et al., 2020; Liu et al., 2017; & Wang et al., 2020). A rising number of studies indicated that the inflammatory response is the "common soil" of multiple illnesses such as cancer, metabolic and cardiovascular diseases, and neurodegenerative disorders (Demir et al., 2020; Julius et al., 2022; Maccari & Ottanà, 2015; & Song et al., 2017).

The inflammation process entails the immune system reacting and intensifying the formation of ROS and reactive nitrogen species (RNS), which increases the action of inflammatory mediators (Cosme et al., 2020). Pro-inflammatory cytokines, including interleukin (IL)-1β, IL-6, and tumour necrosis factor-alpha (TNF-α), are overproduced and are responsible for severe diseases such as cancer, atherosclerosis, arthritis, and allergies. Therefore, reducing the overproduction of pro-inflammatory cytokines is essential to stop the onset of associated diseases. Managing inflammation is difficult and expensive since it often involves using a combination of different analgesics and anti-inflammatory drugs, each of which has its own set of risks. Anti-inflammatory drugs have harmful side effects such as liver damage, kidney damage and stomach ulcers (Moriasi et al., 2021).

Since ancient times, plant-derived phytochemicals have been widely utilized to treat inflammation and other related illnesses (Shahidi & Yeo, 2018). Phenolic compounds are essential for inhibiting inflammation among phytochemicals (Pragasam et al., 2013). The anti-inflammatory effect of phenolic substances disrupts the ROS-dependent inflammation cycle and inhibits pro-inflammatory mediators such as tumour necrosis factor (TNF- α), interleukin (IL)-1β, IL-6, and IL-8, inducible nitric oxide synthase (iNOS), COX, and leukotrienes. Caffeic and ellagic acid treatments reduced the production of inflammatory mediators like IL-6, IL-1β, and tumour necrosis factor-alpha (TNF α) (Chao et al., 2010). Furthermore, kaempferol altered pro-inflammatory enzyme activity, inflammation-related gene expression, and the suppression of transcription factors such as NF-kB (Kasi et al., 2015). Different phenolic compound metabolites were also shown to have anti-inflammatory properties. For example, 4'-O-methyl-gallic acid is a metabolite produced after drinking fruit juice that lowers the release of pro-inflammatory cytokines and suppresses the expression of COX-2 and iNOS genes in macrophages by suppressing NF-kB activation (Serreli & Deiana, 2019). Thus, phenolic substances were proven to inhibit pro-inflammatory mediators and have anti-inflammatory activities (Cosme et al., 2020; & Shahidi & Yeo, 2018).

Tamarindus indica (Tamarind) is a tree with a dense canopy of feathery, alternating compound leaves that are widely planted worldwide. Many medicinally important compounds have been identified in *Tamarindus indica*, including polyphenolic compounds, caffeic acid, and vitamin C. The plant also contains terpenoids, tartaric acid, orientin, lupeol, luteolin, limonene, palmitic acid, flavonoids, and benzyl benzoate, which has a role in antibacterial, antioxidant, hepatoprotective, and wound-healing properties. However, there is currently relatively little research on tamarind leaves' effect on lifestyle disorders (Adeniyi et al., 2021; & Bhadoriya et al., 2011).

The literature review suggested that tamarind leaves are not studied before for their anti-inflammatory properties. Therefore, the present research aimed to demonstrate the anti-inflammatory properties of tamarind leaves through modulation of gene expression and protein levels of inflammatory mediators in Wistar rats.

MATERIALS AND METHODS

2.1 Procedure of plant extract preparation

The extract was made by mixing a measured quantity of powdered tamarind leaves with distilled water. The powder was incubated overnight at room temperature on an orbital shaker, and the extract was filtered. Approximately three to four cycles of this were performed until the filtrate was completely colourless. In order to distil and concentrate the filtrate, a rotary vacuum evaporator (RV 10 Digital/IKA HB 10 Digital, IKA, Germany) was used. After concentrating, total phenolic content was evaluated following the Folin-Ciocalteu method (Singleton et al., 1999).

2.2 Animal ethical statement

Institutional Animal Ethics Committee (ethical committee: 486/GO/Re-s/Re Bi-L/01/CPCSEA; internal reference number: 323/AGB/2020) of the College of Veterinary Science and Animal Husbandry, Anand Agricultural University, Anand-Gujarat, reviewed and approved all animal experiments. All procedures involving the care of animals and the performance of the experiment were in accordance with the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA).

2.3 Experimental animals and study design

Male Wistar rats, aged 6-7 weeks (120–150 g), were procured from the Zydus Research Centre (ZRC), Ahmedabad. The rats were given free access to a standard pellet diet and water and maintained on a 12-hr light/dark cycle at 25±2° C. Rats were divided into 3 groups:

1. Group 1 (Control)
2. Group 2 (Tamarind leaves-1) (dose: 150 mg/kg body weight/day)
3. Group 3 (Tamarind leaves-2) (dose: 300 mg/kg body weight/day)

The rats were given oral gavages of aqueous extracts from tamarind leaves for 1 month.

2.4 blood and tissues collection

At the end of the experiment, all the overnight fasted rats were sacrificed, and samples (blood, kidney and liver) were collected. Serum was separated and used to analyze triglycerides, cholesterol, HDL and inflammatory cytokines. Liver tissues were snap-frozen and stored at -80° C for analyzing antioxidant enzyme activity assays (SOD, CAT, and GSH). Kidney tissues were collected in RNAlater and stored at -80° C for gene expression analysis.

2.5 Serum biochemistry

Sigma Diagnostic (India) Pvt. Ltd. kits were used to measure serum total cholesterol, total triglyceride, and HDL concentrations in conformance with the manufacturer's instructions. The standard formula was used to determine LDL and VLDL values.

2.6 Liver homogenate preparation

To make a 10% tissue homogenate (W/V), liver tissues were homogenized in phosphate buffer (pH 7), following centrifugation at 7000 RPM for 20 minutes in a cooling centrifuge. The resulting supernatant was stored in a freezer at - 20°C for analysis of various parameters.

2.7 Assessment of antioxidant enzymes activities assay (SOD, CAT and GSH)

Serum superoxide dismutase activity was evaluated by monitoring pyrogallol autoxidation inhibition in accordance with a modified method developed by (Marklund & Marklund, 1974). Catalase activity in serum was assayed by monitoring the rate of hydrogen Peroxide (H_2O_2) hydrolysis and expressed as U/mg protein according to the method of (Aebi, 1984). The GSH content in serum was measured by following the (Ellman, 1959) method and represented as mg%.

2.8 Determination of protein concentration

The protein concentration in liver tissue was determined using the method described by (Lowry et al., 1951).

2.9 Assessment of inflammatory and anti-inflammatory cytokines

Following the manufacturer's protocol, TNF-, IL-6, and IL-10 were measured quantitatively using ELISA kits (Thermo Fisher Scientific, USA).

2.10 Quantitative Real-Time PCR (gene expression)

RNA was isolated from kidney tissue using the TRIzol technique and the Pure Link RNA mini kit following the instructions provided by the manufacturer (Invitrogen, Life Technologies, USA; Catalog No. 12183018A). cDNA was synthesized using a high-capacity reverse transcription kit (Thermo Fisher Scientific, Catalog No. 4368814). Light Cycler® 480II real-time PCR detection equipment (Roche, USA) was used to run PCR in duplicate using SYBR green master mix (Thermo Fisher Scientific, Catalog No. A25742). The thermal cycling procedure for PCR consisted of 45 cycles with the following temperatures: 95 ° C for 15 seconds, 60 ° C or 58 °C (IL-6) for 30 seconds, and 72 ° C for 1 minute. Inflammatory and pro-inflammatory cytokines, Interlukine-6 (IL-6) (F-AAGTCCGGAGAGGAGACTTCA, R-GCCATTGCACAACTCTTTTCTCATT), Interlukine-10 (IL-10) (F-GAGAGAAGCTGAAGACCCTCTG, R-TCATTCATGGCCTTGTAGACAC), Tumer Necrosis factor-α (TNF-α) (F-TCTCAAAACTCGAGTGACAAGC, R-GGTTGTCTTTGAGATCCATGC), Cyclooxigenase-1 (COX-1) (F-GCCTCGAACCACTACCAATGT, R-GTGGTGGGTGAAGTGTTGTG), Cyclooxigenase-2 (COX-2) (F-GATTGACAGCCCACCAACTT, R-ACGTGGGGAGGGTAGATCAT) and 5-Lipooxigenase (5-LOX) (F-TCAAGCAGCACAGGCGTAAAG, R-GTCCACGATGAAAATGTTCCCTTC) were analyzed. β- actin was used as a housekeeping gene. The $2^{-\Delta\Delta CT}$ method was used for relative quantification of gene expression (Livak & Piña, 2001).

2.11 Statistical analysis

Statistical analysis was done using SPSS 20. All of the results were represented as Mean ± S.D. A one-way ANOVA ($p \leq 0.001$) was carried out to assess the differences between the groups, followed by Duncan's post hoc test.

RESULTS

In the current investigation, two different dosages of tamarind leaf extract were supplemented with food for a period of 30 days to Wistar rats. Blood and tissue (liver and kidney) samples were collected from rats after they were euthanized at the end of the experimental period. Inflammatory cytokines (gene expression and protein levels) (IL-6, TNF-α, and IL-10) and pro-inflammatory enzymes (gene expression) (COX-1, COX-2, and 5-LOX) were analyzed.

3.1 Effect of tamarind leaves supplementation on lipid profile

The lipid profile data shown in Figure 1 concluded that all the lipid profile parameters improved significantly when rats were given tamarind leaves supplementation. Both dosages of tamarind leaf supplementation showed a significant ($p \leq 0.01$) decrease in cholesterol, and VLDL levels, while a non-significant increase in HDL and decrease in triglycerides and LDL levels were noted at both levels.

3.2 Effect of tamarind leaves on oxidative stress enzymes (SOD, CAT, GSH)

The antioxidant enzymes assay data depicted in Figures 2 and 3 showed no significant change in catalase and glutathione levels, but SOD levels were increased significantly ($p \leq 0.001$) after rats were given tamarind leaves supplementation.

3.3 Effect of tamarind leaves on Inflammatory and Anti-inflammatory cytokines (gene expression and protein levels)

The gene expression of IL-6, IL-10, and TNF-α is depicted in Figure 4, which showed no significant change, although IL-6 and TNF-α showed non-significant downregulation. Serum inflammatory markers analysis (protein levels) data shown in Figure 5 concluded that tamarind leaves supplementation significantly ($p \leq 0.001$) decreased IL-6 levels and significantly ($p \leq 0.001$) increased IL-10 levels. TNF-α levels decreased in the second dosage of tamarind leaves aqueous extract, but not significantly.

3.4 Effect of tamarind leaves on mRNA expression of pro-inflammatory enzymes

The pro-inflammatory enzymes gene expression data are shown in Figure 6. When rats were given tamarind leaves, their COX-1 gene expression decreased significantly ($p \leq 0.01$). COX-2 and 5-LOX gene expression showed no significant change in mRNA expression.

DISCUSSION

Inflammation and oxidative stress are common roots for multiple illnesses such as cancer, metabolic diseases, and neurodegenerative disorders. These diseases can be ameliorated by reducing oxidative stress and inflammation. Natural products are potentially safe and affordable in reducing oxidative stress and inflammation. Tamarind leaves are rich in polyphenols and other active compound terpenoids, tartaric acid, orientin, lupeol, luteolin, limonene, palmitic acid, flavonoids, and benzyl benzoate hence proven to be beneficial in the prevention of various diseases (Adeniyi et al., 2021; & Bhadoriya et al., 2011).

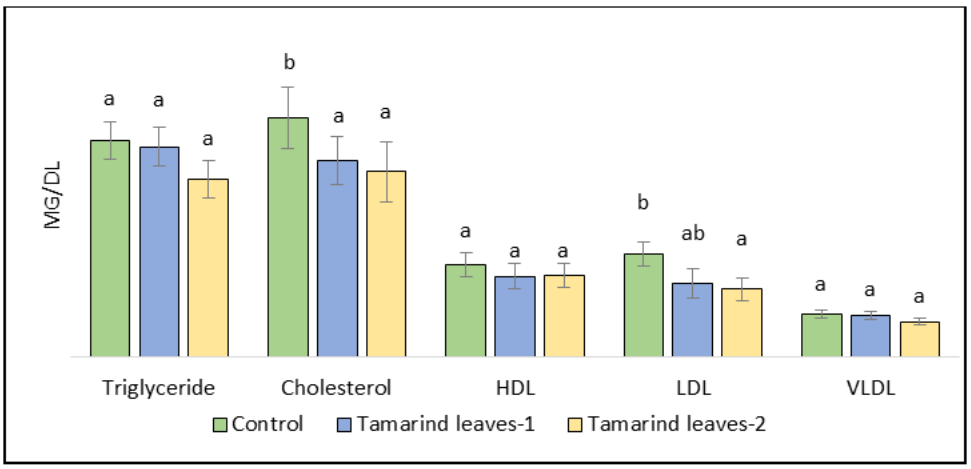
The present study showed that tamarind leaf supplementation has beneficial effects on lipid profile. The lipid-lowering effects of tamarind leaves have been supported by research and highlighted that the saponin, flavonoids, and epicatechin in tamarind leaves were responsible for the hypolipidemic effect. We inferred that tamarind leaves' bioactive components might be responsible for the hypolipidemic effect observed in the supplemented rats. Saponin from tamarind leaves reacts with bile acid to make a large mixed micelle, which blocks the absorption of cholesterol. Flavonoids accelerate LDL-C clearance and lower total cholesterol levels through increased activation of the LDL-C receptor in the liver. The epicatechin in tamarind leaves reduces triglyceride levels and increases free fatty acid and sterol acid clearance during bowel movements (Aprilia et al., 2017).

The antioxidant enzyme analysis showed tamarind leaf supplementation replenished SOD levels, indicating antioxidant properties. Extensive studies on tamarind seed and fruit juice confirmed its high levels of chlorogenic acid, catechin, and epicatechin are responsible for its powerful antioxidant activity, which is effective in ameliorating oxidative stress (Ameeramja & Perumal, 2018; Ghoneim & Eldahshan, 2012; Sadi et al., 2021; & Sandesh et al., 2014). This led us to conclude that the bioactive compounds in tamarind leaves (like chlorogenic acid, catechin, and epicatechin) may have antioxidant properties and that supplemental tamarind leaf extract effectively reduced oxidative flux and helped in the homeostasis of the endogenous antioxidant system by regulating SOD levels.

Tamarind leaves supplementation showed beneficial effects on Inflammatory and anti-inflammatory cytokines (gene expression and protein levels). Supportive research has previously shown a similar anti-inflammatory activity of tamarind seed extract. The research highlighted that embelin, rutin, catechin, and procyanidin B2 are all effective antioxidants and anti-inflammatory agents. This can suppress oxidative stress and helps in reducing inflammation (Sundaram et al., 2015). Present research concluded that tamarind leaves, like tamarind seeds, contain bioactive compounds (flavonoids, catechins, and tannins) that serve as antioxidants and decrease inflammation. These bioactive substances, therefore, provide antioxidant and anti-inflammatory properties.

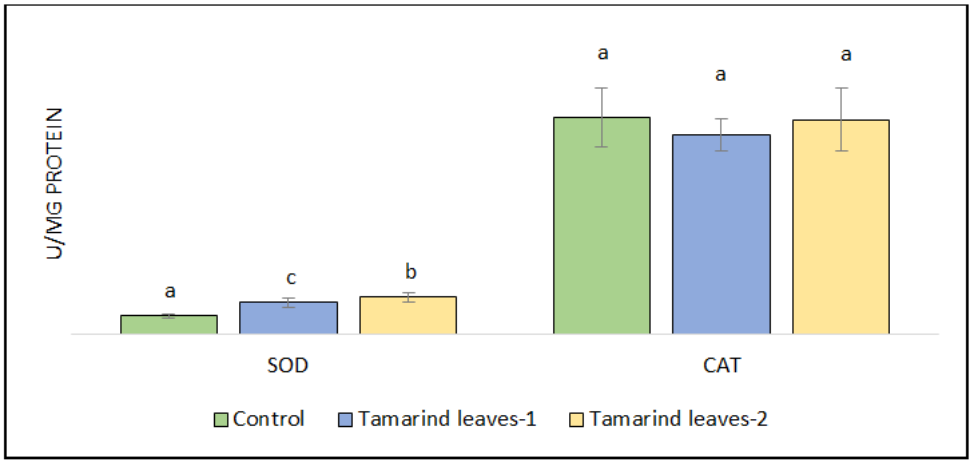
There was a lack of evidence on the impact of supplemental tamarind leaves on pro-inflammatory enzymes. We are the first to discover that consuming tamarind leaves reduces the pro-inflammatory enzyme COX-1. There was a decrease in COX-1 gene expression after taking tamarind leaves supplements, which may aid in inflammation reduction. Arachidonic acid is converted into prostaglandin H2 when COX-1 attaches to prostaglandin synthase (PGH2). PGH2 is a forerunner of TXA2, which promotes platelet activation and recruitment through a positive feedback loop. A COX-1 inhibitor that blocks PGH2 also blocks arachidonic acid metabolism, which in turn blocks TXA2 synthesis, which helps reduce inflammation.

Figure-1 Tamarind leaves supplementation effect on lipid profile



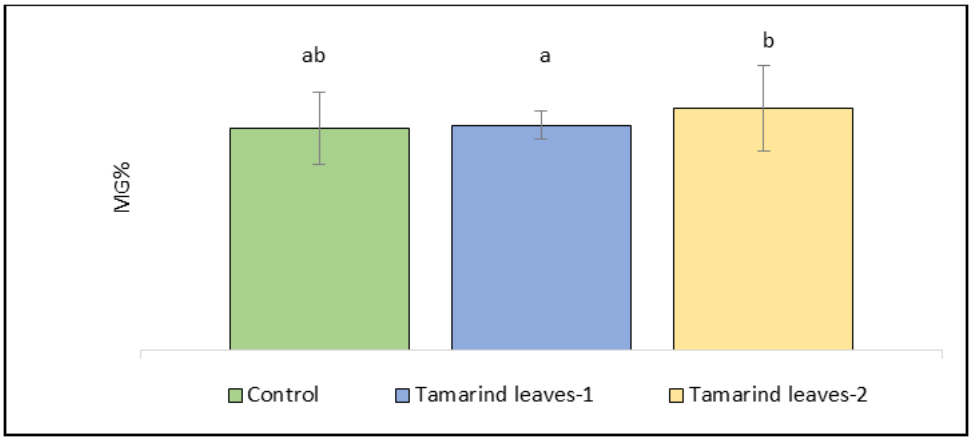
The values are Mean ± S.D (n=6). Bars with different alphabets differ significantly (p≤ 0.01) (ANOVA followed by Duncan's post hoc analysis).

Figure-2 Tamarind leaves supplementation effect on oxidative stress enzymes



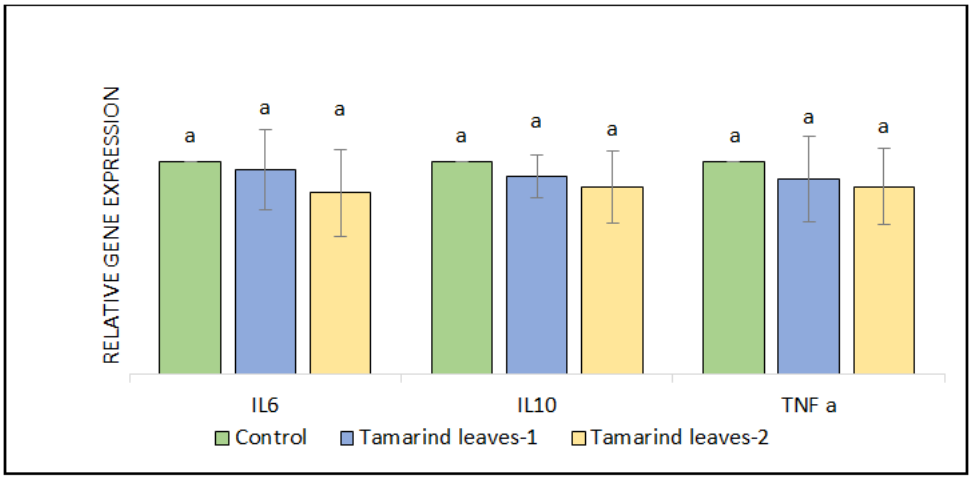
The values are Mean ± S.D (n=6). Bars with different alphabets differ significantly (p≤ 0.001) (ANOVA followed by Duncan's post hoc analysis).

Figure-3 Tamarind leaves supplementation effect on reduced glutathione (GSH)



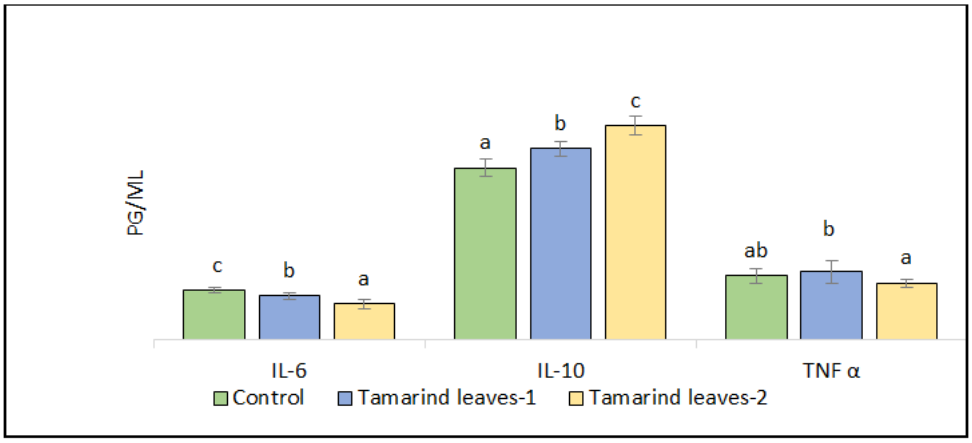
The values are Mean ± S.D (n=6). Bars with different alphabets differ significantly (p≤ 0.05) (ANOVA followed by Duncan's post hoc analysis).

Figure-4 Tamarind leaves supplementation effect on mRNA expression inflammatory and anti-inflammatory cytokines



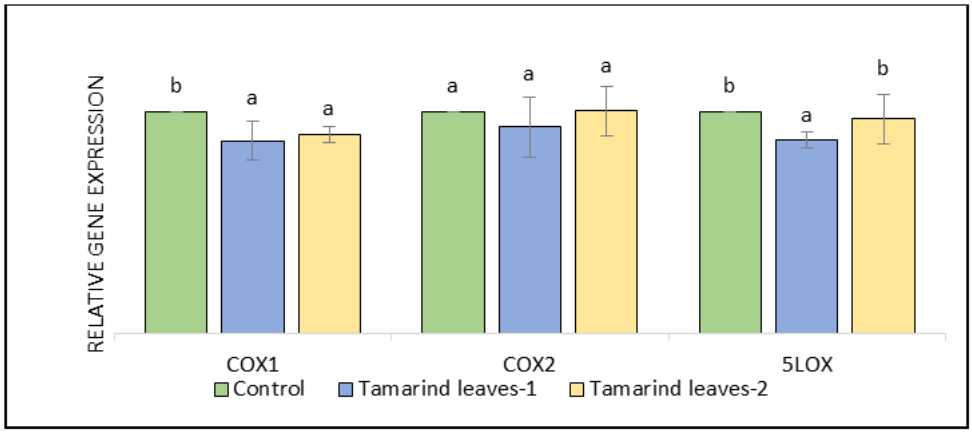
Values are Mean ± S.D (n=6). Bars with different alphabets are significantly (p≤0.001) (ANOVA followed by Duncan's post hoc analysis) different from each other.

Figure- 5 Tamarind leaves supplementation effect on protein levels of pro-inflammatory and anti-inflammatory cytokines



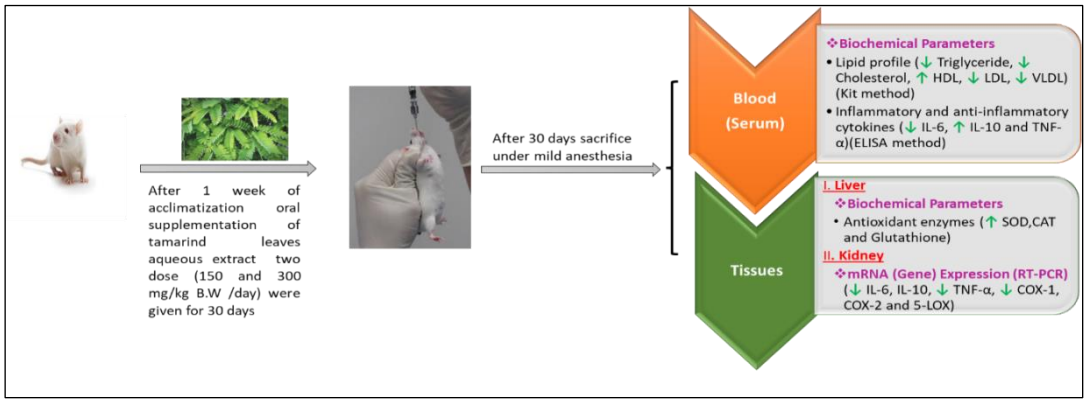
The values are Mean ± S.D (n=6). Bars with different alphabets differ significantly (p≤ 0.001) (ANOVA followed by Duncan's post hoc analysis).

Figure-6 Tamarind leaves supplementation effect on mRNA expression of pro-inflammatory enzymes



Values are Mean ± S.D (n=6). Bars with different alphabets are significantly (p≤0.01) (ANOVA followed by Duncan's post hoc analysis) different from each other.

Figure-7 Effect of tamarind leaves supplementation on Oxidative stress and inflammation in Wistar rats



This figure showed a beneficial effect of tamarind leaves supplementation in Wistar rats. This research concluded that the tamarind leaves had a hypolipidemic effect through decreases in triglyceride, cholesterol, LDL, and VLDL, as well as increased HDL levels in the blood and antioxidant effects through increasing SOD levels in liver tissue. Tamarind leaves supplementation also showed an anti-inflammatory effect by decreasing IL-6 and COX-1 and increasing IL-10 levels in serum and kidney.

CONCLUSION

The present investigation concluded that tamarind leaf supplementation positively affected lipid profile (figure-7). Tamarind leaves supplementation also showed an antioxidant effect and restored endogenous antioxidant homeostasis, as well as modified levels of inflammatory mediators at the molecular and protein levels. All of these mechanisms contribute to a reduction in the heightened circumstances of oxidative stress and inflammation. As a result, tamarind leaves function as a therapeutic agent, having an anti-inflammatory impact. Thus, tamarind leaves can be used as a functional food and nutraceutical to reduce inflammation. Therefore, in future, our findings lend credence to conducting an investigation on tamarind leaves' effects on different inflammation-related illnesses.

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Conflict of Interest: There is no Conflict of interest.

Author's Contribution:

KD conceived and carried out the experiment and wrote the manuscript; DNR supervised the work; and VHP supervised the work and edited the MS.

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