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Quercetin as a Potent Modulator of Innate and Adaptive Immunity: An *In Vivo* Evaluation in Wistar Rats

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Abstract

Background: The immune system maintains host defines through coordinated innate and adaptive responses, and its imbalance can lead to increased susceptibility to infections and inflammatory disorders. Plant-derived flavonoids have attracted attention for their potential immunomodulatory properties. Quercetin, a naturally occurring flavonoid, has shown anti-inflammatory and antioxidant effects, but its effect on different arms of the immune response requires further experimental evaluation. **Aim:** The aim of the current study was to examine the effect of quercetin on immune system modulation. **Methods:** Quercetin suspension was administered orally to rats at dose levels of 50,100 and 150mg/kg for 21days. The carbon clearance test, Delayed Type Hypersensitivity (DTH) reaction, and Hemagglutination Antibody (HA) titer were used to examine the immunomodulatory effect on both specific and non-specific immunity. Rats were given cyclophosphamide (100mg/kg p.o.) as an immunosuppression agent. In the processes of delayed type hypersensitivity response and hemagglutinating antibody titers, Sheep Red Blood Cells (SRBCs) were used as an antigen (0.1mL 20% SRBCs). **Results:** Quercetin significantly reduced antibody titers in response to the SRBC antigen. When compared to the negative control, the immunosuppressed group receiving quercetin showed a significant reduction in first and second HA titers. When immunosuppressed rats were treated with quercetin and pre-sensitized with SRBC antigen, the DTH response was significantly reduced. Quercetin significantly reduced the phagocytic index as compared to the control group, showing that the reticuloendothelial system is inhibited. **Conclusion:** The study found that quercetin inhibits both targeted and nonspecific immune responses. By reducing leucocyte recruitment, chemokine levels, and levels of the lipid peroxidation end-product malondialdehyde, quercetin decreased the histological signs of acute inflammation in the treated rat in a dose-dependent way.

Major Findings: The study demonstrated that quercetin exerts a significant immunomodulatory effect by influencing humoral, cell-mediated, and non-specific immune responses, enhanced antibody and phagocytic responses, and reduced inflammation, showing dose-dependent immunomodulatory potential. These findings suggest that quercetin may have therapeutic potential in conditions involving immune dysregulation and immunosuppression.

Keywords: Delayed Type Hypersensitivity, Immunomodulation, Primary and Secondary Antibody Titer, Phagocytic Index, Quercetin

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Abbreviations: DTH- Delayed Type Hypersensitivity; HA- Haemagglutination Antibody; SRBCs- Sheep Red Blood Cells; SRBC- Sheep red Blood Cell; RES- Reticuloendothelial System, CYP- Cyclophosphamide.

1. Introduction

The immune system plays a fundamental role in protecting the host against invading pathogens and foreign antigens through a coordinated network of innate and adaptive immune mechanisms[1]. Innate immunity provides the first line of defense by promoting rapid, non-specific responses such as phagocytosis, while adaptive immunity generates antigen-specific responses that involve both humoral and cell-mediated components, as shown in Figure 1. A balanced interaction between these two arms of immunity is essential for maintaining immune homeostasis and preventing pathological inflammation[2,3].

Alterations in immune function, whether excessive activation or suppression, can increase susceptibility to infections and inflammatory disorders. Consequently, there is growing interest in identifying agents capable of modulating immune responses in a controlled manner[4]. Natural bioactive compounds have received particular attention due to their broad pharmacological activities and relatively favorable safety profiles when compared to synthetic immunomodulators[5-7]. Quercetin, a plant-derived flavonoid abundantly present in fruits and vegetables, has been reported to exhibit antioxidant, anti-inflammatory, and immunoregulatory properties[8,9]. Experimental evidence suggests that quercetin can influence immune cell activity by regulating cytokine production, leukocyte migration, and oxidative stress–related pathways. In addition, quercetin has been shown to affect macrophage-mediated phagocytosis and lymphocyte-dependent immune responses, indicating its potential role in modulating both innate and adaptive immunity[10]. Despite increasing evidence supporting the biological activities of quercetin, it's *in vivo* effects on specific and non-specific immune responses under immunosuppressed conditions remain incompletely characterized[11,12]. In particular, systematic evaluation

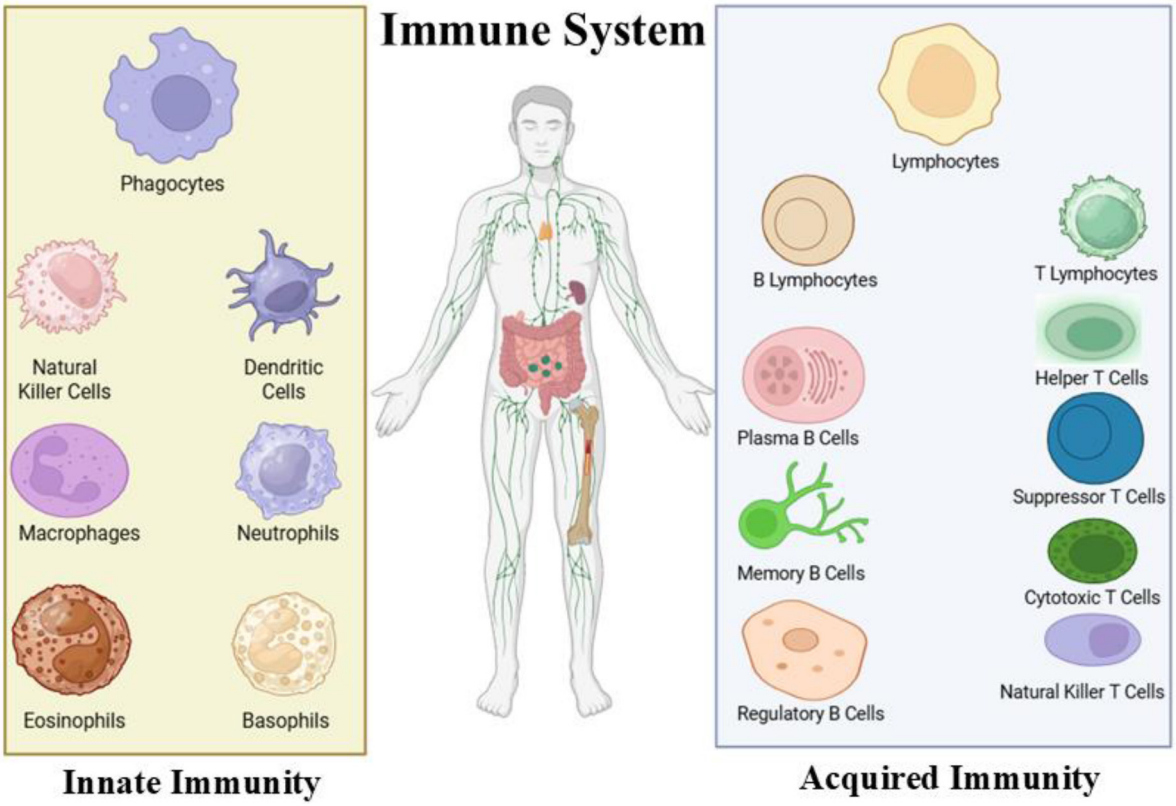


Figure 1. A schematic representation of the innate and adaptive immune systems and their cellular components.

of its influence on humoral antibody production, cell-mediated immunity, and reticuloendothelial system function is limited. Therefore, the present study was undertaken to investigate the immunomodulatory effects of quercetin in Wistar rats using established models of innate and adaptive immune function, including the carbon clearance test, delayed-type hypersensitivity reaction, and hemagglutination antibody titer, under cyclophosphamide-induced immunosuppression.

2. Materials and Methods

2.1 Drugs and Chemicals

We obtained quercetin, manufactured by Yarrow Chem Products in Mumbai. Cyclophosphamide was purchased from Celon Laboratories Ltd. in Hyderabad as their advertised product "Cyclocel". All other chemicals were of analytical grade and were bought commercially, with the exception of colloidal carbon (Pelikan fount Indian ink, Hannover, Germany). Throughout the investigation, double-distilled water was used.

2.2 Experimental Animals

For the investigation, healthy Wistar rats weighing 150-250g of either sex were selected. Water and a typical pellet meal were given to the animals, who were kept in polypropylene cages with five animals per cage. They were reared in a typical setting with 12-12 hours of darkness and light, with a temperature of 24±1°C and a humidity of 55±5%. In accordance with CPCSEA norms, the experimental procedure was approved by the institutional animal ethics committee (Reg no: 1670/PO/ ReBiBt/S/12/ CPCSEA). As per Protocol no: 05/2019, and has been verified from the records by IAEC. (COPH/IAEC/PG/05/2019)

2.3 Preparation of Different Solutions

Before being given orally to animals, quercetin suspension was made in 0.5%w/v Carboxymethyl Cellulose (CMC) in double distilled water[13]. Citric acid 0.055g, sodium citrate 0.8g, glucose 2.05g, sodium chloride 0.42g, and distilled water were used to manufacture Alsever's solution, which had a volume of 100ml[14]. A refrigerator was used to keep the solution. Blood from a healthy sheep from the nearby slaughterhouses was drawn and placed in newly made, sterile Alsever's solution in a 1:1 ratio to create the SRBC suspension. It was kept between 2 and 8 degrees Celsius. The sample of blood was centrifuged for 10 minutes at 2000rpm on the day of the vaccination, and it was then rinsed three times with a 0.9% NaCl solution. Next, 0.9% sodium chloride solution was used to make the SRBC (20% v/v) suspension[15,16]. The carbon clearance test was conducted using a saline solution that had been diluted eight times to create colloidal carbon ink[17].

2.4. Evaluation of Humoral Immunological Activity to SRBC

2.4.1 Hemagglutination Antibody (HA) Titer

The animals were divided into 5 different groups; each group contained six animals. For 21 days, Group I (Normal control) was given double distilled water (1ml/kg, p.o.). On days 9 and 16, Group II (Negative control) was given a single dose of cyclophosphamide-CYP (100 mg/kg, p.o.). For 21 days, groups III, IV, and V were given quercetin at doses of 50,100 and 150mg/kg, p.o., respectively. All groups (*i.e.*, Groups I through V) received SRBCs in normal saline group (0.1 ml of 20% SRBCs, i.p.) for vaccination and challenge on days seven and fourteen, respectively. All antigen-sensitized and challenged rats had their blood extracted from the retro-orbital plexus on day 14 and 21, respectively, while under light ether anesthesia. Serum was obtained by centrifuging blood; the SRBC count was corrected to 0.1% of SRBCs and normal saline was used as a diluent. Twenty microliters of saline were first added to each well of a microtiter plate, and in the first well, twenty microliters of serum were added. In order to obtain double dilutions of the serum's antibodies, the 20 µl of diluted serum was then taken out of the first well and added to the second. To ensure that the antibody concentration in each dilution was half of the preceding dilution, additional in order to obtain double dilutions of this diluted serum were carried out in a similar manner until the final well of the second row (the 24th well). Each of these dilutions received 20µl of SRBC (0.1% of SRBCs), and before the plates were examined for hemagglutination, they were incubated for an hour at 37°C. The antibody titer was determined to be the greatest dilution that produced hemagglutination. The minimum dilution

(1/2) was determined as 1 in the graded expression of the antibody titer, and the mean ranks of the several groups were compared for statistical significance. The main and secondary humoral immune responses were determined by measuring the antibody titer acquired on the fourteenth day following vaccination on the seventh day and on fourteenth day following challenge with SRBCs, respectively[18-20].

2.5 Evaluation of the Cellular Immunological Response Based on by SRBC

2.5.1 Response to Delayed-Type Hypersensitivity (DTH)

Medication regimen was identical to that which was outlined for the HA titer. SRBCs in normal saline groups were administered to groups I through V on the fourteenth day of the study. Every animal in every group was challenged on the twenty-first day with 0.03 milliliters of 20% SRBCs in the right hind paw's sub plantar area and he same volume of saline in the left hind paw. Rat's foot pad oedema was employed to measure the cellular immunological response. After 24 hours, the footpad's response was evaluated. A digital plethysmometer was used to measure the paw volume of the right hind footpad on the 22nd day in order to assess the increase in footpad thickness caused by the hypersensitive reaction brought on by oedema. The volume difference between the right footpad that received an SRBC injection and the left footpad that received a normal saline injection was used to represent the footpad response[21-24].

2.6 Evaluation of Nonspecific Immune Response

2.6.1 Test for Carbon Clearance

The animals were divided into 4 different groups; each group contained six animals. For 14 days, double distilled water (1ml/kg, p.o.) was given to Group I (Normal control). For 14 days, groups II, III, and IV were given quercetin at doses of 50,100 and 150mg/kg,p.o., respectively. Colloidal carbon was administered intravenously to all animals in each group on the fourteenth day, three hours after the last treatment, in a volume of 1ml/100g. Following the injection of colloidal carbon ink, 25µl of blood was taken by the retroorbital plexus and combined with 3ml of a 0.1% Na_2CO_3 solution. At 650nm, optical density was determined using spectrophotometry[25-27]. The Phagocytic Index (K) was calculated by these the formula:

$$K = \frac{In\ OD1 - In\ OD2}{t2 - t1}$$

Where the optical densities at periods t1 and t2 are denoted by OD1 and OD2, respectively.

2.7 Statistical Analysis

The study results were presented as mean ± SEM. Data were analyzed using a one-way Analysis of Variance (ANOVA) followed by the Tukey-Kramer multiple comparison test. Statistical significance was established at a minimum threshold of $P < 0.05$.

3. Results

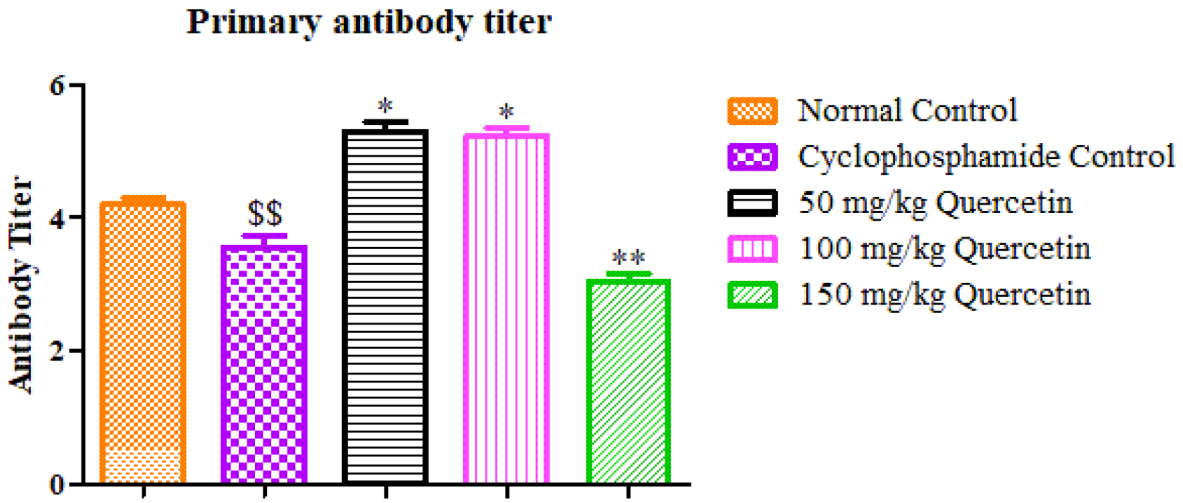
3.1 Primary Humoral Immune Response

At the end of 14 days of prophylactic treatment of quercetin 50,100,150mg/kg the animals of each group were divided to main or primary (on 7th day) and secondary (on 14thday) antigen challenge by sheep RBCs. Figure 2 indicates the primary antibody titre that was identified. Compared to the vehicle control, the cyclophosphamide control group's animals had a considerably lower antibody titer. In the group of rats with normal immunological group, quercetin 50mg/kg and quercetin 100mg/kg considerably raised the primary antibody titer, whereas quercetin 150mg/kg significantly increased the primary antibody titer. Quercetin 50 mg/kg, quercetin 100mg/kg, and quercetin 150mg/kg significantly increased the main antibody titer in the immunosuppressed rat groups treated with cyclophosphamide.

Values are indicated as mean ± SEM; (n=6). Statistics analysis was performed using Graph Pad Prism 5.0, employing one way ANOVA followed by Tukey-Kramer multiple comparisons test. Statistical significance $^{\$\$}$ = $p<0.01$ compared to normal and all test group * = $p<0.05$, ** = $p<0.01$, compared to CYP control group.

3.2 Secondary Humoral Immune Response

At the end of 14 days of prophylactic treatment of quercetin 50,100,150mg/kg, the animals of each group



Values are indicated as mean ± SEM; (n=6). Statistics analysis was performed using graph pad prism 5.0, employing one way ANOVA followed by Tukey-Kramer multiple comparisons test. Statistical significance $$= p<0.01 compared to normal, and all test group *= p<0.05, **= p<0.01, compared to CYP control group.

Figure 2. Effect of quercetin treatment on primary antibody titer.

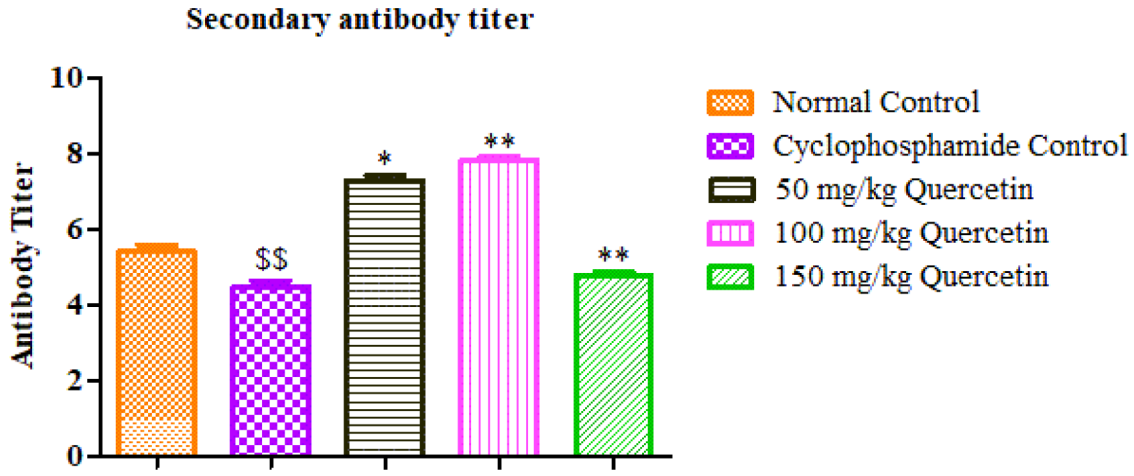


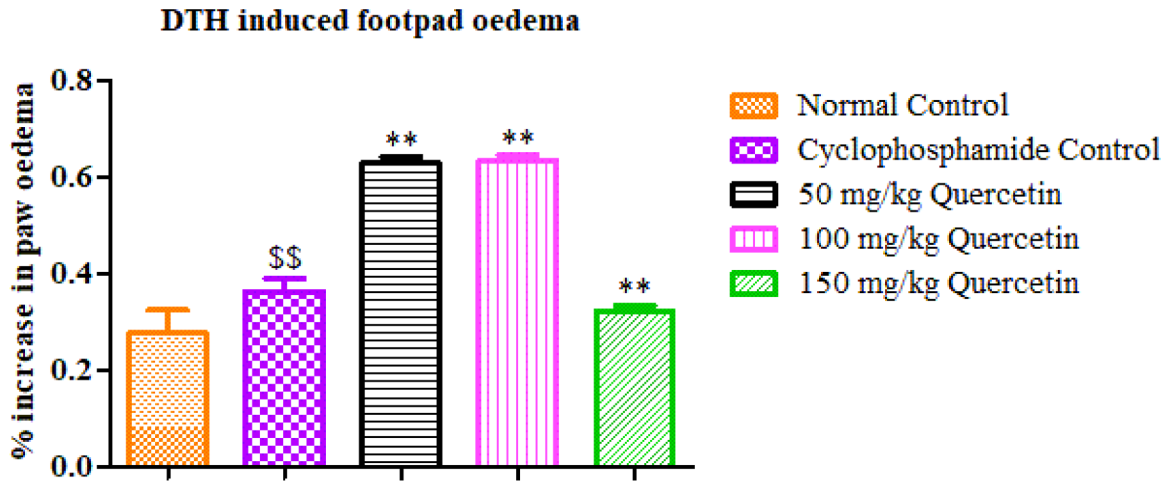
Figure 3. Effect of quercetin treatment on primary and secondary antibody titer.

were divided into main or primary (on 7th day) and secondary (on 14th day) antigen challenge by sheep RBCs. Figure 3 indicates the primary antibody titre that was identified. Compared to the vehicle control, the cyclophosphamide control group's animals had a considerably lower antibody titer. In the group of rats with normal immunological group, quercetin 50mg/kg kg, quercetin 100mg/kg, and Quercetin 150mg/kg raised the secondary antibody titer. Quercetin 50mg/kg, quercetin 100mg/kg, and quercetin 150mg/kg significantly increased secondary antibody titre in the immunosuppressed rat groups treated with cyclophosphamide.

3.3 Assessment of Cell-mediated Immune Response

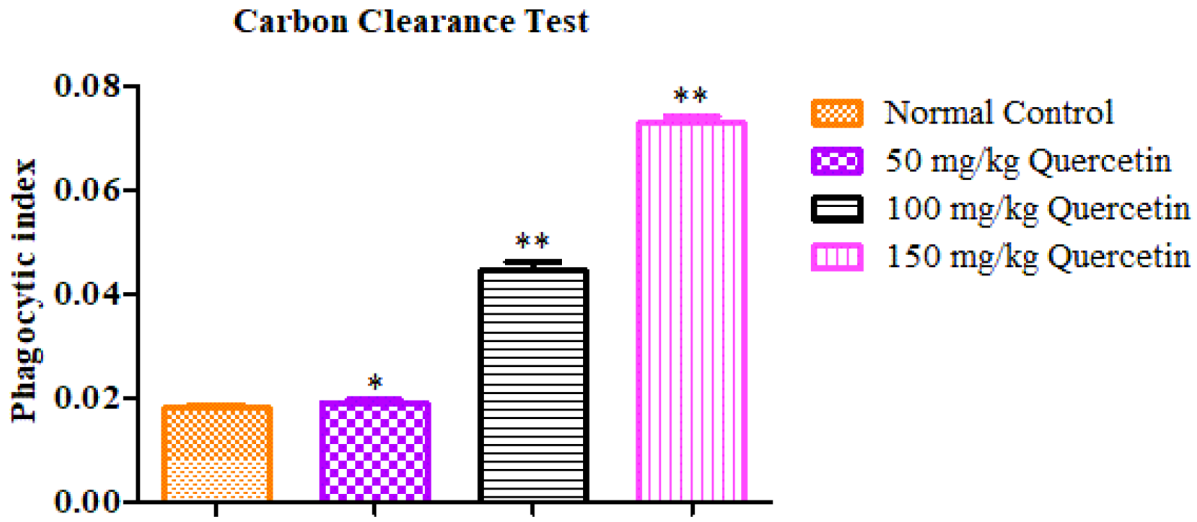
3.3.1 Delayed Type Hypersensitivity-induced Footpad Oedema

Figure 4 displays the impact of quercetin 50,100 and 150mg/kg on the cell-mediated immune response via DTH-induced footpad edema. On the twenty-first day, the mean difference in paw volume was significantly lower in the group treated with cyclophosphamide than in the control group. Quercetin 50, 100 and 150mg/kg significantly potentiated the DTH response in the groups of rats treated with normal immunological group, as indicated by an increase in the mean



Values are indicated as mean ± SEM; (n=6). Statistics analysis was performed using graph pad prism 5.0, employing one way ANOVA followed by Tukey-Kramer multiple comparisons test. Statistical significance $^{\$\$}$ = p<0.01 compared to normal, and all test group **= p<0.01, compared to CYP control group.

Figure 4. Effect of quercetin treatment on cell-mediated immune response by delayed type hypersensitivity induced footpad oedema.



Values are indicated as mean ± SEM; (n=6). Statistics analysis was performed using graph pad prism 5.0, employing one way ANOVA followed by Tukey-Kramer multiple comparisons test. Statistical significance all test group *= p<0.05, **= p<0.01, compared to normal.

Figure 5. Effect of quercetin treatment on reticuloendothelial system by carbon clearance test.

difference in paw volume when compared to the control group. Quercetin 50, 100 and 150mg/kg significantly potentiated the DTH response in all groups of rats treated with cyclophosphamide immunosuppressed rats, as measured by an increase in the mean difference in paw volume in comparison to the cyclophosphamide group. The cellular immune system may be activated in response to a delayed-type hypersensitivity reaction. The DTH skin response causes inflammation and needs antigen-specific memory T cells. Many neutrophils and mononuclear cells are attracted to the injection site as a result of chemotaxis and the generation of local cytokines, which causes inflammation.

3.4 Assessment of Non-specific Immune Response (Phagocytic Capacity)

3.4.1 Test for Carbon Clearance

Figure 5 displays the impact of quercetin at 50, 100, and 150mg/kg on phagocytic activity as determined by the carbon clearance test. The reticuloendothelial system's phagocytic activity is often assessed by how quickly carbon particles are eliminated from the

blood. The test medication, which was administered to all groups in the carbon clearance test, showed a significantly increased phagocytic index. Comparing quercetins 50,100 and 150mg/kg to the control group indicated a substantial increase in the phagocytic index. This suggests that the reticuloendothelial system is being stimulated.

4. Discussion

A process known as immunomodulation can control an organism's immune system by interfering with its normal function. An individual can maintain a disease-free condition by stimulating or suppressing their immune system. As a result, immunomodulatory have been employed to treat diseases all over the world[28]. By assessing its impact on the Hemagglutination Antibody (HA) titer, DTH responses, and the reticuloendothelial system's phagocytic capability, the study investigated quercetin's immunomodulatory effect. Quercetin's impact on humoral immunity was assessed using a hemagglutination test. B lymphocytes mediate humoral immunity by the interactions of B cells with the antigen, followed by their proliferation and differentiation into plasma cells, which produce and release certain proteins known as antibodies. By attaching itself to the antigen and neutralizing or aiding in its removal, the antibody acts as the effector of the humoral response[29]. To evaluate the effect of quercetin on humoral response, its influence was tested by using SRBCs as antigen in the HA titer. The antibody titer response was significantly inhibited by cyclophosphamide because it inhibits the proliferation of B cells, whereas quercetin reversed the suppression of primary and secondary humoral responses brought on by cyclophosphamide. The study's findings showed that quercetin increases an immunocompromised animal's generation of antibodies[30]. Sensitized T cells interacting with a particular antigen because the DTH reaction, a type IV delayed or cell-mediated hypersensitivity reaction. Either direct cytotoxicity or lymphokine release mediates the subsequent cell-mediated immune response, which activates and accumulates macrophages, raises vascular permeability, causes vasodilation, and generates inflammation[31,32]. In animals that have already had vaccinations, this causes the footpad's thickness to increase. According to this study, the rats that received quercetin treatment had thicker footpads. This could be explained by quercetin's capacity to stimulate lymphocytes and boost antibody production in the immunocompromised animal, which in turn increases cell-mediated immunity[33]. Through the rate of carbon clearance by the Reticuloendothelial System (RES) cells, quercetin demonstrated a stimulatory impact on the phagocytic capacity. Phagocytosis's function is to eliminate dead or damaged cells, foreign objects, and microbes. The improvement in nonspecific immunity and the phagocytic activity of mononuclear macrophages is reflected in the rise in the carbon clearance rate[34].

5. Conclusion

According to the study's results, quercetin demonstrated inhibitory effects on humoral and cell-mediated immunity, two distinct immune system arms, and nonspecific immune system activation through reticuloendothelial system activation due to saponin glycoside. Therefore, it can be said that quercetin is helpful in reducing illness states and has potential therapeutic efficacy in immunosuppressed clinical situations. By inhibiting leucocyte recruitment, lowering chemokine levels, and lowering levels of the lipid peroxidation end-product malondialdehyde, quercetin reduced the histological indicators of acute inflammation in the treated rats in a dose-dependent way.

6. Acknowledgment

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7. References

1. Baniyash M. Chronic inflammation, immunosuppression and cancer:new insights and outlook. Semin Cancer Biol. 2006; 16:80-88. https://doi.org/10.1016/j.semcancer.2005.12.002 PMid:16420981.
2. Manu KA, Kuttan G. Immunomodulatory activities of Punarnavine, an alkaloid from *Boerhaavia diffusa*.

Immunopharmacol Immunotoxicol. 2009; 31(3):377-387. https://doi.org/10.1080/08923970802702036 PMid:19555203.
3. Iwasaki A, Medzhitov R. Regulation of adaptive immunity by the innate immune system. Science. 2010; 327(5963):291-295. https://doi.org/10.1126/science.1183021 PMid:20075244 PMCid: PMC3645875.
4. Chaplin DD. Overview of the immune response. J Allergy Clin Immunol. 2010; 125(2):S3-S23. https://doi.org/10.1016/j.jaci.2009.12.980 PMid:20176265 PMCid: PMC2923430.
5. Felsburg PJ. Overview of the immune system and immunodeficiency diseases. Vet Clin North Am Small Anim Pract. 1994; 24(4):629-653. https://doi.org/10.1016/S0195-5616(94)50076-7 PMid:7975040
6. Moser M, Leo O. Key concepts in immunology. Vaccine. 2010; 28:C2-C13. https://doi.org/10.1016/j.vaccine.2010.07.022 PMid:20713253.
7. Murphy K, Travers P, Walport M. *Janeway's Immunobiology.* 7th ed. New York: Garland Science. 2008. https://doi.org/10.1007/978-3-8274-2219-4
8. Medina KL. Overview of the immune system. In: Handbook of Clinical Neurology. Elsevier. 2016; 133:61-76. https://doi.org/10.1016/B978-0-444-63432-0.00004-9
9. Jung JH, Kang JI, Kim HS. Effect of quercetin on impaired immune function in mice exposed to irradiation. Nutr Res Pract. 2012; 6(4):301-307. https://doi.org/10.4162/nrp.2012.6.4.301 PMid:22977683 PMCid: PMC3439573.
10. Middleton E, Kandaswami C. The impact of plant flavonoids on mammalian biology: Implications for immunity, inflammation and cancer. In: Harborne JB, editor. *The flavonoids: Advances in research since 1986*. London: Chapman and Hall. 1994. https://doi.org/10.1007/978-1-4899-2911-2_15
11. Zheng J, Wu J, Chen J, Liu J, Lu Y, Huang C, Hu G, Wang X, Zeng Y. Therapeutic effects of quercetin on early inflammation in hypertriglyceridemia-related acute pancreatitis and its mechanism. Pancreatology. 2016; 16(2):200-210. https://doi.org/10.1016/j.pan.2016.01.005 PMid:26873426.
12. Mlcek J, Jurikova T, Skrovankova S, Sochor J. Quercetin and its anti-allergic immune response. Molecules. 2016; 21(5):623. https://doi.org/10.3390/molecules21050623 PMid:27187333 PMCid: PMC6273625.
13. Chis IC, Coseriu A, Simedrea R, Oros A, Nagy AL, Clichici S. *In vivo* effects of quercetin in association with moderate exercise training in improving streptozotocin-induced aortic tissue injuries. Molecules. 2015; 20(12):21770-21786. https://doi.org/10.3390/molecules201219802 PMid:26690102 PMCid: PMC6331973.
14. Gandhidasan R, Thamaraichelvan A, Baburaj S. Anti-inflammatory action of *Lannea coromandelica* by HRBC membrane stabilization. Fitoterapia. 1991; 62(1):81-83.
15. Yadav R, Yadav N, Kharya MD. Immunomodulation potential of *Andrographis paniculata* and *Tinospora cordifolia* methanolic extracts in combination forms. Int J Pharmacol Res. 2016; 6(1):29-40.
16. Ahirwal L, Singh S, Dubey MK, Bharti V, Mehta A, Shukla S. *In vivo* immunomodulatory effects of the methanolic leaf extract of *Gymnema sylvestre* in Swiss albino mice. Arch Biol Sci. 2015; 67(2):561-570. https://doi.org/10.2298/ABS141027018A
17. Abebe D, Karim A, Bitew H, Periasamy G. *In-vivo* evaluation of immunomodulatory activity of crude extract and solvent fractions of *Cyphostemma adenocaule* (Steud. ex A. Rich). Heliyon. 2022; 8(12):e12345. https://doi.org/10.1016/j.heliyon.2022.e12377 PMid:36590494 PMCid: PMC9798168.
18. Dashputre NL, Naikwade NS. Immunomodulatory activity of *Abutilon indicum* Linn on albino mice. Int J Pharm Sci Res. 2010; 1(3):178-184.
19. Singh S, Yadav CP, Noolvi MN. Immunomodulatory activity of butanol fraction of *Gentiana olivieri* Griseb. on Balb/C mice. Asian Pac J Trop Biomed. 2012; 2(6):433-437. https://doi.org/10.1016/S2221-1691(12)60071-9 PMid:23569945.
20. Fulzele SV, Satturwar PM, Joshi SB, Dorle AK. Study of the immunomodulatory activity of *Haridradi ghrita* in rats. Indian J Pharmacol. 2003; 35(1):51-54.
21. Arunabha M, Satish N. Evaluation of immunomodulatory activity of *Sesbania grandiflora* flowers extract in mice. Indones J Pharm. 2014; 25(4):277-282. https://doi.org/10.14499/indonesianjpharm25iss4pp277
22. Gokhale AB, Damre AS, Saraf MN. Investigations into the immunomodulatory activity of *Argyreia speciosa*. J Ethnopharmacol. 2003; 84(1):109-114. https://doi.org/10.1016/S0378-8741(02)00168-X PMid:12499085.
23. Puri A, Saxena R, Saxena RP, Saxena KC, Srivastava V, Tandon JS. Immunostimulant agents from *Andrographis paniculata*. J Nat Prod. 1993; 56(7):995-999. https://doi.org/10.1021/np50097a002 PMid:8377022.
24. Chandu AC, Kumar S, Bhattacharjee C, Debnath S, Kannan KK. Studies on immunomodulatory activity of *Aloe vera (Linn)*. Int J Appl Biol Pharm Technol. 2011; 2:19-22.
25. Gaur K, Kori ML, Nema RK. Comparative screening of immunomodulatory activity of hydro-alcoholic extract of *Hibiscus rosasinensis* Linn. and ethanolic extract of *Cleome gynandra* Linn. Glob J Pharmacol. 2009; 3(2):85-89.
26. Shukla S, Mehta A, John J, Mehta P, Vyas SP, Shukla S. Immunomodulatory activities of the ethanolic extract of *Caesalpinia bonducella* seeds. J Ethnopharmacol. 2009; 125(2):252-256. https://doi.org/10.1016/j.jep.2009.07.002 PMid:19607900.
27. Rao CS, Raju C, Gopumadhavan S, Chauhan BL, Kulkarni RD, Mitra SK. Immunotherapeutic modification by an Ayurvedic formulation Septilin. Indian J Exp Biol. 1994; 32:553-558.

28. Bascones-Martinez A, Mattila R, Gomez-Font R, Meurman JH. Immunomodulatory drugs: oral and systemic adverse effects. Med Oral Patol Oral Cir Bucal. 2013; 19(1):e24. https://doi.org/10.4317/medoral.19087 PMid:23986016 PMCid: PMC3909428.
29. Singh D, Tanwar H, Jayashankar B, Sharma J, Murthy S, Chanda S, Singh SB, Ganju L. Quercetin exhibits adjuvant activity by enhancing Th2 immune response in ovalbumin-immunized mice. Biomed Pharmacother. 2017; 90:354-360. https://doi.org/10.1016/j.biopha.2017.03.067 PMid:28380410.
30. Turedi S. Protective/preventive effects of quercetin against cyclophosphamide-induced hepatic inflammation, apoptosis and fibrosis in rats. In: *Hepatology Forum.* 2023; 4(3):135141. https://doi.org/10.14744/hf.2023.2023.0026 PMid:37822313 PMCid: PMC10564257.
31. Askenase PW, Van Loveren H. Delayed-type hypersensitivity: activation of mast cells by antigen-specific T-cell factors initiates the cascade of cellular interactions. Immunol Today. 1983; 4(9):259-264. https://doi.org/10.1016/0167-5699(83)90046-4 PMid:25290305.
32. Männel DN, Falk W. Interferon-γ is required in activation of macrophages for tumor cytotoxicity. Cell Immunol. 1983; 79(2):396-402. https://doi.org/10.1016/0008-8749(83)90082-5 PMid:6307534.
33. Farhadi L, Mohammadi-Motlagh HR, Seyfi P, Mostafaie A. Low concentrations of flavonoid-rich fraction of shallot extract induce delayed-type hypersensitivity and TH1 cytokine IFNγ expression in Balb/c mice. Int J Mol Cell Med. 2014; 3(1):16-25.
34. Liang Y, Han Y, Xiao L, Su Y, Bao T, Ji X, Jia L, Zhang J. Coenzyme Q10 modulates the immunity by enhancing mononuclear macrophage, NK cell activity, and regulating gut microbiota. Front Nutr. 2025; 12:1504831. https://doi.org/10.3389/fnut.2025.1504831 PMid:40165818 PMCid:PMC11955478.

Author Contribution

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