ACUTE AND CHRONIC ANTI-INFLAMMATORY EFFECTS OF MEKONG CISSUS CAPSULES IN EXPERIMENTAL ANIMALS

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Inflammation is a biological response of the immune system that can be triggered by a variety of factors, including pathogens, damaged cells, and toxic compounds. These factors may induce acute and/or chronic inflammatory responses leading to tissue damage or disease. Current anti-inflammatory drug groups have not met treatment effectiveness and cause many unwanted side effects for patients. Therefore, this study was conducted to evaluate the anti-inflammatory effect of Mekong Cissus capsules in an experimental study. Before carrageenin-induced acute edema, Wistar rats were randomly divided into four groups (normal, positive control, Mekong Cissus capsules 168 and 504 mg/kg/24h) and given water/test solution for five consecutive days. The results showed that Mekong Cissus capsules at 504 mg/kg/24h had the effect of reducing the volume of peritoneal exudate and the number of leukocytes in the fluid after injection of a mixture of carrageenin and formaldehyde, similar to aspirin, and also tended to reduce the volume of carrageenin-induced mouse paw edema. However, Mekong Cissus capsules have not shown any effect against chronic inflammation caused by asbestos in Swiss mice. This study demonstrated the potential in vivo efficacy of Mekong Cissus capsules in the treatment of inflammatory diseases as a promising therapeutic product.

Keywords: Mekong Cissus capsules, acute anti-inflammatory effects, chronic anti-inflammatory effects, herbal medicine, *Wistar* rats, *Swiss* mice.

I. INTRODUTION

Inflammation is a reaction of the body in connective tissue expressed by local phagocytosis, which has the effect of eliminating inflammatory agents and repairing damage; at the same time, it is accompanied by pathological manifestations, acting as the body's first line of defense against harmful stimuli.[1] Inflammation has four external manifestations: swelling, heat, redness, pain, and disruption of body functions. Inflammation is both a protective response of the body against pathogens and a pathological reaction because the inflammatory process causes damage, necrosis, and organ dysfunction, which can be at a dangerously severe level.[1] The etiologies of inflammation can be infectious (bacteria, viruses, and other microorganisms) or non-infectious (such as physical: burn, physical injury, lionizing radiation; Chemical: toxins, alcohol, chemical irritants; biological: damaged cells, and psychological: excitement). Inflammatory reactions are classified in many ways; the most commonly used clinical method is classification by time. Acute inflammation is

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short-lived (a few minutes to a few days) and is characterized by secretions containing a lot of plasma proteins and the exudation of many neutrophils.[2] In acute inflammation, circulatory disorders occur first, with arteriolar constriction occurring in a very short period of time, followed by arteriolar dilation and increased vascular permeability due to endothelial cell contraction, creating gaps between cells, facilitating the extravasation of cells and plasma proteins. Chronic inflammation that may last for months or even years when acute inflammation fails to settle, and subacute which is a transformational period from acute to chronic, lasting from 2 to 6 weeks.[3] Chronic inflammation is characterized by infiltration of macrophages and lymphocytes. Granulomas begin when the monocytes, unable to sequester the inflammatory agent, differentiate into epitheloid cells, which are cells that lack phagocytic capacity but can engulf small plaques.[3] Changes in inflammatory tissue include: release of chemical mediators, circulatory and metabolic disorders, proliferation of capillaries and cells in connective tissue to form granulomas. The main groups of drugs used to treat inflammation today are corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs). These groups of drugs have a fast, strong anti-inflammatory effect but cause many unwanted effects such as gastric and duodenal ulcers, bleeding, metabolic disorders, kidney toxicity, and ototoxicity. Therefore, the research direction of natural origin drugs is receiving much attention and has achieved certain successes. Some herbs containing aponin, flavonoid, alkaloid, polysaccharide, components which have been proven to have anti-inflammatory effects, such as *Siegesbeckia orientalis* L., *Panax ginseng* CA Mey, *Aesculus chinensis* Bge.[4,5]

In this study, we used Mekong Cissus capsules with the main ingredient being *Cissus quadragularis* L. extract. *Cissus quadragularis* L. belongs to the family Vitaceae and is a climbing vine. This species is often distributed in hot and humid climates such as southern Vietnam, India, Arabia, Thailand, and Africa. Chemical composition of *Cissus quadragularis* L. includes: calcium oxalate, carotene (267mg), ascorbic acid (vine and stem have 398mg; stem fiber has 232mg; soybean juice has 479mg), 3-ketosteroid.[6] According to traditional medicine, *Cissus quadrangularis* L. has a cooling effect, aids digestion (leaves and young shoots), and enriches blood (whole plant). *Cissus quadrangularis* L. is commonly used to relieve bone and joint pain and promote bone health. Several studies have been conducted to evaluate the pharmacological effects of *Cissus quadrangularis* L., showing that *Cissus quadrangularis* L. protects against isoniazid-induced liver damage in mice, reduces chronic ulcers. However, there is a lack of studies demonstrating the anti-inflammatory effects of *Cissus quadrangularis* L. in Vietnam. Therefore, we conducted this study to evaluate the acute and chronic anti-inflammatory effects in vitro, providing further basis for the development of anti-inflammatory drugs from *Cissus quadrangularis* L.

II. MARTERIAL AND METHODS

1. Subjects

Plant material

Mekong Cissus is formulated as 400mg capsules, containing mainly Cissus quadrangularis L. extract (1ml of extract is equivalent to 6g of medicinal material).

Drug and chemicals

The control drug of the acute inflammation model was aspirin 500mg (trade name Aspirin pH8 enteric-coated tablets), product

of Mekophar Chemical - Pharmaceutical Joint Stock Company, Vietnam. The control drug of the chronic inflammation model was methylprednisolone 16mg tablets (brand name Medrol) from Pfizer, Italy. We induced inflammation using Carrageenin powder from BHD Chemicals Ltd., UK. 0.9% NaCl infusion solution of B. Braun Company, Vietnam. Protein quantification kit from Hospitex Diagnostics, Italy. Plethylmometer No 7250 of Ugo-Basile, Italy; Erba Semi-Automatic Biochemistry Analyzer from India; Exigo-VET automatic hematology analyzer by Exigo, Sweden; Japanese four-digit electronic scale.

Animals

Swiss mice, both genders, healthy, weighing 20 ± 2g, provided by the National Institute of Hygiene and Epidemiology (NIHE). *Wistar* rats, both genders, healthy, weighing 180 ± 20g, provided by Dan Phuong Laboratory Animal Supply Center - Hanoi. Animals were grouped into individual cages of ten animals each and housed under standard room conditions (temperature 27 ± 2°C; humidity 80 ± 10%; 12-h light/dark cycle). After randomized grouping and before initiation of the experiment, animals were allowed to feed on the standard diet and water ad libitum, and were acclimatized to the laboratory conditions for 7 days in the Department of Pharmacology, Hanoi Medical University.

2. Methods

Carrageenin-induced acute inflammation model

Group *Wistar* rats were randomly divided into four groups, ten rats in each group, and were orally treated for 5 days as follows:

- Group 1 (normal control group): distilled water at 1 mL/100g b.w.
- Group 2 (Aspirin): Aspirin at 200 mg/kg b.w.
- Group 3 (MC-168): Mekong Cissus capsules at 168 mg/kg b.w.
- Group 4 (MC-504): Mekong Cissus capsules at 504 mg/kg b.w.

After 5 days, animals were induced with inflammation by subcutaneous injection of 1% Carrageenin solution (volume 0.05 mL/mouse) into the sole of the right hind paw.[7] The volume of the mouse paw (measured at the exact location) was measured using Plethylsmometer No 7250 of Ugo-Basile, Italy, at pre-injection (V0), 2, 4, 6, and 24 hours after injection (V1, V2, V3, V4). The increase in paw volume of each mouse was calculated using the Fontaine formula:

$$\Delta V\% = \frac{V_t - V_0}{V_0} \times 100$$

The anti-inflammatory effect of the drug is evaluated by its ability to inhibit the edema reaction:

$$I\% = \frac{\Delta \bar{V}_c\% - \Delta \bar{V}_t\%}{\Delta \bar{V}_c\%} \times 100$$

Carrageenin and formaldehyde mixture induced acute peritonitis model

Wistar rats were randomly divided into four groups, ten rats in each group, and were orally treated for 5 days as follows:

- Group 1 (normal control group): distilled water at 1 mL/100g b.w.
- Group 2 (Aspirin): aspirin at 200 mg/kg b.w.
- Group 3 (MC-168): Mekong Cissus capsules at 168 mg/kg b.w.
- Group 4 (MC-504): Mekong Cissus capsules at 504 mg/kg b.w.

After 5 days, animals were injected intraperitoneally with a Carrageenin solution (containing 50mg Carrageenin and 1.4ml formaldehyde) to induce local inflammation.[8] Twenty-four hours after the intraperitoneal injection, *Wistar* rats were euthanized, and their abdominal cavities were opened to collect the inflammatory fluid. Volume, number of

leukocytes per ml, and protein content in the inflammatory exudate will be quantified.

Asbestos-induced chronic inflammation model

Swiss mice were randomly divided into four groups, ten rats in each group. Each mice was induced to become inflamed by implanting sterile (120°C for 1 hour) asbestos fibers (6mg) immersed in 1% Carrageenin solution into the nape of the neck.[9] After, mice were orally treated for 10 days as follows:

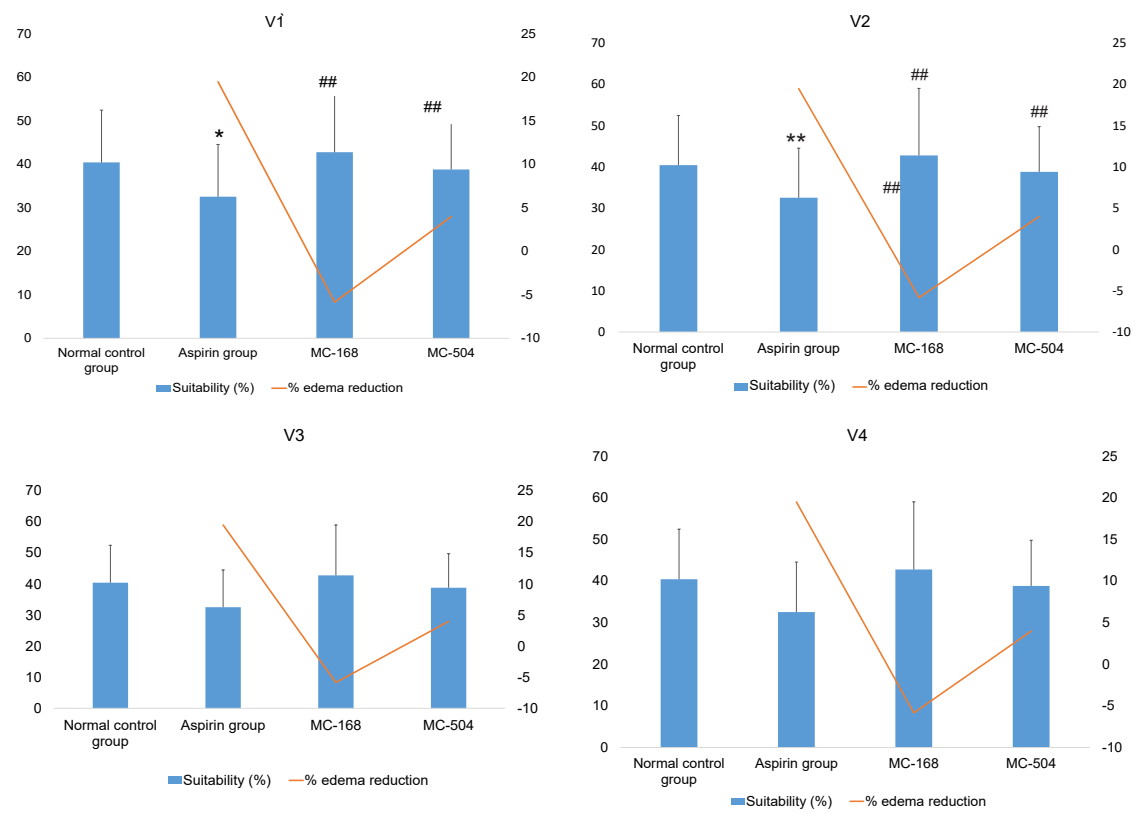
- Group 1 (normal control group): distilled water at 0.2 mL/10g b.w.
- Group 2 (Methylprednisolone): methylprednisolone at 10 mg/kg b.w.
- Group 3 (MC-288): Mekong Cissus capsules at 288 mg/kg b.w.
- Group 4 (MC-864): Mekong Cissus capsules at 864 mg/kg b.w.

After 10 days, the granulomas were collected for wet weight, and three tumors from each group were randomly selected for histopathological examination. The remaining granulomas were dried at 56°C for 18 hours, and the dry weight was reweighed.

Statistical analysis

The data were expressed as the mean ± standard deviation (SD), and statistical analysis was carried out employing Student's T-test. In the study of histological grading, nonparametric tests (Mann-Whitney U test) were used. Both analyses were performed using SPSS 25.0. The p-value < 0.05 was statistically significant.

III. RESULTS



**, **: p < 0.05; p < 0.01 compared to normal control group*

##, ###: p < 0.01; p < 0.001 compared to aspirin group

Chart 1. Effect of Mekong Cissus capsules on rat paw edema model

Chart 1 shows the change in paw edema of mice over time after injection of 1% Carrageenin. Aspirin demonstrated an acute anti-inflammatory effect, as evidenced by a significant reduction in paw volume of mice compared with the normal group at 2 hours (V1) ($p < 0.05$) and 4 hours (V2) ($p < 0.01$). Mekong Cissus at 504 mg/kg tended to reduce the volume of mouse paws compared with the aspirin group after 4 hours (V2), and 6 hours (V3); however, the difference was not statistically significant ($p > 0.05$).

Table 1. Effects of Mekong Cissus capsules on volume, leukocyte, and protein concentration in fluid

Group	Volume (mL/100g)	Protein (g/dL)	Leukocyte (G/L)
Normal control group	5.71 ± 1.91	3.26 ± 0.21	7.20 ± 2.22
Aspirin	3.42 ± 1.72*	3.18 ± 0.32	4.92 ± 1.57*
MC-168	5.29 ± 1.93#	3.40 ± 0.27	6.03 ± 2.67
MC-504	3.79 ± 1.44*	3.37 ± 0.34	5.36 ± 1.48*

**: p < 0.05 compared to normal control group; #: p < 0.05 compared to aspirin group*

Aspirin 200 mg/kg reduced the volume of peritoneal effusion compared with the normal group ($p < 0.05$). Similarly, the Mekong Cissus at 504 mg/kg also reduced the volume of peritoneal inflammatory fluid compared with the normal group ($p < 0.05$), but there was no difference with the Aspirin group. Meanwhile, Mekong Cissus at 168 mg/kg only tended to reduce the volume of peritoneal effusion ($p > 0.05$). Aspirin and Mekong Cissus groups at 504 mg/kg both tended to reduce protein content in peritoneal effusion; however, the difference was not statistically significant ($p > 0.05$). In contrast, these two groups had a statistically significant reduction in the number of leukocytes in the peritoneal effusion ($p < 0.05$) and no difference when compared with each other. Mekong Cissus group 168 mg/kg did not show these effects ($p > 0.05$).

Table 2. Effect of Mekong Cissus on granuloma weight before and after drying

Group	Pre-granuloma weight (mg)	Reduction rate compared to the normal group (%)	Posterior granuloma weight (mg)	Reduction rate compared to the normal group (%)
Normal control group	97.15 ± 35.89		27.18 ± 5.34	
Methylprednisolone	67.13 ± 22.11**	30.90	19.71 ± 6.20**	27.48
MC-288	97.41 ± 33.13#	-0.27	27.62 ± 8.65#	-1.62
MC-864	88.57 ± 24.53	8.83	25.97 ± 8.41	4.45

***: p < 0.01 compared to normal control group; p < 0.05 compared to methylprednisolone group*

Methylprednisolone reduced granuloma weight both before and after drying compared with the normal group by about 30% ($p < 0.01$). In the Mekong Cissus group, neither dose level showed any effect in reducing granuloma weight at 2 time points ($p > 0.05$).

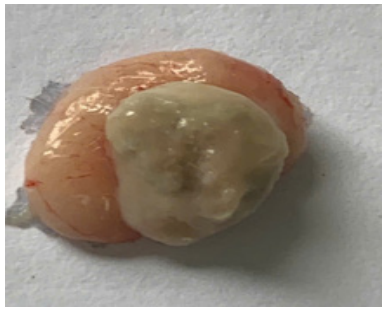
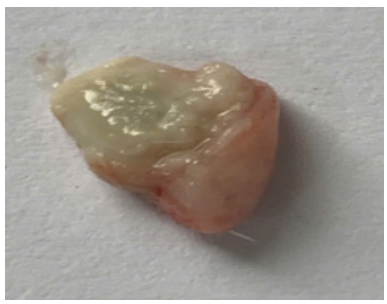
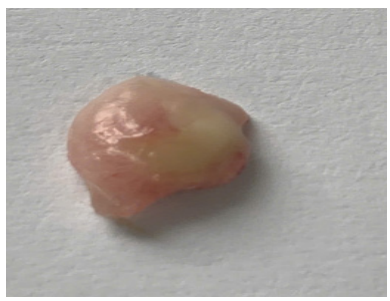
Group	Macroscopic image	
Normal control group	The granuloma is large in size, surrounded by many inflammatory tissues.	
Methylprednisolone	Granuloma size and inflammation were reduced compared with the normacontrol group.	
MC-288	The granuloma size and inflammation status were not special, so there was a normal control group.	
MC-864	Granulomas tended to decrease in size and inflammation compared with normal control group.	

Figure 1. Macroscopic image of granuloma

IV. DISCUSSION

Inflammation is the immune system's response to harmful stimuli, such as pathogens, damaged cells, toxic compounds, or irradiation.[10] Inflammation is therefore a defense mechanism that is vital to health, by removing injurious stimuli and initiating the healing process. Usually, during acute inflammatory responses, cellular and molecular

events and interactions efficiently minimize impending injury or infection. This mitigation process contributes to the restoration of tissue homeostasis and the resolution of the acute inflammation. However, uncontrolled acute inflammation may become chronic, contributing to a variety of chronic inflammatory diseases.[11] The inflammatory response is the coordinated activation of signaling pathways that regulate inflammatory mediator levels in resident tissue cells and inflammatory cells recruited from the blood.[1] Although inflammatory response processes depend on the precise nature of the initial stimulus and its location in the body, they all share a common mechanism, which can be summarized as follows: cell surface pattern receptors recognize detrimental stimuli; inflammatory pathways are activated; inflammatory markers are released; and inflammatory cells are recruited. In addition to chemical mediators secreted by cells at the site of inflammation, immune cells also secrete cytokines that block or amplify the inflammatory response. Cytokines are predominantly released from immune cells, including monocytes, macrophages, and lymphocytes. Inflammatory cytokines are classified as ILs, colony-stimulating factors (CSF), IFNs, TNFs, TGFs, and chemokines. They are produced by cells primarily to recruit leukocytes to the site of infection or injury.[12] However, excessive inflammatory cytokine production can lead to tissue damage, hemodynamic changes, organ failure, and ultimately death.

The essential mechanisms of acute inflammation are the release of chemical mediators such as histamine, serotonin, bradykinin, substance P... In the early phase (0 – 1h), histamine, serotonin, and bradykinin are the first mediators involved, whereas prostaglandins and various cytokines such as IL-1β, IL-6, IL-10, and TNF-α are implicated in the second phase.[13] And, subcutaneous injection of carrageenan into the rat paw caused a significant increase in substance P levels. While injection of substance P alone caused mild edema, coadministration of submaximal doses of carrageenan and substance P resulted in a synergistic exacerbation in the degree of inflammation.[14] A solution of carrageenan in saline injected subcutaneously in rats induces an acute swelling that becomes maximal 3 – 5 hours after the injection and subsides by 24 hours. Cutaneous inflammation can be assessed in tissue innervated by the lumbar dorsal root ganglion neurons (footpad) and by the trigeminal ganglion neurons (vibrissal pad).[15] This protocol focuses on the induction of inflammation in rats; however, it can easily be adapted for mice > 20g by using smaller injection volumes (i.e., 50 µl for the vibrissal pad and 25 – 50µl for the footpad) and a 3 mm biopsy punch.[16-18] In this study, we induced acute inflammation by injecting 1% carrageenan solution (50 µl) into the sole of right foot of mice. Inflammation was assessed through symptoms of swelling, heat, redness, and pain (mouse paws were swollen, increased in volume, and hyperresponsive to touch). Aspirin inhibits the enzyme cyclooxygenase (COX), reducing prostaglandin production, so it has an acute anti-inflammatory effect in phase 2 (> 1 hour). This was demonstrated in the results of the study: aspirin reduced the volume of the rat's paw at 2 and 4 hours after administration. Meanwhile, Mekong Cissus capsules at different doses did not show any effect in reducing the volume of mouse paw edema, suggesting that the anti-inflammatory mechanism of Mekong Cissus capsules is not related to the COX enzyme.

Carrageenan is a polysaccharide derived from red seaweed, commonly used as a thickening agent in food. Formaldehyde is a

known irritant and can cause tissue damage and inflammation upon exposure. It reacts with proteins and nucleic acids, leading to cellular stress and the activation of inflammatory pathways.[8] The inhalation of formaldehyde gas in even small quantities is followed by bronchitis and pneumonia. And, intraperitoneal injections of formalin cause peritonitis of a fibrino-haemorrhagic character. The inflammation that follows subcutaneous injections of formalin is characterized by intense exudation.[19] Formalin is, directly or indirectly, chemotactic for leucocytes. The first appearance of eosinophils, is followed by other polynuclear leucocytes, and last appear the large and small mononuclear leucocytes. Aspirin has the effect of stabilizing lysosomal membranes, preventing the release of mitotic enzymes. In addition, it also affects the mobility of leukocytes, inhibiting their movement to the site of inflammation. The above mechanisms are shown in the results of the study, aspirin significantly reduced the volume and number of leukocytes in peritoneal fluid compared with the normal control group. Similar effects were also observed in the Mekong Cissus capsule group at 504 mg/kg. This suggests that the mechanism of anti-inflammatory action of Mekong Cissus capsules induced by formaldehyde may be similar to that of aspirin.

Asbestos is the name given to six minerals that occur naturally in the environment as bundles of fibers that can be separated into thin, durable threads for use in commercial and industrial applications. Upon asbestos exposure, mesothelial cells release HMGB1 from the nucleus to the cytoplasm and extracellular space, where HMGB1 initiates an inflammatory response.[20] Asbestos has been classified as a known human carcinogen (a substance that causes cancer) by the U.S. Department of Health and Human Services (HHS), the U.S. Environmental Protection Agency (EPA), and the International Agency for Research on Cancer (IARC). In efforts to remove asbestos fibers, macrophages and mesothelial cells attempt to envelop and phagocytize these fibers, which causes a wide range of cytotoxic effects, including intracellular oxidation, DNA damage, cell cycle delay, cell death, and release of superoxide and cytokines.[20] Methylprednisolone has the effect of increasing the transcription of the synthesis gene lipocortin, a protein that inhibits the secretion of BC, IL-1 receptor antagonist. Furthermore, it inhibits the transcription of inflammatory cytokine synthesis genes, inhibits the release of chemical mediators, inhibits the synthesis of endothelial nitric oxide synthase (eNOS), and inhibits leukocyte migration and phagocytosis. Therefore, methylprednisolone significantly reduced granuloma mass after 10 days of subcutaneous implantation of asbestos fibers in the nape of mice. Mekong Cissus capsules have not been able to show this effect, so the mechanism may not be through gene transcription or eNOS inhibition.

Mekong Cissus capsules with the main ingredient *Cissus quadragularis* L., a perennial herb with medicinal properties distributed throughout the tropical world, are one of the most frequently used medicinal plants in India.[21] The plant consists of various constituents such as flavonoides like quercetin, daidzein and genistein, triterpenoids like friedelin, acid ascobic, stilbene derivatives like quadrangularin-A, resveratrol and piceatannol, iridoids like 6-0-meta-methoxy-benzozyl catapol, picroside and pallidol and phytosterols like β-sitosterol and calcium were identified as major constituents of the plant. The stem parts of the plant contain A and β-amyrins, β-sitosterol, ketosetosterol, phenols, tannins, vitamins, carotene, Calcium

oxalate, 31 methyl tritiacontanoic acid, taraxeryl acetate, taraxeroliso-pentadecanoic acid, calcium ions, and phosphorus.[21] Among them, components such as ascorbic acid, β-sitosterol, quercetin, and carotene have been shown to have anti-inflammatory effects through various mechanisms.[22–25]as a one of the basic exogenous vitamins, occurs in the body in the form of ascorbate, known for its strong antioxidant and anti-inflammatory properties. The presented review shows not only the importance of ascorbate as a free radical scavenger but also summarizes its antioxidant action based on other mechanisms, including the activation of intracellular antioxidant systems and its effect on the NFκB/TNFα pathway and apoptosis. Ascorbate interacts with small-molecule antioxidants, including tocopherol, glutathione, and thioredoxin; it can also stimulate biosynthesis and the activation of antioxidant enzymes, such as superoxide dismutase, catalase, or glutathione peroxidase. Moreover, ascorbate promotes the activity of transcription factors (Nrf2, Ref-1, AP-1 In this study, Mekong Cissus capsules at 504 mg/kg showed a tendency to suppress carrageenin-induced acute inflammation and reduce the volume of formaldehyde-induced intra-abdominal inflammatory fluid. These results suggest that it is a potential anti-inflammatory drug, especially in the acute phase.

V. CONCLUSION

Mekong Cissus capsules at 504 mg/kg exhibited an anti-inflammatory effect against carrageenan - formaldehyde-induced acute inflammation in experimental studies. A tendency of chronic anti-inflammatory effects have been observed at high dose (864 mg/kg) of Mekong Cissus capsules. To further clarify the anti-inflammatory mechanism of Mekong Cissus, further studies should be conducted to evaluate histopathology and the concentrations of inflammatory cytokines.

REFERRENCES

1. Chen L, Deng H, Cui H, et al. Inflammatory responses and inflammation-associated diseases in organs. *Oncotarget*. 2017;9(6):7204-7218. doi:10.18632/oncotarget.23208

2. Acute Inflammatory Response - StatPearls - NCBI Bookshelf. ResearchGate. Accessed October 2, 2025.

3. Pahwa R, Goyal A, Jialal I. Chronic Inflammation. In: *StatPearls*. StatPearls Publishing; 2025. Accessed October 2, 2025. http://www.ncbi.nlm.nih.gov/books/NBK493173/

4. Hong YH, Weng LW, Chang CC, et al. Anti-Inflammatory Effects of Siegesbeckia orientalis Ethanol Extract in In Vitro and In Vivo Models. *BioMed Res Int*. 2014;2014:329712. doi:10.1155/2014/329712

5. Zheng Q, Wang T, Wang S, et al. The anti-inflammatory effects of saponins from natural herbs. *Pharmacol Ther*. 2025;269:108827. doi:10.1016/j.pharmthera.2025.108827

6. Bafna PS, Patil PH, Maru SK, et al. Cissus quadrangularis L: A comprehensive multidisciplinary review. *J Ethnopharmacol*. 2021;279:114355. doi:10.1016/j.jep.2021.114355

7. Winter CA, Risley EA, Nuss GW. Carrageenin-induced edema in hind paw of the rat as an assay for antiiflammatory drugs. *Proc Soc Exp Biol Med Soc Exp Biol Med N Y N*. 1962;111:544-547. doi:10.3181/00379727-111-27849

8. Hunskaar S, Hole K. The formalin test in mice: dissociation between inflammatory and non-inflammatory pain. *Pain*. 1987;30(1):103-114. doi:10.1016/0304-3959(87)90088-1

9. Mann Jr. DE. Screening methods in pharmacology. By Robert A. Turner. Academic

Press Inc., 111 Fifth Ave., New York, N. Y., 1965. xv + 332 pp. 15.5 × 23.5 cm. Price $12. *J Pharm Sci*. 1965;54(9):1394-1394. doi:10.1002/jps.2600540943

10. Medzhitov R. Inflammation 2010: new adventures of an old flame. *Cell*. 2010;140(6):771-776. doi:10.1016/j.cell.2010.03.006

11. Zhou Y, Hong Y, Huang H. Triptolide Attenuates Inflammatory Response in Membranous Glomerulo-Nephritis Rat via Downregulation of NF-κB Signaling Pathway. *Kidney Blood Press Res*. 2016;41(6):901-910. doi:10.1159/000452591

12. Turner MD, Nedjai B, Hurst T, et al. Cytokines and chemokines: At the crossroads of cell signalling and inflammatory disease. *Biochim Biophys Acta*. 2014;1843(11):2563-2582. doi:10.1016/j.bbamcr.2014.05.014

13. Carrageenan-Induced Inflammation - an overview | ScienceDirect Topics. Accessed October 4, 2025.

14. Gilligan JP, Lovato SJ, Erion MD, et al. Modulation of carrageenan-induced hind paw edema by substance P. *Inflammation*. 1994;18(3):285-292. doi:10.1007/BF01534269

15. Fehrenbacher JC, Vasko MR, Duarte DB. Models of Inflammation: Carrageenan- or Complete Freund's Adjuvant-Induced Edema and Hypersensitivity in the Rat. *Curr Protoc Pharmacol Editor Board SJ Enna Ed--Chief Al*. 2012;0 5:Unit5.4. doi:10.1002/0471141755.ph0504s56

16. Cunha TM, Verri WA, Vivancos GG, et al. An electronic pressure-meter nociception paw test for mice. *Braz J Med Biol Res Rev Bras Pesqui Medicas E Biol*. 2004;37(3):401-407. doi:10.1590/s0100-879x2004000300018

17. Schreiber KL, Beitz AJ, Wilcox GL. Activation of spinal microglia in a murine model of peripheral inflammation-induced, long-lasting contralateral allodynia. *Neurosci Lett*. 2008;440(1):63-67. doi:10.1016/j.neulet.2008.05.044

18. Poh KW, Lutfun N, Manikandan J, et al. Global gene expression analysis in the mouse brainstem after hyperalgesia induced by facial carrageenan injection--evidence for a form of neurovascular coupling? *Pain*. 2009;142(1-2):133-141. doi:10.1016/j.pain.2008.12.029

19. Fischer MH. The toxic effects of formaldehyde and formalin. *J Exp Med*. 1905;6(4-6):487-518. doi:10.1084/jem.6.4-6.487

20. Zolondick AA, Gaudino G, Xue J, et al. Asbestos-induced chronic inflammation in malignant pleural mesothelioma and related therapeutic approaches-a narrative review. *Precis Cancer Med*. 2021;4:27. doi:10.21037/pcm-21-12

21. Sundaran J, begum R, Vasanthi M, et al. A short review on pharmacological activity of Cissus quadrangularis. *Bioinformation*. 2020;16(8):579-585. doi:10.6026/97320630016579

22. Gęgotek A, Skrzydlewska E. Antioxidative and Anti-Inflammatory Activity of Ascorbic Acid. *Antioxidants*. 2022;11(10):1993. doi:10.3390/antiox11101993

23. Wu S, Chen R, Chen J, et al. Study of the Anti-Inflammatory Mechanism of β-Carotene Based on Network Pharmacology. *Molecules*. 2023;28(22):7540. doi:10.3390/molecules28227540

24. Sun Y, Gao L, Hou W, et al. β-Sitosterol Alleviates Inflammatory Response via Inhibiting the Activation of ERK/p38 and NF-κB Pathways in LPS-Exposed BV2 Cells. *BioMed Res Int*. 2020;2020:7532306. doi:10.1155/2020/7532306

25. Li Y, Yao J, Han C, et al. Quercetin, Inflammation and Immunity. *Nutrients*. 2016;8(3):167. doi:10.3390/nu8030167