

ANTIOXIDANT ROLE OF PUNICALAGIN IN MANAGEMENT AND EARLY RECOVERY OF POST COVID-19 PATIENTS - A SYSTEMATIC REVIEW

Faiza Ismail¹, Saim Hasan², Abhishek Sharma³, Najmul Islam⁴

¹Tutor, Department of Biochemistry, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, Uttar Pradesh, India.

²Professor, Department of Anatomy, Shaheed Hasan Khan Mewati, Government Medical College, Nalhar, Nuh, Haryana, India.

³Professor, Government Medical College, Datia, Madhya Pradesh, India

⁴Professor, Department of Biochemistry, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, Uttar Pradesh, India.

Received : 15/09/2023
Received in revised form : 02/10/2023
Accepted : 11/10/2023

Keywords:

Punicalagin, antioxidant, Covid-19, Pomegranate peel extract.

Corresponding Author:

Dr. Saim Hasan,

Email: saimhasan99@gmail.com

ORCID: 0000-0002-1614-7491

DOI: 10.47009/jamp.2023.5.5.221

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2023; 5 (5); 1129-1133



Abstract

Background: Chronic inflammation is a factor in many diseases, such as cancer and cardiovascular illnesses, and it plays a crucial role in both health and disease. The COVID-19 epidemic has brought attention to the need for efficient therapies, and while conventional medications currently dominate research, natural substances like punicalagin from pomegranates provide intriguing alternatives. Punicalagin has strong anti-inflammatory and antioxidant effects that have an impact on immunological responses, different cell types, and the prevention of cell necrosis. Additionally, it targets important signaling pathways implicated in disorders that cause chronic inflammation. The objective is to investigate Punicalagin's antioxidant capacity in the treatment as well as rapid recovery of post-COVID-19 patients. **Materials and Methods:** Peer-reviewed articles published between 2000 until 2022 were searched for in PubMed, Google Scholar, and MedLine Plus. The articles were then evaluated for relevance to the subject and included. **Result:** Punicalagin, gallic acid, and ellagic acid are just a few of the bioactive substances that can be found in pomegranate peel, an often-overlooked food source. These substances exhibit exceptional antibacterial, antifungal, and antiviral characteristics, and they may be effective against COVID-19. **Conclusion:** Despite encouraging laboratory results, more study is needed to understand punicalagin's gastrointestinal destiny, molecular interactions and therapeutic uses.

INTRODUCTION

Health and disease are significantly influenced by inflammation, which is the body's response to numerous stressors. It comprises two unique phases: acute and chronic, each of which is defined by a different type of immunological reaction. Chronic inflammation, a factor in many diseases, can develop if acute inflammation is not controlled. Initiators, sensors, mediators, and effectors all participate in the inflammatory process^[1] and immune cells pattern recognition receptors play a critical role in identifying various stimuli. In order to fight infections and eliminate damaged cells, inflammatory cytokines are generated, immune cells are enlisted, and enzymes are used. Osteoarthritis, rheumatoid arthritis, osteoporosis, stomach ulcers, and diseases like atherosclerosis, Parkinson's disease, Alzheimer's disease, and diabetes can all be

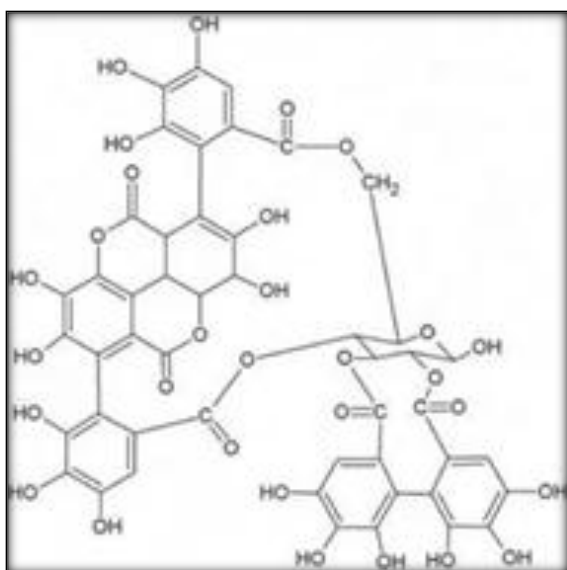
brought on by the dysregulation of the inflammatory response.

The COVID-19 pandemic has had a significant influence on the world, resulting in numerous fatalities, economic turmoil, and interruptions to daily life. Globally scientists and researchers are assiduously working on extensive drug discovery and analysis to create COVID-19 vaccines and treatments. However, conventional allopathic drugs, which are frequently linked to unfavorable side effects, make up the bulk of studied treatments. Despite the fact that there have been over 160 million COVID-19 instances documented, the possibility of using natural remedies to treat the virus has not received much attention. Thus in comparison to synthetic pharmaceutical drugs, natural chemicals from plants, notably polyphenols, has drawn interest for their affordability, bioavailability and decreased toxicity.

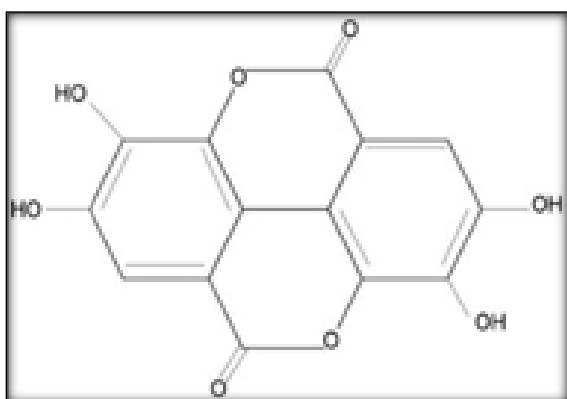
MATERIALS AND METHODS

In this review study, the titles and abstracts of articles published between 2000 and 2022 in reputable international scientific databases like Google Scholar, Science Direct, Scopus, and PubMed were searched for the keywords Punicalagin, bioavailability of Punicalagin, oxidative stress, metabolism of ellagitannins, Covid-19 patient recovery, role of Punicalagin in immune system.

Punicalagin: Punicalagin, one of the polyphenols found in pomegranates, has shown to have strong anti-inflammatory and antioxidant effects. Punicalagin, the most prevalent polyphenol in pomegranates, has demonstrated potential for reducing both acute and chronic inflammation. Its effects include altering immunological responses, having an impact on different cell types, and helping to avoid cell necrosis. Punicalagin, for instance, has been shown to suppress the expression of interleukin-2 and prevent the activation of nuclear factor of activated T cells in murine splenic CD4+ T cells. In conclusion, punicalagin, a substance found in pomegranates, has the potential to be used therapeutically and as a natural remedy for treating inflammation and related disorders.



Structure of Punicalagin.^[2]



Structure of Ellagic acid.^[2]

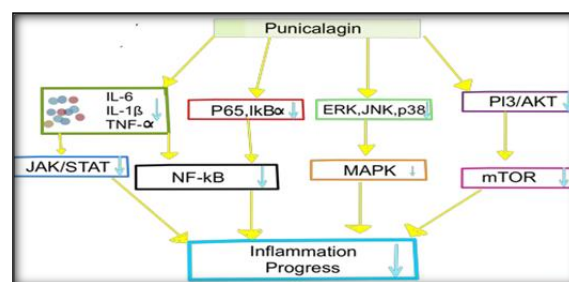
The pomegranate, or *Punica granatum* L., is a tropical fruit of Asian origins that has a long history of therapeutic use that dates back to 3000 BC. Greek, Chinese, Indian, and traditional medicine in Cuba and Cuba acknowledge its medicinal usefulness.^[2] The quantity of antioxidants in pomegranates raises the possibility of health benefits by treating oxidative stress in many living forms.

The nutritional and health benefits of this plant extend beyond its edible sections to encompass its non-edible parts, such as the peel and blossoms. Surprisingly, these inedible parts frequently have higher levels of bioactive substances. Pomegranate production around the globe exceeds 4.5 million tons, highlighting the fruit's economic importance. Surprisingly, the pomegranate peel, which was formerly thought to as agro-industrial trash, has a higher concentration of beneficial chemicals than the aril and seeds.^[3]

Nearly 50 phenolic components, including anthocyanins, catechins, and hydrolyzable tannins including punicalagin, gallic acid, and ellagic acid,^[4] may be found in pomegranate peel. Many other extraction techniques have been investigated, however polar solvents like ethanol have proven to be the most productive because of their potent antioxidant extraction properties while still maintaining safety standards.

The pomegranate has gained attention due to its historical relevance, health advantages, and economic value, notably due to the underutilized potential of its peel as a rich source of bioactive chemicals.

Anti-inflammatory role of Punicalagin: Punicalagin and its metabolites have shown anti-inflammatory properties via affecting a number of signaling pathways^[5] such as IL-6/JAK/STAT3, PI3K/Akt/mTOR, NF- κ B, MAPK, and others. These pathways present prospective targets for treating chronic disorders linked to inflammation and its symptoms.



Punicalagin has a number of molecular targets in inflammation^[5].

Antioxidant and antibacterial role of Punicalagin: Antioxidant and antibacterial qualities of pomegranate peel make it a valuable food^[6]. Its ability to fight against conditions like cancer and cardiovascular disorders that are linked to oxidative

stress is directly correlated with its antioxidant capability. On breast, prostate, and colon cancer cell lines, it has demonstrated anti-proliferative properties. Pomegranate peel extracts also showed strong antioxidant activity, which is due to their abundant phenolic content. In terms of antioxidant capacity, they fared better than extracts from other fruits like mango, kinnow, banana, and loquat.

Pomegranate peel extracts have also proven to have antibacterial qualities. *Giardia lamblia*, *Eimeria papillata*, as well as dangerous bacteria like *Staphylococcus aureus*, *Propionibacterium acnes*, *Bacillus subtilis*, *Streptococcus mutans*, *Shigella dysenteriae*, *Salmonella typhimurium*, and *Escherichia coli* have all been successfully eradicated by them.^[7]

Additionally, these extracts shown antifungal activity in the presence of fungi including *Penicillium expansum*, *Penicillium digitatum*, *Botrytis cinerea*, *Trichophyton mentagrophytes*, *T. rubrum*, *Microsporium canis*, and *M. gypseum*. Their potential for a variety of uses, from treating infections to providing dental care and food preservation, is suggested by their broad-spectrum antibacterial action.^[8]

Antiviral Role of Punicalagin in Covid -19 management: Pomegranate peel's capacity to prevent viral RNA replication has been linked to its substantial antiviral potential, especially against the influenza virus. Punicalagin compounds have shown substantial inhibitory action against viral RNA replication at doses up to 40 mg/ml.

Effective antiviral therapies are desperately needed in light of the COVID-19 pandemic's extremely contagious SARS-CoV-2 virus's appearance. Patients with COVID-19 cannot currently access any specific antiviral medications.^[9] The possible antiviral effects of secondary metabolites generated from fruits and vegetables are being investigated.

Additionally, urolithin A, a naturally occurring substance produced in the human gut microbiota, is present in pomegranate peel extracts that have showed promise in preventing S-glycoprotein-ACE2 interactions.

Gallic acid, ellagic acid, punicalagin, and punicalin from pomegranate peel extract may interact with important protein targets involved in the virus's entry into host cells, such as the SARS-CoV-2 spike glycoprotein and angiotensin-converting enzyme two, according to research by Surui et al. (2021). These results imply that punicalagin and punicalin may be taken into account for additional in vivo studies as COVID-19 therapy possibilities.

Punicalin and punicalagin have been shown to weaken the S-glycoprotein, which is essential for a virus to connect to a host cell's receptor, indicating that they may play a part in preventing virus-host cell interactions.^[10]

DISCUSSION

A complicated biological response called inflammation is important in both health and illness. It serves as the body's line of defense against a variety of stressors like infections, wounds, and poisons. Acute and chronic inflammation have two separate phases, making it a two-edged sword. While acute inflammation is a quick and protective reaction characterized by an increase in blood flow, the recruitment of immune cells, and the production of cytokines, chronic inflammation is a long-lasting, low-level activity that, if left unchecked, can result in a number of disorders.

Numerous diseases, including as cancer, rheumatoid arthritis, diabetes, cardiovascular illnesses, and neurological disorders, are linked to the emergence of a chronic inflammatory state. Interventions that effectively control inflammation therefore have the potential to significantly ameliorate these chronic illnesses.

The recognition of stimuli (initiators), the detection of inflammatory signals (sensors), the production of inflammatory mediators (cytokines), and the recruitment of immune cells (effectors) are all part of a carefully organized set of events that make up the inflammatory process. Immune cells like macrophages and dendritic cells include pattern recognition receptors (PRRs) that are essential for detecting numerous stimuli, including infections and injured cells.

The moment the inflammatory signals are recognized; a series of events are triggered. Immune cells are attracted to the site of infection or tissue injury as a result of the release of inflammatory cytokines. These immune cells, which include neutrophils, lymphocytes, and macrophages, release enzymes and other chemicals to fend off pathogens and eliminate damaged cells.

Chronic acute inflammation can develop if acute inflammation is not controlled. Inability to control acute inflammation can cause the inflammatory response to persist, resulting in chronic inflammation. Chronic diseases can start and advance as a result of this imbalance. For instance, the persistent inflammatory response in arthritis affects the joints and results in pain and tissue destruction. Similar to how it does in disorders like atherosclerosis, Parkinson's disease, Alzheimer's disease, and diabetes, chronic inflammation is a common trait in these diseases, where it promotes tissue damage and the development of the illness.

When compared to manufactured pharmacological medicines, these natural chemicals have advantages such as affordability, bioavailability, and lower toxicity.

The rich polyphenol punicalagin, which is present in pomegranates, has drawn attention for its significant anti-inflammatory and antioxidant activities. It has proven to be able to control immunological responses, have an impact on different cell types,

and stop cell necrosis. Punicalagin, for instance, has been demonstrated to decrease nuclear factor of activated T cells activation and limit the expression of interleukin-2 (IL-2) in murine splenic CD4+ T cells, indicating a potential function in controlling immunological responses.

This highlights the pomegranate peel's unrealized potential as a valuable source of bioactive compounds.

Pomegranate peel is an important dietary and medicinal resource since it demonstrates exceptional antioxidant and antibacterial qualities. In the context of illnesses like cancer and cardiovascular conditions, which are linked to the destructive effects of reactive oxygen species (ROS) on biological substrates like DNA, RNA, lipids, and plasma membrane proteins, its capacity to combat oxidative stress is particularly pertinent.

Pomegranate peel extracts have been shown in numerous studies to have anti-proliferative effects on a variety of cancer cell lines, including breast, prostate, and colon cancer. These extracts have additionally demonstrated strong antioxidant activity, outperforming extracts from other fruits like mango, kinnow, banana, and loquat.

Pomegranate peel extracts also demonstrated potent antimicrobial properties. Extracts from the pomegranate peel have also proven to have potent antibacterial and antifungal effects. They have been effective against a number of pathogenic bacteria, including *Salmonella typhimurium*, *Escherichia coli*, *Bacillus subtilis*, *Propionibacterium acnes*, *Shigella dysenteriae*, and *Bacillus subtilis*. They have also proven to be antifungal in their ability to combat fungi such *Penicillium expansum*, *Penicillium digitatum*, *Botrytis cinerea*, *Trichophyton mentagrophytes*, *T. rubrum*, *Microsporium canis*, and *M. gypseum*.^[11]

The effectiveness of pomegranate peel against the influenza virus is one of the noteworthy discoveries about this fruit's antiviral capabilities. The pomegranate peel's punicalagin chemicals have shown inhibitory effect against viral RNA replication, making them interesting candidates for antiviral treatments.

The development of the extremely contagious COVID-19-causing SARS-CoV-2 virus has made the need for efficient antiviral medications critical.^[12] The development of the extremely contagious COVID-19-causing SARS-CoV-2 virus has made the need for efficient antiviral medications critical. Because there are currently no particular antiviral medications for COVID-19, researchers are looking into secondary metabolites from fruits and vegetables as prospective therapeutic possibilities. In this situation, punicalin and punicalagin-rich pomegranate peel extracts have shown the capacity to reduce the virus's S-glycoprotein's affinity for the ACE2 receptor on host cells.

Additionally, studies have demonstrated that key protein targets involved in the virus's entrance into host cells, such as the SARS-CoV-2 spike

glycoprotein and angiotensin-converting enzyme 2 (ACE2),^[13] can interact with gallic acid, ellagic acid, punicalagin, and punicalin from pomegranate peel extract. These interactions imply that punicalagin and punicalin may require more in vivo testing as COVID-19 treatment options.

CONCLUSION

Punicalagin's ability to successfully treat chronic disorders linked to inflammation is supported by the processes presented in a convincing manner. But crucial topics that need to be covered in future study include: Understanding punicalagin's path in the digestive system and how bioactive substances are absorbed by cells still has to be better understood, therefore this area of research is in need of more attention.

Molecular interactions: Despite the effects research is urgently needed to delve into the real molecular interactions behind punicalagin's actions notwithstanding the effects that have been shown and the paths that have been suggested.

While many basic investigations employing punicalagin have been carried out in laboratories, further clinical studies are necessary to verify its potential advantages before developing treatment techniques involving it.

In conclusion, punicalagin, a polyphenol that is rich in pomegranates, has significant promise as a complimentary treatment for viral infections and conditions connected to inflammation. Pomegranate peel's ability to improve health and fight disease is highlighted by its broad anti-inflammatory and antioxidant actions as well as the wide range of bioactive chemicals present in pomegranate peel. To fully utilize punicalagin's therapeutic potential and maximize its positive effects on global health and wellbeing, more research and clinical investigations are required.

REFERENCES

1. Xu J, Cao K, Liu X, Zhao L, Feng Z, Liu J. Punicalagin Regulates Signaling Pathways in Inflammation-Associated Chronic Diseases. *Antioxidants*. 2022;11(1):29.
2. Valero-Mendoza AG, Meléndez-Rentería NP, Chávez-González ML, Flores-Gallegos AC, Wong-Paz JE, Govea-Salas M, Zugasti-Cruz A, Ascacio-Valdés JA. The whole pomegranate (*Punica granatum* L), biological properties and important findings: A review.
3. Espín JC, Larrosa M, García-Conesa MT, Tomás-Barberán F. Biological significance of urolithins, the gut microbial ellagic acid-derived metabolites: The evidence so far. *Evidence Based Complementary and Alternative Medicine*. 2013;2013:15.
4. Bialonska D, Kasimsetty SG, Schrader KK, Ferreira D. The effect of pomegranate (*Punica granatum* L.) byproducts and ellagitannins on the growth of human gut bacteria. *Journal of Agricultural and Food Chemistry*. 2009;57.
5. George NS, Cheung L, Luthria DL, Santin M, Dawson HD, Bhagwat AA, et al. Pomegranate peel extract alters the microbiome in mice and dysbiosis is caused by *Citrobacter rodentium* infection. *Food Science and Nutrition*. 2019;7:2565-2576.
6. Li Destri Nicosia MG, Pangallo S, Raphael G, Romeo FV, Strano MC, Rapisarda M, et al. Control of postharvest fungal

- rots on citrus fruit and sweet cherries using a pomegranate peel extract. *Postharvest Biology and Technology*. 2016;114:54-61.
7. Foss SR, Nakamura CV, Ueda-Nakamura T, Cortez DAG, Endo EH, Dias Filho BP. Antifungal activity of pomegranate peel extract and isolated compound punicalagin against dermatophytes. *Annals of Clinical Microbiology and Antimicrobials*. 2014;13:1-6.
 8. Smaoui S, Ben Hlima H, Mtibaa AC, Fourati M, Sellem I, Elhadeif K, et al. Pomegranate peel as phenolic compounds source: Advanced analytical strategies and practical use in meat products. *Meat Science*. 2019;158.
 9. Islam SS, Midya S, Sinha S, Saadi SMAI. Natural medicinal plant products as immune-boosters: A possible role to lessen the impact of COVID-19. *Case Studies in Chemical and Environmental Engineering*. 2021;4.
 10. Kumar S, Singh B, Kumari P, Kumar PV, Agnihotri G, Khan S, et al. Identification of multipotent drugs for COVID-19 therapeutics with the evaluation of their SARS-CoV2 inhibitory activity. *Computational and Structural Biotechnology Journal*. 2021;19:1998-2017.
 11. Annaka S. Political regime, data transparency, and COVID-19 death cases. *SSM Population Health*. 2021;15.
 12. Haidari M, Ali M, Ward Casscells S, Madjid M. Pomegranate (*Punica granatum*) purified polyphenol extract inhibits influenza virus and has a synergistic effect with oseltamivir. *Phytomedicine*. 2009;16:1127-1136.
 13. Suru R, Stojiljkovi P, Savikin K, Zduni G, Skrbic R. Pomegranate peel extract polyphenols attenuate the SARS-CoV-2 S-glycoprotein binding ability to ACE2 receptor: In silico and in vitro studies. *Bioorganic Chemistry*. 2021;114.