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Knowing the unknown medicinal benefits of *Punica granatum* L. on oral health - A Review

Review Article

Gunjan Kumar[1*], Samikshya Jena[2], Ranjan Mani Tripathi[3], Rajnish Kumar Verma[4], Mohammad Jalaluddin[5], Dheeraj Sharma[6]

1. Department of Public Health Dentistry, 4. Department of Pediatric & Preventive Dentistry, 5. Department of Periodontics and Oral Implantology, Kalinga Institute of Dental Sciences (KIDS), Kalinga Institute of Industrial Technology (KIIT) Deemed to be University, Bhubaneswar. Odisha, India.
2. Public Health Dentistry, Sai Laproscopic Hospital, Rourkela, Odisha, India.
3. Department of Public Health Dentistry, 6. Department of Oral and Maxillofacial Pathology & Oral Microbiology, Index Institute of Dental Sciences, Indore. India.

Abstract

For centuries, Ayurvedic medicines have been used for the treatment of large variety of diseases. Many types of plants are rich in medicinal properties and have been utilised to treat oral and systemic illnesses. A growing number of people are becoming interested in using different ayurvedic medications for dental health. *Punica granatum* L., often known as a "pomegranate," is a member of the Punicaceae family. According to researches, various extracts of pomegranate peels have been found to contain a broad range of phytochemicals. Pomegranates and their compounds have been suggested as a healthy substitute treatment for a variety of ailments. The combinatorial characteristics of these substances are much greater than the efficiency of the separate components. Pomegranate fruit has been shown to have antioxidative and anti-inflammatory properties. Ellagitannins is one of the most essential bioactive constituents, may combine with the intestinal microbiota and impact its metabolic activity. Certain pathogens, such as Clostridia species, S. aureus, and P. aeruginosa, have already been demonstrated to be inhibited by punicalin and punicalagin. Pomegranate is quickly gaining popularity as an antioxidant booster, antioxidants extracted from pomegranate are polyphenols, hydrolyzable tannins, and anthocyanins. The extracts were proven to be effective over several bacteria, methicillin-resistant and methicillin-sensitive *S. aureus, E. coli, S. typhi*, and other streptococci. Many studies have also shown positive results and more are still on the go. Even though there is a lot of information for antioxidant, antibacterial, anti-inflammatory, and antifungal activities, additional clinical trials are required to explore the unexplored properties of this fruit.

Keywords: *Pomegranate,* Plaque, Anti-inflammatory, Mouthrinse.

Introduction

For centuries, Ayurvedic medicines have been used for the treatment of large variety of diseases. Many types of plants are rich in medicinal properties and have been utilised to treat oral and systemic illnesses. A growing number of people are becoming interested in using different ayurvedic medications for dental health. (1) People are conscious of the potential risks of medication resistance as well as the negative impacts of prescribing an excessive amount antibiotics. Following nature's lead is therefore quite natural.(2)

Punica granatum L., belongs to the Punicaceae family and is commonly called as "pomegranate,". In the latter part of the 16th century, it was mentioned in Spanish America.(3) The fruit is mostly cultivated during winter season in the Northern Hemisphere and during spring and summer seasons in the Southern Hemisphere. Pomegranates are grown commonly in the Middle East, north and tropical Africa, Iran, the Indian subcontinent, Central Asia, Southeast Asia's drier regions, and the Mediterranean Basin. The fruit is spherical and has a dense crimson skin.(4) A whitish, skinny mesocarp creates compartments inside the husk, enclosing edible arils and seeds within. Due to an increased quantity of polyphenols, particularly anthocyanins, the arils are dark reddish in colour. Pomegranate is a potent and distinctive antioxidant, with stronger antioxidant capacity over vitamins E, A, and C due to its significant polyphenol content.(5) Among other regularly ingested polyphenol-rich drinks and fruit drinks, such as green tea, orange, grape fruit, or cranberry juice, its juice has the greatest antioxidant content. Pomegranate peel is the component of the fruit that is not consumable. Several studies have proved that the skin of a pomegranate is rich in compounds which have nutritious and medical values.(6) Near about 48 phenolic components has been recognised in the peel

*** Corresponding Author:**

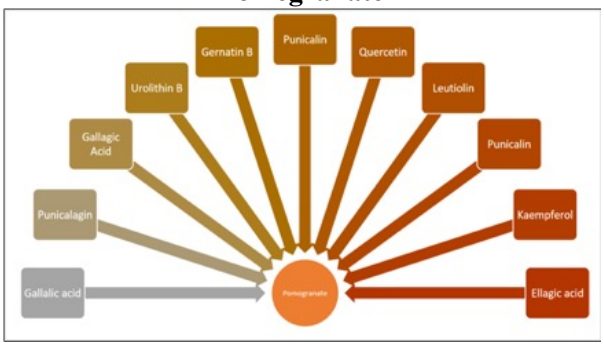
Gunjan Kumar

Department of Public Health Dentistry, Kalinga Institute of Dental Sciences (KIDS), Kalinga Institute of Industrial Technology (KIIT) Deemed to be University, Bhubaneswar-751024, Odisha, India.

Email Id: drgk1014@gmail.com

and other sections of the fruit those contain (polyphenols, flavonoids, ellagitannins, and proanthocyanidins). According to researches, various extracts of pomegranate peels have been found to contain a broad range of phytochemicals.(7)

Figure 1: Common bioactive molecules seen in Pomegranate



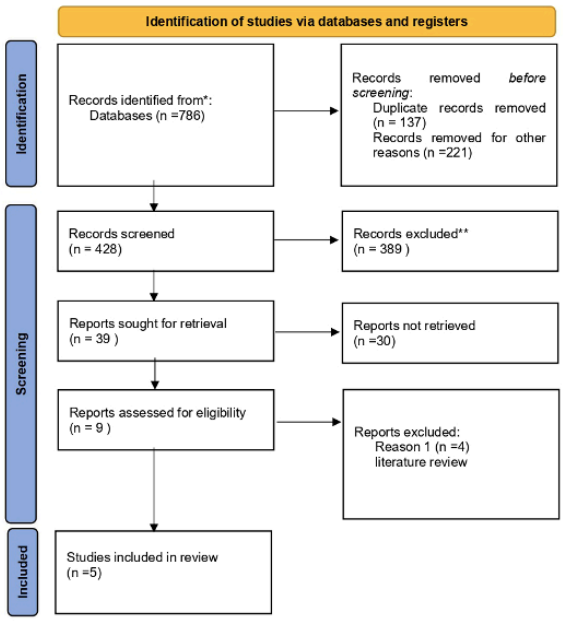
It is also known for its several beneficial properties, notably antibacterial, antifungal, anti-inflammatory, and antioxidant properties, for centuries. Pomegranates and their compounds have been suggested as a healthy substitute treatment for a variety of ailments. These behaviours are linked to ellagic acid and ellagitannins, particularly punicalagins, punicalins, and gallagic acid.(8) It has also been discovered that anthocyanins and a specific fatty acid profile contribute to the stated qualities.(9) The combinatorial characteristics of these substances are much greater than the efficiency of the separate components.(10) Thus this systematic review is conducted to assess the benefits of pomegranate on oral health.

Materials and Methods

Study Protocol and Registration

The PRISMA 2020 (Preferred Reporting Items for Systematic review and Meta analysis) guidelines were strictly followed.(Figure 2)

Figure 2: Prisma flowchart



Search Strategies

The research question was formulated as follows: what is the benefit of Pomegranate on oral health.

A systematic and comprehensive search was performed for research publications based on specific keywords analysing the benefit of Pomegranate on Oral health and published until June 2024. Using keywords from the Medical Subject Headings (MeSH), the full-text studies were searched electronically in 4 journal databases. The studies were analysed in PubMed, Scopus, Google scholar and Web of Science.

Two analysts conducted an electronic literature search on September 30, 2024. Suitable studies that met the inclusion criteria were searched using various databases. The Boolean operators used to combine the keywords were “OR” and “AND”. (Table 1) To eliminate duplicate studies Rayyan a tool for systematic review was utilised. Additionally two authors screened the title and abstract of the articles. The finalised articles were then thoroughly read by the same authors to access the eligibility of the article for according to the inclusion criteria of the study.

Eligibility Criteria

Articles in full text with study design either RCT or in vivo studies, and indexed in PubMed or Scopus or Google scholar or Web of Science, results analysing benefits of pomegranate on oral health, in English language was considered.

Data extraction and Synthesis

The articles which satisfied the eligibility criteria were selected and the data was manually extracted by the two authors(A1 and A2). The titles and summaries of the literature search results were reviewed separately by the primary evaluating author (A1) and a designated co-screener. (A2) and (A3) supervised and verified the selection process. In case of conflicts, discussions were held and, if necessary, either author (A2) or author (A3) was consulted before a decision was made. Subsequently, A1 and the selected co-screener evaluated each full-text article separately to decide whether it should be included and undergo further review. An exclusive Excel spreadsheet was created to collect the data obtained from the studies. The following information was collected individually by two separate authors(A4 and A5) using the data extraction sheet for each article included in the review, based on the eligibility requirements. The data included were- Author name, year of publication, name of the Journal for basic data further for methodological data study design, sampling method, sample size data, tool used assess the pain and the result outcome.

Results

Pomegranate plays a multifaceted role in oral cavity health, offering antibacterial, antioxidant, anti-inflammatory, wound-healing, and saliva-stimulating effects.(16) It is quickly gaining popularity as an antioxidant booster, antioxidants extracted from pomegranate are polyphenols, hydrolysable tannins and anthocyanins. These antioxidants aid in the binding of

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hazardous oxygen-containing molecules in our bodies known as free radicals and peroxides, which may sometimes disrupt DNA, cell membranes, and other cellular constituents.(17)

Table 1: Result summary of the included study

Journal	Year	Author	Study design	Sample size	Study Group	Material uesd in control	Part of Pomegranat	Form of Pomegranat	Result	Conclusion
J Int Oral Health (11)	2015	Sahgal A	RCT	40	Patients with chronic periodontitis	Placebo gel, Alovera gel, chlorhexidine gel	Seeds	Gel	Significant reduction in the quantitative bacterial levels in the	The gel containing Punica granatum extract was efficient in
J Dent Res Rev (12)	2016	Kiany F	RCT	104	Individuals with mild to moderate gingivitits	Persica mouthwashes, matrica mouthwash, placebo	Juice	Mouthwash	No significant difference in reducing plaque, but	Pomegranate mouthwash was beneficial in
Int Dent & Med J Adv Res (13)	2018	Kunte S,	Invitro	-	-	Chlorhexidine, Herbal toothpaste	-	Mouthwash	Zone of inhibition of the solutions against S. Mutans and Lactobacillu	pomegranate peel extract has antibacterial property
Pharm Med Sci (14)	2019	Darakhshan S	RCT	56	Patients with Recurrent apthous ulcer	Placebo	Peel	Gel	significantly effective in reducing the pain, ulcer size and healing	Pomegranate peel,pulp and seed extract in gel form if effective in
Advanced dental J (15)	2020	Zakaria M	RCT	42	Patients with Atrophic oral lichen planus	Steroid gel	Peel and Seed	Gel	Significant decrease in atrophic oral lichen planus	topical pomegranate seeds and peel extracts gel offer a new promising

Table 2: Role of Pomegranate on oral cavity

Antimicrobial Effects	Pomegranate extracts have shown antimicrobial activity against various oral pathogens, including Streptococcus mutans, which is a major contributor to tooth decay. Incorporating pomegranate extracts into mouthwashes or dental products could help in combating oral bacteria.(18)
Anti-inflammatory Properties	Compounds found in pomegranate, such as polyphenols and flavonoids, possess anti-inflammatory properties. These properties may aid in reducing inflammation associated with gum disease (gingivitis and periodontitis) and promoting gum health.(12)
Wound Healing	Pomegranate extracts have been studied for their potential to promote wound healing, which could be beneficial in oral surgery procedures or in treating oral ulcers.(13)
Periodontal Disease Management	Some research suggests that pomegranate extract may help in managing periodontal disease by reducing inflammation and inhibiting the growth of periodontal pathogens.(11)
Antioxidant Activity	The high antioxidant content in pomegranate, particularly polyphenols, helps neutralize free radicals and reduce oxidative stress in oral tissues. This antioxidant activity contributes to overall oral health by protecting against cellular damage and inflammation.(4)
Anticancer effect	Pomegranate has shown promise in the prevention and management of oral cancer through its rich array of bioactive compounds, such as polyphenols, flavonoids, tannins, and anthocyanins. (24)

Anti-microbial action

The antibacterial qualities of pomegranates (Punica granatum) have been extensively researched, especially in relation to dental health. Its potent antimicrobial properties are attributed to the abundance of polyphenols, flavonoids, tannins, and other bioactive substances found in it.(18)

Key Antibacterial Compounds are: Punicalagins are potent polyphenols with high antibacterial properties that are present in pomegranates. Another important polyphenol with proven antibacterial qualities is ellagic acid. Tannins are substances that have astringent qualities that aid in preventing the growth of microorganisms. Pomegranate's general antibacterial effects are attributed to flavonoids, which are well-

known for their antimicrobial and antioxidant properties.

These extracts were proven to be effective over several bacteria, methicillin-resistant and methicillin-sensitive S. aureus, E. coli, S. typhi, and other streptococci. According to studies, pomegranate extract reduces the capacity of these germs to cling to the tooth's structure.(19) It hinders prevalent streptococcus species, limiting them from generating compounds that promote the growth of fungus and numerous different bacteria. Pomegranate inhibits the plaque bacteria's capacity to cling to the tooth surface by interfering with the development of the compounds that the bacteria utilize as adhesive.(20)

Anti-inflammatory action

Its anti-inflammatory properties can be linked to its significant immunological control function over macrophages, T lymphocytes, and B lymphocytes(Ross et al). Grindwit et al. investigated the benefits of mixed preparations from *Centella asiatica* and Pomegranate peel on gingival tissue regeneration, subgibgivally after scaling and root planing in an in vivo study published in 2003. After 90 days, the therapy locations showed a propensity towards lowering plaque, with considerable reductions in the probing depth and attachment level in comparison to the control. They also discovered that IL-1 and IL-6 levels were considerably reduced at 3 and 6 months in comparison to start of the treatment.(12)

Wound Healing effect

Pomegranate has been studied for its possible health advantages, including its effects on wound healing, due to its significant presence of bioactive chemicals and antioxidants. Promotion of the synthesis of collagen: Collagen is an essential part of connective tissue and is essential to the healing of wounds.(13) Pomegranate extracts have been linked in certain studies to increased collagen synthesis, which can speed up the growth of new tissue and enhance wound closure. Stimulation of angiogenesis: Bringing nutrition and oxygen to the site of a wound requires angiogenesis, the growth of new blood vessels. It has been shown that chemicals present in pomegranates encourage angiogenesis, which can improve tissue regeneration and quicken recovery.(14)

Periodontal Disease Management

Pomegranate has garnered interest for its potential role in managing periodontal disease, a condition characterised by inflammation and infection of the gums and supporting structures of the teeth. Pomegranates include substances called ellagitannins and punicalagins that have been shown to have antibacterial activity against bacteria linked to periodontal disease, such as Aggregatibacter actinomycetemcomitans and Porphyromonas gingivalis. Pomegranate extract may help maintain gum health and stop the advancement of periodontal disease by lowering the bacterial load in the oral cavity.(11)

Periodontal disease is mostly responsible for the onset and progression of chronic inflammation. Strong anti-inflammatory polyphenols found in pomegranates can help lessen gum swelling and inflammation. Pomegranate may lessen periodontal disease symptoms and encourage tissue healing by regulating the inflammatory response.(21)

Gingival tissue regeneration: Some studies suggest that pomegranate extracts may stimulate the regeneration of gum tissue damaged by periodontal disease. Compounds found in pomegranate, such as epigallocatechin gallate (EGCG) and urolithins, have been shown to promote fibroblast proliferation and collagen synthesis, which are essential processes for tissue repair and regeneration in the gums.(13)

Antioxidant Activity

Pomegranates are known for having a high level of antioxidants, which may have various advantages for dental health. Oxidative stress is a persistent threat to the oral cavity, originating from a variety of sources including dietary variables, microbiological activity, and environmental contaminants.(13) Antioxidants found in pomegranates include vitamin C, flavonoids, and polyphenols including punicalagins and ellagic acid. These antioxidants can scavenge free radicals and lessen oxidative damage to oral tissues. The anti-inflammatory and tissue-destroying enzymes in the gums have been demonstrated to be inhibited by pomegranate antioxidants, which may prevent the advancement of periodontal disease.(4) The anti-inflammatory and tissue-destroying enzymes in the gums have been demonstrated to be inhibited by pomegranate antioxidants, which may prevent the advancement of periodontal disease. Chronic oxidative stress is a risk factor for oral cancer development. Pomegranate antioxidants have been studied for their potential chemopreventive effects against oral cancer by inhibiting the growth of cancer cells and inducing apoptosis (cell death) in malignant cells.(14)

Anticancer Activity

Pomegranate's wide range of bioactive substances, including polyphenols, flavonoids, tannins, and anthocyanins, has demonstrated promise in the management and prevention of oral cancer. Antioxidants, which are rich in it, aid in reducing oxidative stress and neutralising free radicals. Oxidative stress can cause DNA alterations and damage, which can aid in the development of cancer. Pomegranate may reduce the incidence of mouth cancer by lowering oxidative damage.(19)

Oral cancer development is significantly predisposed to by chronic inflammation. The anti-inflammatory properties found in pomegranates can aid in reducing oral cavity inflammation. Inflammation reduction can reduce the chance that oral tissues will develop cancerous changes. Research has demonstrated that pomegranate extracts can stop oral cancer cells from proliferating. Cell cycle arrest may result from the bioactive chemicals in pomegranates interfering with the cell cycle. As a result, cancer cells are unable to divide and spread.(22)

Programmed cell death, or apoptosis, is a technique that can be used to destroy cancer cells. Pomegranate components, namely punicalagins and ellagic acid, can trigger oral cancer cells' apoptotic pathways, killing the cells and slowing the growth of tumours. The development of new blood vessels, or angiogenesis, is essential for the growth and spread of tumours. It has been discovered that pomegranate contains anti-angiogenic qualities, which means it can prevent the creation of new blood vessels that provide nutrients to tumours.(23)

One of the biggest obstacles to treating cancer is metastasis, or the spread of cancer cells to other areas of the body. By limiting the ability of oral cancer cells to spread, pomegranate chemicals can help keep the disease localised in its initial site and stop it from spreading to other locations. Clinical studies on pomegranate and oral cancer are limited, the existing research suggests potential benefits.(12) Pomegranate affects a number of biological signalling pathways linked to the development of cancer. For example, it can block the NF-κB pathway, which is frequently linked to inflammation and the ability of cancer cells to survive. Pomegranate can inhibit the development and survival of cancer cells via modifying several mechanisms.(24)

Epigenetic modifications, or variations in gene expression without alterations to the DNA sequence, are influenced by chemicals found in pomegranates. These changes may have an impact on the expression of genes that are involved in the activation and repression of cancer, which may aid in the detection and management of the disease.(25)

Discussion

Despite the encouraging outcomes of the great majority of randomised clinical trials using P. granatum products to treat gingivitis, it is still important to assess the actual physiological effects of these medications. Pharmacokinetic and toxicokinetic studies of mouthwashes containing P. granatum are crucial in this regard to guarantee the products' efficacy and safety. Some clinical investigations indicate that natural, even though there is a lack of sophisticated pharmacological data.

Conclusion

Pomagranate has a spectacular gift of nature. It has the potential to provide numerous health benefits. Substantial health benefits of it has recently gained popularity among the public. But then also very little is known about its dynamic benefits in the field of medicine. This fruit has a lot, which is yet to be explored. Only the juice fruit is being utilized,which commercially available at ease. The leaves, flowers, peel and oil from seeds are yet to be explored. Its components work harmoniously to boost up the fruit's health benefits. Many clinical trials are being conducted in current time to prove the efficacy of the fruit for different types of conditions. Many studies have also shown positive results and more are still on the go.

Even though there are a lot of information for antioxidant, antibacterial, antiinflammatory, and antifungal activities, additional clinical trials are required to explore the unexplored properties of this fruit.

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