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POMEGRANATE AS A BIOACTIVE TREASURE: A COMPHREHENSIVE REVIEW OF ITS ANTIOXIDENT AND ANTIMICROBIAL MECHANISM

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ABSTRACT:

Pomegranate (Punica granatum L.) peel, a by-product of the fruit industry, is rich in bioactive compounds and possesses remarkable medicinal potential. This review highlights the antioxidant and antimicrobial properties of pomegranate peel and its importance in promoting human health. The peel contains a high amount of polyphenols, flavonoids, tannins, and ellagitannins, which are responsible for its strong free radical scavenging and antibacterial activities. It has been proven effective against several pathogenic microorganisms, making it a useful natural alternative to synthetic preservatives and antibiotics. Additionally, the bioactive compounds present in the peel exhibit anti-inflammatory and cytoprotective properties, making it valuable for pharmaceutical, cosmetic, and food industry applications. Overall, this review emphasizes the potential of pomegranate peel as a natural source of antioxidants and antimicrobials and encourages further research for its industrial and medical utilization.

KEYWORDS:

Antimicrobial activity, Antioxidants, Bioactive compounds, Natural therapeutics, Pharmacological potential, Pomegranate peel, Punica granatum.

1. INTRODUCTION:

Pomegranate (Punica granatum L.), belonging to the family Lythraceae and genus Punica, stands as one of humanity's oldest cultivated fruits, with its origins tracing back to Persia (modern-day Iran) around 3000 B.C. This ancient fruit has traversed millennia and continents, spreading from its native regions to encompass Asia, North Africa, the Mediterranean basin, and eventually North and South America and the Caucasus region (1). Today, pomegranate cultivation has expanded globally, with an estimated total cultivation area exceeding 300,000 hectares and an annual production of approximately 3.8 million tons as of 2017 (2). India emerged as the world's largest pomegranate producer in 2018, with a cultivation area of 234,000 hectares yielding 2.84 million metric tons (3).

Pomegranates are becoming more and more popular throughout the world for reasons other than their unique flavour and nutritional value. For thousands of years, pomegranates have been an essential part of traditional medical systems in many different countries. Their therapeutic qualities were acknowledged long before they were validated by contemporary science. Pomegranate peel has been used medicinally throughout history. The Romans used it as an anthelmintic, while ethnic groups in the Middle East and South America used boiled pomegranate peel to cure diarrhoea. Pomegranate peel is also acknowledged by Ayurvedic medicine as a successful treatment for mouth infections.

These historical benefits have been confirmed by current scientific research, which has shown pomegranates to be a real gold mine of bioactive chemicals. Juice, seeds, and peels (which make about 26–30% of the fruit's weight) are its three main constituents. However, significant amounts of by-products are produced during industrial juice processing; pomegranate peel alone makes up almost half of the fruit's mass. This corresponds to an annual production of about 1.6 million tonnes of pomegranate peel trash worldwide. By-products from the processing of fruits and vegetables make up 25% to 30% of the raw materials. Skin, rind, seeds, and pomace are good sources of dietary fibre, polyphenols, and other notable bioactive compounds like carotenoids.

The disposal of such massive quantities of pomegranate peel waste presents significant environmental challenges, contributing to resource wastage while negatively impacting natural resources such as land and water. Paradoxically, this "waste" material harbors exceptional nutritional and medicinal value. Pomegranate peel is extraordinarily rich in bioactive metabolites, particularly polyphenolic compounds, with total phenolic content ranging from 18 to 510 mg/g dry matter depending on species, extraction solvents, and methodologies employed. The peel fraction contains significantly higher concentrations of bioactive compounds compared to the edible portions of the fruit, making it a prime candidate for valorization and functional food development.

The phytochemical profile of pomegranate peel encompasses a broad range of bioactive constituents, including ellagitannins, flavonoids, phenolic acids, dietary fiber, alkaloids, vitamins, and minerals. Among these, ellagitannins represent the predominant class of polyphenols, with punicalagin identified as the characteristic and most abundant compound, present in concentrations ranging from 16.67 to 245.47 mg/g dry matter. Other significant ellagitannins include punicalin, corilagin, pedunculagin, castalagin, corilagin, gallagyl dilactone, and tellimagrandin. The flavonoid fraction encompasses quercetin, catechin, kaempferol, granatin A, and granatin B, while phenolic acids identified include gallic acid, ellagic acid, protocatechuic acid, chlorogenic acid, syringic acid, ferulic acid, caffeic acid, vanillic acid, p-coumaric acid, and cinnamic acid.

Pomegranate peel offers broad-spectrum antibacterial activity against a variety of pathogenic microorganisms in addition to its antioxidant qualities. Both Gram-positive and Gram-negative bacteria, such as Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, and Salmonella species, as well as fungal pathogens, such as Candida albicans, Penicillium digitatum, and Fusarium sambucinum, have been shown to be susceptible to the antimicrobial's effectiveness (4). Pomegranate peel compounds have a variety of antimicrobial mechanisms, such as inhibition of enzyme activity, precipitation of membrane proteins, depletion of metal ions, disruption of bacterial membrane integrity, interference with bacterial metabolism, and inhibition of biofilm formation.

Pomegranate peel has emerged as a promising natural source for the development of functional foods, nutraceuticals, pharmaceutical formulations, and biomedical materials due to the convergence of traditional knowledge and contemporary scientific findings. Pomegranate peel bioactive components have been shown in numerous in vitro and in vivo studies to offer a variety of health advantages, including as anti-inflammatory, anticancer, cardioprotective, hepatoprotective, neuroprotective, immunomodulatory, and wound-healing qualities (5). Cardiovascular illnesses, diabetes, obesity, and neurodegenerative disorders are among the chronic metabolic diseases that these biological processes help prevent and treat (6).

Objectives:

- To provide a comprehensive phytochemical characterization of pomegranate peel.
- To elucidate the antioxidant and antimicrobial mechanisms.
- To bridge traditional knowledge with modern scientific evidence.
- To explore the valorization potential of pomegranate peel waste.
- To establish a scientific foundation for future applications

- To synthesize evidence on the nutraceutical and therapeutic properties of pomegranate peel.

Fig.1: Pomegranate fruit (A), pomegranate seeds (B), sundried pomegranate peel (C), Pomegranate peel powder (D).

2. MAJOR BIOACTIVE COMPOUNDS:

Pomegranates are now grown all over the world, notably in the Caucasus region, North and tropical Africa, and North and South America. Peels, juice, and seeds are the fruit's three primary components. Peels make up about 26–30% of the overall fruit weight, and large amounts of by-products are produced during industrial processing into juice. These peels, which are frequently thrown away as waste, contain a wealth of bioactive substances with amazing health-promoting qualities. Pomegranate peel's complex combinations of bioactive substances produce a variety of physiological actions through synergistic effects, making these by-products excellent resources for the creation of functional foods and therapeutic uses.

• Polyphenolic Compounds

The main bioactive components of pomegranates are polyphenolic chemicals, which are especially concentrated in the peel fraction. These secondary metabolites include a variety of water-soluble compounds and originate from the pentose phosphate, phenylpropanoid, and shikimic acid pathways. Pomegranate peel's total phenolic content varies greatly, from 18 to 510 mg/g dry matter, depending on the cultivar, place of origin, extraction solvents, and techniques used (7). At least one aromatic ring with one or more hydroxyl substituents is a structural characteristic of phenolic compounds (8). Tannins, flavonoids, and phenolic acids are the main phenolic compounds found in pomegranate peel; the quantities of tannins and flavonoids are 193–420 mg/g and 84–134 mg/g dry matter, respectively.

- **Tannins**

Gallotannins, ellagitannins, complex tannins, and condensed tannins are the four primary structural types of tannins found in pomegranate peel, which are remarkably rich in hydrolysable tannins (9). With concentrations ranging from 16.67 to 245.47 mg/g dry matter, punicalagin—a special ellagitannin—serves as both the defining ingredient and the primary component of pomegranate peel, significantly surpassing other components (10). The hexahydroxybenzoic acid structure of this chemical undergoes spontaneous endo-esterification hydrolysis to produce ellagic acid, which then interacts with sugar ligands and polymerises to generate structurally complex ellagitannins (11).
Tannins' polyphenol hydroxyl groups, which successfully lower free radical concentrations, are responsible for their antioxidant qualities. Furthermore, complex and condensed tannins' catechol hydroxyl groups provide them the ability to chelate metals, especially iron and transition metals (12). Tannins have antibacterial qualities in addition to antioxidant action through a variety of methods, including depletion of vital metal ions needed for bacterial development, precipitation of membrane proteins, and inhibition of microbial enzyme function. Tannins are important components of pomegranate's medicinal potential because of these diverse actions (12).

- **Flavonoids**

Pomegranate peels contain a wide range of flavonoids, a diversified class of chemicals generated from flavanone (2-phenylchromanone). The basic structure, which consists of two aromatic rings (labelled A and B) joined by a heterocyclic ring (C ring) bonded to a third carbon chain, is made up of 15 carbon atoms arranged in a C_3–C_3–C_6 configuration (14). Flavonoids, flavonols, proanthocyanidins, and anthocyanidins are some of the subclasses that result from variations in substitution patterns within these rings.
Certain structural characteristics and substitution properties control the antioxidant activity of flavonoids. The location and number of hydroxyl groups on the A and B rings, the existence of a double bond between the C_2 and C_3 positions (which conjugates with the 4-keto group on the C ring to improve free radical scavenging capacity), and the partial conjugation of the C_2–C_3 double bond with the 3-hydroxyl group on the C ring are important factors. Notably, antioxidant activity is decreased when hydroxyl groups are glycosylated. Flavonoids' strong antioxidant activity has led to their categorisation as phytoestrogens, substances whose oestrogenic and antioxidant qualities may potentially lower the prevalence of hormone-dependent malignancies (15, 16).

- **Phenolic Acids**

Numerous phenolic acids, such as gallic, ellagic, caffeic, chlorogenic, butyric, erucic, ferulic, and cinnamic acids, are found in pomegranate peels. The geographical context of cultivation has a significant impact on the phenolic acid composition and concentrations. For example, examination of six ecotypes of Tunisian pomegranates showed average amounts of gallic acid of 123.79 mg/100 g, ellagic acid of 35.89 mg/100 g, and caffeic acid of 20.56 mg/100 g. Hydroxybenzoic acids (C_3–C_1) and hydroxycinnamic acids (C_6–C_3) are the two main families of phenolic acids, which are structurally composed of a phenolic ring joined to an organic carboxylic acid (C_6–C_1) backbone (17).
Phenolic acids' antibacterial action requires transmembrane diffusion, which causes cytoplasmic acidification and, in certain situations, bacterial cell death. It's interesting to note that hydroxybenzoic acids with more hydroxyl groups have less antibacterial action, according to the link between structure and antibacterial activity. On the other hand, the presence of the double bond in the side chain is crucial for the antibacterial action of hydroxycinnamic acids, underscoring the significance of structural characteristics in influencing biological activity.

- **Dietary Fiber**

Pomegranate peels are an excellent natural source of fibre since dietary fibre makes up the majority of their composition (33–62%) (18). Lignin, cellulose, uronic acid, and neutral sugars have been shown to be the main components after fractionation in comparative investigations of dietary fibre quantity and composition among 12 pomegranate cultivars. Among these components, lignin has the highest concentration, while cellulose and uronic acid have comparable values, ranging from 16 to 22 g/100 g, making them the second most prevalent parts (19). Xylose, arabinose, and galactose make up the majority of the neutral sugar fraction (20).

The nearly 1:1 ratio of insoluble to soluble fibre, which has a notable impact on the kinetics of cholesterol absorption in the gastrointestinal tract, is a property of pomegranate peel dietary fibre. Pomegranate peel dietary fibre has been shown to have superior physicochemical and functional qualities when compared to other fruit by-products, such as citrus, grape, and lemon. Additionally, novel uses have surfaced, such as the addition of dietary fibre from pomegranate peels to alginate microsphere formulations, which show antioxidant activity higher than that of commercial goods (21). These results highlight pomegranate peel's adaptability and exceptional functionality as a dietary fibre source for food and medicinal uses (22).

- ### Other Bioactive Components

Pomegranate peels have additional bioactive compounds that add to their overall nutritional and medicinal value, such as alkaloids, vitamins, steroids, and different mineral elements, in addition to polyphenols and dietary fibre. Two isomers including acetyl grenadine, 2-(2-hydroxypropyl)-1′-piperidine, sedridine, and N-acetyl sedridine have been identified by alkaloid identification investigations (23). Other discovered alkaloids that contribute to the pharmacological characteristics of pomegranate peel include pseudo-grenadine, N-methyl grenadine, and iso-grenadine.

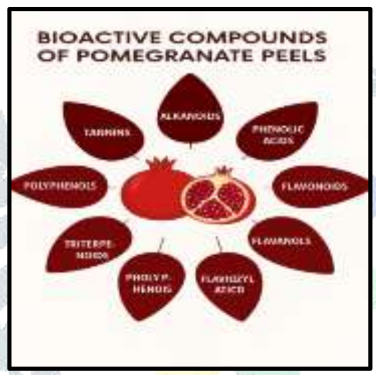

Fig.2: Pomegranate Peels' Bioactive Components

Pomegranate peels have a remarkably varied mineral makeup that includes vital components including potassium (K), phosphorus (P), sodium (Na), calcium (Ca), magnesium (Mg), and nitrogen (N). The human body's basic physiological activities, such as electrolyte balance, bone health, nerve transmission, and metabolic processes, depend heavily on these mineral elements (24). These minerals improve the nutritional profile of pomegranate peel extracts and facilitate their use as dietary supplements or functional food ingredients when combined with vitamins and other micronutrients. Pomegranate peels' potential to promote health is enhanced by the synergistic interactions between these various bioactive components, such as polyphenols, dietary fibre, alkaloids, vitamins, and minerals, which form a complex matrix.

3. ANTIOXIDENT PROPERTIES OF POMEGRANATE PEEL

Pomegranate peel exhibits a much higher antioxidant capacity than other fruit parts. Because of its polyphenolic structure, pomegranate peel extract has an antioxidant capacity that is almost ten times higher than that of other pomegranate fruit parts. The abundance of bioactive substances, especially flavonoids, phenolic acids, and ellagitannins, is responsible for this exceptional antioxidant potential.

- **Key Antioxidant Compounds and Mechanisms**

a. Ellagitannins and Punicalagin

Pomegranate product's antioxidant qualities are mostly attributed to punicalagin, which has a high total phenolic concentration. In contrast to ellagic acid, which has a lower antioxidant capacity of just 3% per molecule, it has an exceptionally high antioxidant capacity of over 50%. Punicalin and ellagic acid are released when the galloyl groups that bind punicalagin to glucose hydrolyse. By effectively neutralising free radicals and reducing cellular oxidative damage, punicalin demonstrates great antioxidant activity and plays a crucial role in postponing ageing and avoiding related illnesses (25).

b. Flavonoids

The following structural characteristics of flavonoids determine their antioxidant activity:
(a) Where and how many hydroxyl groups are present in the A and B rings.

(b) The double bond between C_2 and C_3 increases the ability to scavenge free radicals because it is conjugated to the 4-keto group on the C ring.

(c) The ability to scavenge free radicals is improved by the double bond between C_2 and C_3, which is partially conjugated to the 3-hydroxyl group on the C ring.

(d) Antioxidant activity is decreased when hydroxyl groups are replaced by glycosylation.

By binding metal ions that encourage oxidative damage and neutralising reactive oxygen species (ROS), quercetin demonstrates its antioxidant potential. Quercetin reduced oxidative stress in a 3-nitropropionic acid-induced oxidative stress model by increasing SIRT1 expression, triggering the SIRT1/ROS/AMPK signalling pathway, preventing oxidative stress-induced ROS accumulation, controlling autophagy levels, lowering cell apoptosis, and eventually restoring ovarian function. In a chronic unpredictable moderate stress depression paradigm, catechin reduced oxidative stress-induced depression by replenishing antioxidant indices like catalase, glutathione, and superoxide dismutase levels.

c. Phenolic Acids

Protocatechuic acid (PCA) promotes the removal of ROS and reduces oxidative stress in cells by increasing the activity of intracellular antioxidant enzymes such glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD) (26). Additionally, PCA prevents metal ions (such as Fe^{2+} and Cu^{2+}) from catalysing the Fenton reaction, which lowers the generation of hydroxyl radicals and mitigates oxidative stress at its source. Ellagic acid showed protective effects against oxidative stress and cisplatin-induced nephrotoxicity in rats, possibly because of its strong scavenging action against hydroxyl radicals and superoxide anions. By preserving Ca^{2+} homeostasis in HepG2 cells and suppressing CYP1A1 activity, ellagic acid increased antioxidant capacity. Ellagic acid has shown promise in reducing atherosclerosis by scavenging RO• or ROO• free radicals, suppressing lipid peroxidation, and preventing the generation of hydrogen peroxide and singlet oxygen. By activating nuclear factor erythroid 2-related factor 2 (Nrf2), lowering oxidative damage, and raising sperm count, punicalagin considerably decreased the generation of the potent oxidant NO and lessened oxidative stress in the testes. By boosting liver superoxide dismutase (SOD), glutathione peroxidase (GPx) activity, and Nrf2 protein expression, punicalagin reduced oxidative stress and prevented CCl_4-induced liver damage.

- **In Vivo and Clinical Evidence**

a. Animal Studies

Pomegranate peel extracts show possible antioxidant effect by lowering levels of oxidised low density lipoprotein (Ox-LDL), thiobarbituric acid reactive substances (TBARS), lipid peroxidation, and oxidative indicators linked to cardiovascular risk in healthy individuals. In vivo, urolithin A protected the mice's kidneys against renal oxidative damage caused by cisplatin. In an ovarian oxidative stress paradigm caused by 3-

nitropropionate acid, gallic acid inhibited death in ovarian granulosa cells by drastically lowering glucose fasting levels, raising antioxidant enzyme activity, and lowering the mRNA expression levels of pro-apoptotic genes.

b. Human Studies

Animals and humans fed diets rich in pomegranate showed improvements in diminishing of cut wounds, fracture strength, and epithelialization. Volunteers taking pomegranate juice showed significantly higher antioxidant capacity compared to those not consuming pomegranate.

c. Urolithin Metabolites

The gut microbiota breaks down ellagitannins to produce the health-promoting urolithins (Uros). Consuming foods high in ellagitannin over time can raise the amount of Uros in physiological fluids like urine and plasma as well as in tissues like the breast and bones. Inflammatory indicators such inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and prostaglandin E synthase (PTGES) were markedly decreased in the inflammatory rats when pomegranate extract was administered in an inflammatory bowel disease model. Urolithins were discovered in the brains of the Parkinson's disease rat model after pomegranate extract was administered, and the animals' motor and olfactory abilities improved.

- ### Mechanisms of Antioxidant Action

Numerous important biological pathways, such as nuclear factor-kappa B (NF-κB), cysteine-aspartic acid-specific proteases, mitogen-activated protein kinases, and peroxisome proliferator-activated receptors, can be modulated by PPE. The antioxidant properties of tannins are given by polyphenol hydroxyl groups that can diminish the concentration of free radicals. Additionally, complex and condensed tannins have the capacity to chelate iron and transition metals due to their catechol hydroxyl groups.

4. Antimicrobial Properties of Pomegranate Peel

Pomegranate peel has broad-spectrum antibacterial activity against a variety of harmful microbes, such as viruses, fungi, and bacteria. Its high phenolic content is largely responsible for its antibacterial potential (27).

- ### Antibacterial Activity:

a. Gram-Positive and Gram-Negative Bacteria

Both Gram-positive and Gram-negative bacteria were susceptible to the antibacterial activity of pomegranate peel extract, with peel extracts showing the most inhibitory impact. Pomegranate peel ethyl acetate extract, which has significant tannin concentrations, is highly effective against strains of Staphylococcus aureus (28). Both Gram-positive and Gram-negative microbes, such as E. coli, B. subtilis, Enterobacter aerogenes, Serratia marcescens, and Brucella species, as well as yeasts like Saccharomyces cerevisiae and Rhodotorula glutinis, have been demonstrated to be inhibited in their growth by pomegranate peel water extract. Salmonella sp., Pseudomonas aeruginosa, Escherichia coli, Listeria monocytogenes, and Staphylococcus aureus were all effectively combatted by a 30–60 mg/mL methanol extract. With minimal bactericidal doses of 11.5 and 10.75 mg/mL, an ethanolic extract of Tunisian pomegranate peel was effective against a strain of Salmonella Kentucky isolated from chicken meat.

b. Specific Pathogenic Bacteria

Ellagic acid showed strong anti-H. pylori actions by repairing and restoring the damage that H. pylori had caused to the stomach mucosa. Ellagic acid therapy preserved intestinal villi integrity, showed antibacterial action against Aeromonas hydrophila, and markedly raised levels of anti-LPS and anti-ECP IgM in infected mice. Gallic acid dramatically reduced bacterial burdens in organs including the liver, raised levels of cytokines like IFN-γ, and decreased mortality in Salmonella Typhimurium-infected mice. By preventing F-actin polymerisation and downregulating mitogen-activated protein kinases (MAPKs), gallic acid prevented Brucella abortus invasion and caused the release of protective cytokines like IL-12. Ellagic acid showed strong anti-H. pylori actions by repairing and restoring the damage that H. pylori had caused to the stomach mucosa. Ellagic acid therapy preserved intestinal villi integrity, showed antibacterial action against Aeromonas hydrophila, and markedly raised levels of anti-LPS and anti-ECP IgM in infected mice. Gallic acid dramatically reduced bacterial burdens in organs including the liver, raised levels of cytokines like IFN-γ, and decreased mortality in Salmonella Typhimurium-infected mice. By preventing F-actin polymerisation and downregulating mitogen-activated protein kinases (MAPKs), gallic acid prevented Brucella abortus invasion and caused the release of protective cytokines like IL-12. In mice infected with extensively drug-resistant P. aeruginosa and multidrug-resistant Escherichia coli, gallic acid dose-dependently increased the survival rate and dramatically reduced the expression of genes linked to quorum sensing. Punicalagin bound to the functional domains of the bacterial transcriptional regulator PhcA, causing the regulatory network to become disorganised and ultimately leading to bacterial impairment in Ralstonia solanacearum. Pomegranate peel polyphenols significantly reduced bacterial growth and motility.

- ## Mechanisms of Antibacterial Action

By precipitating membrane proteins, depleting metal ions, and inhibiting enzyme activity, tannins may have antimicrobial effects. Phenolic acid diffusion across the cell membrane can cause cytoplasmic acidification, which can sometimes cause cell death. The hydroxybenzoic acid has less antibacterial action when it contains more hydroxyl groups. The presence of the double bond on the side chain of hydroxycinnamic acid has a significant impact on its antibacterial efficacy. Phenolic chemicals have antibacterial properties and can cause bacterial mortality by precipitating membrane proteins and inhibiting enzyme function. These substances can prevent lipid oxidation in fatty diets and neutralise free radicals.

Bacteria	Mechanism of action	Reference
Eight different food contaminants/pathogenic bacteria	Beacause of high antioxidant activity and high total phenolic content	40
B. coagulans, B. cereus, B. subtilis, S. aureus, E. coli, K. pneumoniae, and P. aeruginosa	High levels of phytocompounds, such as phenols, tannins, and flavonoids, are thought to be the cause..	41
S. aureus and Salmonella	6lms inhibition against specific microbes.	42
S. aureus	Beacause of the high concentrations of tannins	28
Gram-positive and Gram-negative bacteria including E. coli, B. subtilis, E. aerogenes, S. marcescens, Brucella spp., S. cerevisiae, and R. glutinis.	Beacause of high tannins content	43

Table 1: Antibacterial effects of pomegranate peel against different pathogens.

- ## Antifungal Activity

a. Pathogenic Fungi

Fusarium sambucinum spore germination was completely inhibited by pomegranate peel extract (20 mg/ml), and mycelia growth was inhibited by 75.5%. Pomegranate peel extract has been shown to have strong fungicidal action against Botrytis cinerea, Penicillium digitatum, and Penicillium expansum. After 20 hours of incubation, all fungal spores on lemons and grapefruits were nearly completely inhibited. Penicillium digitatum was considerably reduced by 28% and 49%, respectively, when 0.361 g of aqueous pomegranate peel extract was added to locust bean gum and chitosan coatings. Saccharomyces cerevisiae and Penicillium digitatum are more susceptible to methanol extraction. The control of mycelia growth in brown rot (induced by Monilinia laxa and M. fructigena) was inhibited by aqueous pomegranate peel extracts in a range of 76.65% to 90%. When tested against Fusarium oxysporum f. sp. lycopersici, all of the pomegranate genotypes showed differing antifungal activity; some even totally suppressed the pathogen (29).

b. Candida Species

The growth of Candida albicans was inhibited by pomegranate peel extract at doses of 125, 250, and 500 mg/kg/day BW, with 100% efficacy at all doses as opposed to nystatin's 80% efficacy. The tongue's lamina propria, muscle core, and epithelium all retained their normal structure after treatment.

c. Parasitic Infections:

The level of Giardia antigen in the faeces of the experimental groups steadily dropped when pomegranate peel extract (300 mg/kg) was added. This resulted in a considerable cure rate and a reduction in cyst formation.

Fungi	Mechanism of action	Reference
F. sambucinum	Beacause of the high contents of phenolic compounds	44
P. digitatum and Saccharomyces cerevisiae.	Inhibit cellular receptors of pathogens	5
Brown rot (caused by Monilinia laxa and M. fructigena)	Beacause of the high total phenolic and Flavonoid contents	45
B. cinerea, P. digitatum, and P. expansum	Beacause of the high concentrations of ellagitannins	46
F. oxysporum f. sp. lycopersici	Beacause of the high levels of total phenol and punicalagin contents.	47
P. digitatum	Beacause of the high contents of phenolic compounds	48

Table 2: Antifungal effects of pomegranate peel against different pathogens.

- ## Anti-inflammatory Effects Related to Antimicrobial Action

Ellagic acid efficiently inhibited Nuclear Factor-kappa B (NF-κB) activation by blocking the phosphorylation of IκB-α and NF-κB p65, hence lowering inflammation and minimising liver damage. It also greatly reduced the generation of pro-inflammatory cytokines like TNF-α. Punicalagin showed promise as a safe and efficient treatment by dramatically lowering IL-1β levels, lipid peroxidation, and catalase activity in models of collagen-induced arthritis and pelvic inflammatory illness. In addition to reducing cellular infiltration, synovial hyperplasia, cartilage degradation, and limb swelling, punicalagin dramatically lowered serum levels of TNF-α and IL-6. Corilagin effectively protected against LPS-induced acute lung injury by reducing inflammatory cell infiltration in lung tissues and inhibiting the production of pro-inflammatory cytokines TNF-α, IL-6, and IL-1β.

- ## Antiviral Properties

Gallic acid, ellagic acid, punicalin, and punicalagin may be essential for antiviral activity, influencing influenza and respiratory diseases. The polyphenol extracts' ability to prevent influenza viruses' RNA replication is the primary cause of their antiviral qualities. At concentrations as high as 40 mg/mL, punicalagin successfully inhibited viral RNA replication, whereas casuarinin showed antiviral qualities by blocking the attachment and entrance of herpes simplex virus type 2. On the sixth day after infection with Listeria monocytogenes EGD, kaempferol treatment increased the survival rate of infected mice by more than 20% and dramatically decreased the bacterial load in major target organs.

- ## Applications in Food Preservation

Pomegranate peel can be used as a natural preservative in food products to stop spoiling and increase shelf life because of its phenolic content, which gives it antibacterial and antioxidant qualities. Pomegranate peel extract improved the antibacterial qualities of chitosan and starch-based films by completely inhibiting the growth of Staphylococcus aureus and 50% inhibiting the growth of Escherichia coli. In addition to inhibiting pH and total volatile organic nitrogen levels in seafood items, pomegranate peel extract added to edible coatings dramatically decreased the total number of aerobic plaques (30). It is advised to use pomegranate peel extract sanitisers for complete control of green mould in citrus fruits since pomegranate peel extracts were efficient against Penicillium digitatum. Pomegranate peel extract sprayed at a rate of 12 g/L on olive plants prevented premature defoliation and decreased the risk of olive anthracnose by 84.5% (31).

- **Synergistic Effects**

Protocatechuic acid exhibits synergistic effects with antibiotics, increasing its antibacterial activity. Pomegranate peel aqueous extract dramatically reduced oxidative stress indices and inflammatory indicators in paracetamol-induced hepatotoxicity when combined with N-acetyl cysteine.

5. Bioavailability and Pharmacokinetics

- **Understanding Pomegranate Polyphenol Absorption and Metabolism**

Pomegranate product's exceptional in vitro antioxidant potential has been mainly ascribed to their high polyphenolic content, especially ellagitannins like punicalagins and punicalins. However, determining these chemicals' bioavailability is essential to connecting their observed health impacts to in vivo antioxidant activity. Pomegranate polyphenols undergo a complicated metabolic change that profoundly affects their biological activity as they pass through the human digestive system (32).

- **Ellagitannin Metabolism and Absorption**

The results of studies on the bioavailability of ellagitannin in humans have been fascinating and occasionally seemingly contradicting. After consuming pomegranate juice, ellagic acid and its metabolites were found in plasma in a number of studies. When standardised to equivalent polyphenol content, there were no discernible variations in the bioavailability of pomegranate juice, liquid extract, or powdered extract. Ellagic acid was shown to have a comparatively short half-life in plasma, ranging from 0.65 to 1.79 hours, suggesting quick bloodstream clearance. However, another comprehensive investigation indicated that neither ellagic acid, punicalagin, anthocyanins, nor their rapid breakdown products were identified in plasma following ingestion of one liter of pomegranate juice per day. Rather, urolithin metabolites were found in urine and plasma samples. By taking into account the timing of plasma sample and the quick metabolism of these substances, this apparent disparity can be explained. The identification of urolithins revealed that the conversion of pomegranate polyphenols into accessible chemicals is mostly dependent on intestinal bacteria metabolism.

- **The Role of Gut Microbiota**

Pomegranate ellagitannin metabolism is mediated by the gut flora. A multi-stage metabolic process is suggested by current evidence: ellagitannins are initially hydrolysed in the stomach's acidic environment, where some of the produced ellagic acid may be taken straight into the bloodstream. The residual ellagic acid travels to the colon, where gut microbiota further breaks it down to create derivatives of urolithin. The less polar urolithins A and B are the metabolites that are taken into the bloodstream and then metabolised by the liver to produce glucuronide conjugates. This metabolic pathway has been better understood thanks to animal models. Thirty-one ellagitannin metabolites were identified in a study employing Iberian pigs fed acorns as a model system; however, only urolithin A, urolithin B, dimethyl ellagic acid, and their glucuronide derivatives were found in plasma. In mouse models, urolithin metabolites accumulated preferentially in the prostate, colon, and intestinal tissues—organs commonly investigated for pomegranate's health benefits—further confirming this selective absorption pattern (33).

- **Tissue Distribution and Biological Activity**

Pomegranate metabolites' tissue-specific accumulation is very important for comprehending the fruit's medicinal potential. The only ellagitannin metabolites found in human prostate tissue after three days of pomegranate juice supplementation were urolithin A glucuronide, urolithin B glucuronide, and dimethylellagic acid. This result implies that animal models could be suitable stand-ins for researching the bioavailability and metabolism of ellagitannin in humans.

Numerous experimental systems have shown the biological action of these metabolites. In cell-based tests, urolithins A, C, and D shown antioxidant action; in an in vitro colon fibroblast model, urolithin A demonstrated notable anti-inflammatory activity. According to these results, pomegranate polyphenolic compounds may have a variety of beneficial effects. Some are directly absorbed and function as systemic antioxidants, while others are metabolised by colonic microflora to create physiologically active metabolites that may target particular tissues (34).

• Clinical Implications and Standardization

Pomegranate chemicals' intricate metabolism and fluctuating bioavailability offer opportunities and problems for product development and clinical use. Analytical tests have shown that most commercial pomegranate extracts do not include punicalagins, which emphasises the necessity for more thorough standardisation criteria. Since urolithin metabolites seem to be the main circulating and tissue-accumulated forms, many commercial products are now standardised based on ellagic acid concentration, which may not adequately reflect the bioactive potential of the product.

Optimising dosage schedules and product formulations requires an understanding of the pharmacokinetic profile of pomegranate components. Ellagic acid's quick plasma clearance indicates that numerous daily dosages or formulations with extended release may be necessary for sustained bioavailability. Additionally, individual differences in the makeup of the gut microbiota may affect how much urolithin is produced, which could help to explain why different populations respond differently to treatment.

A complex interaction between chemical composition, gastrointestinal processing, microbial metabolism, and tissue-specific accumulation is revealed by the developing picture of pomegranate bioavailability. This research not only enriches our understanding of how pomegranate exerts its health advantages but also provides a foundation for designing more effective nutraceutical products and providing evidence-based dosing guidelines for clinical applications.

6. Traditional medicinal uses

Pomegranate peel (PoP) has long been prized for its medicinal qualities in many cultures and traditional medical systems, both in industrialised and developing nations. Traditionally, the peel is boiled for 10 to 40 minutes to create an aqueous extract that is used as a douche or enema and to treat conditions like diarrhoea, dysentery, and dental plaque. Decoctions or infusions made from the dried peel, bark, and flowers have been used to treat ulcers, bleeding noses, intestinal worms, and diarrhoea throughout the Indian subcontinent. Additionally, pomegranate peel extract (PoPx) is frequently used as a gargle to relieve hoarseness and sore throats. Rind powder applied topically has been shown to help individuals with periodontitis repair their bleeding gums and dental plaque (Amrutesh, 2011). For the treatment of hyperacidity, it is also customary to take 5–10 g of peel powder orally, two to three times a day.

7. Pomegranate and Peel Extracts' Nutraceutical Characteristics

• Cardiovascular Defence Function

One of the main causes of death, especially in industrialised nations, is atherosclerosis, which is caused by oxidised low-density lipoproteins building up in artery walls and producing dangerous reactive species. Pomegranate peel extract has the potential to significantly reduce arterial foam cell levels and slow the course of atherosclerosis by inhibiting LDL oxidation. Punicalagin, gallic acid, and ellagic acid are examples of active polyphenolic substances that boost hepatocyte paraoxonase 1 expression and secretion in a dose-dependent way, hence lowering the risk of developing atherosclerosis.

Although pomegranate peel ellagitannins have shown cardioprotective effects in vitro at concentrations of 10–100 μM, comparatively smaller effects were seen in vivo, indicating that these advantages are linked to lower bioavailability of the antioxidant fractions (35). However, pomegranate extracts at 100 mg/kg have demonstrated cardioprotective benefits in rat models by lowering levels of glutathione, lactate dehydrogenase, and creatine kinase-MB. Pomegranate polyphenols have been shown in numerous studies to have beneficial effects on oxidation-sensitive genes, such as the potential to decrease nitrous oxide synthase production and the downregulation of redox-sensitive ELK-1 and p-JUN genes under endothelium wall shear stress conditions.

Pomegranate peel powder has been tested as a dietary fibre source for the treatment of atherosclerosis and hypercholesterolaemia beyond biochemical causes. In hypercholesterolemic rats, dietary treatment with peel powder at concentrations of 5, 10, and 15 g/100 g for four weeks markedly decreased serum levels of LDL, triglycerides, total cholesterol, and lipid peroxidation.

- **Anti-inflammatory and Anti-allergic Properties**

Pomegranate rind methanolic extract has been shown by strong scientific evidence to have anti-inflammatory and anti-allergic properties (36). By preventing the expression of pro-inflammatory proteins, the anti-inflammatory substances punicalagin, punicalin, strictinin A, and granatin B considerably lower nitric oxide and prostaglandin E2 synthesis. Neutrophils, macrophages, and monocytes are examples of inflammatory cells that can harm surrounding tissues and contribute to the pathophysiology of many diseases, including rheumatoid arthritis, emphysema, acute respiratory distress syndrome, atherosclerosis, reperfusion injury, and cancer.

Aqueous pomegranate peel extract directly reduced neutrophil myeloperoxidase activity and the enzymatic synthesis of hypochloric acid from hydrogen peroxide at a concentration of 50 ng/ml, according to research on isolated human neutrophils. Research has shown anti-inflammatory effects after intraperitoneal (25, 50, and 100 mg/kg) and intracerebroventricular (10, 25, and 50 µg/3 ml/rat) administration. At these dosage levels, the pain index was reduced by 52–82%, and the inflammation caused by egg albumin in the hind paws was significantly reduced. Additionally, during carrageenan-induced paw oedema in mice, granatin B given orally at 2.5 and 10 mg/kg demonstrated robust inhibitory effects against inflammation stimulators, with notable inhibitory effects seen after 6 hours in comparison to indomethacin.

- **Anticancer Properties**

Cancer represents the leading cause of death in both developed and developing countries, with 12.7 million new cases and 7.6 million deaths occurring in 2008 across 20 world regions. Early detection and implementation of appropriate preventive measures are essential to reduce the cancer burden. With significant ROS damage to DNA ultimately resulting in somatic mutations and organ malignancies, reactive oxygen species are both causative and concausal factors in the genesis of cancer. Macromolecules' copper and iron binding sites are key locations for the generation of free radicals, which are prevented by antioxidant chelation of metal ions. By initiating the multistage process of apoptosis, ellagic acid and punicalagin prevent the proliferation of cancer cells.

a. Prostate and Colon Cancer

Pomegranate ellagitannins' anticarcinogenic properties have been linked to hydrolysed products, particularly ellagic acid and punicalagin, which at concentrations of 100 µg/ml caused colon cancer cells (HT-29, HCT116) and prostate cancer cells to undergo apoptosis. These effects were achieved by up-regulating Bax and down-modulating Bcl-2, as well as by bringing cytochrome c into the cell cytoplasm (37).

When standardised pomegranate extract (10 µg/ml) containing 37% punicalagin was applied to Los Angeles prostate cancer cells, it caused apoptosis and reduced cell proliferation. IGFBP-3 therapy in combination decreased the activity of cell growth promoters (mTOR and Akt), which had pro-apoptotic effects. With IC50 values of 6.7±0.5 µg/ml and 2.2±0.2 µg/ml under reduced and normal oxygen supply, respectively, in vitro incubation with 37% standardised ellagitannin-rich pomegranate extract inhibited the proliferation of both prostate cancer and umbilical vein endothelial cells under hypoxic and normoxic conditions. Prostate cancer xenograft size, tumour vascular density, and cancer cell proliferation were all significantly reduced after four weeks of oral dosing following subcutaneous injection.

b. Melanogenesis and Skin Cancer

By blocking tyrosinase activity at levels similar to arbutin, pomegranate peel extract (IC50 = 182.2 µg/ml) prevents melanocyte growth and melanin formation. In brown guinea pigs, oral treatment of an extract containing 90% ellagic acid at a dose of 1000 mg/kg prevented UV-induced skin colouring. At concentrations of 500–10,000 µg/L, pomegranate peel extract and ellagitannins prevent the production of free radicals in UVA and UVB-irradiated human skin, shielding it from depigmentation, skin burns, and DNA fragmentation brought on by monochromatic light activation of photosensitisers that produce genotoxic singlet oxygen species (38). Before UVB-induced skin damage, epidermal pretreatment with pomegranate extract (5–10 µg/0.1 ml/well) suppresses indicators of oxidative stress and genotoxicity as well as matrix metalloproteinases implicated in the breakdown of skin connective tissues and collagen components.

c. Breast Cancer

Human breast cancer cells (MCF-7) undergo apoptosis when exposed to pomegranate peel extract. Significantly greater MCF-7 inhibitory and cytotoxic effects were demonstrated by application of genistein, which also showed capacity to reduce angiogenesis marker expression, cell proliferation, phosphorylation of p38 and C-Jun mitogen-activated protein kinases, and activation of pro-survival signalling pathways. Additionally, it suppressed the expression of nuclear factor kappa B-dependent reporter genes linked to invasion, motility, and proliferation in aggressive breast cancer morphologies.

When combined with 1 µM tamoxifen, pomegranate extract showed anticancer activities at 300 µg/ml, sensitising and enhancing efficacy in suppressing resistant MCF-7 cell proliferation. Anti-aromatase drugs can regulate estrogen-stimulated processes such as the growth of breast cancer cells and the development of oestrogen receptor-positive tumours. The active component with the highest anti-aromatase action was found to be urolithin B, a metabolite of pomegranate ellagitannin that also prevented testosterone-induced MCF7 cell growth (39).

8. CONCLUSION

A profitable by-product of the fruit business, pomegranate (Punica granatum) peel has substantial therapeutic potential and is rich in naturally occurring bioactive chemicals. The peel's potent antioxidant and antibacterial properties are attributed to its polyphenols, flavonoids, and tannins, according to numerous studies. These substances aid in the removal of free radicals, prevent the growth of germs, and enhance general health. Pomegranate peel is valuable in the food, cosmetic, and pharmaceutical industries due to its many uses. To standardise extraction techniques, establish safe dosage ranges, and confirm its effectiveness through human clinical trials, more research is necessary. All things considered, pomegranate peel is a sustainable, economical, and environmentally friendly natural resource with enormous potential for use in the industrial and medicinal fields in the future.

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