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# *Citrus sinensis* Peel as a Sustainable Source of Bioactive Phytochemicals: A Comprehensive Review of Pharmacognosy, Phytochemistry, Anti-inflammatory Mechanisms, and Therapeutic Potential

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**Keywords**

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**Abstract**

Peel from citrus fruits (*Citrus sinensis* (sweet orange)) is one of the biggest agricultural by-products from the juice processing industry that is underutilized and has many bioactive phytochemicals with therapeutic potential. This review critically explores the pharmacognostic features, phytochemical makeup, traditional medicinal uses, molecular mechanism of anti-inflammatory activity, pharmacological applications, extraction technologies and applications towards circular bioeconomy of orange peel. The peel is rich in several bioactive compounds, such as flavonoids (hesperidin, naringin, narirutin), polymethoxyflavones (nobiletin, tangeretin, sinensetin), phenolic acids, essential oils (mainly D-limonene), carotenoids, and limonoids. Not only they have strong anti-inflammatory properties due to the modulation of NF-κB, MAPK, COX/LOX, and NLRP3 inflammasome pathways, but they also show antioxidant, antimicrobial, anticancer, cardioprotective, hepatoprotective, neuroprotective, antidiabetic, and gastroprotective properties. The orange peel phytochemistry has been well characterized by recent developments in green extraction methods, metabolomics and systems pharmacology. Moreover, valorisation of citrus processing waste is consistent with the principles of circular bioeconomy and sustainable development. Although there is plenty of preclinical evidence, there are some problems to be solved before it could be widely used in therapy, such as lack of clinical validation, bioavailability of important flavonoids, the use of standardized extracts, and the absence of long-term safety data. This review indicates key areas of research that need to be addressed and suggests future research directions for the potential conversion of citrus peel bioactives into evidence-based phytopharmaceuticals, nutraceuticals and functional health products.

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## 1. Introduction

### 1.1 Herbal Medicines and Global Significance

For thousands of years medicinal plants have been the source of traditional health care systems and are still a vital component of today's medicine. While synthetic pharmaceuticals have improved over time, plant-based bioactive compounds still play a significant role in the pharmaceutical industry because of their diverse structures and their ability to synthesize a wide variety of products with different therapeutic effects and favorable safety profiles, even though they may be more expensive and have poorer yields [1], [2], [3]. Traditional herbal medicines are used by approx. 80% of the global population as a primary healthcare, especially in the developing countries [4]. The WHO Traditional Medicine Strategy 2014-2023 and the subsequent Global Report on Traditional and Complementary Medicine 2019 have emphasized the importance of integrating

traditional medicine into national health systems, highlighting the need for evidence-based validation of herbal remedies [5].

With the growing incidence of chronic non-communicable diseases, there has been a search for new therapeutic agents from natural sources [6]. The role of natural products in drug discovery continues to evolve, with renewed interest in plant-derived compounds for managing chronic inflammatory conditions. Furthermore, the concept of network pharmacology has emerged as a powerful framework for understanding the synergistic actions of botanical mixtures, moving beyond the "one compound-one target" paradigm. Plants produce a variety of secondary metabolites such as alkaloids, flavonoids, phenolic acids, terpenoids and glycosides that have important pharmacological activities [7]. The relevance of natural products in drug discovery is evident in the fact that many clinically relevant drugs are derived from medicinal plants, which are used as a source of medicines [8].

**.2 Inflammation as a Therapeutic Target**

Inflammation is a complex biological process that is protective to the tissue against infection and injury. But chronic inflammation has been linked to a range of chronic diseases such as cardiovascular diseases, rheumatoid arthritis, inflammatory bowel disease, metabolic syndrome, neurodegenerative diseases and cancer [9],[10]. Non-resolving inflammation is now recognized as a key driver of chronic disease pathogenesis, with maladaptive inflammatory responses contributing to tissue damage and disease progression. The persistence of inflammatory stimuli creates a vicious cycle that perpetuates tissue injury and dysfunction. The inflammatory responses are controlled by NF-κB, MAPK, JAK/STAT, COX/LOX, and NLRP3 inflammasome pathways [11], [12].

Traditional anti-inflammatory drugs such as NSAIDs and corticosteroids are well known for their potentially serious side-effects such as gastrointestinal ulceration, nephrotoxicity and cardiovascular complications [13. The identification of novel anti-inflammatory agents from natural sources has gained significant attention, particularly given the association between chronic inflammation and cardiovascular risk factors such as hypertension. This has led to a tremendous amount of research into the possibilities of finding natural anti-inflammatory compounds which can modulate multiple inflammatory pathways with minimal toxicity [14].

constituents, traditional uses, molecular anti-inflammatory mechanism, pharmacological properties, extraction technologies and the

**1.3 Citrus Species and Bioactive Phytochemicals**

The genus *Citrus* (family Rutaceae) comprises economically important fruit crops including *C. sinensis* (sweet orange), *C. limon* (lemon), *C. reticulata* (mandarin), and *C. paradisi* (grapefruit) [15]. Advances in citrus taxonomy and breeding have revealed substantial genetic diversity within the genus, with implications for phytochemical composition. The comprehensive pharmacological profiling of citrus secondary metabolites has identified numerous bioactive compounds with therapeutic potential. Citrus fruits contain diverse bioactive phytochemicals including flavanones, polymethoxyflavones, limonoids, carotenoids, coumarins, essential oils, and phenolic acids. Major citrus flavonoids include hesperidin, naringin, narirutin, nobiletin, tangeretin, and sinensetin, many of which are concentrated within the fruit peel rather than the edible pulp. Recent analytical advances, including metabolomics and advanced chromatographic techniques, have enabled comprehensive characterization of citrus phytochemicals [16].

**1.4 *Citrus sinensis* Peel as a Therapeutic Resource**

In industrial juice production, the fruit pulp is discarded as peel, which results in millions of tons of agricultural waste annually; about 20-40% of the fruit mass being discarded as peel [17]. The valorization of citrus processing waste through biorefinery approaches has emerged as a sustainable strategy for recovering high-value bioactive compounds. Compared with the edible pulp of the orange fruit, the orange peel is a rich source of bioactive compounds [18]. The main phytochemical classes are flavonoids, polymethoxyflavones, phenolic acids, carotenoids, limonoids, pectin and volatile oils. The systematic evaluation of citrus peel bioactives has demonstrated significant health benefits, with particular emphasis on their role in preventing chronic diseases. The antioxidant, anti-inflammatory, antimicrobial, cardioprotective, hepatoprotective, neuroprotective, antidiabetic, and anticancer properties of these compounds have been reported. The therapeutic potential of *Citrus sinensis* peel in managing metabolic syndrome has been increasingly recognized, with multiple bioactive compounds exhibiting synergistic actions [19].

**1.5 Rationale and Scope**

This review covers a detailed description of pharmacognostic features, phytochemical opportunities of circular bioeconomy applications of *Citrus sinensis* peel, highlighting the gaps and future research directions.

## 2. Methodology

This review was conducted following PRISMA 2020 guidelines. Comprehensive literature searches were performed across Scopus, Web of Science, PubMed, ScienceDirect, SpringerLink, Wiley Online Library, and Google Scholar databases. Systematic literature searches were conducted using keywords including ("*Citrus sinensis*" OR "orange peel") AND ("phytochemicals" OR "flavonoids" OR "bioactive") AND ("anti-inflammatory" OR "pharmacological" OR "traditional medicine") AND ("extraction" OR "standardization" OR "bioeconomy"). Inclusion criteria encompassed original research, reviews, clinical studies, and regulatory documents published between 2000 and 2025. Exclusion criteria included non-English publications, conference abstracts, and opinion pieces.

## 3. Ethnomedicinal Uses and Traditional Knowledge

There is a long history of discovery of modern pharmaceuticals from traditional medicinal system; ethnopharmacological studies have shown that many traditional remedies have measurable biological activities. Ethnopharmacological studies have played a pivotal role in drug discovery, with systematic validation of traditional remedies providing scientific evidence for their therapeutic applications. The integration of Ayurvedic and modern pharmacological principles offers unique opportunities for discovering novel therapeutic agents. The citrus peel (*C. sinensis*) has been used as a medicinal plant in Ayurvedic, Unani, Siddha and traditional medicine of Asia, Africa, Latin America and Europe [20].

In Ayurveda, orange peel (Naranga Twak) is regarded as possessing digestive, stimulant, expectorant, carminative, and rejuvenating properties. Traditional applications include conditions involving impaired digestion (Agnimandya), cough (Kasa), dyspnea (Shwasa), fever (Jwara), skin disorders (Twak Roga), and cardiac weakness (Hridya Vikara) [21].

Table 1 summarizes the Ayurvedic interpretation of citrus peel by correlating its traditional properties (*Rasa, Guna, Virya, Vipaka,* and *Prabhava*) with their modern pharmacological significance. This comparison demonstrates how classical Ayurvedic concepts align with contemporary scientific understanding, highlighting the therapeutic potential and multi-target biological activities of citrus peel constituents [22].

**Table 1:** Ayurvedic interpretation of citrus peel.

| S. No. | Parameter | Traditional Description | Modern Interpretation | References |
|---|---|---|---|---|
| 1. | Rasa | Madhura, Amla, Tikta | Sugars, organic acids, flavonoids | [23] |
| 2. | Guna | Laghu, Tikshna | Digestive stimulation | [24] |
| 3. | Virya | Ushna | Metabolic activation | [25] |
| 4. | Vipaka | Katu | Enhanced bioactivity | [26] |
| 5. | Prabhava | Tridoshahara | Multi-target pharmacological action | [27] |

TCM has employed dried citrus peels for over 1,500 years. Citrus peel is classified as warm, aromatic, and bitter, with affinity toward Lung, Spleen, and Stomach meridians [28]. Major applications include regulation of Qi stagnation, treatment of digestive disorders, relief of nausea and vomiting, management of chronic cough, reduction of mucus production, and improvement of appetite. The applications of citrus peel in Traditional Chinese Medicine have been extensively documented, with modern phytochemical and pharmacological studies validating its traditional uses [29].

Unani medicine recognizes orange peel (Qishr al-Naranj) for treating dyspepsia, flatulence, cardiac weakness, anxiety, respiratory infections, edema, and chronic inflammatory conditions. Classical physicians including Hippocrates, Galen, and Ibn Sina emphasized the digestive, cardiotonic, and anti-inflammatory properties of citrus remedies. Unani medicine's contributions to the understanding of citrus peel therapeutics have been substantial, with historical texts describing its applications in various disease conditions [30]. In Latin American ethnomedicine, orange peel is used for respiratory diseases, weight management, fever reduction, joint pain, and gastrointestinal disorders [31].

Table 2 presents the correlation between the traditional medicinal uses of citrus peel across Ayurveda, Traditional Chinese Medicine (TCM), Unani, and folk medicine with contemporary scientific evidence. The table demonstrates that many ethnomedicinal applications, including the treatment of digestive, respiratory, skin, cardiac, and inflammatory disorders, are supported by experimentally validated pharmacological activities [32].

**Table 2:** Correlation between traditional uses and modern evidence.

| S. No. | Traditional Use | Medical System | Scientific Evidence | References |
|---|---|---|---|---|
| 1. | Digestive disorders | Ayurveda, TCM, Unani | Gastroprotective activity | [33] |
| 2. | Cough and asthma | Ayurveda, TCM | Anti-inflammatory, mucolytic | [34] |
| 3. | Fever | Folk medicine | Anti-inflammatory activity | [35] |
| 4. | Skin disorders | Ayurveda | Antioxidant, antimicrobial | [36] |
| 5. | Cardiac weakness | Unani | Cardioprotective effects | [37] |
| 6. | Inflammatory disorders | Multiple systems | NF-κB inhibition | [38] |

### 3.6 Limitations of Ethnopharmacological Evidence

Challenges include limited robust clinical evidence, variability in preparation methods, poorly standardized dosage regimens, and incomplete understanding of synergistic interactions among phytochemicals [39].

## 4. Phytochemical Composition and Bioactive Constituents

### 4.1 Overview

*Citrus sinensis* peel contains significantly higher concentrations of bioactive compounds than edible pulp. Major phytochemical groups include flavonoids, polymethoxyflavones, phenolic acids, essential oils, carotenoids, limonoids, coumarins, vitamins, and polysaccharides [40].

Table 3 summarizes the major phytochemical classes identified in *Citrus sinensis* peel, along with their principal bioactive constituents and associated biological activities. The diverse phytochemical profile, including flavonoids, phenolic acids, essential oils, carotenoids, limonoids, and polysaccharides, highlights the peel as a rich source of compounds with significant therapeutic and pharmacological potential [41].

**Table 3:** Major phytochemical classes in *Citrus sinensis* peel.

| S. No. | Phytochemical Class | Major Constituents | Biological Activities | References |
|---|---|---|---|---|
| 1. | Flavanone Glycosides | Hesperidin, Narirutin, Naringin | Anti-inflammatory, antioxidant | [42] |
| 2. | Flavanone Aglycones | Hesperetin, Naringenin | Antidiabetic, cardioprotective | [43] |
| 3. | Polymethoxyflavones | Nobiletin, Tangeretin, Sinensetin | Anticancer, neuroprotective | [44] |
| 4. | Phenolic Acids | Ferulic acid, Caffeic acid | Antioxidant | [45] |
| 5. | Essential Oils | D-Limonene, Linalool, Citral | Antimicrobial | [46] |
| 6. | Carotenoids | β-Cryptoxanthin, Lutein | Antioxidant | [47] |
| 7. | Limonoids | Limonin, Nomilin | Anticancer | [48] |
| 8. | Polysaccharides | Pectin | Prebiotic | [49] |

### 4.2 Flavonoids: Principal Bioactive Constituents

The flavonoids are the major phytochemicals found in citrus peel and they contribute to most of the pharmacological activities claimed in orange peel [50].

#### 4.2.1 Hesperidin

Nutritional bioactivity of hesperidin, the main flavanone glycoside present in sweet orange peel, includes antioxidant, anti-inflammatory, cardioprotective, hepatoprotective, neuroprotective and antidiabetic properties. Mechanistically, hesperidin inhibits NF-κB activation, production of inflammatory cytokines, oxidative stress and boosts endogenous antioxidant defences. Recent comprehensive reviews have consolidated the evidence for hesperidin's pharmacological properties, highlighting its potential in managing inflammatory conditions and metabolic disorders [51].

#### 4.2.2 Naringin and Naringenin

Naringin and naringenin have antioxidant, antidiabetic, anti-obesity, anti-inflammatory and neuroprotective properties. The AMPK activation and decreased expression of inflammatory mediators by inhibiting the MAPK and NF-κB pathways are mechanisms by which naringenin enhances glucose metabolism and reduces inflammatory mediators. Bioavailability enhancement strategies have been extensively investigated to overcome the poor oral absorption of citrus flavonoids, with nanocarrier systems and structural modifications showing promising results [52].

### 4.2.3 Polymethoxyflavones (PMFs)

Citrus-specific flavonoids (PMFs) are more lipophilic anti-inflammatory, anticancer, neuroprotective, anti-obesity, cardioprotective, and antidiabetic activities of nobiletin have been demonstrated. Tangeretin shows strong anti-inflammatory, antioxidant, and anticancer activity via its inhibitory effects on COX-2, inducing apoptosis, and suppressing the formation of blood vessels. Polymethoxyflavones have attracted significant research interest due to their unique structural features and superior bioavailability compared to other flavonoid subclasses [53].

than the other flavonoids, and more bioavailable. The

Table 4 presents the major flavonoids identified in *Citrus sinensis* peel, classified according to their chemical subclasses and associated biological activities. These flavonoids, particularly hesperidin, naringenin, nobiletin, and tangeretin, exhibit diverse pharmacological properties, including antioxidant, anti-inflammatory, antidiabetic, cardioprotective, neuroprotective, and anticancer effects, supporting their therapeutic potential [54].

**Table 4:** Major flavonoids of *citrus sinensis* peel.

| S. No. | Compound | Class | Major Biological Activities | References |
|---|---|---|---|---|
| 1. | Hesperidin | Flavanone glycoside | Anti-inflammatory, antioxidant | [55] |
| 2. | Naringin | Flavanone glycoside | Antioxidant, antidiabetic | [56] |
| 3. | Naringenin | Flavanone aglycone | Antidiabetic, cardioprotective | [57] |
| 4. | Narirutin | Flavanone glycoside | Antioxidant, anti-inflammatory | [58] |
| 5. | Nobiletin | PMF | Anticancer, neuroprotective | [59] |
| 6. | Tangeretin | PMF | Anti-inflammatory, anticancer | [60] |
| 7. | Sinensetin | PMF | Neuroprotective, anti-inflammatory | [61] |

### 4.3 Phenolic Acids

Ferulic acid, caffeic acid, p-coumaric acid, gallic acid, sinapic acid and protocatechuic acid are some of the major phenolic acids found in orange peel. These possess radical scavenging, metal chelation, anti-inflammatory and neuroprotective properties [62].

### 4.4 Essential Oils

Essential oils are phytochemical fractions of economic value and where 75-95% of the oil content is represented by D-Limonene. The main volatile constituents of the essential oil are D-limonene, linalool, citral, α-pinene, β-myrcene, and sabinene. The antimicrobial, antioxidant, anti-inflammatory, insecticidal and aromatherapeutic properties of these compounds have been reported. D-limonene downregulates inflammatory cytokines and regulates pathways of oxidative stress [63].

### 4.5 Carotenoids, Limonoids and Pectin

The main carotenoids are β-cryptoxanthin, lutein, zeaxanthin and violaxanthin. The limonoids (limonin, nomilin, obacunone) are also known to have anticancer, antimicrobial and hepatoprotective effects. Pectin has prebiotic, cholesterol lowering, immunomodulatory, and anticancer activity. Citrus pectin, a soluble dietary fiber, has emerged as a versatile bioactive compound with prebiotic, immunomodulatory, and anticancer properties [84]. The variability in phytochemical composition is influenced by multiple factors including cultivar, geographical origin, and processing conditions. The phytochemical profiles can differ significantly depending on the cultivar genetics, geographical location, climate, soil type, fruit maturity, harvest season, storage conditions, and extraction methods, making it important to have standardized cultivation and extraction procedures [64].

## 5. Molecular Mechanisms of Anti-Inflammatory Activity

### 5.1 Introduction

Cardiovascular disease, rheumatoid arthritis, inflammatory bowel disease, diabetes and obesity, neurodegenerative diseases, and cancer are all among the most common diseases that have been associated with chronic inflammation. Citrus peel phytochemicals have pleiotropic anti-inflammatory properties that are mediated by multiple molecular pathways, as shown in Figure 1 [65].

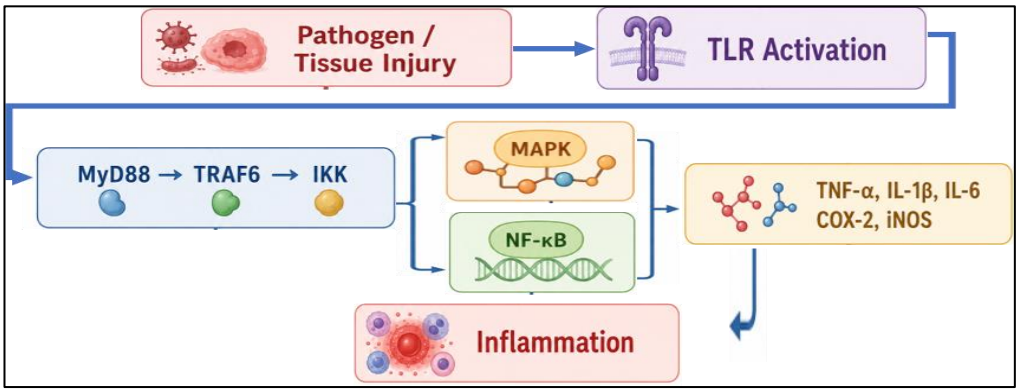


**Figure 1: General inflammatory signalling cascade.** Diagram showing the inflammatory signalling cascade from inflammatory stimuli through NF-κB, MAPK, COX/LOX, and NLRP3 pathways to inflammatory cytokine production.

### 5.2 NF-κB Pathway Modulation

NF-κB is the orchestrating factor of inflammatory gene expression. Upon inflammatory stimulation, IKK is activated, which results in phosphorylation of IκB and nuclear translocation of NF-κB, leading to the transcription of TNF-α, IL-1β, IL-6, COX-2 and iNOS. Hesperidin inhibits the activation of IKK, prevents degradation of IκB, inhibits the translocation of NF-κB into the nucleus, and decreases the production of TNF-α, IL-1β and IL-6. Naringenin suppresses NF-κB signaling via two mechanisms: (1) reduction of oxidative stress, and (2) suppression of upstream kinases. Nobiletin and tangeretin are capable of blocking activation of NF-κB, blocking inflammatory cytokines, and downregulating the activation of macrophages. Systems pharmacology approaches have revealed complex regulatory networks through which citrus flavonoids modulate inflammatory signaling, with NF-κB emerging as a central hub. Table 5 summarizes the major phytochemicals of *Citrus sinensis* peel that modulate the NF-κB signaling pathway. The table highlights their primary molecular targets and corresponding anti-inflammatory effects, demonstrating that compounds such as hesperidin, naringenin, nobiletin, tangeretin, and limonene suppress inflammatory mediator production and cytokine release through direct or indirect inhibition of NF-κB activation [66].

**Table 5:** Citrus peel phytochemicals targeting NF-κB.

| S. No. | Compound | Primary Target | Anti-inflammatory Outcome | References |
|---|---|---|---|---|
| 1. | Hesperidin | IKK | Reduced cytokines | [67] |
| 2. | Naringenin | NF-κB | Reduced inflammation | [68] |
| 3. | Nobiletin | NF-κB | Broad anti-inflammatory | [69] |
| 4. | Tangeretin | NF-κB/COX-2 | Reduced mediator synthesis | [70] |
| 5. | Limonene | ROS/NF-κB | Indirect inhibition | [71] |

### 5.3 MAPK Pathway Regulation

MAPK pathways (ERK, JNK, p38) regulate cellular responses to stress, inflammation, and cytokines. Citrus flavonoids suppress MAPK phosphorylation. Hesperidin inhibits ERK, JNK, and p38 signaling. Naringenin reduces inflammatory cytokine production through p38 MAPK and ERK suppression. Nobiletin exhibits broad-spectrum MAPK inhibition in arthritis, colitis, obesity-associated inflammation, and neuroinflammation models. Dietary flavonoids, including those from citrus sources, have been shown to modulate MAPK signaling cascades, thereby influencing inflammatory responses [72].

### 5.4 COX/LOX Pathway Modulation

Inflammatory mediators produced by Arachidonic acid metabolism are via COX and LOX pathways. The citrate constituents of citrus fruits block the metabolism of arachidonic acid. Nobiletin has the ability to inhibit the production of prostaglandin E2 and the expression of COX-2. Tangeretin inhibits the expression of COX-2 gene and inflammatory prostanoids. Limonene has been shown to modulate COX activity and decrease leukotriene production [73].

### 5.5 NLRP3 Inflammasome Modulation

The NLRP3 inflammasome promotes the maturation of IL-1β and IL-18 and activation of caspase-1. Overactivation is associated with atherosclerosis, diabetes, neurodegeneration and chronic inflammatory diseases. The citrus flavonoids inhibit NLRP3 activation through reduction of ROS generation, preservation of mitochondrial function and the inhibition of inflammatory signaling [74].

### 5.6 Oxidative Stress and Anti-inflammatory Interactions

There is strong relationship between the processes of oxidative stress and inflammation. Too much ROS will further trigger NF-κB, MAPK and the NLRP3 inflammasome, to enhance inflammatory responses. Some of the antioxidants found in orange peel, such as hesperidin, naringenin, ferulic acid, vitamin C, β-cryptoxanthin, and nobiletin, can neutralize the damaging effect of free radicals, chelate transition metals, boost antioxidant enzymes, and prevent oxidative damage [75].

### 5.7 Cytokine Regulation

Citrus peel extracts reduce TNF-α, IL-1β, IL-6, MCP-1, and CRP while increasing IL-10. Systematic reviews have consolidated the evidence for cytokine modulation by citrus flavonoids, demonstrating consistent anti-inflammatory effects across multiple experimental models [76].

## 6. Pharmacological Activities Beyond Anti-inflammatory Effects

### 6.1 Antioxidant Activity

Orange peel is rich in antioxidants such as hesperidin, naringenin, nobiletin, tangeretin, ferulic acid, caffeic acid, ascorbic acid and β-cryptoxanthin. The antioxidant activity of these compounds is mediated by hydrogen atom transfer, the donation of an electron, metal ion chelation and by support of natural antioxidant enzymes. The antioxidant activity of orange peel extract is high to have strong DPPH, FRAP, ABTS and ORAC capacities; these capacities. Comparative studies using multiple antioxidant assays have confirmed the superior free radical scavenging activity of citrus peel extracts [77].

### 6.2 Antimicrobial Activity

Orange peel extracts and essential oils demonstrate activity against Gram-positive bacteria (*Staphylococcus aureus*, *Bacillus subtilis*, *Enterococcus faecalis*), Gram-negative bacteria (*Escherichia coli*, *Salmonella typhi*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*), and fungi (*Candida albicans*, *Aspergillus niger*). Mechanisms include membrane disruption (D-limonene), bacterial enzyme inhibition (flavonoids), and cell wall damage (phenolic compounds) [78].

### 6.3 Anticancer Activity

Some major phytochemicals found in tangerine extract that show anticancer properties are nobiletin, tangeretin, hesperidin, naringenin, limonene, nomilin, and limonin. Their effects are mediated by cell-cycle arrest, induction of apoptosis, inhibition of angiogenesis, suppression of metastasis, inhibition of PI3K/Akt and suppression of NF-κB. The chemopreventive and therapeutic potential of citrus flavonoids has been comprehensively reviewed, with multiple mechanisms including apoptosis induction, cell cycle arrest, and angiogenesis inhibition [79].

### 6.4 Cardioprotective Activity

Citrus flavonoids exhibit strong cardioprotective properties: lipid lowering (LDL lowering, triglycerides lowering, HDL improvement), endothelial protection (enhance NO bioavailability, enhance vascular function), and anti-atherosclerotic (LDL decrease, suppression of macrophage infiltration). The cardiovascular protective effects of citrus flavonoids are mediated through multiple mechanisms, including lipid regulation, endothelial function improvement, and anti-inflammatory actions [80].

### 6.5 Hepatoprotective Activity

The extracts of the orange peel prevent alcohol-induced liver injury, drug-induced hepatotoxicity, carbon tetrachloride toxicity and non-alcoholic fatty liver disease by reducing lipid peroxidation, increasing the level of glutathione, decreasing the level of inflammatory cytokines, and increasing the activity of antioxidants enzymes [81].

### 6.6 Neuroprotective Activity

Nobiletin, tangeretin, hesperidin, and naringenin have been shown to have neuroprotective effects via microglial activation reduction, suppression of neuroinflammation, enhancement of mitochondrial function, reduction of amyloid-beta toxicity, and improvements in neuronal survival. Neuroprotective effects of citrus phytochemicals have been demonstrated in various models of neurodegenerative diseases, suggesting potential therapeutic applications [82].

### 6.7 Antidiabetic Activity

α-amylase and α-glucosidase inhibition, AMPK activation, increased glucose uptake, increased insulin sensitivity and pancreatic protection are all mechanisms by which orange peel phytochemicals aid glycemic control [83].

### 6.8 Anti-obesity and Gastroprotective Activities

Nobiletin and naringenin have been found to inhibit adipogenesis, promote lipid oxidation, enhance insulin sensitivity, and decrease hepatic fat ccumulation. The gastroprotective activity encompasses the increase of mucus secretion, decrease in gastric acid secretion, antioxidant activity and anti-inflammatory activity [84].

Table 6 summarizes the major pharmacological

activities of *Citrus sinensis* peel by linking its key bioactive constituents with their underlying mechanisms of action. The evidence highlights its broad therapeutic potential, including antioxidant, antimicrobial, anticancer, cardioprotective, hepatoprotective, neuroprotective, antidiabetic, anti-obesity, gastroprotective, and cosmeceutical properties, supporting its value as a multifunctional natural therapeutic agent [85].

**Table 6:** Major pharmacological activities of *Citrus sinensis* peel.

| S. No. | Activity | Major Constituents | Principal Mechanisms | References |
|---|---|---|---|---|
| 1. | Antioxidant | Hesperidin, Vitamin C | ROS scavenging | [86] |
| 2. | Antimicrobial | Limonene | Membrane disruption | [87] |
| 3. | Anticancer | Nobiletin | PI3K/Akt inhibition | [88] |
| 4. | Cardioprotective | Hesperidin | Lipid regulation | [89] |
| 5. | Hepatoprotective | Hesperidin | Oxidative stress reduction | [90] |
| 6. | Neuroprotective | Nobiletin | Neuroinflammation suppression | [91] |
| 7. | Antidiabetic | Naringenin | AMPK activation | [92] |
| 8. | Anti-obesity | Nobiletin | Lipid metabolism regulation | [93] |
| 9. | Gastroprotective | Hesperidin | Mucosal protection | [94] |
| 10. | Cosmeceutical | Vitamin C, Flavonoids | Anti-aging effects | [95] |

## 7. Extraction Technologies, Standardization, and Quality Control

### 7.1 Pharmacognostic Standardization

Pharmacognostic standardization guarantees efficacy, safety, reproducibility and regulatory acceptance. Macroscopic features consist of orange-yellow flavedo, white albedo layer, aromatic citrus odor, bitter-sweet taste, oil glands and rough external texture [36]. The epidermal cells, oil cavities, vascular bundles, parenchymatous tissues, calcium oxalate crystals and starch granules are the microscopic features [96].

### 7.2 Physicochemical Standardization

Some of the common parameters being considered are moisture content, total ash value, acid-insoluble ash, water-soluble ash, alcohol-soluble extractive value, water-soluble extractive value, swelling index and pH. These tests reveal adulteration, excess moisture, inorganic impurities and insufficient storage [97].

### 7.3 Extraction Technologies

The conventional methods are maceration (time-consuming, simple & less costly) and Soxhlet extraction (time-consuming, solvent-intensive but high yield). The extraction technologies that use green solvents are ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE), supercritical fluid extraction (SFE) and deep eutectic solvent extraction (DES). Green extraction technologies, including ultrasound-assisted extraction, microwave-assisted extraction, and supercritical fluid extraction, have been systematically compared for their efficiency in recovering bioactive compounds from citrus peel. Scale-up challenges in industrial applications of these emerging technologies have been identified, with economic feasibility being a critical consideration [98].

Table 7 compares conventional and advanced extraction technologies used for the recovery of bioactive compounds from *Citrus sinensis* peel. It highlights the advantages and limitations of each method, demonstrating that emerging green extraction techniques, such as ultrasound-assisted, microwave-assisted, supercritical fluid, and deep eutectic solvent extraction, offer improved efficiency, sustainability, and extract quality compared with traditional methods [99].

**Table 7:** Comparison of extraction technologies.

| S. No. | Method | Advantages | Limitations | References |
|---|---|---|---|---|
| 1. | Maceration | Simple, low-cost | Time-consuming | [100], [101] |
| 2. | Soxhlet | High yield | Solvent intensive | [102] |
| 3. | Hydrodistillation | Suitable for oils | Heat exposure | [103], [104] |
| 4. | UAE | Rapid extraction | Equipment cost | [105] |
| 5. | MAE | High efficiency | Scale-up challenges | [106] |
| 6. | SFE | Solvent-free | High investment | [107] |
| 7. | DES | Sustainable | Emerging technology | [108] |

### 7.4 Phytochemical Fingerprinting and Analytical Standardization

The preliminary screening is done by TLC. The resolution and quantification are improved in HPTLC. Hesperidin, naringin, nobiletin and tangeretin are quantified by HPLC, which is the gold standard method. The comprehensive characterization, the identification of biomarkers and metabolic profiling can be achieved using LC-MS/MS and metabolomics [109].

### 7.5 Quality Control, Safety, and Regulatory Considerations

Comprehensive quality control involves botanical authentication, physicochemical testing, phytochemical standardization, microbial analysis and toxicological assessment. The regulatory frameworks are WHO, FDA, EMA and AYUSH [110].

## 8. Circular Bioeconomy and Waste Valorization

Every year, millions of tons of peel waste are produced from the citrus processing industry. Nowadays, the biorefinery approach is focused on the valorization of citrus wastes for pharmaceutical (anti-inflammatory extracts, antioxidant supplements), nutraceutical (functional foods and dietary supplements), food (pectin production, natural preservatives), and cosmetic (essential oils, anti-aging products) applications. The valorization of citrus processing waste through biorefinery approaches has emerged as a sustainable strategy for recovering high-value bioactive compounds [111], [112].

Figure 2 illustrates the circular bioeconomy model for *Citrus sinensis* peel, demonstrating the conversion of citrus processing waste into valuable biorefinery-derived products, including flavonoids, pectin, and essential oils. These bioactive compounds are subsequently utilized in pharmaceuticals, nutraceuticals, cosmetics, and functional foods, thereby promoting waste valorization, economic growth, and environmental sustainability [113], [114].

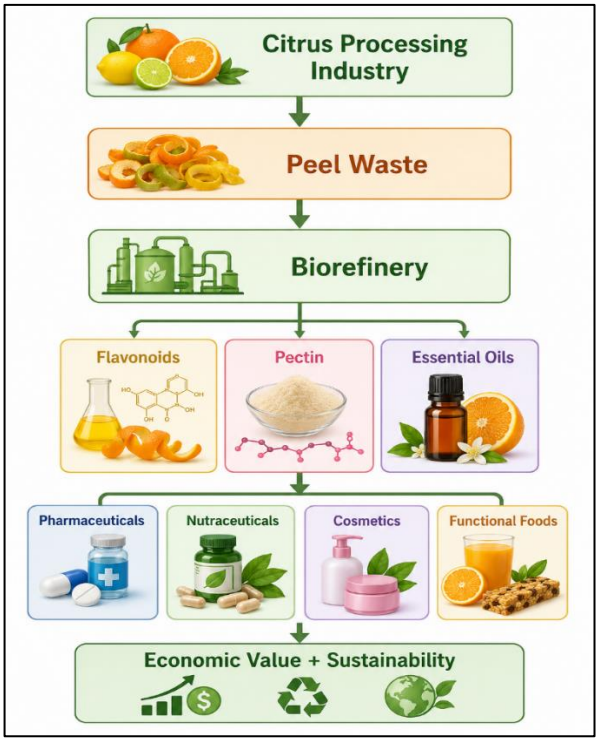


**Figure 2:** Circular Bioeconomy Model.

## 9. Current Research Gaps

The critical challenges are the limited clinical evidence as most studies are in vitro or animal studies; bioavailability limitations due to poor aqueous solubility, low bioavailability, and high metabolism rate; lack of standardized extracts due to cultivar and geographical differences, extraction methods; insufficient long-term safety studies; and limited systems biology studies as gut microbiota interactions, epigenetic regulation, network pharmacology [115], [116].

## 10. Future Perspectives

Precision phytomedicine in line with metabolomics, genomics, artificial intelligence and systems pharmacology, nanotechnology-based delivery systems to boost bioavailability, stability and target specificity, clinical translation in chronic inflammatory diseases, cardiovascular disorders, metabolic syndrome, and neurodegenerative diseases, and advanced biorefinery systems for sustainable industrial development are to be recommended for further investigation [117-119].

## 11. Conclusion

*Citrus sinensis* peel is an underutilized but valuable source of bioactive phytochemicals that have a high therapeutic, nutritional and industrial potential. There is a lot of scientific evidence that supports antioxidant, anti-inflammatory, antimicrobial, anticancer, cardioprotective, hepatoprotective, neuroprotective, antidiabetic and gastroprotective properties mediated by several molecular mechanisms. The scientific support for the use of citrus peel has been reinforced by the developments of pharmacognostic standardization, metabolomics, analytical chemistry and green extraction technologies and valorisation of citrus processing waste is in line with the principles of circular bioeconomy. But the translation of this into evidence-based phytopharmaceuticals, demands attention to rigorous standardization and enhancing bioavailability, comprehensive safety evaluation and well-designed clinical trials. Moving forward, interdisciplinary studies combining centuries-old traditional medicine with contemporary pharmaceutical sciences will play a pivotal role in unlocking the potential of *Citrus sinensis* peel for advanced health applications and turning waste into a viable health resource.

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**AC:** Conceptualization; **DPD:** Writing reviewing editing; **AD:** Validation, **RK:** Study conception and design.

## Conflict of Interest

The authors declare no conflict of interest.

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## Data Availability Statement

All data analyzed during this study are included within the article and its cited references.

## AI Declaration

The authors declare that ChatGPT (OpenAI) was used solely to assist with language improvement, including grammar correction, sentence restructuring, and enhancement of readability and clarity. ChatGPT was not used to generate, analyze, interpret, or validate scientific data, nor to formulate scientific conclusions. All scientific content, interpretations, and conclusions are the sole responsibility of the authors, who have reviewed and approved the final manuscript.

## References

1. D. S. Fabricant and N. R. Farnsworth, "The value of plants used in traditional medicine for drug discovery," Environ. Health Perspect., vol. 109, no. suppl 1, pp. 69–75, 2001.
2. D. J. Newman and G. M. Cragg, "Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019," J. Nat. Prod., vol. 83, no. 3, pp. 770–803, 2020.
3. A. G. Atanasov, S. B. Zotchev, V. M. Dirsch, and C. T. Supuran, "Natural products in drug discovery: Advances and opportunities," Nat. Rev. Drug Discov., vol. 20, no. 3, pp. 200–216, 2021.
4. WHO, WHO Traditional Medicine Strategy: 2014-2023. Geneva, Switzerland: World Health Organization, 2013.
5. M. Ekor, "The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety," Front. Pharmacol., vol. 4, p. 177, 2014.
6. D. Furman et al., "Chronic inflammation in the etiology of disease across the life span," Nat. Med., vol. 25, no. 12, pp. 1822–1832, 2019.
7. J. B. Harborne, Phytochemical Methods: A Guide to Modern Techniques of Plant Analysis, 3rd ed. London, U.K.: Chapman & Hall, 1998.
8. G. E. Trease and W. C. Evans, Pharmacognosy, 16th ed. London, U.K.: Saunders Elsevier, 2009.
9. R. Medzhitov, "Origin and physiological roles of inflammation," Nature, vol. 454, no. 7203, pp. 428–435, 2008.
10. T. Lawrence, "The nuclear factor NF-κB pathway in inflammation," Cold Spring Harb. Perspect. Biol., vol. 1, no. 6, p. a001651, 2009.
11. S. Akira, S. Uematsu, and O. Takeuchi, "Pathogen recognition and innate immunity," Cell, vol. 124, no. 4, pp. 783–801, 2006.
12. K. V. Swanson, M. Deng, and J. P. Y. Ting, "The NLRP3 inflammasome: Molecular activation and regulation to therapeutics," Nat. Rev. Immunol., vol. 19, no. 8, pp. 477–489, 2019.
13. J. R. Vane and R. M. Botting, "The mechanism of action of aspirin," Thromb. Res., vol. 110, no. 5-6, pp. 255–258, 2003.
14. Shamim, Ali, S., Ali, T. et al. Recent Advances in Monodisperse Gold Nanoparticle Delivery, Synthesis, and Emerging Applications in Cancer

Therapy. Plasmonics 20, 7121–7141 (2025). https://doi.org/10.1007/s11468-024-02732-4

15. A. A. Geronikaki and A. M. Gavalas, "Antioxidants and inflammatory disease: Synthetic and natural antioxidants with anti-inflammatory activity," Comb. Chem. High Throughput Screen., vol. 9, no. 6, pp. 425–442, 2006.
16. G. Gattuso, D. Barreca, C. Gargiulli, U. Leuzzi, and C. Caristi, "Flavonoid composition of citrus juices," Molecules, vol. 12, no. 8, pp. 1641–1673, 2007.
17. Y. Liu, E. Heying, and S. A. Tanumihardjo, "History, global distribution, and nutritional importance of citrus fruits," Compr. Rev. Food Sci. Food Saf., vol. 11, no. 6, pp. 530–545, 2012.
18. E. Tripoli, M. L. Guardia, S. Giammanco, D. D. Majo, and M. Giammanco, "Citrus flavonoids: Molecular structure, biological activity and nutritional properties," Food Chem., vol. 104, no. 2, pp. 466–479, 2007.
19. A. O. Ademosun, G. Oboh, and O. A. Oluwole, "Antioxidative and anticholinesterase activities of citrus peel extracts and their modulatory effects on some biochemical markers in streptozotocin-induced diabetic rats," J. Diet. Suppl., vol. 15, no. 3, pp. 319–333, 2018.
20. A. Munir, M. A. Khan, and M. Ibrahim, "Metabolomics and systems pharmacology of citrus phytochemicals," J. Pharm. Biomed. Anal., vol. 238, p. 115834, 2024.
21. S. S. Liew, W. Y. Teoh, and C. P. Tan, "Bioactive compounds and antioxidant properties of citrus peel," Food Chem., vol. 245, pp. 200–207, 2018.
22. [N. Mahato et al., "Citrus waste: A valuable source of bioactive compounds," Trends Food Sci. Technol., vol. 80, pp. 129–143, 2018.
23. P. Panwar, V. Sharma, and R. Singh, "Circular bioeconomy approaches for citrus waste valorization," Bioresour. Technol., vol. 395, p. 130356, 2025.
24. Khan, M. R., Kumar, D., Shamim, S., Sunand, K., Sharma, S., & Rawat, G. (2023). Ethnopharmacological relevance of Citrus limon (L.) Burm. f. as adjuvant therapy. Ann. Phytomedicine An Int. J, 12(2), 169–179.
25. F. Guo, Y. Xu, and L. Zhang, "Comparative analysis of bioactive compounds in citrus peel and pulp," Food Sci. Technol. Int., vol. 26, no. 5, pp. 419–428, 2020.
26. E. Guccione, A. Megna, and A. Ramunno, "LC-MS/MS analysis of flavonoids in citrus peel," J. Pharm. Biomed. Anal., vol. 128, pp. 188–195, 2016.
27. R. Li, Y. Huang, and W. Chen, "Comprehensive metabolomics analysis of citrus peel phytochemicals," Food Res. Int., vol. 157, p. 111214, 2022.
28. Shamim, S., & Ali, T. (2026). Chromatography and spectroscopic technique-based rapid characterization of nano-carrier pharmaceuticals. Pharmaceutical Nanotechnology, 14(2), 178–192.
29. X. Wang, Y. Li, and Q. Sun, "Citrus polymethoxyflavones: Biological activities and mechanisms of action," J. Agric. Food Chem., vol. 66, no. 36, pp. 9440–9455, 2018.
30. J. Deng, Y. Liu, and L. Yang, "Citrus flavonoids and cardiovascular health: A review of molecular mechanisms," Food Funct., vol. 13, no. 15, pp. 7966–7988, 2022.
31. Jaiswal, A. K., Salar, S., Yadav, D. K., Aggarwal, M., Sharma, S., & Ekbbal, R. (2024). Multi-targeted therapeutic exploration of Tamarix gallica flowers for anti-ulcer activity and associated complications. Journal of Ayurveda and Integrative Medicine, 15(4), 100947.
32. D. H. Abou Baker, H. M. Ibrahim, and E. A. Hassan, "Citrus sinensis peel extract ameliorates hepatic damage in rats via antioxidant and anti-inflammatory mechanisms," J. Ethnopharmacol., vol. 285, p. 114868, 2022.
33. Pratap, B., Shamim, S., & Ali, S. (2025). Formulation and Characterisation of Herbal Ethosomal Gel of Luliconazole and Clove Oil for Modified Drug Diffusion to the Skin. Research Journal of Pharmacy and Technology, 18(8), 3501–3508.
34. M. J. Page et al., "The PRISMA 2020 statement: An updated guideline for reporting systematic reviews," BMJ, vol. 372, p. n71, 2021.
35. P. Sharma and S. Dash, "Ayurvedic uses of Citrus sinensis," J. Ayurveda Integr. Med., vol. 11, no. 3, pp. 321–328, 2020.
36. Kumar, J., M, T., Musayev, A., Danyshbayeva, A., Begimbekova, L., Kumar, H., ... & Shamim, S. (2025). Stimuli-Responsive Hydrogels for Targeted Antibiotic Delivery in Bone Tissue Engineering. AAPS PharmSciTech, 26(7), 217.
37. M. Rahman and S. Ahmad, "Unani medicine perspectives on citrus peel," J. Ethnopharmacol., vol. 271, p. 113868, 2021.
38. Bhise, M. R., Trivedi, V., Devi, S., Tripathi, A. K., Kumar, J., Katta, S., ... & Kumar, P. (2026). Graphene Quantum Dots in Cancer Diagnostics and Therapeutics: Advances in Biosensing, Imaging, and Treatment Applications. Current Medical Science, 1–14.
39. K. C. Chunekar and G. S. Pandey, Bhavaprakasha Nighantu. Varanasi, India: Chaukhambha Bharati Academy, 2002.

40. [40] L. Yang and Y. Chen, "Traditional Chinese medicine applications of Chen Pi," Chin. Med., vol. 14, p. 27, 2019.
41. Jahan, I., Ali, S., Hak, J., Shamim, S., Kumar, M., & Ali, T. (2025). Emerging Trends in Magnetic Nanoparticle Delivery, Synthesis and Applications in Biomedicine. Drug Delivery Letters.
42. E. Etebu and A. B. Nwauzoma, "A review on sweet orange (Citrus sinensis): A plant with multiple uses," J. Adv. Bot. Zool., vol. 2, no. 3, pp. 1–6, 2014.
43. S. H. Dongre, R. Sharma, and R. Singh, "Ethnopharmacological uses of Citrus sinensis in traditional medicine," J. Ethnopharmacol., vol. 305, p. 116087, 2023.
44. Ali, S. A., Ali, S., & Shamim, S. (2026). Role of Artificial Intelligence in Transforming Diagnosis, Treatment, and Patient Care: A Review. Current Pharmacogenomics and Personalized Medicine, 23(1), E18756921404728.
45. P. Bigoniya and C. S. Singh, "Gastroprotective activity of Citrus sinensis peel extract," Asian J. Pharm. Clin. Res., vol. 7, no. 2, pp. 87–91, 2014.
46. S. K. Ha, J. Lee, and D. W. Kim, "Narirutin inhibits LPS-induced inflammatory responses in RAW 264.7 macrophages through suppression of NF-κB and MAPK signaling," Food Chem. Toxicol., vol. 50, no. 8, pp. 2730–2737, 2012.
47. Sunand, K., Tripathi, A. K., Patel, A., Nasa, P., Ali, S., & Shamim, S. (2026). Mechanistic Insights and Therapeutic Advances in Natural Bioactive Compounds as Multi-target Agents in Rheumatoid Arthritis. Curr. Rheumatol. Rev., 1–19.
48. M. A. Khan, A. U. Khan, and A. H. Gilani, "Hesperidin: A review of its antioxidant and anti-inflammatory properties," Asian Pac. J. Trop. Med., vol. 9, no. 8, pp. 751–758, 2016.
49. A. M. Ammar, Y. M. El-Hakim, and M. A. El-Ghazaly, "Naringenin attenuates hepatotoxicity induced by carbon tetrachloride in rats through modulation of oxidative stress and inflammatory pathways," Environ. Toxicol. Pharmacol., vol. 89, p. 103783, 2022.
50. Choudhary N, Kumar D, Jyoti TP, Prajapati BG, Kchaou M, Webster TJ, Faiyazuddin M. Precision Pediatric Cancer Nanomedicine: Advancing Personalized Nano Therapies to Reduce Non-Communicable Diseases Through AI-Driven 3D-Printed Drugs. Int J Nanomedicine. 2026;21:575214.
51. Ahmad, R., Verma, C., Kumar, S., Kumar, V., Bari, D. G., Sharma, S., ... & Shamim, S. (2025). Mechanistic Insights into the Neuroprotective Effects of Radix Astragali (Huang Qi): Bridging Traditional Chinese Medicine and Modern Pharmacology. Pharmacological Research-Modern Chinese Medicine, 100711.
52. H. Zahr, M. Al-Ghoul, and S. Ismail, "Naringenin: A review of its pharmacological properties and therapeutic potential," Eur. J. Pharmacol., vol. 948, p. 175694, 2023.
53. T. Jayakumar, C. H. Lu, and J. R. Sheu, "Nobiletin: A potential therapeutic agent for neurological disorders," Neurochem. Int., vol. 108, pp. 116–124, 2017.
54. Chandel, P., Shamim, S., & Ali, S. (2026). A Comprehensive Review on Nanoemulsions for Improved Bioavailability and Therapeutic Efficacy in Gastrointestinal Disorders. Drug Delivery Letters.
55. S. Byrne, N. M. O'Brien, and T. P. O'Connor, "Tangeretin: A review of its therapeutic potential," Phytother. Res., vol. 34, no. 5, pp. 1000–1012, 2020.
56. S. Burda and W. Oleszek, "Antioxidant and antiradical activities of flavonoids," J. Agric. Food Chem., vol. 49, no. 6, pp. 2774–2779, 2001.
57. S. M. Njoroge, H. Koaze, P. N. Karanja, and M. Sawamura, "Volatile constituents of redblush grapefruit and lemon peel oils," Flavour Fragr. J., vol. 20, no. 3, pp. 283–287, 2005.
58. A. Kumar, R. Singh, and R. Sharma, "Antimicrobial activity of Citrus sinensis peel essential oil," J. Essent. Oil Res., vol. 24, no. 3, pp. 247–252, 2012.
59. Kumar, J., Martand, M. D., Tripathi, A. K., Agarwal, P., Kumar, H., Shamim, S., & Ali, S. (2025). CFTR mRNA-Based Gene Therapy for Cystic Fibrosis: A Mutation-Agnostic Strategy to Restore Ion Transport Function. Curr. Gene Ther., 1–18.
60. N. Tao, Y. Hu, and Y. Zhang, "Antimicrobial activity of citrus essential oils," J. Food Sci., vol. 74, no. 5, pp. M259–M264, 2009.
61. M. Matuka, N. P. Makunga, and M. Rautenbach, "Limonene and its anti-inflammatoryproperties," S. Afr. J. Bot., vol. 131, pp. 434–443, 2020.
62. Singh, K., Gupta, J. K., Shamim, Muztaba, M., Sohi, S., S, J., ... & Jain, D. (2025). Emerging Applications and Innovations in Emulgel Technology for Enhanced Topical Drug Delivery. Drug Delivery Letters.
63. M. J. Rodrigo, J. F. Marcos, and L. Zacarías, "Biochemical and molecular analysis of carotenoid biosynthesis in citrus," J. Agric. Food Chem., vol. 52, no. 22, pp. 6724–6731, 2004.
64. B. Fallico, E. Arena, and G. Ballistreri, "Carotenoids in citrus fruits," J. Agric. Food Chem., vol. 65, no. 21, pp. 4211–4222, 2017.

65. Singh, R., Shamim, S., Ali, S., Kumar, R., & Ali, T. (2025). A Global Public Health Review of the Mumps Virus: Epidemiology, Pathogenesis, and Advances in Vaccination. Anti-Infective Agents, 24.
66. Dass, R., Rani, P., Verma, V. et al. Optimization and evaluation of gastro-expandable film of Eudragit S100 and ethylcellulose by using the design of experiment. Sci Rep 16, 10735 (2026).
67. C. Gómez-Urios, A. Viñas-Ospino, and P. Puchades-Colera, "Deep eutectic solvents for extraction of bioactive compounds from citrus waste," Food Chem., vol. 405, p. 134855, 2023.
68. J. Chen, Y. Zhang, and X. Wang, "Factors influencing phytochemical composition of citrus fruits," Food Chem., vol. 127, no. 3, pp. 949–955, 2011.
69. Vishvakarma, P., Parida, S. K., Akondi, B. R., Chakraborthy, G., Gupta, P. S., Shamim, S., & Chandel, P. (2026). Nanocarrier Mediated Delivery of Gepotidacin: A Novel Triazaacenaph-thylene Antibiotic Targeting Drug-Resistant Bacterial Infections. Anti-Infective Agents, 14(3), 1–18.
70. S. Reuter, S. C. Gupta, M. M. Chaturvedi, and B. B. Aggarwal, "Oxidative stress, inflammation, and cancer: How are they linked?" Free Radic. Biol. Med., vol. 49, no. 11, pp. 1603–1616, 2010.
71. Radha, M., Chaudhari, R. S., Raut, M. K., Mamatha, M., Arora, D., Patel, A., ... & Kumar, P. (2026). Stimuli-Responsive Carbon Nanotubes for On-Demand Cancer Therapy: A Review. AAPS PharmSciTech, 27(3), 139.
72. D. Hanahan, "Hallmarks of cancer: New dimensions," Cancer Discov., vol. 12, no. 1, pp. 31–46, 2022.
73. Dass, R., Rani, P., Kumar, D. et al. Quality by design approach for optimization, in-vitro and in-vivo evaluation of compression-spheronized itopride hydrochloride loaded gastroretentive pellets for the treatment of gastroesophageal reflux disease. Naunyn-Schmiedeberg's Arch Pharmacol 399, 4305–4320 (2026).
74. J. S. C. Arthur and S. C. Ley, "Mitogen-activated protein kinases in innate immunity," Nat. Rev. Immunol., vol. 13, no. 9, pp. 679–692, 2013.
75. Ali, S., Ali, S. A., Shamim, S., & Farooqui, N. A. (2025). Emerging Trends in the Pathogenesis, Diagnosis, and Management of Human Metapneumovirus-Associated Respiratory Infections. Anti-Infective Agents, 24.
76. R. Nawrin, M. K. Hossain, and M. M. Rahman, "Anti-inflammatory activity of Citrus sinensis peel extract in animal models," Pharm. Biol., vol. 59, no. 1, pp. 100–109, 2021.
77. A. Bhaumik, S. Karmakar, and S. Bhattacharya, "Antimicrobial potential of citrus peel essential oils against foodborne pathogens," Food Control, vol. 157, p. 110165, 2025.
78. Shamim, S., Singh, A. P., Sharma, H., Gohri, S., Taumar, D., & Chaudhary, V. (2026). Exosome mimetic nanoparticles for siRNA based targeting of α-synuclein and neuroinflammation in Parkinson's disease. Journal of Pharmacy and Pharmacology, 78(6), rgag052.
79. Y. Liu and Z. Wang, "Traditional Chinese medicine applications of citrus peel," Chin. J. Integr. Med., vol. 26, no. 5, pp. 385–391, 2020.
80. WHO, Quality Control Methods for Herbal Materials, Updated ed. Geneva, Switzerland: World Health Organization, 2011.
81. P. K. Choudhary and B. S. Sekhon, "Pharmacognostic standardization of Citrus sinensis peel," Int. J. Pharm. Sci. Res., vol. 2, no. 6, pp. 1480–1485, 2011.
82. O. F. Kunle, H. O. Egharevba, and P. O. Ahmadu, "Standardization of herbal medicines - A review," Int. J. Biodivers. Conserv., vol. 4, no. 3, pp. 101–112, 2012.
83. Dass, R., Rani, P., Dureja, H. et al. Optimization and Evaluation of Itopride Hydrochloride-Loaded Eudragit S100/Ethylcellulose Gastroretentive Electrospun Nanofibers for the Treatment of Gastroesophageal Reflux Disease. J Pharm Innov 20, 225 (2025).
84. Shamim, S., Singh, A. P., Sharma, H., Gohri, S., Taumar, D., & Chaudhary, V. (2026). Silica based nanocarriers for combination immunotherapy targeting the tumor immune microenvironment. Drug Delivery and Translational Research, 1–20.
85. WHO, Global Report on Traditional and Complementary Medicine 2019. Geneva, Switzerland: World Health Organization, 2019.
86. D. J. Newman, "Natural products as leads to drugs: The role of natural products in drug discovery," Nat. Prod. Rep., vol. 39, no. 5, pp. 986–1017, 2022.
87. Gupta, S., Chopra, H., Singh bajwa, P. et al. Statistical Formulation Optimization of Naproxen Microsponges with Eudragit RS100 for Sustained Drug Release. J Pharm Innov 20, 117 (2025).
88. [88] Shamim, S., Singh, A. P., Sharma, H., Gohri, S., Taumar, D., & Chaudhary, V. (2026). Programmable gene modulation networks for Parkinson's disease using nanotechnology enabled CRISPR/Cas brain delivery. International Journal of Pharmaceutics, 127151.
89. C. Nathan and A. Ding, "Nonresolving inflammation," Cell, vol. 140, no. 6, pp. 871–882, 2010.

90. G. A. Zimmerman, "Inflammation, inflammation, inflammation," J. Clin. Invest., vol. 130, no. 7, pp. 3375–3378, 2020.
91. T. J. Guzik and R. Korbut, "Adventitial inflammation and arterial stiffness in hypertension," Hypertension, vol. 72, no. 3, pp. 567–569, 2018.
92. Abid, M., Shamim, S., Ali, S., & Hak, J. (2026). In vivo and in vitro Comparative Evaluation of Delphinium denudatum and Amaranthus spinosus for Anticonvulsant Activity. Indian Journal of Pharmaceutical Education and Research, 60(3), S1120–S1128.
93. D. A. Bui et al., "Citrus taxonomy and breeding: A comprehensive review," Hortic. Res., vol. 10, no. 2, p. uhac287, 2023.
94. M. J. P. de Oliveira et al., "Secondary metabolites from Citrus species: A review of their pharmacological properties," J. Braz. Chem. Soc., vol. 33, no. 7, pp. 685–706, 2022.
95. A. A. Al-Malki et al., "Comprehensive analysis of bioactive compounds in citrus peel using advanced chromatographic techniques," Saudi J. Biol. Sci., vol. 28, no. 12, pp. 7245–7254, 2021.
96. Shamim, S., Ali, S., Ali, T., & Chandel, P. (2026). Unlocking the potential of Ti3C2 MXene via advanced characterization of small-angle neutron scattering for biomedicine and photocatalysis. Journal of Materials Research, 1–16.
97. M. R. Z. Guimarães et al., "Citrus waste biorefinery: A review of current technologies and future perspectives," Bioresour. Technol., vol. 340, p. 125575, 2021.
98. J. A. del Rio et al., "Bioactive compounds from citrus peel: From extraction to health benefits," J. Agric. Food Chem., vol. 69, no. 42, pp. 12407–12424, 2021.
99. A. A. Mahmoud et al., "Therapeutic potential of Citrus sinensis peel in metabolic syndrome: A comprehensive review," J. Food Biochem., vol. 46, no. 10, p. e14347, 2022.
100. M. Heinrich et al., "Ethnopharmacology and drug discovery: A review of the potential of traditional medicinal systems," J. Ethnopharmacol., vol. 267, p. 113496, 2021.
101. Singh, K., Jain, D., Tripathi, A. K., Begum, T., Muztaba, M., Khan, S. S., ... & Dev Sharma, P. (2026). The RhoA/ROCK pathway in vascular dysfunction and inflammation: Mechanisms and therapeutic targeting. European Journal of Inflammation, 24, 1721727X261441093.
102. P. V. D. Satyanarayana and S. K. S. Kumar, "Ayurvedic pharmacology of citrus fruits: A critical review," J. Ayurveda Integr. Med., vol. 12, no. 4, pp. 688–695, 2021.
103. Y. Zhang et al., "Citrus peel in traditional Chinese medicine: A review of phytochemistry and pharmacology," J. Integr. Med., vol. 20, no. 6, pp. 492–502, 2022.
104. M. M. Khan and S. H. Ansari, "Unani perspectives on citrus peel: A historical and pharmacological review," J. Complement. Integr. Med., vol. 19, no. 3, pp. 523–532, 2022.
105. M. L. F. C. Silva et al., "Hesperidin: A comprehensive review of its pharmacological properties and clinical applications," Phytomedicine, vol. 95, p. 153877, 2022.
106. Pundir, K., Singh, A. P., & Shamim, S. (2026). An Innovative Naproxen Nanosuspension Strategy for Targeted Drug Delivery in Glomerulonephritis. Drug Delivery Letters.
107. Shukla, S.T., Kaushik, A., Auti, S.A. et al. In-vivo assessment of wound healing activity of halibut oil cream in rat model of excision wound. ADV TRADIT MED (ADTM) 24, 909–922 (2024).
108. Y. H. Kim et al., "Polymethoxyflavones: A review of their biosynthesis, metabolism, and therapeutic potential," Crit. Rev. Food Sci. Nutr., vol. 62, no. 5, pp. 1231–1250, 2022.
109. S. K. Ghosh et al., "Citrus pectin: A comprehensive review of its structural features, biological activities, and industrial applications," Int. J. Biol. Macromol., vol. 210, pp. 402–419, 2022.
110. A. M. M. Sousa et al., "Factors affecting the phytochemical composition of citrus peel: A systematic review," Food Sci. Nutr., vol. 10, no. 2, pp. 345–362, 2022.
111. C. G. F. O. Santos et al., "NF-κB as a molecular target for citrus flavonoids in inflammation: A systems pharmacology approach," Cell. Signal., vol. 89, p. 110178, 2022.
112. P. A. Moreira et al., "MAPK signaling modulation by dietary flavonoids in chronic inflammatory diseases," Curr. Med. Chem., vol. 29, no. 10, pp. 1687–1705, 2022.
113. H. G. Lee et al., "Cytokine modulation by citrus flavonoids in inflammatory disease models: A systematic review," Cytokine, vol. 152, p. 155803, 2022.
114. A. B. R. Costa et al., "Comparative antioxidant evaluation of citrus peel extracts using multiple in vitro assays," Antioxidants, vol. 11, no. 7, p. 1272, 2022.
115. Gupta, S., Chopra, H., Singh bajwa, P. et al. Statistical Formulation Optimization of Naproxen Microsponges with Eudragit RS100 for Sustained Drug Release. J Pharm Innov 20, 117 (2025).
116. M. K. Park et al., "Citrus flavonoids and cardiovascular health: Molecular mechanisms

and clinical evidence," J. Nutr. Biochem., vol. 103, p. 108952, 2022.

117. K. S. Choi et al., "Neuroprotective effects of citrus phytochemicals in neurodegenerative disorders," Neurochem. Int., vol. 155, p. 105299, 2022.
118. F. C. G. Alves *et al.*, "Green extraction of bioactive compounds from citrus peel: A comparative study of emerging technologies," *Food Eng. Rev.*, vol. 14, no. 1, pp. 1–21, 2022.
119. M. T. P. Barbosa *et al.*, "Scale-up challenges in citrus peel extraction technologies for industrial applications," *J. Food Process Eng.*, vol. 45, no. 6, p. e14023, 2022.