Nutraceutical Potential and Toxicological Concerns of Citrus Fruit Phytoconstituents: A Review

Olorunfemi R. Molehin[a,*], Olulope O. Ajayi[b], Stephen A. Adefegha[c], Adenike C. Ogunro[d] Aderonke E. Fakayode[e]

[a]*Department of Biochemistry, Faculty of Life Sciences, Ekiti State University, Ado-Ekiti, P.M.B. 5363, Ado-Ekiti, 360001, Nigeria*

[b]*Department of Biochemistry, Edo State University Uzairue (Formerly Edo University Iyamho), Edo State, Nigeria*

[c]*Functional Foods and Nutraceuticals Unit, Department of Biochemistry, Federal University of Technology, Akure, P.M.B.704. Akure, 340001, Nigeria*

[d]*Department of Biochemistry, School of Life Sciences, Federal University of Minna, Bosso campus, Minna, Niger State, Nigeria*

[e]*Bioinformatics and Molecular Biology Unit, Department of Biochemistry, Federal University of Technology, P.M.B. 704, Akure, 340001, Nigeria*

*Corresponding Author: Olorunfemi R. Molehin, PhD, MNSBMB, AMRSC
Email: *olorunfemi.molehin@eksu.edu.ng*; Tel: +234-803-462-1267

Abstract

Citrus refers to a genus of flowering shrubs and trees belonging to the Rutaceae family. Citrus fruits are among the most widely cultivated and consumed fruits globally, serving as important sources of nutrients and nutraceuticals. Major species include *Citrus sinensis* (sweet orange), *Citrus limon* (lemon), *Citrus paradisi* (grapefruit), *Citrus medica* (citron), *Citrus aurantium* (sour orange), *Citrus maxima* (pummelo), *Citrus reticulata* (tangerine), and *Citrus clementina* (clementine). These fruits are valued not only for their refreshing juices but also for their bioactive-rich by-products (peels, pulp, and seeds), which exhibit diverse pharmacological properties. This review was conducted through a structured literature search of major scientific databases, including Scopus, Web of Science, PubMed, and Google Scholar, covering publications from 2000 to 2024. Keywords such as "citrus phytochemicals," "citrus flavonoids," "limonoids," "citrus essential oils," "bioactivity," and "toxicity" were used. Peer-reviewed experimental, clinical, and review articles published in English were included, with emphasis on studies addressing both health benefits and toxicological outcomes of citrus-derived compounds. Reported biological activities include antidiabetic, anticancer, antihypertensive, antihypercholesterolemic, anti-obesity, antiviral, antifungal, antibacterial, anti-inflammatory, and antioxidant effects. These health-promoting properties are largely attributed to the diverse phytoconstituents present in citrus fruits, including flavonoids, limonoids, carotenoids, coumarins, and essential oils. However, despite these benefits, emerging evidence indicates that excessive intake or high concentrations of certain citrus phytochemicals may elicit toxic effects, highlighting important safety concerns. This review critically examines both the nutraceutical benefits and potential toxicities of citrus phytoconstituents, emphasizing their dual biological roles. Furthermore, it underscores the need for mechanistic and dose–response studies to better define toxicity pathways and establish safe consumption thresholds.

Keywords: Citrus fruits; phytochemicals; bioactive compounds; citrus essential oils; nutraceuticals; toxicity

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Introduction

Citrus fruits are among the most widely produced, traded, and consumed fruits globally, with annual production reaching several hundred million tonnes and spanning diverse agroecological regions across Asia, the Americas, Africa, and the Mediterranean basin. Sweet orange (Citrus sinensis), mandarin (*C. reticulata*), grapefruit (*C. paradisi*), lemon (*C. limon*), lime (*C. aurantifolia*), and related species constitute staple components of daily diets, consumed as fresh fruits, juices, and processed products. Their widespread availability, affordability, pleasant sensory attributes, and long history of safe dietary use have firmly positioned citrus fruits as integral contributors to global food security and human nutrition. Beyond their role as sources of basic nutrients, rising consumer interest in health-promoting foods has intensified scientific and industrial focus on citrus fruits as functional foods and reservoirs of nutraceutical ingredients. [1, 8,15].

The health relevance of citrus consumption is underpinned by their exceptional phytochemical richness. In addition to providing essential nutrients such as vitamin C, folate, potassium, and dietary fibre, citrus fruits contain a wide array of secondary metabolites with marked biological activity. These phytochemicals are unevenly distributed across the pulp, peel, albedo, and seeds, rendering both edible portions and processing by-products valuable from a bioactive standpoint. Notably, citrus peels and other residues generated by the juice and food industries represent concentrated sources of phytoconstituents and have attracted growing attention within the context of circular bioeconomy and waste valorisation strategies [2, 10,12].

Among the diverse bioactive classes present in citrus fruits, flavonoids are the most extensively studied. These include flavanones (such as hesperidin, naringin, and eriocitrin), flavones, flavonols, and polymethoxylated flavones (including nobiletin and tangeretin), many of which are unique or particularly abundant in citrus species. Limonoids, a group of highly oxygenated triterpenoids derived from tetracyclic triterpene precursors, represent another characteristic class, contributing to the bitter taste of some citrus varieties while exhibiting notable anticancer, anti-inflammatory, and detoxification-related activities. Carotenoids, responsible for the distinctive yellow, orange, and red pigmentation of citrus fruits, play important roles as antioxidants and vitamin A precursors, whereas phenolic acids and coumarins further contribute to redox modulation and metabolic effects. Citrus essential oils, dominated by monoterpenes such as d-limonene, linalool, and β-pinene, are concentrated predominantly in the peel and are widely used in foods, cosmetics, and pharmaceuticals for their antimicrobial, sensory, and therapeutic properties [11,13,14,20,29–32].

A substantial body of experimental and clinical evidence supports the positive contribution of citrus phytochemicals to human health. Regular citrus intake has been associated with reduced risk of cardiometabolic disorders, attenuation of oxidative stress and inflammation, modulation of gut microbiota, and protective effects against certain cancers. These benefits are mediated through multiple molecular mechanisms, including free-radical scavenging, regulation of inflammatory and apoptotic pathways, modulation of lipid and glucose metabolism, and interaction with xenobiotic-metabolising enzymes. Such multifunctional activities have driven the incorporation of citrus extracts and isolated compounds into functional foods, dietary supplements, and nutraceutical formulations [11,13,14,20,29–32].

However, alongside these beneficial attributes, emerging evidence has highlighted that citrus phytochemicals may also exert adverse or toxicological effects under specific conditions. In particular, excessive intake, prolonged exposure, or use of highly concentrated extracts and essential oils can lead to hepatotoxicity, genotoxicity, endocrine disruption, or neurotoxicity in experimental models. Citrus essential oils and isolated terpenoids, while generally recognised as safe at dietary or flavouring levels, have demonstrated dose-dependent toxicity in vivo, underscoring the importance of exposure level, route of administration, and duration. Furthermore, certain citrus compounds are known to interact with drug-metabolising enzymes and transporters, raising concerns regarding herb–drug interactions and vulnerable populations [29–32].

These apparently paradoxical effects illustrate a fundamental principle in nutritional toxicology: the distinction between health benefit and toxicity is often determined by dose and context. While citrus fruits consumed as part of a balanced diet are widely regarded as safe and beneficial, the increasing use of citrus-derived phytochemicals in concentrated or isolated forms necessitates a careful and evidence-based evaluation of their safety profiles. Balancing efficacy with safety is therefore critical to ensure that citrus nutraceuticals deliver health benefits without unintended harm [14,20,29–32].

In this context, the present review critically examines citrus fruit phytoconstituents as "two sides of the same coin," integrating current knowledge on their nutraceutical benefits and toxicological concerns. Emphasis is placed on major bioactive classes, mechanisms of action, dose-dependent responses, and safety considerations, including insights derived from citrus by-products. By synthesising evidence from nutritional, pharmacological, and toxicological perspectives, this review aims to inform the safe and effective utilisation of citrus-derived compounds in foods, nutraceuticals, and related applications while highlighting key research gaps that must be addressed to support responsible innovation.

Overview of Citrus Fruits and Their Nutritional Importance

Citrus fruits contribute substantially to daily micronutrient intake in many populations and are frequently recommended in dietary guidelines for disease prevention and health promotion [7,10]. Their bioactive constituents act synergistically within the food matrix, influencing bioavailability, metabolism, and biological activity [9,13].

Nutrients in Citrus Fruits

Citrus fruits are rich sources of essential nutrients, including vitamin C, potassium, folate, and dietary fibre [7,10]. Vitamin C plays a key role in antioxidant defence, immune modulation, and collagen synthesis [10,19], while dietary fibre supports gastrointestinal health, glycaemic control, and cholesterol regulation. The major biomolecules; carbohydrates, fatty acids, amino acids and organic acids are also present in citrus fruits (Table 1). They influence the aroma, flavour and nutritional value of citrus fruits [6,8-9].

Table 1: Major Nutrients in Citrus Fruits, Principal Sources, and Biological Relevance

Nutrient	Major citrus sources	Biological relevance	References
Vitamin C	Orange, lemon, grapefruit	Antioxidant defence; immune support; collagen synthesis	[1,10,19]
Carotenoids (vitamin A)	Orange, mandarin, pomelo	Vision; epithelial integrity; antioxidant activity	[12,34]
Dietary fibre	Citrus peel and pulp	Gut health; cholesterol reduction; glycaemic control	[6,9]
Potassium	Orange, lime	Blood pressure regulation; electrolyte balance	[7,13]

Note: Data summarizes selected major nutrients relevant to citrus nutritional quality.

Global Consumption Patterns, Processing, and Exposure Implications

Although traditionally consumed as whole fruits, citrus products are increasingly processed into juices, concentrates, flavouring agents, essential oils, and nutraceutical formulations (Figure 1) [52,71]. Industrial processing can markedly alter phytochemical profiles, often concentrating lipophilic compounds such as terpenoids while reducing thermolabile constituents [10,52]. Whole-fruit consumption delivers phytochemicals within a complex food matrix that modulates digestion and metabolism, whereas concentrated extracts may result in substantially higher systemic exposure, with important toxicological implications [9,13,58].

Citrus Phytoconstituents

Citrus fruits contain a diverse array of phytoconstituents, including flavonoids, limonoids, carotenoids, phenolic acids, coumarins, and volatile terpenoids [15,16,33]. These compounds are unevenly distributed across fruit tissues, with peels generally containing higher concentrations than edible pulp or juice [6,34].

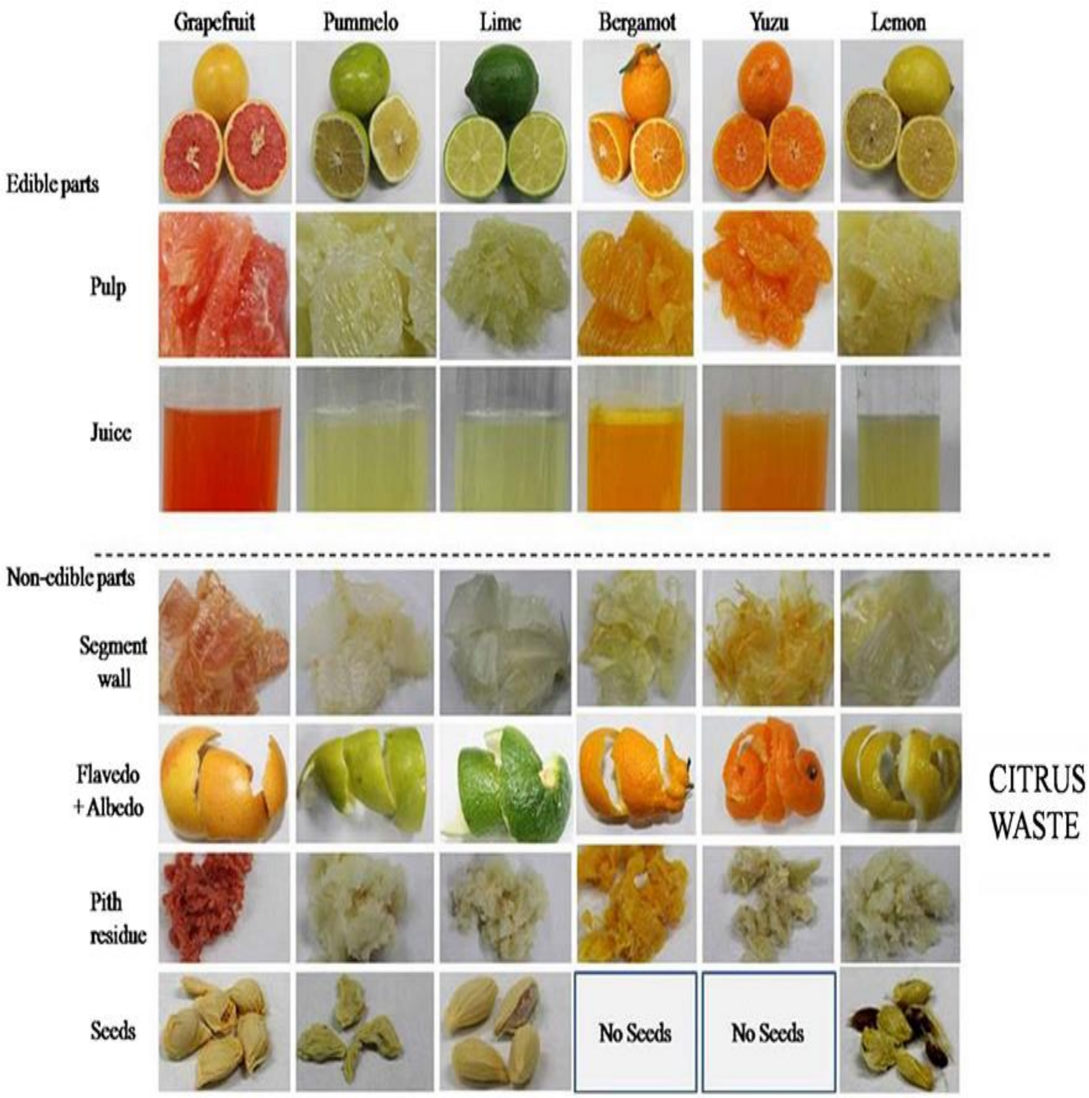

Fig. 1: Edible, non-edible and waste proportions of the main citrus fruit varieties commercially grown across the globe. Mahato et al. [9].

Classification and Distribution of Citrus Phytochemicals

Phytochemicals are differentially localised in citrus peel, pulp, seeds, and juice, reflecting both physiological function and industrial relevance [6,34]. Citrus peels are particularly rich in flavonoids and essential oil constituents, making them a major source of value-added nutraceutical ingredients [6,52].

Major Classes of Citrus Phytoconstituents

Flavonoids, including flavanones and poly-methoxylated flavones, represent the most extensively studied class of citrus phytochemicals [16,20,31]. Limonoids, a group of highly oxygenated triterpenoids, are characteristic of citrus species and contribute to bitterness as well as anti-inflammatory, anticancer, and enzyme-modulating activities [35–44]. Carotenoids and phenolic acids further contribute to antioxidant and health-promoting effects [15,33].

Flavonoids

Flavonoids are plant-based products with potent health properties such as anti-neoplastic, hypo-lipidaemic, anti-inflammatory, hypoglycaemic etc. [13]. The oxidation state, glycosylation and substituents in the aromatic rings of flavonoids correlate with their biological functions including antioxidant and antiproliferative effects [11]. There are over 9000 flavonoids [11]. They are classified into flavanols, flavones, flavanones, isoflavones and anthocyanidins [14]. Citrus flavonoids exist as glycoside or aglycone [15]. Citrus fruits are good sources of the following flavonoids; naringenin, diosmin, rutin, nobiletin, hesperetin, naringin, hesperidin, nobiletin, tangeretin [13]. In Citrus limon, the following flavonones are present; eriodictyol, neohesperidin, hesperetin, hesperidin, naringin; flavones-diosmin, apigenin, eriocitrin. Quercetin, limocitrin, spinacetin and their derivatives are major flavonols present. Furthermore, orientin and vitexin are common flavones. The ability of flavonoids to stall LDL oxidation allows them to protect against cardiovascular diseases [16]. There are reports that naringenin represses protein carbonylation and lipid peroxidation. However, it boosts antioxidant capacity of the body, thereby protecting the body against different pathologies [17-18]. The antioxidant potential of rutin is in its ability to inhibit xanthine oxidase [13]. The anti-malignant, antioxidant, antihypertensive, anti-inflammatory potentials of citrus hesperidin have been reported [13].

Nobiletin, tangeretin and their metabolites possess antioxidant potentials [20]. The bio-defensive abilities of nobiletin are facilitated by phosphoinositide 3-kinase/Akt signaling pathway [21]. The overwhelming effect of Naringenin and hesperetin on microsomal triglyceride transfer protein as well as acyl-CoA:cholesterol acyltransferase indicates their importance in lipid metabolism [22]. The ability of naringenin to quash pro-inflammatory cytokines; TNF-alpha and IL-6 indicates its anti-inflammatory effects [23]. Eriodictyol has been reported to mediate antioxidant effects via reduction of nitric oxide, TNF-alpha and ICAM [24].

Anti-cancer Mechanisms of Flavonoids

Cell Cycle Obstruction

Obstruction of the protein kinase C pathway could be the anti-proliferative mechanism of quercetin. Upregulation of inhibitors of CYP1B1 and CYP1A1 appears to be the mechanism by which nobiletin boosts the cytostatic effect in MCF-7 (breast cancer) cells [11]. Apigenin halted cell cycle at the G2/M phase in human prostate cancer cells by triggering WAF1/p21, a cyclin kinase suppressor [25]. There are evidence that citrus peel extracts alter proteins concerned with the development of cells such as; epidermal growth factor receptor and reticular activating system [11]. Furthermore, they cause over-expression of cyclin-dependent kinase inhibitor1 (p21) as well as tumour suppressor protein (p53), thus, resulting in halting of G1 of the cell cycle in breast and prostate cancers [25].

Apoptosis

Citrus peel flavonoids lowered inhibitors of apoptosis proteins (IAPs) including cellular IAP (cIAP) and X-linked IAP (XIAP). It also elevated caspase 3 and 9 in some cancers [26-27]. Nobiletin stimulates apoptosis by boosting the expression of Bax and p53 protein, halting Bcl-2 protein and increasing Bax:Bcl-2 proteins in lung cancer [28].

Anti-angiogenesis

Reported mechanisms of anti-angiogenesis of flavonoids include; halting the expression of VEGF, control of endothelial cell migration and reduction of matrix metalloproteinases 2 and 9 [29]. Luteolin and apigenin inhibit angiogenesis by hindering the release of pro-inflammmatory cytokine, IL-6 [30]. The control of cell cycle by halting G0/G1, reduction of thrombospondin1 and CD36 expression are anti-angiogenic mechanism of nobiletin [31-32].

Inhibition of Metastasis

The anti-metastatic mechanism of luteolin, apigenin, genistein, quercine is via down regulation of MMP 2 and 9. Furthermore, nobiletin averts the migration of A549 cancer cells and improves the expression of TIMP-1 via triggering of PKCβII/epsilon-JNK pathway. Naringin suppresses PI3K/AKT/mTOR/p70S6K signaling pathway, while hesperidin inhibits the ANGPT1 gene [11].

Limonoids

Limonoids are extremely oxidized triterpenoids found in different species of citrus fruits; Citrus sinensis (sweet orange), C. limon (lemon), C. paradisi (grapefruit), C. aurantium (sour orange), C. aurantiifolia (lime), C. maxima (pummelo) [33]. They are usually present in the pulp, peels and seeds of citrus fruits [34]. They exist as aglycones (typically in the seeds) and D-glucosides [35].

Ichangin, nomilin, obacunone, limonin and deacetylnomilin are hydrophobic limonoid aglycones found primarily in citrus seeds and peels. Hydrophilic limonoid glucosides including nomilin, limonin, obacunone, limonin and nomilic acid glucosides are found in citrus pulps and juices [36].

Biological Effects of Limonoids

Anti-malignant Effects

In human colon cancer cell, limonin was significant in β-catenin signalling and concomitantly hampered the transcription of T-cytokine/lymphocyte-enhancing factor [37]. The inhibitory effects of isolimonic acid, ichanexic acid and limonexic acid on colon cancer have been reported [33]. The antioxidative ability of citrus limonoids is a potent anti-malignant mechanism [38]. Limonin and nomilin have been reported to have glutathione S transferase stimulating ability [39] Furthermore, their propensity to elevate the activities of certain phase 2 detoxifying enzymes is also a mechanism [40]. Upregulation of Bax expression, inhibition of Bcl-2 expression as well as induction of apoptosis are mechanisms by which obacunone exerts its anticancer effects on breast cancer cells [41]. Inhibition of important enzymes implicated in carcinogenesis by nomilinic acid glycoside [42]. Obacunone and its glucoside were reported to hinder human prostate cancer cell growth [43].

Anti-inflammatory, Anti-viral and Anti-bacterial Effects of limonoids

The anti-inflammatory effects of limonoids are well documented. Nomilin inhibited p38 MAP kinase activity in cells of human aortic smooth muscle [44]. This is via mechanisms involving decreased phosphorylation of IκBα, an effective inhibitor of NF-κB [26]. The immunomodulatory effects of nomilin have been reported. This is because of its ability to inhibit type-4 hypersensitivity [45]. The antiviral effects of limonin and nomilin, as well as the antibacterial effect of obacunone have been reported [33].

Phytohormones

In addition to the terpenoids, phytohormones play important roles in citrus fruits. The phytohormones include abscisic acid, indole acetic acid, jasmonic and salicylic acids [46]. They are involved in regulating fruit colour, pigment, nutritional content, maturation, ripening and other metabolic activities [47-51]. There are indications that jasmonic and salicylic acids are important in the anabolism of terpenoids in citrus fruit [46].

Bioavailability, Metabolism, and Biotransformation

The biological effects of citrus phytochemicals are strongly influenced by bioavailability and metabolic transformation [16,18]. Most flavonoids occur as glycosides that require enzymatic hydrolysis prior to absorption, followed by extensive phase II metabolism [16,23]. Limonoids and terpenoids undergo cytochrome P450-mediated metabolism, raising the potential for food–drug interactions and dose-dependent toxicity [39,42,83–85].

Citrus Essential Oils

Citrus essential oils are complex mixtures of volatile terpenoids derived primarily from fruit peels [52–54]. d-Limonene is the dominant constituent, accompanied by β-pinene, γ-terpinene, linalool, and citral [53,54]. These oils are widely used in food preservation, cosmetics, and complementary medicine due to their antimicrobial, antifungal, and anti-inflammatory properties [55–57,66].

Composition and Extraction of Citrus Essential Oils

Extraction methods such as cold pressing and steam distillation strongly influence the qualitative and quantitative composition of citrus essential oils [52–54]. Concentration of lipophilic terpenoids during processing can markedly increase biological potency and toxicological risk [58,95].

Biological Effects of Essential Oils

Food Safety

The antibacterial, antifungal and insecticidal effects of essential oils (Eos) have been described. These are important in food preservation because they are non-toxic, environmentally friendly and inexpensive substitutes to artificial preservatives. There is evidence that phenolic compounds in EOs hold a potential of preserving fish and meat from deterioration [52]. Furthermore, using EOs alongside edible films and coatings also hold high potentials of minimizing food spoilage [55]. The stability of food with encapsulated EO is preserved by inhibiting direct contact with food matrices [52]. Essential oil can act cooperatively with antimicrobial carriers, thereby boosting antimicrobial effect of the nano-encapsulated EO [56]. A study showed that citrus essential oil nano-emulsion inhibited bacterial growth in refrigerated rainbow trout fillets [57].

Anticancer Effects

The anticancer potentials of limonene are known. Its lipophilic nature enhances its bioaccumulation in breast tissues and its body retention for an extended time frame [58]. The mechanisms of action of limonene are still being studied. A report showed that limonene destroyed cancer cells by apoptosis [59]. Another report showed the ability of limonene to induce apoptosis via stimulation of caspase-3 [60]. Reports showed a decline in the expression of cyclin D1, a marker of cell cycle progression in breast tumours [58,61]. Its ability to act as cancer chemoprotective drug has also been stated [62]. Limonene reduced the growth of secondary tumours as well as caused the regression of already formed secondary tumours in another study [63]. The tumour regression potentials of d-limonene derivatives; sobrerol, perillyl alcohol, carveol and uroterpenol have been reported [58]. In a study, their administration at the promotion and progression stages resulted in considerably decline in tumour growth [64].

Antidepressant

The interaction of beta-pinene and linalool with 5HT1A, adrenergic and dopaminergic receptors result in anti-depressive effects [65-66].

Antifungal Effects

Studies have reported the antifungal effect of citrus fruit oil which was attributed to high concentration of limonene. Citrus essential oil inhibited the growth of *Sclerotinia sclerotiorum*, *Trichophyton rubrum*, *Fusarium oxysporum*, *Penicelium* sp., *Alternaria* sp [67-69]. Plausible mechanisms include cell wall breakdown, seepage of cytoplasmic content and ultimately cell death [70].

Citrus Wastes

Citrus waste constitutes a huge environmental bio-pollutant in areas of large cultivation. There are evidence that waste is produced at every stage of citrus fruit handling, right from production until prior to consumption [71]. Peel, rag and seeds constitute citrus waste, of which the peel account for about 65% [72]. Furthermore, amino acids, proteins, carbohydrates, lipids, minerals, essential oils and phenolic compounds are present in citrus wastes [73]. Citrus peels contain between 2.5% and 9% protein [71] Citrus waste phytochemicals have been reported to exert health-promoting effects including; anticancer, antidiabetic, antimicrobial effects [74]. Galactose, glucose, fructose, arabinose and xylose have been reportedly present in sweet lemon and sweet orange peels [75-76]. Citrus wastes are good sources of dietary fibres constituting about 60% of cellulose and hemi-celluloses. Pectin, gum and mucus are the major soluble fibre, while lignin and cellulose are major indigestible fibres [77].

The main limonoid in citrus peel are obacunone and nomilin acid glucosides. Additionally, 7-methoxy-8-(2-oxo-3-methylbutyl) coumarin, epoxyaurapten, 5-geranyloxy-7-methoxycoumarin, limettin, and auraptene as well as furanocoumarins such as epoxybergamottin, xanthotoxin, bergamottin, and psoralen are the principal coumarins. Foremost phenolic acids include; benzoic and cinnamic acids. Moreover, *β*-carotene and xanthophylls; β-cryptoxanthin, lutein, β-citraurin, violaxanthin, and zeaxanthin are the major carotenoids. D-limonene is the major essential oil [11].

Caution should be exercised in the disposal of citrus wastes, because the antimicrobial effects of its constituents may delay microbial decay process at nitrogen content less than 0.14% [11].

Benefits of Citrus Wastes

Modulation of Blood Lipids

Citrus peel extracts have been reported to modulate blood lipids. This has been attributed to the phytochemicals in citrus peel. There was a considerable reduction in total cholesterol in rats fed with high doses of citrus peel extract relative to the control group fed with low doses [78]. Triglycerides, low density lipoproteins (LDL) and total cholesterol significantly reduced while high density lipoproteins (HDL) significantly improved in rats with hypercholesterolemia placed in citrus peel extract over a period of one month [79]. Citrus peel phytochemicals stimulate receptor cells that take in extra LDL and triglycerides into liver the adipose tissue, thereby preventing plaque formation [80]. Furthermore, efficacy of citrus peel in reducing liver lipids has been widely reported [6].

Hypoglycaemic Effects of Citrus Peel

There are evidence of hypoglycaemic effects of citrus peel. Citrus peel flavonoids were observed to enhance insulin production by activating the beta cells of the pancreas [81]. [82] observed hypoglycaemia in diabetic rats fed with citrus peel extract due to reenergizing of insulin-producing cells. [74] reported the glycaemic control of citrus limetta peel via downregulating the activities of α-amylase and α-glucosidase.

Cancer Therapy

The use of citrus peel bioactive compounds as adjuvant in conventional chemotherapy, thereby, reducing their toxicity has also been reported [83]. Flavonoids have been reported to be effective natural non-steroidal anti-oestrogenic and aromatase inhibitors [84-85]. Quercetin, naringenin and naringin possess prophylactic and therapeutic potentials in both pre-and post-menopausal breast cancers.The anti-oestrogenic and anti-aromatase effects of quercetin, naringenin and naringin isolated from citrus peel in breast cancer have been reported. The modulation of oestrogen signaling pathways as well as inhibition of aromatase are the plausible mechanisms [83]. These three flavonoids considerably reduce tumour sizes and aromatase levels.

Other Health Benefits of Citrus Waste

Citrus fibre contains phytochemicals with antioxidative properties. This can be used to deter rancidity of fat in meat products, hence, extending their shelf stability. It also reduces nitrite levels hence, nitrosamines [6, 74]. Citrus fiber enhances cooking yield of meat products due to their hydro and lipo-binding potential [86]. Citrus fruits are good sources of citric acid which enhance the conversion of oxalates to citrates, thereby allowing their easy excretion from the body [87]. Furthermore, citrus waste contains a huge quantity of colorants. Hence, are good sources of clouding agents which are important in fizzy drink/beverage production [74]. Molasses obtained from citrus fruits containing between 60 and 65 % sugars and 4-5 % citrus pulp is a good alternative to molasses gotten from sugarcane [74]. The insecticidal effect of citrus peel oil has been reported [88].

Animal Feed Supplements

There is evidence that dried citrus waste is suitable additive in animal feeds. This is predicated on their good sources of soluble carbohydrates. It also enhances a high level of salivation with a positive buffering effect on the pH in the rumen, hence, enhances good digestibility of feeds as well as no adverse effect on milk production [9, 72].

Biogas/Biofuel Production

Citrus waste has a high potential of biogas generation/production. This is because of the presence of both soluble and insoluble carbohydrates [89]. The presence of limonene, which has antimicrobial property in citrus peel was an initial challenge. Mechanism of limonene removal from citrus wastes was reported by [90]. Their study showed a higher production of methane in substrates pretreated with orange peel and hexane (1:12) in comparison with wastes not treated with orange peel.

Bio-sorbents

[91] reported the bio-absorptive ability of citrus waste. Carbon biochar obtained from citrus waste are cheap, effective and safe bio-sorbents which can be used for the elimination of toxic metals and dyes from effluents. Furthermore, limonene, richly present in citrus waste is used to produce Bronsted acid which is important in the production of levulinic acid and lignin [92]. Lignocellulosic from citrus waste is one of the most affordable sources of bio-sorbent production. High rate of adsorption and efficient removal of contaminants at low concentration are some benefits of biosorbents [93].

Biopolymers

The demand for eco-friendly polymers is on the rise. Hence, plant starch and hemicellulose. Their hydrophilicity and retrogradability at storage are major problems. This calls for cross linking of functional groups on the starch surface. Citric acid has been reported as a good cross-linking agent. Limonene is also crucial in eco-friendly polymer production [92] Organic acids; succinic, lactic and citric acids derived from citrus wastes are raw materials in the production of ecofriendly/ biodegradable polymers [92]. Furthermore, wastes from citrus fruit could be used as a base for 3D printing, bio-imaging as well as nanostructured materials [92].

Microcrystalline cellulose and Carbon nanodots

Citrus mesocarp is an ideal source of microcrystalline cellulose which has a range of pharmaceutical significance. Its ability to absorb water and ease of disintegration make it serves as diluent in oral tablet and capsule formulations [92]. Carbon nanodots produced from citrus are safe, cheap, strong, stable and easily absorbed by living cells for imaging [92]. Carbon nanodots produced from orange juice produced good results as an investigative material in cellular imaging [94].

Molecular Mechanisms Underpinning Nutraceutical Effects

Citrus phytochemicals modulate multiple molecular pathways, including activation of the Nrf2 antioxidant response and inhibition of NF-κB-mediated inflammatory signalling [13,16,44]. Limonoids and polymethoxylated flavones induce apoptosis and inhibit angiogenesis through modulation of PI3K/Akt and Wnt/β-catenin pathways [28,31,32,37–43].

Toxicological Considerations

Toxicological evidence indicates that adverse effects associated with citrus phytochemicals are primarily dose-dependent, with toxicity most frequently reported at supra-dietary exposure levels [95–98]. Evidence of toxicity were observed in the rats fed with d-limonene at 25 and 75 mg/kg. Leucocyte infiltration, hydropic deterioration and necrosis were observed in hepatic lesions obtained from the rats. Hydropic deterioration was indicated by intracellular oedema that is reversible, brought about by assault on the hepatocytes by infective or toxic agent [95].Toxicity could also be attributed to metabolites of d-limonene including limonene-8-9-diol, dihydroperilic and perillic acids. Hepatic steatosis was also observed in some animals treated with d-limonene [95]. Inflammation coupled with attendant mononuclear cells as well as fibrosis were found in the liver of rats fed with d-limonene [95]. Immunohistochemical assessment of the hepatic lesions showed the occurrence of T lymphocytes in the parenchymal cells of the liver [95].

In a study on mediterranean fruit flies, limonene, α-pinene and linalool were reported to exert toxic effect on the larvae of medfly, with α-pinene exerting the least toxicity [96]. Gender variation was observed in the toxicity of α-pinene, with a higher toxicity observed in females [97]. The hormetic effects of limonene were also reported in the study [97]. The toxic effect of *Citrus latifolia* essential oil on human oral epithelial cells was observed at 21.8 µg [98]. In another study, minimal adverse effects of d-limonene were observed in breast cancer study participants using $8g/m^2$/day as the maximum tolerable dose. Moreover, GIT disturbances including vomiting, nausea and diarrhoea were observed in some studies in which perillyl alcohol was administered [58]. Elevated level of IGF-1 was observed in breast cancer patients to which d-limonene was administered. This suggests its pro-cancer effect attributable to toxicity [58]. Furthermore, the induction of cytostasis by d-limonene via discriminatory inhibition of isopreylation of small G proteins has been proposed [63].

General Toxicological Evidences

High-dose exposure to certain citrus phytochemicals has been associated with hepatic and renal toxicity, oxidative stress, mitochondrial dysfunction, and cellular damage in experimental models [91,95,98].

Dose–Response Relationships and Hormesis

Many citrus phytochemicals exhibit hormetic behaviour, characterized by beneficial effects at low doses and adverse effects at higher exposure levels [93]. d-Limonene exemplifies this duality, demonstrating chemopreventive activity at low doses but hepatotoxicity and nephrotoxicity at high doses due to reactive metabolite formation [58–64,95].

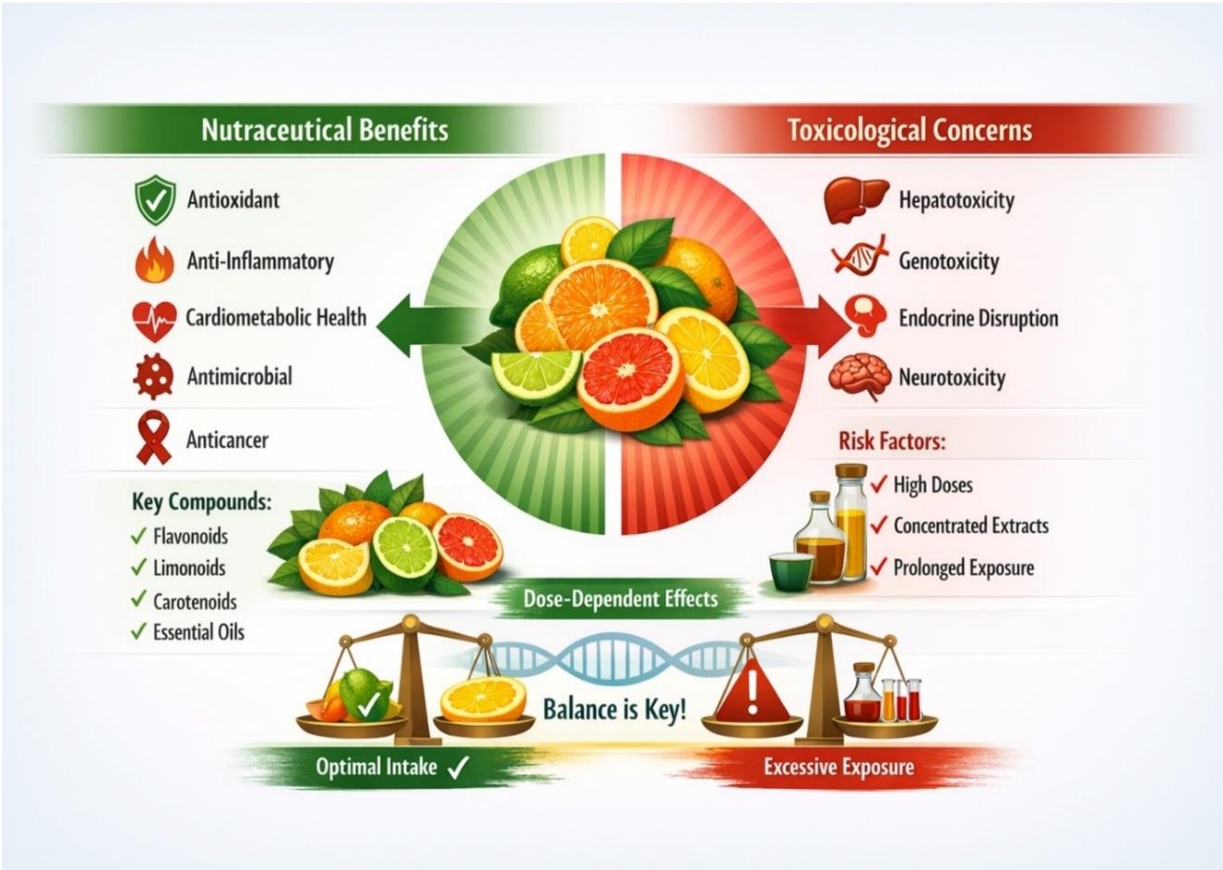

Fig. 2: The dual dose nature of citrus phytochemicals encompassing both nutraceuticals benefits and toxicological risks is summarized schematically in the above figure 2.

Citrus fruits contain diverse bioactive compounds, including flavonoids, limonoids, and essential oils, which exert antioxidant, anti-inflammatory, cardiometabolic, antimicrobial, and anticancer effects at dietary exposure levels. However, excessive intake or exposure to concentrated citrus phytochemicals may result in adverse outcomes, including hepatotoxicity, nephrotoxicity, genotoxicity, cytochrome P450-mediated drug interactions, and increased risk in vulnerable populations. The central schematic highlights the dose-dependent (hormetic) relationship, illustrating the transition from beneficial effects within the dietary "safe zone" to toxicological risks associated with high-dose or concentrated formulations (figure 2).

Vulnerable Populations

Individuals with hepatic or renal impairment, pregnant individuals, children, and those receiving long-term pharmacotherapy may be particularly susceptible to adverse effects due to altered metabolism and food–drug interactions [42,83–85,95].

Regulatory and Safety Challenges

Despite extensive dietary exposure, many citrus-derived compounds are designated as generally recognized as safe based on historical consumption, without adequate consideration of concentrated formulations, chronic intake, or mixture effects [52,95].

Table 2: Integrated Safety Profile of Major Citrus Phytoconstituents: Biological Benefits, Toxic Effects and Dose Ranges

Compound	Primary source	Key biological benefits	Reported toxic effects	Dose range / model	References
Hesperidin	Citrus pulp and peel	Antioxidant; cardioprotective; antiviral	No significant toxicity at dietary intake	In vitro; animal; limited human data	[13,19]
Naringenin / naringin	Grapefruit, orange, lemon	Antioxidant; hypolipidaemic; anti-inflammatory	Drug–enzyme interaction; pro-oxidant effects at high dose	>100 µM (in vitro); animal models	[17,18,22,23]
Quercetin	Citrus peel	Antioxidant; anticancer	Pro-oxidant effects at high concentrations	>100 µM (in vitro)	[11,16]
Limonoids (limonin, nomilin)	Seeds, peel, pulp	Anticancer; antioxidant	Minimal toxicity at dietary exposure	In vitro; animal models	[33–41]
d-Limonene	Citrus peel essential oil	Anticancer; antimicrobial	Hepatotoxicity; inflammation	25–75 mg/kg (rats); ≤8 g/m²/day (humans)	[58,95]
Perillyl alcohol	Limonene metabolite	Anticancer	Gastrointestinal toxicity	≥1.2–2.4 g/day (humans)	[58,64]

Abbreviations: µM, micromolar. Dose ranges represent values reported in experimental or clinical studies.

Conclusion

Citrus fruits provide substantial health benefits at dietary levels, largely attributable to their diverse phytochemical composition [10,13,79]. However, excessive exposure to isolated or concentrated citrus phytochemicals—particularly essential oils and terpenoids—may pose toxicological risks [95–98]. The balance between benefit and risk is determined by dose, bioavailability, and context of consumption. Future research and regulatory frameworks should prioritize evidence-based dosing and long-term safety evaluation to ensure the responsible use of citrus-derived nutraceuticals.

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