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Review

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Most Known *Citrus* L. Species and Breast Cancer Relationship

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Abstract

The genus *Citrus* L. belongs to the Rutaceae family of flowering plants and shrubs. *Citrus* genus has valuable edible fruits such as oranges, lemons, grapefruits, pomelos, and limes. Australia, Melanesia, Southeast Asia, East Asia, and South Asia are the native habitats of the genus *Citrus.* Indigenous societies in these regions have long utilized and tamed various *Citrus* species. *Citrus* fruits and their secondary metabolites have been reported to be useful agents in numerous studies to possess anti-inflammatory, antioxidant, and anticancer properties. This review gives an overview of *Citrus* species and background information on the potential anticancer properties of the compounds identified, along with the related *in vitro* and *in vivo* research. Studies from the past have revealed a variety of biological functions that *Citrus* compounds can regulate, such as angiogenesis, apoptosis, metastasis, cell cycle regulation, and cell proliferation. These promising data call for more investigation into the chemopreventative activity of *Citrus* and phytoconstituents.

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1. Introduction

Citrus L. fruits offer a treasure trove of bioactive compounds beyond their refreshing taste, with potential for disease prevention and treatment. Studies consistently link high fruit and vegetable intake, including *Citrus* varieties like mandarin, pomelo, orange, and grapefruit, to reduced cancer risk by at least 20%, particularly for breast cancer (Cirmi et al., 2016; Wang et al., 2021). This aligns with the observed protective effect of the Mediterranean diet, which is rich in citrus, likely due to its abundance of fiber, antioxidants, and polyphenols (Koolaji et al., 2020).

Intriguingly, even citrus peels, traditionally used medicinally, contain bioactive compounds with potential for cancer treatment, particularly breast cancer. These peels are rich in flavonoids and other polyphenols, supported by preclinical and epidemiological evidence (Gómez-Mejía et al., 2019). This review delves into the diverse secondary metabolites of *Citrus* species, focusing on their potential connection to breast cancer prevention and treatment.

Beyond their delightful presence, citrus fruits boast a captivating history, originating around 2200 BC in Southeast Asia (Cebadera-Miranda et al., 2020). Traversing continents via trade and exploration, they held religious significance in India and graced the Mediterranean during Alexander the Great's era (Rouseff et al., 2009). However, this rich past presents a tangled taxonomic web. Prolific crossbreeding within and beyond *Citrus*, coupled with ancient cultivation and ambiguous boundaries, obfuscates classification (Agouillal et al., 2017).

The estimated range of 16 to 156 suggested species emphasizes the continuous difficulty with taxonomy (Ollitrault et al., 2020).

Amidst this labyrinth, four "basic taxa" – pomelo, citron, mandarin, and kaffir lime – stand as foundational pillars. Unravelling their role in hybridization and recombination is key to comprehending *Citrus* evolution and securing the future of these treasured fruits (de Araújo et al., 2003).

2. Chemical Composition of *Citrus* species

2.1. Coumarins

Beyond alluring scents, citrus coumarins (Figure 1) unveil an arsenal of potent anti-breast cancer activities. Their versatile structure and diverse substituents enable potent pharmacological effects and the development of active derivatives with enhanced efficacy (Wu et al., 2009)

Citrus coumarins (auraptene, imperatorin, phellopterin, scoparone, myrsellin, triphasiol, umbelliferone, citropten) offer a compelling multi-pronged attack (Kerekes et al., 2022; Prince et al., 2009).

Growth pathway disruption:

They target the vital PI3K/Akt/mTOR pathway, a regulator of cell growth and survival, ultimately inducing cancer cell death (Musa et al., 2008).

Hormone signaling modulation:

By inhibiting key enzymes like sulfatase and aromatase, coumarins decrease estrogen levels, depriving breast cancer cells of a crucial fuel source (Wu et al., 2020).

Resistance mechanism bypass:

Certain coumarin derivatives can bypass multidrug resistance, rendering them effective against established cancer therapies (Musa et al., 2008).

This multifaceted assault positions citrus coumarins as promising candidates for novel breast cancer treatment strategies.

2.2. Flavonoids

Beyond vibrant colors, citrus fruits unveil a treasure trove of flavonoids, and diverse chemical structures (Figure 2) with potent bioactivities (Chen et al., 2023). Their arsenal extends beyond aesthetics, wielding potent antioxidant, anti-inflammatory, and anti-mutagenic properties against chronic diseases like cancer (Panche et al., 2016).

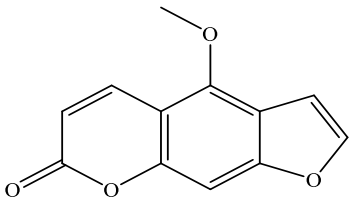
In the fight against cancer, citrus flavonoids (nobiletin, tangeretin, hesperetin, naringenin, eriodictyol, diosmin) become versatile warriors, employing a multifaceted attack (Qiu et al., 2023):

Suppressing cell proliferation:

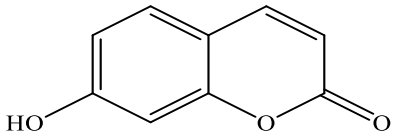
They hinder uncontrolled cell division, slowing tumor growth.

Inducing apoptosis:

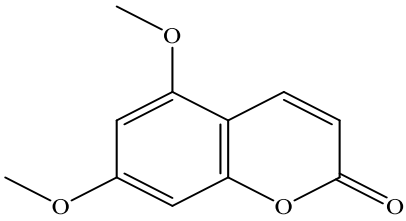
They trigger programmed cell death within cancer cells, leading to their elimination.



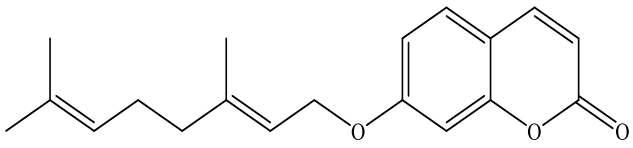
Bergapten



Umbelliferone



Citropten



Auraptene

Figure 1. Chemical structures of some citrus coumarins

Hinder metastasis:

They prevent cancer spread by interfering with cell movement and adhesion.

Notably, their ability to trigger apoptosis through both intrinsic and extrinsic pathways underscores their significant therapeutic potential (Park et al., 2022).

2.3. Terpenes

Beyond captivating fragrances, citrus terpenoids (mainly limonene) unleash a potent anticancer arsenal against this formidable foe (Kłos & Chlubek, 2022). Their diverse and flexible structures (Figure 3) enable a multi-pronged attack on tumor development, encompassing:

Thwarting cell proliferation and angiogenesis:

They curb uncontrolled cell growth and restrict blood vessel formation, which is vital for tumor nourishment (Luo et al., 2019).

Disrupting metastasis:

By interfering with critical cell signaling pathways, these terpenes hinder cancer cell migration and dissemination (Luo et al., 2019).

Targeting key signaling pathways:

They disrupt crucial cascades like NF-kB and JAK-STAT, impacting cell survival and proliferation (Olson, 1999; Saini et al., 2020).

Inhibiting critical enzymes:

By targeting enzymes like DNA topoisomerases and proteinases, they disrupt DNA replication and protein function, hindering tumor growth (Ghantous et al., 2010).

While programmed cell death (apoptosis) is the primary outcome, evidence suggests citrus terpenoids may trigger additional pathways like autophagy, further amplifying their antitumor potential (Kuttan et al., 2011).

2.3.1. Carotenoids

Beyond captivating hues, citrus fruits harbor a wealth of bioactive carotenoids categorized as vitamin A precursors and non-precursors (Young & Lowe, 2018). Key dietary members like α-carotene, β-carotene, and lycopene play significant roles in human health (Alquézar et al., 2008).

Carotenoids excel as antioxidants, shielding cells from oxidative damage (Rowles III & Erdman Jr, 2020). They further influence diverse biological functions, potentially mitigating chronic diseases, bolstering immunity, and exhibiting anti-inflammatory and anti-obesity properties (Rao & Rao, 2007). They demonstrate anticancer potential through mechanisms like free radical scavenging, cell proliferation modulation, and enhanced immune response (Olson, 1999; Saini et al., 2020) . Understanding the specific carotenoid profiles within different citrus varieties is crucial for maximizing their health benefits, as depicted in Figure 4 (Agócs et al., 2007).

The chemical composition of *Citrus* species and the major components of their essential oils were presented in Tables 1 and 2, respectively.

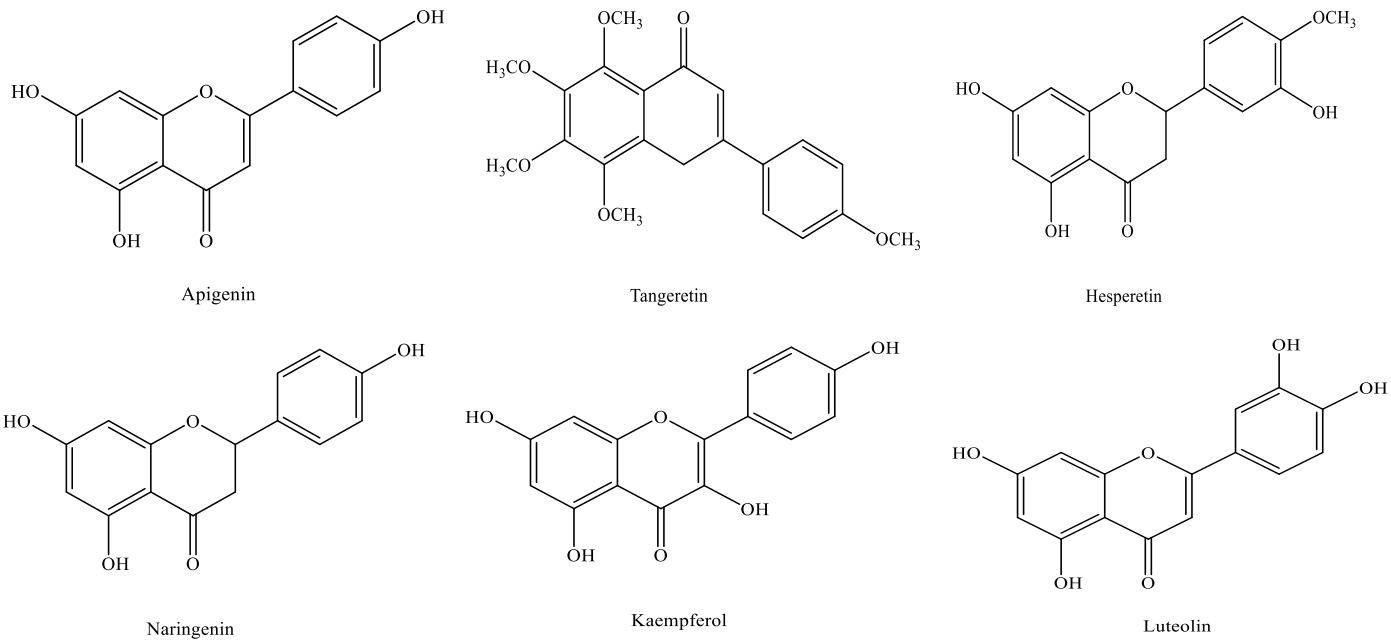


Figure 2. Chemical structures of some citrus flavonoids

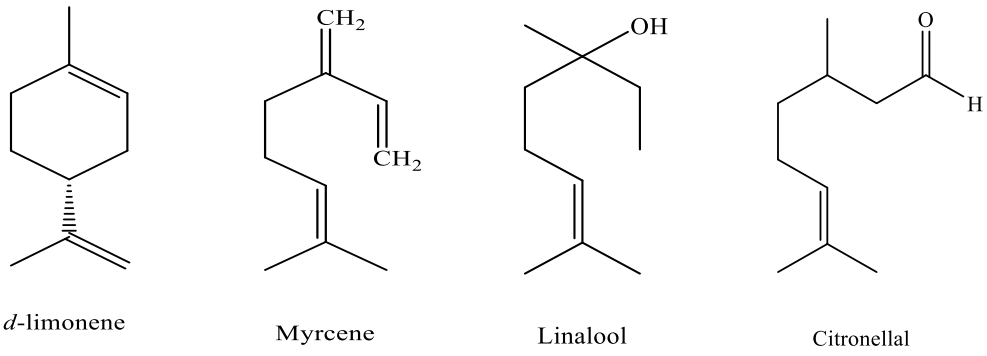


Figure 3. Chemical structures of some citrus terpenoids

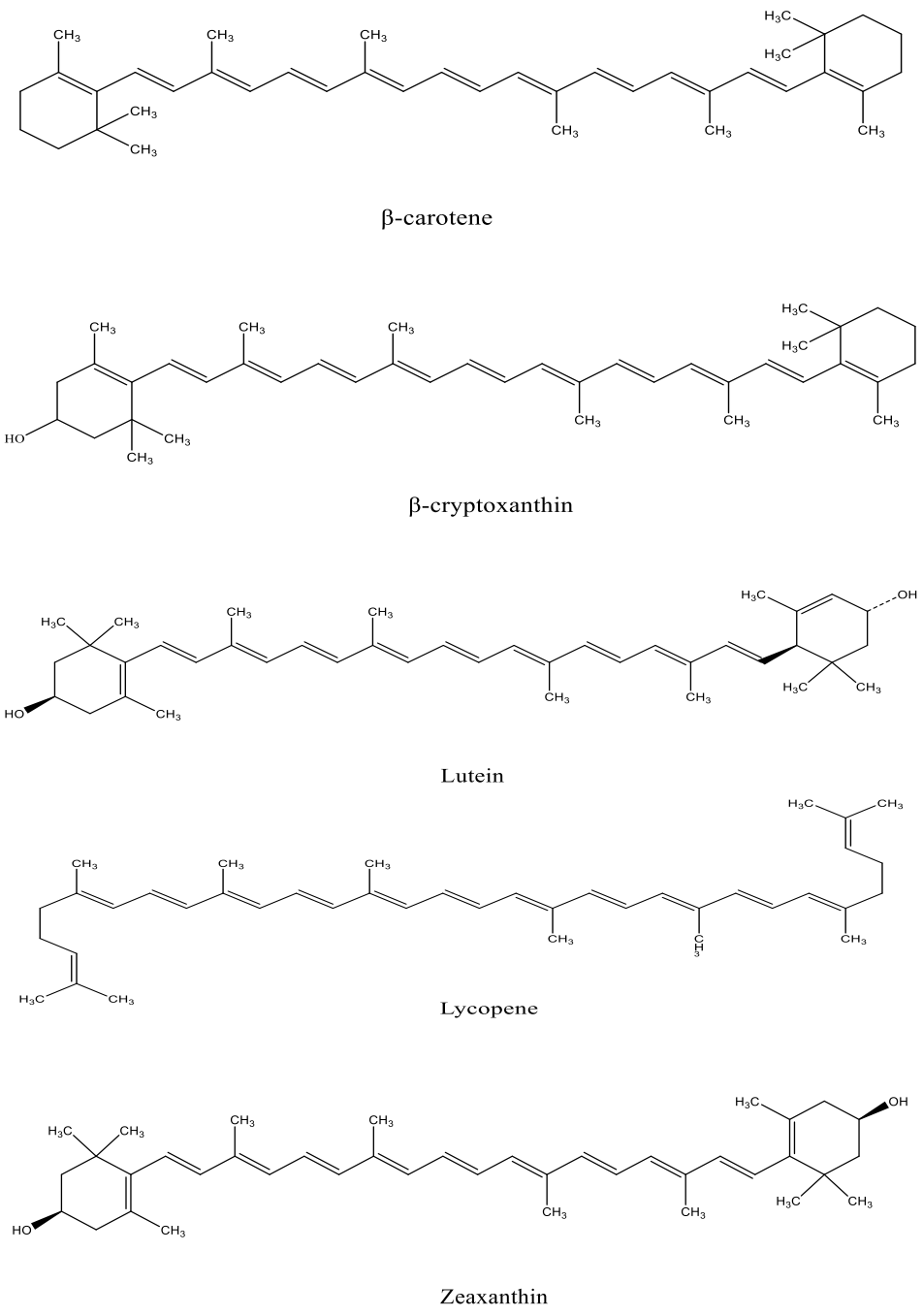


Figure 4. Chemical structures of some citrus carotenoids

Table 1. Chemical composition of *Citrus* sp. (major components)

Latin name	English name	Phytochemical Screening					References
		Carotenoids	Coumarins	Flavonoids	Terpenes	Others	
***Citrus* × *aurantium* L.**	Bitter orange		Osthol **Furanocoumarin**: Bergapten, epoxybergamottin, 6' 7'-dihydroxybergamottin	**Flavanones**: Hesperetin, naringenin **Flavones:** Apigenin, diosmetin, luteolin, nobiletin and tangeretin **Flavonol**: Kaempferol and quercetin	**Limonoids**: Deacetylnomilin, ichangin, limonin, nomilin, obacunone **Monoterpenes:** *β*-Myrcene, limonene, linalool	**Alkaloids**: p-Synephrine,	(Dugrand-Judek et al., 2015)
***Citrus aurantiifolia* (Christm.) Swingle**	Lime		5-Geranyloxy-7-methoxycoumarin, citropten (5,7-dimethoxycoumarin), isopimpinellin, herniarin, umbelliferone, xanthotoxol **Furanocoumarin**: Bergamottin, bergapten		**Monoterpenes:** α-Terpineol, α-thujene, *p*-cymene, camphene, carvone, citral, fenchene, linalool, terpinen-4-ol, geranial, geraniol, limonene, sabinene **Sesquiterpenes:** Bergamotene, caryophyllene, spathulenol *trans*-α-bisabolene	1-methoxy-cyclohexene, 3,7-dimethyl-(Z)-2,6-octadienal, 3-methyl-1,2-cyclopentanedione, methyl cyclopentenolone, palmitic acid, 2-methyltetrahydropyran, 3-methyl-3-penten-2-one, 3-hexen-2-one, 4-hexen-3-one, crysantenile, pinacol resorcinol	(Sandoval-Montemayor et al., 2012)
***Citrus limon* (L.) Osbeck**	Lemon		Citropten, scopoletin **Furanocoumarin**: Bergamottin, bergapten	**Flavones**: Apigenin, diosmetin, diosmin, homoorientin, luteolin, orientin, vitexin (whole fruit)	**Limonoids**: Limonin, nomilin (whole fruit)	**Carboxylic acids:** Citric acid, galacturonic acid, glucuronic acid, glutaric acid, homocitric acid, 3-hydroxymethylglutaric acid, isocitric acid, malic acid, quinic acid **Phenolic acids:** Dihydroferulic acid, p-hydroxybenzoic acid, 3-(2-hydroxy-4-methoxyphenyl) propanoic acid, synapic acid (whole fruit)	(Klimek-Szczykutowicz et al., 2020)

Table 1. Chemical composition of *Citrus* sp. (major components) (continued)

***Citrus maxima* (Burm.) Merr. (syn. *Citrus grandis* (L.) Osbeck)**	Pomelo	Carotene, roseoside	**5-Geranyloxy-7-methoxycoumarin, auraptene, bergamottin (peel), 5-methoxy seselin, 5-methyltodannol, 6-hydroxy methylherniarin (roots, stem bark)**	**Flavones: Acacetin, cosmosiin, diosmetin, diosmin, hesperidin, eriocitrin, naringin, rutin, tangeretin**	**Monoterpenes**:α-Pinene, α-terpineol, anethole, β-pinene, camphene, camphor, citral, citronellal, citroonellol, farnesol, geraniol, myrcene, neral, terpinene **Sesquiterpenes:** α-Bisabolol, α-cadinene, α-copaene, elemol	**Steroids:** β-Sitosterol, campesterol, daucosterol, stigmasterol	(Vijayalakshmi & Radha, 2016)
***Citrus medica* L.**	Citron	*β*-Cryptoxanthin, *β*-carotene, *cis*-violaxanthin, lycopene, lutein, xanthin, violaxanthin, zeaxanthin	Citropten, scoparone, scopoletin, umbelliferone (peel)	**Flavanones**: Hesperidin, 3,4',5-Trihydroxy-3',6,7- trimethoxyflavone neoeriocitrin, neohesperidin, naringin **Flavones:** Apigenin, chrysoeriol, diosmetin	**Monoterpenes**: β-Pinene, γ-terpinene, α-terpinolene, citral (geranial and neral), citronellol, limonene, linalool, geraniol, geranyl acetate, neryl acetate, mycrene, trans-α-bergamotene **Sesquiterpenes:** Valencene	**Steroids:** β-sitosterol	(Favela-Hernández et al., 2016)
***Citrus paradisi* Macfad**	Grapefruit		5-Geranyloxy-7-methoxycoumarin, 6'7'-dihydroxybergamottin (DHB), auraptene, bergamottin, epoxyauraptene, epoxybergamottin, meranzin	**Flavanones:** Isosakuranetin, hesperidin, neohesperidin, naringin, naringenin **Flavones:** 3,3',4',5,6,7,8-Heptamethoxyflavone **Flavonols:** Quercetin	**Limonoids**: limonin, **Monoterpenes**: α-pinene, limonene, myrcene, octanal, sabinene **Sesquiterpenes:** α-copaene, α-farnesene, trans-caryophyllene		(El Kamali et al., 2015; Uckoo et al., 2012; Wangensteen et al., 2003)
***Citrus reticulata* Blanco**	Tangerine		5-Geranyloxy-7-methoxycoumarin, 7-Geranyloxy-6-methoxycoumarin, xanthotoxol, xanthotoxin	**Flavanones**: Didymin, eriodictyol, hesperidin, naringin, naringenin, neohesperidin, poncirin **Flavones:** 5-Demethylnobiletin, diosmetin, luteolin, nobiletin, rhoifolin, sinensetin, tangeretin, quercitrin **Flavonols:** Kaempferol, quercetin	**Diterpenes:** Dehydroabietic acid **Monoterpenes**: α-Pinene, limonene, citronellyl acetate, citronellyl laurate, citronellyl valerate **Tetracylic terpenes:** Cholestane **Triterpenes**: 4,4-Dimethyl-14alpha-formyl-5alpha-cholesta-8,24-dien-3beta-ol, cholest-16-en-3-ol	β-stigmasterol, γ-sitosterol, 2-Methoxy-4-vinylphenol, 3,7,11,15-tetramethyl-2-hexadecene, caffeic acid, citronellyl valerate, ferulic acid, ethyl palmitate, methyl palmitate, linoleic acid, oleic acid, tetracosanoic acid, quinic acid	(Ferreira et al., 2018; Kaushal et al., 2022; Saleem et al., 2005; Zhang et al., 2014)

Table 2. Chemical composition of *Citrus* sp. essential oil (major components)

Latin name	English name	Phytochemical Screening		References
		Leaves	**Peels**	
***Citrus* × *aurantium* L.**	Bitter orange	Eucalyptol, sabinene, β-linalool, α-terpineol, α-pinene, β-myrcene, 4-terpineol, β-pinene, D-limonene, O-cymene, 4-carvomenthenol, linalool, linalyl acetate, 6,9,12,15-docosatetraenoic acid methyl ester, tetraneurin-α-diol	Limonene, linalool, linalyl acetate, myrcene, geranial, β-myrcene, neral, β-pinene, γ-terpinene, sabinene, geranyl acetate, β-caryophyllene, α-terpineol, α-pinene	(Maksoud et al., 2021; Okla et al., 2019)
***Citrus aurantiifolia* (Christm.) Swingle**	Lime	(Z)-Hex-3-en-1-ol, myrcene, limonene, trans-β-ocimene, linalool, citronellal, citronellol, neral, geraniol, geranial, citronellyl acetate, trans-β-caryophyllene	α-Thujene, α-pinene, sabinene, β-pinene, β-myrcene, α-terpinene, o-cymene, limonene, β-ocimene, γ-terpinene, α-terpinolene, α-terpineol, linalool, nerol, geraniol, α-bisabolol, α-citral, β-citral, neryl acetate, trans-α-bergamotene, β-bisabolene	(Lemes et al., 2018; Lin et al., 2019)
***Citrus limon* (L.) Osbeck**	Lemon	Myrcene, limonene, 3-carene, β-ocimene, gamma-terpinene, linalool, 6-octenal,7-methyl-3-methylene, citronellal, isoneral, terpinen-4-ol, isogeranial, α-terpineol, nerol, citronellol, neral, geraniol, geranial, citronellyl-propanoate, neryl acetate, geranyl acetate, z-caryophyllene	Limonene, neral, linalool, nonanal, *trans*-verbenol, decanal, geraniol, *cis*-α-bergamotene, ethyl cinnamate, ethyl p-methoxycinnamate, monoterpene hydrocarbons, oxygenated monoterpenes, sesquiterpenes, ketone	(Paw et al., 2020; Petretto et al., 2023)
***Citrus maxima* (Burm.) Merr.-*Citrus grandis* (L.) Osbeck**	Pomelo	α-Pinene, trans-isolimonene, delta-carene, trans-ocimene, nerol, citronellol, β-caryophyllene, calarene, α-humulene, patchoulene, allo-aromadendrene, germacrene D, β-ionone α-selinene α-farnesene, delta-cadinene, nerolidol, lauric acid, caryophyllene oxide, spathulenol, heptadecane, myristic acid, loliolide neophytadiene, palmitic acid, margaric acid, phytol, ethyl linoleolate, stearic acid, 9,12,15-octadecatrienoic acid, methyl ester	3-carene, cyclohexene, 4-methylene-1-(1-methylethyl), α-pinene, D-limonene, trans-linalool oxide (furanoid), cis-linaloloxide, 1,6-octadien-3-ol, 3,7-dimethyl, α-terpineol, 2,6-octadienal, 3,7-dimethyl-, (Z), citral, 2-carene, geranyl acetate, caryophyllen, α-cubebene, α-guaiene, stigmasterol, desmosterol, (3α,22E) 3-methoxy-stigmasta-5,22-diene, campesterol, α-sitosterol, β-sitosterol, 24-propylidene-, (3á) cholest-5-en-3-ol, allopregnane-3á,7à, 11à-triol-20-one, 9,19-Cyclolanost-24-en-3-ol	(Susandarini et al., 2016; Visakh et al., 2022)
***Citrus medica* L.**	Citron	Limonene,7-oxabicyclo[4.1.0]heptane, 1-methyl-4-(1-methylethenyl)-, 6-octenal, 3,7-dimethyl- cyclohexanone, 2-methyl-5-(1-methylethenyl)-, 1-monolinoleoylglycerol trimethylsilyl ether, 6-octen-1-ol, 3,7-dimethyl-, n-pentyl(1-propenyl)dimethylsilane, citral, 2-octen-1-ol, 3,7-dimethyl-, isobutyrate, (Z)-, 2-oxocycloheptyl acetate, 2,4-dodecadienoic acid, 11-methoxy-3,7,11-trimethyl-, methyl ester, (E,E)-, methoprene, geranyl methyl ether, 13-heptadecyn-1-ol, 1,2-cyclohexanediol, 1-methyl-4-(1-methylethenyl)-, 2,6-octadien-1-ol, 3,7-dimethyl-, acetate, (Z)-, mehp, 3,7-nonadien-2-ol, 4,8-dimethyl-, erucylamide	1R)-2,6,6-Trimethylbicyclo[3.1.1]hept-2-ene, α-pinene, 3-octyn-2-ol, β-myrcene, 2-acetyl-5-methylfuran, cyclooctyl alcohol, limonene, isolimonene, 1,3,6-octatriene, 3,7-dimethyl-, (Z)-, 1-heptanol, 3-methyl-, linalool, nonanal, trans-p-mentha-2,8-dienol, 7-oxabicyclo[4.1.0]heptane, 1-methyl-4-(1-methylethenyl)-, citral, 6-octenal, 3,7-dimethyl-, cis-verbenol, carane, 4,5-epoxy-, trans, 1,2-cyclohexanediol, 1-methyl-4-(1-methylethyl)-, 4-terpineol, terpinyl acetate, β-terpinyl acetate, decanal, neryl acetate, neryl alcohol, undecanal, neryl acetate, dodecanal, (Z,E)-α-farnesene, caryophyllene, α-bergamotene, 1,6,10-dodecatriene, 7,11-dimethyl-3-methylene-, (Z)-, tetrakis(trimethylsiloxy)silane, α-caryophyllene, germacrene D, cis-.α-bisabolene, γ-elemene, β-bisabolene, δ-cadinene, tetradecanal, neoisolongifolane, hydroxy-, β-bisabolol, n-hexadecanoic acid	(Bhuiyan et al., 2009)

Table 2. Chemical composition of *Citrus* sp. essential oil (major components) (continued)

***Citrus sinensis* (L.) Osbeck**	Sweet orange	Sabinene, delta-3-carene, (E)-beta-ocimene, linalool, terpinen-4-ol	α-Pinene, β-pinene, myrcene, terpinolene, D-limonene, aldehyde C8, citronellol, linalool	(Ghadiri et al., 2020; Kasali et al., 2011)
***Citrus paradisi* Macfad.**	Grapefruit	Sabinene, β-pinene, myrcene,limonene, (E)-β-ocimene, γ-terpinene, terpinolene, linalool, terpinen-4-ol, β-sinensal, β-elemene	α-Pinene, β-pinene, myrcene, limonene, n-decanal, (+)-(S)-carvone, 1-cyclohexene-1-carboxaldehyde, alpha-farnesene, α-copaene, trans-caryophyllene, palmitic acid	(El Kamali et al., 2015; Paoli et al., 2016)
***Citrus reticulata* Blanco**	Tangerine	α- Fenchene, sabinene, β-myrcene, iso- sylvestrene, limonene, (E)-β-ocimene, α-cis- bergamotene, γ-terpinene, γ- elemene, linalool, α- selinene δ- elemene, germacrene b, terpinen-4-ol, thymol, methyl ether, β-sinensal, α-sinensal	α-Fenchene, β-pinene, sabinene, limonene, γ-terpinene, linalool, terpinen-4-ol	(Hamdan et al., 2016)

3. Breast Cancer

The 21st century faces a rising flood of chronic diseases, led by cancer, with breast cancer taking center stage despite advances in healthcare (Chhikara & Parang, 2023; Miller et al., 2022). Its complexity lies in its multi-stage progression, inherent heterogeneity, and metastatic potential (Benson et al., 2009; Waks & Winer, 2019). Yet, a glimmer of hope exists in decreasing mortality rates due to improved management strategies (Giaquinto et al., 2022). Recognizing its dual nature, requiring both local and systemic approaches, has sparked renewed interest in natural resources like citrus fruits for therapeutic intervention (Senkus et al., 2015).

Natural products offer compelling potential, with over half of FDA-approved anticancer drugs since 1960 being natural derivatives (Mayer & Gustafson, 2004). *Citrus* species, rich in diverse phytochemicals like coumarins, flavonoids, and limonoids, emerge as promising candidates. These bioactive compounds not only exhibit anticarcinogenic effects but also boast better tolerability compared to synthetic drugs, further propelling research efforts (Silalahi, 2002).

4. Recent Breast Cancer Studies on *Citrus* sp.

Once considered waste, citrus peels are rewriting their narrative as a readily available resource with remarkable potential in breast cancer prevention and treatment. Their diverse bioactivities offer a multifaceted attack:

Dose-Dependent cytotoxicity:

Extracts from various citrus peels exhibit a potent, dose-dependent ability to suppress the proliferation of breast cancer cell lines (MCF-7, MDA-MB-231) (El-Kersh et al., 2021; Narayanankutty et al., 2022).

Apoptosis induction:

Beyond mere growth inhibition, citrus peels actively trigger programmed cell death (apoptosis) in cancer cells. Compounds like naringenin, naringin, quercetin, and *C. limon* extract effectively induce apoptosis through mechanisms like BAX-Caspase 3 activation (Alshatwi et al., 2011; El-Kersh et al., 2021).

Antioxidant shield:

Rich in flavonoids and limonoids, citrus peels act as potent antioxidant shields, scavenging free radicals, limiting oxidative damage, and potentially preventing cancer initiation (Oyebadejo et al., 2019; Saranya et al., 2017).

Angiogenesis suppression and tumor reduction:

Citrus peels show promising effects beyond cellular targets. A lemon and ginger infusion significantly suppressed angiogenesis and induced apoptosis *in vivo*, while also achieving a 50% tumor-free rate and 32.8% tumor reduction in mice (Al-Ataby & Talib, 2022).

Targeted arsenal for personalized therapies:

Beyond broad benefits, specific peel components, like acridone alkaloids, exhibit targeted cytotoxicity against specific breast cancer cell lines (Segun et al., 2018). Citrus peel extract nanoparticles also show

enhanced cytotoxicity, opening doors for personalized drug delivery strategies (Amalina & Wahyuni, 2021).

5. Conclusion

Once discarded as waste, citrus peels are rewriting their narrative as promising allies against breast cancer. Their diverse bioactivities and encouraging *in vivo* results position them as valuable resources for novel cancer prevention and treatment strategies.

However, unlocking their full potential requires further research. A deeper understanding of their anticancer mechanisms is crucial for optimizing therapeutic application. Rigorous clinical trials are essential to bridge the gap between preclinical findings and safe, effective human therapies. Furthermore, exploring synergies between citrus peels and established treatments could lead to more potent and multifaceted regimens.

In conclusion, while citrus peels hold immense promise, continued research and rigorous clinical trials are key to transforming these readily available natural weapons into viable cancer-fighting tools, bringing us closer to a future where they not only nourish but also protect.

Ethical Statement

There is no need to obtain ethics committee permission for this study due to the use of open access sources. However, the study was conducted in accordance with ethical principles.

Financial Support for the Study

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The findings of this study have not been presented at any conference or journal.

Conflicts of Interest

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Author Contributions

All authers contributed to literature search, data collecting and editing the report.

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