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REVIEW ARTICLE
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Volatile and Non-volatile Compounds in Citrus Fruit by-products and their Biological Activities - A Review

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ABSTRACT

Citrus fruits are among the most extensively cultivated crops worldwide, as their fruits and by-products are widely recognized as vital sources of vitamins, minerals, and phytochemicals essential for human health. In recent years, citrus by-products have attracted significant research interest due to their potential as sources of value-added products, such as essential oils, flavonoids, pectin, dietary fibers, and biofuels. Notably, customers have high demands for green, safe, and health-friendly products. Therefore, this paper reviews the importance of both volatile and non-volatile compounds in citrus by-products and their potential health benefits. The results indicate that citrus by-products are rich in essential oils, flavonoids, and limonoids, which possess diverse bioactivities, such as antioxidative, antimicrobial, and anti-inflammatory activities. Therefore, the recovery of essential substances from citrus by-products (peels, leaves, and seeds) not only minimizes environmental impact but also enhances added values of citrus fruits, offering sustainable solutions for economic and health benefits derived from citrus-based products. This information is useful for the food, pharmaceutical and cosmetic industries in developing new and safe products. Regarding future research, the synergistic and antagonistic interactions between volatile and non-volatile compounds in citrus by-products and their impact on bioactivity should be focused to better understand their overall bioactivity.

Keywords: Citrus; Essential oils; Phenolic compounds; Flavonoids; Fruit by-products.

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INTRODUCTION

The term "Citrus" comes from the Latin word "Kedros," referencing its reminiscent odor of cedar, pine, and cypress (Spiegel-Roy & Goldschmidt, 1996). Citrus belongs to the family Rutaceae, subfamily Aurantioideae, which is further divided into two subtribes: Clauseneae (5 genera) and Citrae (28 genera) (Spiegel-Roy & Goldschmidt, 1996; Dugo & Di Giacomo, 2002). Nowadays, citrus fruits are among the most extensively cultivated crops in the world because their fruits and by-products are widely recognized as vital sources of vitamins, minerals, and phytochemicals necessary for human wellness. Citrus is one of major agricultural crops over the world. It is intensively cultivated in many Asian countries, including China, India, Iran, Turkey, Thailand, and Vietnam, due to optimal climatic conditions. The global production of citrus fruits increased significantly from 2016 to 2024, rising from 145.5 megatons in 2016 to 165 megatons in 2024 (Supplementary S1). Notably, annual production increased by nearly 10 megatons from 2018 to 2019, and significantly increased by 20 megatons from 2019 to 2020. The highest annual production of citrus fruits in the 2016 to 2024 was recorded in 2023. Reaching 169.4 megatons. According to FAO statistics in 2023, global citrus

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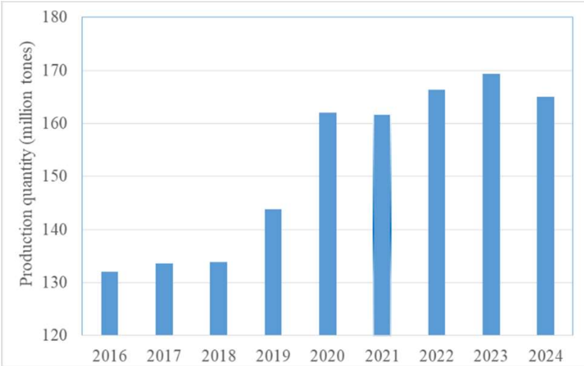
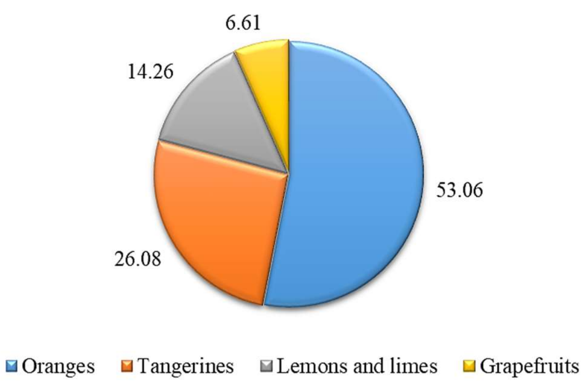


S1: World production of Citrus fruits in the period of 2016 - 2024 (FAO, 2025).

fruit production in 2022 was estimated at 166.3 megatons, with oranges contributing the largest share (over 76.4 megatons) and grapefruits the lowest (slightly above 9.7 megatons). These results are similar to the FAO statistics in 2021 (FAO, 2025) that oranges accounted for the largest share of production (53.06%), followed by tangerines (26.08%), lemons and limes (14.26%), and grapefruits, which had the smallest share (6.61%) (Supplementary S2).



S2: World production of different Citrus fruits in 2019 (FAO, 2021).

Citrus trees are relatively short, ranging from shrubs to medium-sized trees 5-10m in height, although some species can grow up to 15m. Citrus trees have dense, evergreen foliage with simple leaves that typically consist of a single blade and a petiole. The leaves are entire, unifoliate, and relatively thick, measuring 4-8cm in length. The fruits of Citrus, classified as hesperidia, are fleshy, many-seeded berries. Morphologically, these fruits are composed of two main parts: the pericarp (commonly referred to as the peel) and the endocarp, which is the edible portion (referred to as the pulp). The external, colored layer of the peel is the epicarp or exocarp, often called the flavedo, while the internal, white layer is the mesocarp, usually known as the albedo (Fig. 1). The flavedo, composed of layers of cells that protect the fruit from water loss, contains essential oils and pigmented cells within its oil glands (Spiegel-Roy & Goldschmidt, 1996; Dugo & Di Giacomo, 2002). In its immature state, chlorophyll is the primary green pigment in the flavedo, but as the fruit matures, it transitions to the yellow or orange hues of carotenes (Solovchenko et al., 2019). Additionally, the deeper layers of the flavedo merge into the mesocarp, providing further protection for the fruit against external factors. In the early stages of development, the albedo accounts for approximately 60-90% of the total fruit volume. However, as the fruit matures, the endocarp expands and the mesocarp layer becomes thinner. The endocarp, or pulp, is the innermost layer of the fruit and is composed of segments containing juice vesicles, also referred to as juice sacs (Spiegel-Roy & Goldschmidt, 1996; Dugo & Di Giacomo, 2002). These segments are enclosed by thin locular membranes that separate them from adjacent segments, making them easily separable. The juice vesicles are elongated, spindle-shaped, plump cells that extend from a stem at the segment's periphery toward the central axis, where the seeds are located.

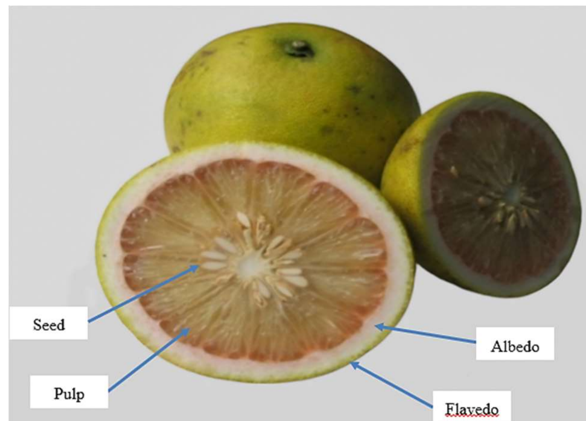


Fig. 1: The overall structure of the Citrus fruits.

Citrus can be consumed fresh or used in various dishes due to its versatility in cooking. Additionally, citrus and its by-products are well-known as sources of numerous beneficial compounds for human health, such as ascorbic acid, polyphenols, flavonoids, essential oils, and dietary fibers. From an industrial perspective, a wide range of products - including dehydrated products, jams, juices, and flavoring agents - can be derived from citrus by-products (Zema et al., 2018). However, only about 34% of citrus fruits are utilized, leaving nearly 50% of the total mass as waste, primarily consisting of peels, seeds, and pulp. The industrial waste from citrus is estimated to exceed 24.3 million tons annually (Consoli et al., 2023) Without proper treatment, citrus waste can contribute to environmental issues, such as methane production, a potent greenhouse gas, due to its high fermentability (Mamma & Christakopoulos, 2013). Traditionally, citrus waste has been reused in the manufacture of cattle feed, which is generally a low-value application. However, numerous approaches have been developed to utilize and manage citrus by-products from an environmental perspective. The most common methods include composting, anaerobic digestion, incineration, thermolysis, and gasification (Sharma et al., 2017). In recent years, citrus by-products have garnered significant research interest due to their potential as sources of value-added products, including essential oils, flavonoids, pectin, dietary fibers, and biofuels (Sharma et al., 2017; Zema et al., 2018). The extraction of essential oils, flavonoids, and dietary fibers not only minimizes waste but also promotes sustainable industrial practices by reducing reliance on synthetic chemicals and fossil fuels. Additionally, converting citrus waste into bioenergy can replace conventional energy sources, further lowering carbon footprints. By integrating citrus by-product utilization into circular economy models, industries can enhance sustainability, reduce greenhouse gas emissions, and contribute to a greener future. Research indicates that citrus by-products, including peels, seeds and leaves, are rich in essential oils, flavonoids, and limonoids, which exhibit diverse bioactivities, including antioxidant, antimicrobial, and anti-inflammatory properties. Recovering these valuable compounds from citrus peels, seeds, and leaves not only reduces environmental impact but also enhances economic and health benefits of citrus-based products. Additionally, it provides a sustainable solution for reducing citrus waste and increasing the added value of citrus fruit. Therefore, the objective of this review paper is to systematically summarize the chemical compositions of essential oils, flavonoids, limonoids and other non-volatile compounds extracted from citrus peels, seeds, and leaves, as well as their associated health benefits, offering sustainable solutions for economic and health benefits derived from citrus-based products.

Study Methodology

The literature review was conducted using bibliographic databases including Web of Science, Scopus, and Google Scholar. The scientific articles are available in searchable web-based scientific databases such as ScienceDirect, Wiley Online Library, ACS publications, Taylor & Francis Online, Springer Nature Link, MDPI, Frontier, , and Google Scholar. The searching keywords used were citrus peels, citrus leaves, citrus seeds, citrus by-products, citrus extraction, citrus essential oils, citrus flavonoid, citrus limonoid, antioxidant, antimicrobial activity, *in vitro* bioactivity, or *in vivo* bioactivity. A total of 115 articles were selected for this review, categorized into three time periods: 15 articles from 1995 to 2005, 36 articles from 2006 to 2015, and 64 articles from 2016 to 2025. Among these, 40 studies on citrus peels, 11 on citrus leaves, 18 on citrus seeds, 35 on essential oils, 35 on flavonoids, and 25 on limonoids were found.

Chemical Composition of Volatile and Non-volatile Compounds Extracted from Citrus by-products

Essential Oils

Essential oils (EOs) derived from citrus fruits are aromatic, oily extracts characterized by the strong essence of fruits such as orange, lemon, lime, and grapefruit. They are complex mixtures of volatile, organic, hydrophobic compounds, including esters, aldehydes, ketones, and alcohols, all of which contribute to the plant's flavor and fragrance (Verma et al., 2022). Additionally, EOs are biologically active compounds associated with numerous beneficial effects. These EOs can be sustainably extracted from the leaves, flowers, and the fruits' flavedo. As a result, citrus EOs are among the most important compounds of citrus fruit processing by-products. They are widely used as natural food additives in various food and beverage products. Notably, they are classified as generally recognized as safe (GRAS) and emerging as novel bio-preservatives effective against resistant pathogens. EOs from citrus peels and leaves were reported to be in the range from 0.005 to 10% depending on the material quality as well as extraction conditions (Phi et al., 2015a). Therefore, processing or extraction techniques of citrus EOs have attracted significant interest from researchers. Traditionally, a high proportion of EOs can be extracted by performing cold pressing or steam distillation. Cold pressing method is usually employed to extract essential oils of citrus peels by pressing the flavedo of fruits with hand to express the oil and then the oil is collected in brine solution on ice, while steam distillation, which employs the boiling water to extract the oil of citrus peel, is also a common method for extraction of citrus essential oils because of high extracted yield of essential oils (Phi et al., 2015a). In addition, a modification of steam distillation method by applying the vacuum pump in the extraction system was used to reduce the heating temperature during extraction. Phi et al. (2015a) reported that the vacuum-distillation is considered to be the promising innovation theme for producing natural fragrance and essential oil with high production efficiency. Another approach is microwave extraction, which has received increasing attention (Singh et al., 2021). The microwave-accelarated distillation showed higher yields (0.24%) than traditional hydrodistillation (0.21%) and cold pressing (0.05%) with shorter extraction time and more environmentally friendly (Ferhat et al., 2007). The primary chemical classes of EO components identified in citrus peels and leaves include monoterpene hydrocarbons, oxygenated monoterpenes, and sesquiterpene hydrocarbons. Monoterpene hydrocarbons are the major components of essential oils extracted from citrus peels, prompting extensive quantitative analyses. The main EO components (% w/w) of several citrus peels and leaves are summarized in Table 1.

Essential oils (EOs) derived from citrus peels and leaves consist predominantly of monoterpene hydrocarbons (51.2–99.4%), with oxygenated monoterpenes present in much smaller amounts (0.40–45.9%), followed by sesquiterpenes (0.18–5.50%). Significant variations in the composition and patterns of citrus EOs are observed, influenced by factors such as geographical location, environmental conditions, genetic background, origin, maturity stage, and the methods used for extraction and analysis. Hsouna et al. (2019) reported that monoterpenes constituted approximately 51.2% of the EOs from Tunisian sour orange peels (*Citrus aurantium*), while Hosni et al. (2010) found that Tunisian orange peels (*Citrus sinensis*) contained 99.4%. Similarly, Bourgou et al. (2012) noted that the compositions of monoterpenes, oxygenated monoterpenes, and sesquiterpenes varied among citrus species and ripening stages. For example, lemon fruits at the immature stage exhibited the highest yield of 1.30% w/w, while mandarins and oranges had the highest yields at the semimature stage, with values of 2.70% and 0.74% w/w, respectively. Bitter oranges, on the other hand, showed the highest yield (0.46% w/w) at the mature stage. The differences in EO yields, even among the same Tunisian citrus species, are attributed to variations in extraction methods and environmental growing conditions, as highlighted by the comparative studies of Hosni et al. (2010) and Bourgou et al. (2012).

Table 1: Main volatile compounds (%w/w) of *Citrus* peels and leaves essential oils*

Compounds	Orange		Pummelo/Grapefruit		Lime/Lemon	
	Peels	Leaves	Peels	Leaves	Peels	Leaves
Monoterpene hydrocarbons	51.2 - 99.4	-	97.6	-	77.7 - 80.9	-
α-pinene	0.49 - 1.80	0.10 - 2.80	0.15 - 1.60	0.97	0.40 - 3.12	0.10 - 1.70
β-pinene	0.02 - 1.82	16.9	0.25 - 1.52	2.69 - 4.90	1.37 - 21.1	0.10 - 19.3
Camphene	-	-	-	-	0.14 - 1.30	-
Sabinene	0.28 - 1.00	4.73 - 44.9	0.19 - 1.00	0.10 - 1.99	0.28 - 2.54	0.10 - 2.00
Mycrene	0.73 - 3.30	1.50 - 4.50	1.40 - 6.43	-	1.30 - 2.20	0.10 - 0.90
α-phellandrene	0.05 - 0.08	2.61	0.79	4.01	0.13	0.12 - 0.80
o-cymene	-	-	-	-	1.30 - 16.62	-
p-cymene	-	0.20 - 0.90	0.10	-	1.60 - 2.50	0.10 - 0.30
D-limonene	48.7 - 97.3	5.5 - 13.8	78.4 - 96.5	1.40 - 21.9	40.3 - 96.9	0.10 - 30.1
β-ocimene	0.27	1.10 - 3.70	0.14 - 0.26	-	0.28 – 0.31	0.50 – 20.0
α-terpinolene	0.02	0.20 - 2.60	0.03 - 0.33	1.60 - 2.39	0.21 - 1.12	0.23
α-terpinene	0.15 - 0.42	1.87	0.17 - 0.33	-	0.18 - 2.10	0.29
ɣ-terpinene	0.02 - 13.5	0.40 - 3.30	7.63 - 10.9	2.58	2.61 - 15.4	0.30 - 1.18
Oxygenated monoterpenes	0.40 - 45.9	-	0.84	-	6.00 - 13.3	-
Terpene alcohols						
Linalool	0.30 - 32.4	0.20 - 5.23	0.09 - 0.20	1.16	0.30 - 0.90	1.00 - 6.10
Nerol	0.01	-	-	1.50 - 10.4	0.85	0.27 - 9.50
Fenchol	-	-	-	-	0.04 -1.40	-
Borneol	-	-	-	-	0.06 - 1.40	-
1-terpineol	0.01	-	0.04	-	0.04 - 2.30	-
4-terpineol (Terpinen-4-ol)	0.43	5.74 - 22.6	0.04	-	0.40 - 1.90	0.40 - 1.80
α-terpineol	0.1 - 0.42	0.20 - 1.50	-	0.46	0.10 - 12.7	0.30 - 3.10
Geraniol	0.01- 0.10	0.40 - 1.90	-	1.40 - 10.7	0.58	0.40 - 7.50
Citronellol	-	0.40 - 1.50	-	3.19	8.19	3.98 - 13.4
Terpene esters						
Linalyl/Linalool acetate	0.28 - 12.0	-	-	-	0.70 - 2.37	-
Citronellyl acetate	0.12 - 0.20	0.10	-	0.30 - 1.80	0.05	1.20 - 4.10
Gernanyl acetate	0.08 - 0.20	0.37	0.10	0.21	0.60	0.10 - 6.60
Neryl acetate	0.10	0.10 - 1.70	0.04 - 0.10	0.61	1.20 - 2.20	-
Terpene aldehydes						
Neral	1.30	0.20 - 5.62	0.10	4.50	0.40 - 2.00	1.94 - 11.4
Geranial	0.20 - 1.80	0.20 - 3.99	0.10	3.28 - 4.5	0.17 - 4.30	19.4
Decanal	0.10 - 0.20	-	0.20	-	0.10	0.37
Tetradecanal	-	-	-		0.12	-
Nonanal	-	-	-	-	-	-
Octanal	0.20 - 1.40	-	-	-	0.10	-
α-citral	-	-	-	-	1.98	-
β-citral	-	-	-	-	1.76	-
Citronellal	0.01	0.10 - 0.70	-	0.50	0.05 - 0.69	61.7 - 72.5
α-sinensal	0.02 - 0.04	0.10 - 0.30	-	-	-	-
β-sinensal	0.04 - 0.14	0.10 - 0.80	-	-	-	-
Sesquiterpene hydrocarbons	0.18 - 2.4	-	0.71	-	4.23 - 5.50	-
β-caryophyllene	0.10	0.20 - 2.80		6.75 - 15.40	0.70 - 1.00	0.90 - 5.70
α-humulene	0.02 - 0.08	-	0.03 - 0.10	1.80	0.11 - 0.15	0.27 - 0.80
α-copaene (more popular)	0.04 - 0.24	-	0.03 - 0.13	0.13	-	0.08
β-copaene	0.01 - 0.09	-	0.06	-	-	-
trans-α-bergamotene	-	-	0.04	-	0.12	0.05
cis-α-bergamotene	-	-	-	-	1.10	-
β-farnesene	0.10	-	-	2.20	0.16	1.90
α-farnesene	3.64	-	-	-	0.41 – 10.0	-
δ-elemene	-	0.10	-	0.17	0.23	0.04 - 2.70
β-elemene	0.02 - 0.17	0.20 - 1.40	0.10 - 0.42	0.04	0.31	0.02 - 1.10
γ-elemene	-	0.05	-	1.01	0.05	0.05
α-santalene	-	-	-	-	0.02	-
β-santalene	-	-	-	0.04	0.07	0.06
β-selinene	-	-	-	-	0.02	-
cis-β-bisabolene	-	-	-	0.04	1.60 - 2.00	0.10 - 1.18
cis-α-bisabolene	-	-	-	-	0.18 - 5.07	-

*Data were collected from different studies on *Citrus* (Bustamante et al., 2016; Caputo et al., 2020; Dosoky & Setzer, 2018; Espina et al., 2011; Hilali et al., 2019; Hosni et al., 2010; Hsouna et al., 2019; Hussain et al., 2008; Khalid et al., 2020; Kirbaşlar et al., 2009; Kirbaşlar et al., 2006; L.-Y. Lin et al., 2019; L. Y. Lin et al., 2019; Liu et al., 2012; Mahmud et al., 2009; Maurya et al., 2018; Ngan et al., 2022; Othman et al., 2016; Phi et al., 2015; Tao et al., 2009; Wu et al., 2013).

Among the monoterpenes in Citrus EOs, limonene, α-pinene, β-pinene, sabinene, myrcene, α-phellandrene, and ɣ-terpinene were identified in the peels and leaves of all Citrus species (Table 1). Limonene (40.3–97.3%) is the major compound with the highest concentration in the EOs of Citrus peels, followed by β-pinene (0.02–21.1%) and ɣ-terpinene (0.02–15.4%). Limonene concentrations in the EOs of Citrus leaves, which range from 0.10% to 30.1% (w/w), are much lower than those in the Citrus peels. In contrast, the EOs of Citrus leaves contain higher concentrations of sabinene and β-pinene compared to those in Citrus peels. Khalid et al. (2020) reported that the EOs of Navel orange leaves contained sabinene concentrations of up to 44.9%, whereas lower concentrations of other monoterpenes, including limonene (5.50%), α-pinene (0.49%), and ɣ-terpinene (0.40%), were recorded. Among Citrus varieties, the chemical compositions of EO peels depend on each species and their growing locations rather than on the different groups of Citrus, such as oranges, pummelos/grapefruits, or limes/lemons. However, the EOs of pummelo leaves contain higher amounts of α-phellandrene than those of orange and lime leaves, whereas the EOs of lime leaves have higher amounts of β-ocimene than those of orange and pummelo leaves.

Alcohol compounds such as linalool and α-terpineol, which are derived from the degradation of limonene, are crucial to the orange flavor profile, contributing to the desirable aromatic and flavor qualities of orange juice (Pérez-López et al., 2006). Linalool was also found to be abundant in sour oranges, with a concentration of 32.4% (Hsouna et al., 2019). Moreover, previous studies have shown that linalool plays a significant role in inhibiting peroxidation activity due to its antioxidant properties (Hussain et al., 2008). Geraniol and terpineols, such as 1-terpineol, 4-terpineol, and α-terpineol, are widely distributed in Citrus peels and leaves. These compounds are valued not only for their aromatic qualities but also for their biological activities, including antimicrobial and antioxidant effects. The results indicate that the EOs of orange and pummelo leaves contain higher amounts of geraniol, 4-terpineol, and α-terpineol than the EOs of orange and pummelo peels. Similarly, the EOs of lime leaves have higher amounts of geraniol than those of lime peels; however, a higher concentration of α-terpineol was found in the EOs of lime peels.

Regarding the groups of terpene esters and terpene aldehydes, the EOs of Citrus peels contain high amounts of linalool acetate (0.28–12.0% w/w for orange peels and 0.70-2.3% w/w for lime peels), neral (0.10-2.0% w/w), geranial (0.10-4.30% w/w), and octanal. In contrast, the EOs of Citrus leaves have higher amounts of citronellyl acetate, neral, geranial, and citronellal. Interestingly, the EOs of lime leaves from Malaysia consist predominantly of citronellal, accounting for 61.7-72.5% w/w (Othman et al., 2016). Citronnellal from Citrus leaves has been identified as having both antifungal and antioxidant acitivity (Li et al., 2013; Warsito et al., 2018).

Sesquiterpene hydrocarbons account for the smallest proportion of Citrus EOs. Compounds such as β-caryophyllene, α-humulene, and β-elemene are widely distributed in Citrus peels and leaves. The EOs of lime peels contain 2-5 times higher concentrations of sesquiterpene hydrocarbons than those of orange or pummelo peels. The major sesquiterpene hydrocarbons in the EOs of lime peels include β-caryophyllene (0.70-1.00% w/w), α-farnesene (0.41-10.0% w/w), cis-β-bisabolene (1.60-2.00% w/w), and cis-α-bisabolene (0.10-5.07% w/w) (Table 1). Additionally, Lin et al. (2019) reported that the EOs of *Citrus aurantifolia* (Christm.) Swingle contains a variety of sesquiterpenes, including α-santalene, β-santalene, β-selinene, cis-β-bisabolene, and cis-α-bisabolene.

Consequently, the citrus peel is the primary source of volatile compounds among fruit matrices, as its oil glands contain highly concentrated EOs. Monoterpene hydrocarbons, particularly D-limonene, are the major volatile compounds, typically accounting for 60–95% of the EOs of Citrus peels (Guo et al., 2025). Although the Citrus leaves share some key volatile compounds like D-limonene and γ-terpinene at much lower levels, they are comparatively richer in linalool and oxygenated sesquiterpene (Hamdan et al., 2024). Overall, the peel remains the most abundant and diverse matrix for aroma compounds. However, the yield and chemical composition of citrus EOs depend mainly on the extraction methods. Although the hydrodistillation and steam distillation are conventional methods used for extracting essential oils from Citrus peels and leaves, they have several drawbacks, including low yield of the essential oil, loss of volatile components, long extraction time, and degradation of some constituents (Pheko-Ofitlhile et al., 2024). Therefore, alternative methods that minimize heat effect should be developed such as ohmic-assisted hydrodistillation (Ikarini et al., 2025), microwave- and enzyme-assisted extraction (Zhang et al., 2025), and sonication-assisted hydrodistillation (Ali et al., 2025) to enhance both the yield and chemical composition of Citrus essential oils.

Flavonoids

Flavonoids, naturally occurring polyphenolic compounds, are secondary metabolites found in a variety of foods, including fruits and vegetables, grains, teas, and wine (Sayre et al., 2012). Flavonoids are structurally characterized by a 15-carbon skeleton, consisting of two phenyl rings (aromatic rings A and B) and a heterocyclic ring (C), which are often depicted as C6-C3-C6. This structure allows for various substitutions and modifications, giving rise to a diverse group of flavonoids with distinct properties and functions. Based on their molecular structure, flavonoids can be classified into seven classes: flavanones, flavonols, flavones, isoflavones, flavanols, anthocyanidins, and chalcones (Panche et al., 2016). Citrus fruits are rich sources of flavonoids, especially in the peels and leaves. The extraction yield of leaf extract from *C. sinensis* were recorded at 7, 11, and 13% with increase in aqueous component of methanol (100, 80, and 50%, respectively), and the highest extraction yield obtained from three different citrus leaf extracts were recorded using distilled water heated at 50℃ (Adnan et al., 2014). Another study by Lachos-Perez et al. (2018) also investigated the extraction yields of different extraction methods on defatted orange peels. Low pressure extraction methods including soxhlet, shaker, and ultrasound produced less yield (2.91, 2.75, and 3.15%, respectively) compared to subcritical water extraction (SWE) approach (10.63%). More than 110 flavonoids have been identified in 62 Citrus germplasms, and they are primarily composed of three main groups: flavanones, flavonols, and flavones (Wang et al., 2017; Addi et al., 2021). According to Khan and Dangles (2014), Citrus flavonoids exist in the forms of aglycones (flavanone aglycones, flavone aglycones, and flavonol aglycones) and glycosides (neohesperidoside and rutinoside).

Flavanones (2-arylchroman-4-ones) are crucial Citrus flavonoids, contributing to the bitterness of the fruits. Among the aglycone forms, the most important ones are naringenin, hesperetin, and eriodictyol; however, most of them exist in glycosidic form. In the glycoside forms, there are two types: neohesperidosides and rutinosides (Wang et al., 2022). Neohesperidosides are flavonoids connected with the disaccharide neohesperidose (rhamnosyl-α-1,2 glucose), while rutinosides are flavonoids linked with the disaccharide rutinose (rhamnosyl-α-1,6 glucose) (Tripoli et al., 2007). Fig. 2A presents the chemical structures of the main flavanone glycosides from Citrus fruits, including rutinosides and neohesperidosides. Neohesperidoside flavanones (naringin, neo-hesperidin, poncirin, and neo-eriocitrin) contribute to a bitter taste and are typically found in grapefruits, bitter oranges, and pummelos, whereas rutinoside flavanones (hesperidin, narirutin, and didymin) are tasteless and occur in sweet oranges, lemons, and mandarins (Nogata et al., 2006; Tripoli et al., 2007).

Table 2 shows the data for the main flavonoid compounds identified in citrus peels and leaves. Flavanone glycosides account for significant quantities in the albedo of citrus peels (Sharma et al., 2019). The amounts of neohesperidoside flavanones in the peels of orange and pummelo varieties were found to be significantly higher than those in the peels of lime varieties. Conversely, the peels of orange and lime varieties contained higher amounts of rutinoside flavanones than the peels of pummelo varieties. Among Citrus peels, naringin and poncirin, the glucoside forms of naringenin, were found at the highest concentrations of 2100 and 462 mg/100g, respectively, in the peels of Marsh grapefruit (*C. paradisi*) (Nogata et al., 2006). Additionally, the three highest concentrations of flavanone glucosides detected in sour orange peels were naringin, neo-hesperidin, and poncirin, with concentrations of 1470, 1090, and 567mg/100g, respectively (Nogata et al., 2006). Furthermore, the peels of orange varieties contained higher amounts of neo-poncirin (2.70 - 78.0mg/100g) than those found in both grapefruits and lime peels (8.40 and 12.6mg/100g, respectively). Regarding the aglycone content in Citrus peels, Pereira et al. (2017) found that Brazilian orange peels (*C. sinensis* L. Osbeck var. Baia) contained naringenin and hesperetin at notable concentrations of 474 and 121mg/100g, respectively. On the other hand, none of the flavanone aglycones were detected in the peel tissues of pummelos or grapefruits.

Flavanones in the leaves of Citrus plants are generally present in smaller amounts compared to the peels. Naringenin and its glucoside forms were not detected in the leaves of Citrus plants. However, the leaves of lime varieties contained noticeable amounts of hesperidin (0.0 – 0.41mg/100g) and eriocitrin (0.0 - 1.13mg/100g) (Kawaii et al., 2000). Additionally, eriocitrin was found to be widely present in the leaves of Tahiti lime (*C. latifolia*), Eureka lemon (*C. limon*), and lumia (*C. lumia*), while it was not detected in the leaves of oranges, pummelos, or grapefruits. The highest amount of naringin was found in the leaves of grapefruits such as Hirado Buntan and Marsh grapefruits (1.08 and 0.40mg/100g, respectively). On the other hand, the highest amount of hesperidin was found in the leaves of Morita Navel oranges (0.74mg/100g), followed by Meyer lemon leaves (0.41mg/100g) (Kawaii et al., 2000). Previous studies have shown that hesperidin and naringin are mutually exclusive and cannot co-exist at high concentrations (Tsuchida et al., 1997; Kawaii et al., 1999; Kawaii et al., 2000).

Flavonols (3-hydroxy-2-phenylchromen-4-one) are characterized by the presence of a hydroxyl group (-OH) at the 3-position on the C ring, with kaempferol, quercetin, catechin, and isorhamnetin being the major flavonol aglycones (Aherne & O'Brien, 2002). However, the 3-OH group can be glycosylated by different sugars, and glycoside flavonols such as rutin are detected in various Citrus plants, although only in trace amounts compared to flavanones and flavones (Wang et al., 2022). Rutin is the only flavonol detected in Citrus peels and leaves, as reported by Kawaii et al. (2000) and Nogata et al. (2006). In Citrus peels, the highest concentration of rutin was found in sour

Table 2: Main flavonoid compounds identified in *Citrus* peels and leaves (mg/100g)*

Compounds	Orange		Pummelo/Grapefruit		Lime/Lemon	
	Peels	Leaves	Peels	Leaves	Peels	Leaves
Flavanones						
Naringin	0.0 - 1470	0.0 – 0.16	333 - 2100	0.40 – 1.08	0.0 - 173	0.0
Poncirin	0.0 - 567	0.0 - 0.15	0.0 - 462	0.14 - 0.30	0.0 - 36.7	0.0
Neo-hesperidin	0.0 - 1090	0.0	4.50 - 20.30	0.0	0.0 - 4.90	0.0
Neo-eriocitrin	0.0 - 220	0.0 – 0.22	0.0 - 4.40	0.0 – 0.07	0.0 - 6.12	0.0
Hesperidin	0.0 - 4117	0.0 – 0.74	0.0	0.0	1.40 - 1210	0.0 – 0.41
Narirutin	22.0 - 228	0.0	0.0 - 190	0.08 – 0.1	0.0 - 56.3	0.0
Naringenin	0.0 - 474	0.0	-	0.0	0.0 - 85	0.0
Hesperitin	0.0 - 121	-	-	-	0.0 - 121	-
Eriodictyol	-	-	-	-	-	-
Eriocitrin	3.80 - 8.10	0.0	0.0 - 9.20	0.0	0.0 - 146	0.0 – 1.13
Neo-poncirin	2.70 - 78.0	Trace	0.0 - 8.40	0.0 - 0.32	0.0 - 12.6	Trace
Flavonols						
Quercetin (3,3',4',5,7-pentahydroxyflavone)	-	0.0	-	0.0	-	0.0
Rutin (quercetin-3-O-rutinoside)	0.0 - 41.3	0.0 – 0.22	4.3 – 16.6	0.0 – 0.1	0.0 - 27.2	0.02 – 1.8
Flavones						
Isorhoifolin	1.10 - 4.20	0.0 – 0.28	0.0	0.0 – 0.11	0.0 - 55.3	0.1 – 0.41
Rhoifolin	3.70 - 108	0.0	2.0 - 18.4	0.0 – 0.56	0.0 - 2.90	0.0
Diosmin	3.80 - 7.10	0.0 – 0.21	0.0 - 0.70	0.0	2.60 - 52.5	0.12 – 0.56
Neo-diosmin	3.00 - 43.8	0.0 – 0.04	0.60 - 11.0	0.0 – 0.05	0.0 -20.4	0.0
Polymethoxylated flavones (PMFs)						
Nobiletin	8.90 - 18.1	0.02 – 0.04	0.0 - 4.60	Trace	0.0 - 1.70	0.0 – 0.06
Tangeretin	0.19 - 444	Tr	0.0 - 0.4	Trace	0.0 - 84	0.0 – 0.13
Sinensetin	0.0 - 34.0	0.0 – 0.02	0.0 - 0.30	Trace	0.0 -2.20	Trace
Heptamethoxyflavone	0.0 - 3.60	0.0	0.0	Trace	0.0 - 4.10	Trace
5-Demethylnobiletin	-	Trace	-	0.0 - 0.25	-	0.0 – 0.05

*Data were reported by (Nogata et al., 2006; Pereira et al., 2017).

orange (41.3mg/100g), followed by lumie (27.2mg/100g) and *C. grandis* cv. Shytian you (16.6mg/100g), while no flavonols were detected in sweet orange peels (Nogata et al., 2006). In citrus leaves, the highest rutin content was found in lumie leaves (1.8mg/100g) when compared to those from oranges, pummelos, or grapefruits (Table 2).

Flavones (2-phenylchromen-4-one) are also present in the peels and leaves of Citrus plants. Unlike flavonols, the absence of the hydroxyl (-OH) group at the third position of the C ring in flavones leads to differences in their biological activities (Panche et al., 2016). Apigenin, luteolin, and diosmin are the aglycone forms of flavones. Additionally, flavones in Citrus are converted into polymethoxylated flavones (PMFs) rather than being glycosylated (Peng et al., 2021). Both the fruit peels and leaves of Citrus plants contain notable amounts of flavones and polymethoxylated flavones (Table 2). Similarly, to flavanones, flavones can exist as aglycones or glycosides, but flavone glucosides such as isorhoifolin, rhoifolin, diosmin, and neo-diosmin are more common. Rhoifolin and neo-diosmin were the most abundant flavones found in sour orange peels, particularly at concentrations of 108 and 43.8mg/100g, respectively (Nogata et al., 2006). The leaves of oranges also contained small amounts of isorhoifolin and diosmin, at 0.28 and 0.21mg/100g, respectively. In addition to orange peels, rhoifolin was also found in grapefruits such as Marsh grapefruit peels and Hirado buntan leaves (Nogata et al., 2006). Isorhoifolin and diosmin were also found in high concentrations in Tahiti lime peel tissues, at 55.3 and 52.5mg/100g, respectively (Nogata et al., 2006).

Fig. 2B illustrates the chemical structure of polymethoxylated flavones (PMFs). PMFs are flavones characterized by methoxy groups attached to positions 3, 5, 6, 7, 8, and 3′, 4′ on the aromatic rings A and B, respectively (Wang et al., 2022). The most common PMFs, such as nobiletin, tangeretin, and sinensetin, are primarily concentrated in orange peels and exhibit various biological properties (Nogata et al., 2006; Tripoli et al., 2007). Among these, nobiletin is the most widely distributed and has been detected in 57 samples (Kawaii et al., 2000; Nogata et al., 2006). The highest concentration of nobiletin was found in Valencia orange peels, measuring 18.1mg/100g. Sinensetin and tangeretin were also detected in the peel tissues of Valencia oranges at notable concentrations of 34.0mg/100g and 8.5mg/100g, respectively. Tangeretin, which is most prevalent in tangerines and pokans, can be detected at a high concentration of 444mg/100g in the peels of mucroot fruit (*Citrus aurantium* × *reticulata* var. murcote), a hybrid of sweet oranges and mandarins (Nogata et al., 2006; Pereira et al., 2017). It has been suggested that two polymethoxylated flavones, nobiletin and tangeretin, as well as hesperidin, are strongly correlated (Kawaii et al., 1999). In addition to peel tissues, the leaves of oranges contain moderate amounts of nobiletin, sinensetin, and 5-demethylnobiletin, while the leaves of lime varieties contain notable amounts of nobiletin, tangeretin, and 5-demethylnobiletin (Table 2).

To sum up, although the flavonoid composition is attributed to the different Citrus matrices and varieties, the citrus peels are the richest source of flavonoids, while the citrus leaves typically contain substantially lower levels (Kawaii et al., 2000). Flavanones (2-arylchroman-4-ones) are key citrus flavonoids responsible for fruit bitterness. Major flavanones in the citrus peels include hesperidin (orange, mandarin) and naringin (grapefruit, lemon), mainly in glycosidic forms (Chakraborty et al., 2025). Polymethoxylated flavones (PMFs) such as nobiletin, tangeretin, and sinensetin are largely concentrated in orange peels and exhibit diverse bioactivities, while the citrus leaves are rich in nobiletin, and 5-demethylnobiletin (Toledo et al., 2024; Wang et al., 2025). Consequently, citrus processing waste (CPW) represents a valuable, sustainable source for flavonoid extraction (Xu et al., 2025). To maximize flavonoid yield from citrus peels and leaves, solvent type/concentration, solid-to-liquid (S/L) ratio, and pretreatment/assisted-extraction technologies emerge as key factors that simultaneously minimize flavonoid degradation and achieve desired bioactivity.

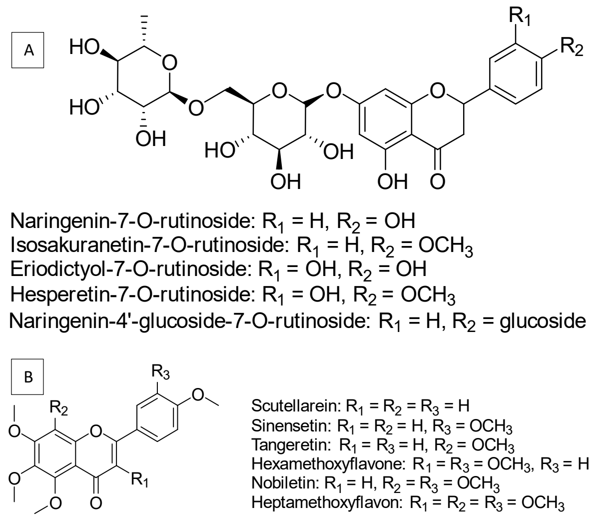


Fig. 2: Chemical structure of the main flavanone glycosides (A) and the main polymethoxyflavone (B) from *Citrus* fruits.

Limonoids

Limonoids are a distinctive class of oxygenated tetracyclic triterpenoid compounds that predominantly occur in citrus fruits and other plant species. In Citrus species, these compounds are primarily found in the seeds, peels, and, to a lesser extent, the pulp. The term "limonoid" was derived from limonin, the first compound identified as contributing to the bitterness in citrus seeds. Limonoids are vital chemical constituents of citrus, acting as one of the two primary contributors to bitterness in the fruit. Matheyambath et al. (2016) indicated that the highest concentrations of limonoids in citrus fruits are found in the seeds. Based on their structural patterns and functional groups, limonoids can be classified into two groups: limonoid aglycones and limonoid glucosides. The limonoid aglycones, most of which are insoluble in water and contribute to the bitter taste, are mainly distributed in the seeds and peels. In contrast, limonoid glucosides, which are not bitter and are soluble in water, are more abundant in juices and pulps (Breksa III et al., 2009). Limonoids have been traditionally extracted and purified by utilizing different organic solvents including ethyl acetate, methanol,

ethanol, and dichloromethane (Melwita & Ju, 2010). However, the extensive use of these solvents can negatively affect the environment and food securities (Narayanan et al., 2022). A study by Yu et al. (2007) on extraction of limonoids from grapfruit seeds by using supercritical carbon dioxide showed a potential approach. The highest yield of limonin was recorded at 6.3mg/g of seeds. Another extraction way is ultrasound-assisted extraction, which was conducted by Yu et al. (2017). The major limonoids in lemon seeds recorded in study were limonin (715.40mg/g), nomilin (270.20mg/g), and obakunone (47.40mg/g). Since limonoid aglycones have low polarity, the hydrotropic technique, which can enhance the solubility of poorly soluble substances in water, has been proposed. By application, the limonin extracted from sour orange seeds and lemon seeds recorded were 0.65 and 6.41mg/g seeds, respectively (Dandekar et al., 2008; Narayanan et al., 2022). Since limonoids and their aglycones are primarily found in seeds and peels, relatively few studies have investigated the contents of Citrus leaves. To date, about 55 limonoid aglycones and 18 limonoid glucosides have been discovered and reported in various citrus fruits, including oranges, lemons, grapefruits, limes, sour oranges, and pummelos (Ozaki et al., 2014; Russo et al., 2016). Both aglycones and glucosides of limonoids have been investigated in different citrus peels and seeds, as shown in Table 3. Hasegawa et al. (1996) reported that the concentrations of limonoid aglycones in Citrus seeds were higher than those of limonoid glucosides, which likely contribute significantly to the antioxidant capacity of limonoids. According to Sun et al. (2005), the predominant aglycones in citrus seeds are limonin, followed by nomilin. Additionally, some predominant acidic limonoids, such as nomilinic acid and diacetylnomilinic acid, make up approximately 20% of the total limonoid glucosides in citrus seeds (Hasegawa et al., 1996).

The total concentration of limonoids significantly varied among different citrus parts and species. Among three citrus varieties, pummelo seeds contained the highest amounts of total limonoid aglycones (44.04µg/g), followed by orange seeds (27.19µg/g) and lime seeds (24.01µg/g) when extracted with EtOAc (Tung et al., 2020). Limonin, the main cause of bitterness in citrus juice, was recorded as the predominant limonoid in most citrus species. The limonin content found in grapefruit seeds was the highest, with a concentration of 19.06mg/g, followed by Valencia orange seeds (10.00mg/g), Fukuhara orange seeds (9.77mg/g), and lemon seeds (8.95mg/g) (Ozaki et al., 2014). On the other hand, the seeds of Reinking pummelo and Pin Shan Kong Yau pummelo contained the lowest concentrations of limonin, at 0.55 and 0.60mg/g, respectively (Ohta & Hasegawa, 1995). Additionally, bergamia fruit, a hybrid of grapefruit and lime, also contained a high concentration of limonin (2.1mg/g) (Russo et al., 2016). Nomilin in the seeds of bergamia fruits also exhibited high concentrations, with 2.57mg/g of dry seeds. The glucoside forms of limonin and nomilin also contribute to limonoid concentrations, at 0.11 and 1.65mg/g of dry seeds, respectively (Russo et al., 2016). In addition to limonoid aglycones, limonoid glucosides, which include deacetylnomilinic acid glucoside, nomilin glucoside, nomilinic acid glucoside, and obacunone glucoside, are also present in small amounts in citrus seeds.

Limonin, as well as limonoid glucosides, were identified at low concentrations in citrus peels. More than 0.8mg/g of total limonoids were present in the peels of bergamot fruit (Russo et al., 2016). Additionally, limonoid aglycones contributed around 70% of the total limonoids in peel tissues, with nomilin and limonin being the most abundant (0.39 and 0.23mg/g, respectively). Another study by Sun et al. (2005) on limonoid contents in different fruit tissues of various citrus species during fruit growth and maturation also showed low concentrations of limonin and nomilin in citrus peels. The levels of limonin and nomilin initially increased, then declined throughout the entire growth and maturation period. The highest concentrations of limonin and nomilin in the flavedo at maturity were recorded in *C. reticulata* (1.35mg/g), while the lowest concentration was in *C. grandis* (0.0067 mg/g) (Sun et al., 2005).

Thus, the pomelo seeds and certain lime/orange seeds yield the richest amounts of total limonoid aglycones, with concentrations in the seeds far exceeding those in the peel (Saber et al., 2025; Panwar et al., 2021). Conversely, the limonoid glucosides are non-bitter and water-soluble, making them more abundant in the juices and pulps (Panwar et al., 2021). These by-products from citrus varieties remains the most cost-effective starting material for industrial-scale extraction targeting maximal yield of limonoids. Consequently, optimization of extraction must focus not only on maximizing total yield but also on preserving the glycoside structure or promoting the conversion necessary for achieving the desired functional health benefits (Meng et al., 2025; Saber et al., 2025).

Table 3: Main limonoid compounds in Citrus peels and seeds (mg/g)*

Compounds	Orange		Pummelo/Grapefruit		Lime/Lemon	
	Peels	Seeds	Peels	Seeds	Peels	Seeds
Neutral limonoid aglycones						
Limonin	0.03 - 2.31	3.95 - 10.0	0.02 - 0.20	0.55 - 19.06	0.26 - 0.32	8.95
Nomilin	0.01 - 3.94	1.02 – 3.88	-	0.11 - 3.73	-	3.03
Obacunone	-	0.08 - 0.37	-	0.06 - 1.86	-	0.58
Deacetylnomilin	-	1.24 - 2.14	-	0.35 - 1.10	-	1.24
Ichangin	0.03	0.16 - 1.16	-	Trace	-	1.16
Limonoid glucosides						
Limonin glucoside	0.12	0.37 - 0.59	-	Trace - 1.48	-	1.44
Nomilin glucoside	0.56	1.13 – 4.48	-	0.06 - 16.5	-	1.53
Obacunone glucoside	-	0.90 - 2.35	-	0.03 - 0.86	-	1.49
Deacetyl nomilin glucoside	0.45	0.69 - 1.69	-	0.37 - 0.68	-	0.55
Deacetyl nomilinic acid glucoside	-	0.13 - 0.48	-	0.42 - 0.75	-	0.14
Nomilinic acid glucoside	0.35	0.55 – 1.29	-	0.0 - 0.89	-	1.39

*Data were reported by (Ohta & Hasegawa, 1995; Ozaki et al., 2014).

Other Non-volatile Compounds of Limonoids in the Extracts of Citrus Peels and Seeds

Vitamin C

Among vegetables and fruits, citrus fruits have always been particularly popular as a dietary source of vitamin C, supplying from 23 to 83 milligrams of ascorbic acid per 100 grams of flesh weight (Matheyambath et al., 2016). The content of vitamin C in citrus fruits varies depending on production factors, climatic conditions, maturity, species and variety, and processing (Magwaza et al., 2017). Despite the fact that fruit juice is a crucial source of vitamin C for human nutrition, more than 50% of the vitamin C in citrus fruits is found in inedible parts, including peels, pulps, and seeds. The grapefruit, orange, and lemon peels were found to contain 113.3, 110.4, and 58.59mg/100 g vitamin C, respectively, while the vitamin C contents of the inner parts (pulp and seeds) of grapefruit, orange, and lemon were 99.2, 89.8, and 46.9mg/g in the, respectively (Elkhatim et al., 2018).

Carotenoids

Carotenoids, a diverse group of natural pigments, are typically found in all citrus tissues. They are responsible for the vibrant yellow, orange, and red colors of the fruits. Classes of carotenoids, such as carotenes (including β-carotene and α-carotene) and xanthophylls (which are oxygenated carotenoids), are both present in citrus varieties. Carotenoids can be synthesized in different parts of the fruit, including peels, pulps, and seeds. Yan et al. (2018) reported that carotenoids, including 9-cis-violaxanthin, violaxanthin, lutein, β-cryptoxanthin, α-carotene, β-carotene, phytofluene, and phytoene, have been identified in the exocarp of citrus fruits. In addition, trace amounts of carotenoids have been detected in seeds, ranging from 0.3 to 26.7mg/kg (Malacrida et al., 2012; Matheyambath et al., 2016; Cabral & Klein, 2017; Ordoudi et al., 2018). Moreover, carotenoids are precursors of the plant hormones ABA and strigolactones (Lado et al., 2019).

Tocopherols

Tocopherols, or vitamin E, are potent antioxidants, anticancer agents, and essential to human health. Compared to nuts, seeds, and vegetable oils, citrus fruits are not typically considered a good source of tocopherols, primarily because they are found in their seed oils. Jorge et al. (2016) indicated that α-tocopherol was the major form detected in seed oil extracted from sweet oranges, with a concentration of 135.6mg/kg. Moreover, Yilmaz and Güneşer (2017) found that different extraction methods affected tocopherol content in the seed oil of *Citrus limon* and concluded that oil prepared by cold pressing had a higher α-tocopherol content (155mg/kg oil) compared to oil extracted using traditional solvent extraction (110mg/kg oil).

Phytosterols

Phytosterols, structurally like cholesterol in animals, are plant bioactive compounds that naturally occur in plant cell membranes. Phytosterols are classified into sterols and stanols, with stanols being saturated and found to a smaller extent compared to sterols. While campesterol, β-sitosterol, and stigmasterol are the most common sterols, β-sitostanol and campestanol are the most well-known stanols (Cabral & Klein, 2017). More than 250 phytosterols have been discovered, and they have been shown to offer various health benefits to humans. Phytosterols can also be found in citrus seed oil, where β-sitosterol and campesterol are predominant and considered key quality determinants (Zayed et al., 2021). Seed oil from sweet oranges has been investigated as a potential source of phytosterols, total carotenoids, and α-tocopherol, with concentrations of 1304.2mg/kg, 19.0mg/kg, and 135.6mg/kg, respectively (Jorge et al., 2016).

Bioactivities of Volatile and non-volatile Compounds from Citrus by-products

Bioactivities of Essential oils Extracted from Citrus Peels and Leaves

Antioxidant Activity of Citrus Essential oils: Antioxidants are biological substances that inhibit the oxidation of molecules, thereby preventing the formation of radicals and subsequent chain reactions that can cause cellular damage. Oxidative stress, a result of natural oxidative processes, is linked to various chronic diseases, including cancer, heart disease, and neurodegenerative disorders (Hayes et al., 2020). By neutralizing free radicals through electron donation, antioxidants help protect cells from damage. Today, antioxidants are widely used in the food industry to prevent the rancidity of fats and oils, extend shelf life, and enhance the nutritional value of food products.

Essential oils (EOs) from natural sources, such as citrus fruits, are known to exhibit significant antioxidant activities. The *in vitro* antioxidant capacity of EOs extracted from different parts of Citrus has been extensively investigated using various chemical assays, including 2,2-diphenyl-1-picrylhydrazyl (DPPH), ferric reducing antioxidant power (FRAP), 2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS), and oxygen radical absorbance capacity (ORAC). Although EOs contain hundreds of volatile components, the main components of EOs can be classified in two structural families with respect to hydrocarbon skeleton: terpenoids, formed by the combination of two (monoterpene), three (sesquiterpene), or four (diterpene) isoprene units, and phenylpropanoids (Amorati et al., 2013). The phenolic compounds of terpenoid and phenylpropanoid families act as antioxidants due to their high reactivity with peroxyl radicals, which are disposed of by formal hydrogen atom transfer (Foti, 2007). Guo et al. (2018) evaluated the antioxidant activities of 14 Citrus varieties using two different assays (Fig. 3). They found that bergamot (*Citrus medica* var. *sarcodactylis* Swing) exhibited the highest antioxidant activity in both the DPPH and ABTS assays, with more than 70% activity, while sour orange (*Citrus aurantium*) showed the best antioxidant performance in the ABTS assay alone (more than 80%). Similarly, Smeriglio et al. (2018) reported that EOs extracted from lumia peels (*Citrus lumia* Risso) demonstrated significant antioxidant activity in various assays, including ORAC (46µg/mL), DPPH (104µg/mL), FRAP (202µg/mL), and ABTS (233µg/mL), expressed as IC_{50} values with standard BHT. IC_{50} values denote the concentration of samples,

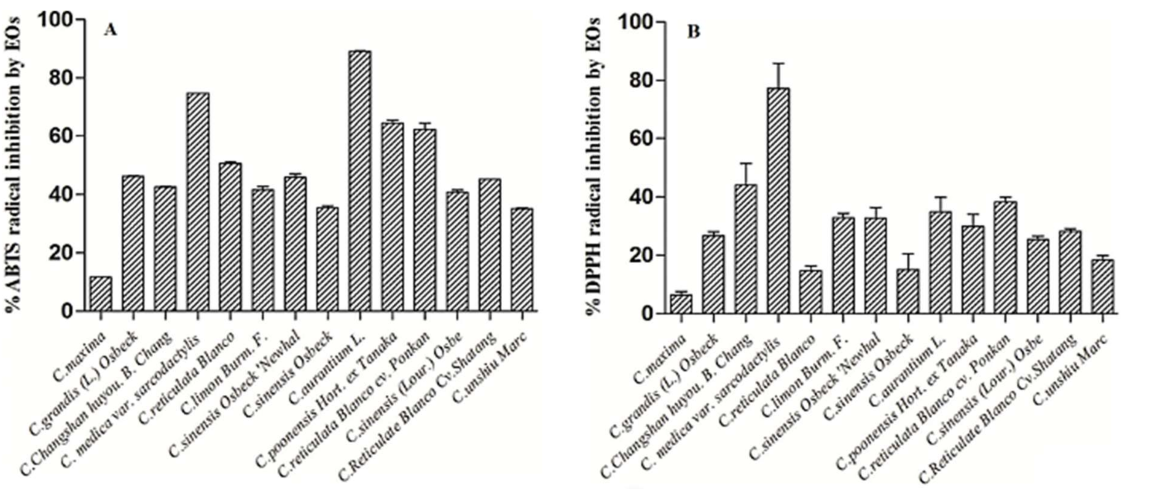


Fig. 3: %ABTS (A) and %DPPH (B) radical inhibitions by essential oils from 14 different *Citrus* fruits (Adapted with permission from Guo et al. (2018), © 2018 Elsevier Ltd. All rights reserved).

which is required to scavenge 50% of DPPH free radicals. The lower IC_{50} value is, the higher antioxidant activity is. Additionally, the EOs of lumia peels were shown to act as chelators, forming chelate complexes. Phi et al. (2015b) reported that peel EOs of Citrus varieties grown in Vietnam exhibited high radical scavenging capacities, which were influenced by the variety and growing locations. The IC_{50} values of EOs extracted from the peels of Long An lime and Da Lat lime were 7.11mg/mL and 60.32mg/mL, respectively, while the IC_{50} values for Xoan orange and Vinh orange EOs were 52.04mg/mL and 63.43mg/mL, respectively. The results also indicated that pummelo EOs demonstrated higher antioxidant capacities than orange EOs. The higher concentrations of sabinene, β-pinene, and γ-terpinene in lime EOs, compared to orange and pummelo EOs, were responsible for the superior antioxidant capacities of lime EOs. In contrast, the high proportions of limonene and myrcene in orange EOs were not associated with radical scavenging activity.

Regarding the antioxidant capacity of EOs derived from Citrus leaves, the volatile compounds have received limited attention in previous literature. A study from Vietnam on the antioxidant activities of leaf EOs reported that the IC_{50} value of *C. grandis* was the highest (2.18mg/mL), followed by *C. sinensis* (1.49mg/mL) and *C. aurantifolia* leaves (1.21mg/mL) (Chi et al., 2020). This indicates that the leaves of *C. aurantifolia* exhibited the strongest scavenging activity among the three species. Similarly, Warsito et al. (2018) found strong antioxidant capacities in citronellal extracted from *C. hystrix* leaves, with values ranging from 2.40 to 6.01µg/mL. Furthermore, the antioxidant activities of Citrus leaves in this study were significantly stronger than those of EOs derived from Citrus peels of the same varieties, as reported by Phi et al. (2015b).

Antimicrobial Activity of Citrus Essential oils

In addition to their antioxidant activity, the EOs exhibit significant antimicrobial properties, which can inhibit growth or destroy harmful microorganisms such as bacteria, fungi, and viruses. This characteristic is essential in healthcare, agriculture, and the food industry, where controlling microbial growth is critical to ensuring the safety and quality of food products. Citrus EOs have demonstrated a strong capacity to inhibit microorganism growth. However, different EOs vary in their effects on the same microbial strain, and different microorganisms exhibit varying susceptibility to the same EO (Guo et al., 2018). Because EOs contain the large number of different groups of chemical compounds, their antibacterial activity is not attributable to a single specific mechanism. Instead, several targets in the cell such as increased permeability of membrane, affecting the integrity of cell membrane, or reducing membrane potential are considered. An important characteristic of EOs and their components is their hydrophobicity, which enables them to partition in the lipids of the bacterial cell membrane and mitochondria, disturbing the structures and rendering them more permeable (Burt, 2004). Dominant compounds in Citrus EOs, such as d-limonene, α-pinene, β-pinene, myrcene, and ocimene, are primarily responsible for their antimicrobial activity. Nonetheless, the contribution of less abundant compounds should not be overlooked (Guo et al., 2018). For example, linalool and β-pinene exhibit strong antimicrobial activity, whereas d-limonene, myrcene, and γ-terpinene showed no significant effects against tested strains (Guo et al., 2018). Similarly, Chi et al. (2020) reported that α-pinene and β-pinene had significantly stronger antimicrobial effects than myrcene and d-limonene. It has been suggested that the antimicrobial efficacy of Citrus EOs results from synergistic or antagonistic interactions among their components (Bounatirou et al., 2007). Quirino et al. (2020) evaluated the antimicrobial activity of *C. bergamia* and highlighted synergism between d-limonene and terpenes against *C. striatum* and between linalool and terpenes against *P. aeruginosa*. Despite these findings, there remains a gap in the literature regarding the specific synergistic and antagonistic interactions among Citrus EO components and their effects on microbial activity.

In the study by Phi et al. (2015b), the Citrus EOs were shown to exhibit strong antimicrobial activities against selected microorganisms. Lime EOs demonstrated the strongest antimicrobial effects compared to those derived from pummelos and oranges in the inhibition zone diameter assay. The EOs of lime and pummelo peels showed significant inhibition effects against all tested microorganisms, with minimum inhibitory concentration (MIC) values ranging from 1.31 to 10.5 mg/mL (Phi et al., 2015b). Another study by Guo et al. (2018) on 14 different Citrus varieties in China also found that peel EOs derived from pummelo and lemon exhibited strong antimicrobial activity against eight different microorganisms. Additionally, geographic locations were found to influence the antimicrobial activities of Citrus peels EOs. The EOs from Vinh oranges showed strong effects against bacteria, including *B. cereus*, *S. typhi*, and *P. aeruginosa*, as well as fungi such as *A. flavus* and *F. solani*, while the peel EOs of Xoan oranges showed strong effects only against fungi (Phi et al., 2015b).

Similarly to citrus peels, the EOs of citrus leaves have been shown to exhibit strong antimicrobial activities (El-hawary et al., 2013; Othman et al., 2016; Chi et al., 2020). According to Pizzo et al. (2023) the hydrophobic nature of EOs allows them to dissolve in the lipid components of bacterial cell membranes. This interaction causes structural alterations and increases membrane permeability. The EOs extracted from the leaves of *C. hystrix* in Malaysia have been shown to strongly inhibit microorganisms, including *E. coli* and *B. subtilis* (Othman et al., 2016). Similarly, a study by Chi et al. (2020) from Vietnam on Citrus leaves EOs demonstrated antibacterial activity against four different species. The antimicrobial activity of *C. grandis* leaves EOs was found to be stronger than that of *C. sinensis* and *C. aurantifolia* leaves. Furthermore, the higher contents of certain EOs, including α-phellandrene, terpinolene, β-caryophyllene, nerol, and geraniol from *C. grandis* leaves, as well as their synergistic interactions, were key factors in the results of this study (Chi et al., 2020).

Bioactivities of Flavonoids Extracted from Citrus Peels and Leaves

Up to date, several epidemiological studies have demonstrated that a diet rich in phenolic compounds, i.e., flavonoids, has positive effects on preventing cardiovascular diseases and cancer (Addi et al., 2021). Antioxidant ability or oxidative stress resistance is one of the most crucial biological activities of citrus flavonoids. They are known to have Fe^{2+}-chelating ability as well as lipid peroxidation and oxido-reductase enzyme-inhibiting functions (Acker et al., 1996). Yu et al. (2005) reported that the active chemicals of flavonoids are polyphenol compounds containing a chromanol ring system with the capacity to stabilize unpaired electrons and thereby scavenge free radicals. Ghasemi et al. (2009) investigated flavonoid contents from the peels of 13 Citrus species, showing a good capacity for radical scavenging with IC_{50} values lower than 3.8mg/mL compared to values of ascorbic acid and quercetin, which were 17.3 ± 0.12 and 19.3 ± 0.43μg/mL, respectively. Citrus flavonoids have also been recorded to have anti-mutagenic, cardioprotective, anti-inflammatory, anti-allergic, and anti-proliferative effects (Cook & Samman, 1996; Benavente-García et al., 1997; Du & Chen, 2010). In several studies, the high anti-inflammatory activities of PMFs, hesperidin, and naringin from Citrus peels have been investigated (Li et al., 2009; Huang & Ho, 2010). Furthermore, the antimicrobial activity of flavonoids and PMFs against *Penicillium digitatum* and *Aspergillus niger* has also been reported (Ortuño et al., 2006; Liu et al., 2012).

A study by Lachos-Perez et al. (2018) on the antioxidant capacity of orange peel extract obtained through subcritical water extraction recorded the highest values of 16.26, 73.27, and 319.40g TE/g of raw material for DPPH, FRAP, and ORAC assays, respectively. Similarly to EOs, it is suggested that the antioxidant capacity of citrus extracts cannot be fully evaluated by a single assay. Another study by Li et al. (2022) showed the overall antioxidant capacity of 14 Chinese citrus peel extracts, expressed using the antioxidant potency composite (APC) index. The APC index quantifies a substance's overall antioxidant power, with a high APC value indicating a strong ability to combat oxidative stress and neutralize free radicals. The grapefruit was recorded to have the highest APC index (92.19%), followed by *Chachiensis* (89.13%), satsuma orange (87.68%), and lemon (86.86%). Additionally, the extracts were shown to encourage the growth of *Bifidobacterium* spp. in the intestine and increase acetic acid levels in the human gut (Li et al., 2022).

Regarding the bioactivity of flavonoids in Citrus leaf extracts, this topic has not been as extensively investigated compared to peel-derived extracts. A study by Loizzo et al. (2012) on *Citrus aurantifolia* leaf extract showed that citrus leaves collected in Italy are a potential accessible source of bioactive compounds. The leaf extract demonstrated good scavenging activity of the DPPH radical and the $ABTS^{+}$ radical cation, with IC_{50} values of 76.9μg/mL and 28.8 TEAC, respectively (Loizzo et al., 2012). The aqueous leaf extract of *C. aurantifolia* from Algeria also showed similar results, with a DPPH IC_{50} value of 65.42μg/mL (Khettal et al., 2017). The highest scavenging effect of DPPH was observed in the leaf extract of *Citrus limon*, with an IC_{50} value of 35.35μg/mL. Additionally, the citrus leaf extracts exhibited potential antioxidant activity in both ABTS and FRAP assays. *C. clementina* and *C. limon* leaf extracts were recorded to have the best $ABTS^{+}$ cation scavenging activities (1174 and 874μM TE/g, respectively), while *C. clementina* and *C. aurantifolia* had the strongest ferric reducing power (30.6 and 28.86 BHAE/g, respectively) (Khettal et al., 2017).

As potential sources of bioactives, the *in vivo* bioactivity of flavonoids derived from citrus peels and leaves were reported in various studies. By increasing insulin sensitvity and GLUT4 function, citrus flavonoids including heperidin and naringin have been recorded to have antidiabetic effects (Mahmoud et al., 2015). Additionally, naringin has been demonstrated to have highly potential anticancer effects on numerous cancer types such as brain, breast, colon, liver, prostate, and skin (Ghanbari-Movahed et al., 2021). The study by Nair et al. (2018) also showed that the extracts from *C. reticulata* peels exhibited strong activity against Dalton's Lymphoma Ascites (DLA) cell line in MTT assay. In addition, the peel extract showed both prophylactic and therapeutic anti-tumor activity, in which 50% of pre - treated mice with were protected from DLA cells without any apparent toxic effects (Nair et al., 2018).

Bioactivities of Limonoids Extracted from Citrus Seeds and Peels

Limonoids are highly oxygenated triterpenoids with fewer hydroxyl groups than flavonoids. Regarding antioxidant activity, citrus limonoids have been shown to have weaker effects compared to flavonoids and ascorbic acid due to the absence of hydroxyl groups in their structure (Zou et al., 2016). However, a broad spectrum of activities of citrus limonoids has been identified, and they have been linked as potential anti-carcinogenic agents. Citrus limonoids have been confirmed to possess a variety of biological activities, including antitumor, antioxidant, anti-inflammatory, antimicrobial, anti-obesity, and anti-hyperglycemic effects (Shi et al., 2020). The limonoid extract from pummelo seeds exhibited the strongest DPPH radical scavenging ability (38.53%), while both orange- and lime-sourced methanolic extracts showed no significant difference (37.21% and 36.75%, respectively) (Tung et al., 2020). Similarly, the pummelo seed MeOH-based extract had the best ABTS radical scavenging activity (50.77%), followed by extracts from orange (33.75%) and lime (32.26%) seeds. Another study by Sun et al. (2005) also demonstrated the antiviral activity of seed extract from *C. bergamia*. The seed extract showed strong inhibition against HTLV-1 RT, with an RTIC50 value of 3.95ng/ml. Additionally, the seed extract exhibited low cytotoxicity, indicating its potential application in functional foods and drug development.

A study on the total limonoid content from *Adalia* lemon peels and its bioactivity was conducted by El-Feky et al. (2024). The limonoid-rich extract exhibited good antioxidant activity with a total antioxidant capacity (TAC) of 59.13mg gallic acid/g and iron-reducing power (IRP) of 42.82μg/ml. The IC_{50} values of the lemon peel extract against DPPH, ABTS, and NO radicals were also evaluated, with values of 7.46, 7.39, and 9.5μg/ml, respectively. In addition, the limonoid-rich extract exhibited anti-diabetic activities by inhibiting enzymes, including α-amylase and α-glucosidase. The IC_{50} values were 6.57 and 5.81μg/ml, respectively, indicating its potential in the prevention of diabetes (El-Feky et al., 2024).

In *in vivo* experiments, Citrus limonoids were reported to exhibit a wide array of biological activities, particularly inhibitory effects on the proliferation of various cancer cell lines (Shi et al., 2020). Limonin has been shown to inhibit the development of colon polyps in Apc-mutant mice and the proliferation of the human colon carcinoma cell line (Caco-2) (Shimizu et al., 2015). Furthermore, limonin can inhibit the proliferation of Hep3B, HepG2, and MCF-7 cells (Yao et al., 2018; Tian et al., 2001). Similarly, obacunone and its glycosides have the ability to inhibit the growth of colon cancer cells (SW480) (Murthy et al., 2011) and prostate cancer cells (LNCaP) (Murthy et al., 2015). Nomilin and limonin have also been shown to inhibit the formation of benzo[α]-pyrene, which induces the formation of lung tumors (Shi et al., 2020). Nomilin was reported to act as an agonist of the pregnane X receptor (PXR), which regulates the expression of genes associated with the metabolism and detoxification of many substances, thereby increasing lifespan, healthspan, and toxic resistance in animals (Fan et al., 2023). Additionally, nobiletin, which is a polymethoxyflavones found in citrus peels, has been revealed to reduce eotaxin levels, which consequently mitigates eosinophil infiltration and airway inflammation in asthmatic mice (Pan et al., 2010). Another study by Jin et al. (2021) also showed that limonin can have therapeutic effect on osteoarthritis (OA) by activating the Nrf2/HO-1 pathway, which inhibits the NF-κB and suppress inflammation.

In summary, the single most consistently abundant compound in virtually all citrus EOs, particularly those derived from the peel and leaves of orange, grapefruit, and lime, is the monoterpene D-limonene, a major structural component to possess anti-inflammatory, antioxidant, and anti-carcinogenic activities (Brah et al., 2023). This monoterpene primarily functions as an antioxidant by directly neutralizing free radicals and modulating gene expression related to oxidative stress response. Although D-limonene provides the foundational antioxidant activity, several minor, more reactive terpenoids often drive the overall potency of the essential oil. Brah et al. (2023) further reported that linalool has shown good antifungal, anticancer, sedative, antidepressant, and pesticide activities. In addition, γ-terpinene and terpinolene demonstrate antioxidant activity, whereas α- terpineol and β-pinene exhibit anti-carcinogenic activity, anti-proliferative, and cytotoxic activities, and geranyl acetate also has anti-inflammatory, and anti-fungal activities. This difference is often attributed to their chemical structure, which allows for easier electron donation. Thus, the observed biological effects of certain citrus cultivars (e.g., specific hybrids) is frequently a result of the synergistic interaction between the major component (D-limonene) and these highly active minor oxygenated monoterpenes like linalool and γ-terpinene, confirming that total antioxidant strength is a function of composition heterogeneity, not just concentration (Hamdan et al., 2024).

It is also crucial to note that the total concentration of flavonoids and limonoids, which are structurally known for superior antioxidant effects, is generally low in the essential oil, as these compounds are largely non-volatile and remain in the peel or seed extract (Toledo et al., 2024). Toledo et al. (2024) reported that polymethoxyflavones (PMFs) occur naturally in citrus peels and citrus-derived foods shows potentially relevant biological effects including anticancer, anti-inflammatory, anti-atherosclerosis, and neuroprotective activities. Likewise, limonin, a highly oxygenated nor-triterpenoid phytochemical abundant in Citrus plants, possesses significant anti-inflammatory, antioxidant, anticancer, antifungal, and antiviral activities and is associated with the modulation of multiple signaling pathways, highlighting its potential as a valuable lead compound for therapeutic development (Meng et al., 2025).

The traditional extraction methods are associated with limitations such as long extraction time, high energy consumption, CO_2 emissions, degradation of major biological constituents, and reduction in the yield and quality of the extract components. However, technological advancement has helped volotile and non-volatile component extraction through the development of innovative, efficient, and eco-friendly extraction techniques. As new methods continue to evolve each day, techniques such as ultrasound, microwaves, and supercritical fluid extraction have demonstrated promising extraction efficiency and could be used for large-scale production of Citrus bioactive compounds (Brah et al., 2024). At the same time, advancements in extraction and purification technologies have facilitated the development and application of citrus essential oils, flavonoids and limonoids in the fields of food, medicine, and functional materials (Xu et al., 2025).

Conclusion

Citrus by-products are potential sources of both volatile and non-volatile compounds, including essential oil found in citrus peels and leaves, flavonoids found in citrus peels and leaves, and limonoids in citrus peels and seeds. Both volatile and non-volatile compounds from citrus by-products are well known for their diverse bioactivities, such as antioxidative, antimicrobial, and anti-inflammatory effects, which contribute to the potential value and health benefits of citrus-derived products. However, the chemical compositions and bioactivity of these compounds vary depending on the species and their growing locations. The extraction and application of these valuable compounds from citrus peels, seeds, and leaves are necessary to provide a sustainable solution for reducing citrus waste and increasing the added value of citrus fruit. Nevertheless, a significant research gap remains, particularly in investigating the synergistic and antagonistic effects between volatile and non-volatile compounds in citrus on their bioactivity. Most studies have focused on individual components and their properties, while interactions among them, which could result in enhanced or reduced activity, have been underexplored. Effective applications in food preservation, cosmetics, and pharmaceuticals could be achieved if the combined effects of these compounds are better understood. Additionally, while citrus peel tissues and seeds have been widely explored, citrus leaves remain understudied despite their potential as a source of bioactive compounds. Future research should focus on the chemical composition and bioactive potential of citrus leaves, as well as the interactions among different compounds, to better understand their overall bioactivity. Recent innovative, efficient, and eco-friendly extraction techniques such as ultrasound, microwaves, and supercritical fluid extraction should be employed for large-scale production of Citrus bioactive compounds. Furthermore, the mechanism of action, optimal dosage, and standardization of assays for determining the biological effects of Citrus bioactive compounds as antimicrobial and anticancer therapeutic agents should be further investigated.

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