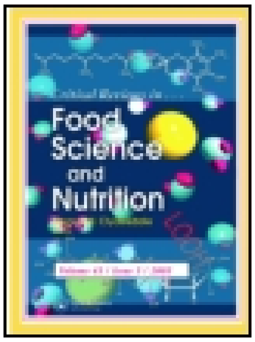

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Outgoing and potential trends of composition, health benefits, juice production and waste management of the multi-faceted Grapefruit *Citrus* X *paradisi*: A comprehensive review for maximizing its value

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REVIEW

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Outgoing and potential trends of composition, health benefits, juice production and waste management of the multi-faceted Grapefruit *Citrus X paradisi*: A comprehensive review for maximizing its value

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ABSTRACT
Grapefruit (GF) *Citrus X paradisi* Macfad (F. Rutaceae) is one of the major citrus fruits that encompass a myriad of bioactive chemicals and most unique among citrus fruits. Nevertheless, no study has yet to assess comprehensively its multitudinous constituents, health benefits, and valuable waste products. Hereto, the present review provides an updated comprehensive review on the different aspects of GF, its juice production, waste valorization, enhancement of its byproducts quality, and compared to other citrus fruits. Grapefruit uniqueness among other citrus fruits stands from its unique taste, flavor, and underlying complex chemical composition. Despite limonene abundance in peel oil and grapefruit juice (GFJ) aroma, nootkatone and sulfur compounds are the key determinants of its flavor, whereas flavanones contribute to its bitter taste and in conjunction with limonoids. Different postharvest treatments and juice processing are reviewed and in context to its influence on final product quality and or biological effects. Flavanones, furanocoumarins, and limonoids appear as the most prominent in GF drug interactions affecting its metabolism and or excretion. Valorization of GF peel is overviewed for its utilization as biosrobent, its oil in aromatherapy, limonene as antimicrobial or in cosmetics, fruit pectin for bioethanol production, or as biosorbent, and peel phenolics biotransformation. The present review capitalizes on all of the aforementioned aspects in GF and further explore novel aspects of its juice quality presenting the full potential of this valued multi-faceted citrus fruit.

KEYWORDS
Grapefruit; terpenoids; flavonoids; juice; valorization; debittering

Introduction

Sustainable production of edible crops and its wastes utilization are two challenging issues for humanity and ecology. Continually, farmers select varieties with higher crop yield and better sensory traits. Postharvest, a small portion of the waste could be utilized as fertilizers, however, the larger portion is burnt especially, if the waste is slowly biodegradable and occupies a large space or volume of the land (Sabiiti 2011; Tamelová, Malaťák, and Velebil 2018). Therefore, a surplus of researches is dictated for two purposes. First, old and new varieties are continuously compared on different levels, to decipher genetic, metabolic and biological differences. Second, valorization of the waste to incite industry and farmers to utilize the waste in an eco-friendly and profitable way.

Hereto, we explore the scientific progress achieved for an important *Citrus* variety, namely, Grapefruit (GF). GF is unique among other *Citrus* fruits in terms of its taste, odor, and utilities. The current review explores this uniqueness by defining the botanical origin of GF and its varieties; then an updated concise report about its phytochemicals, health benefits, juice production, and valorization of its waste is presented.

Grapefruit (GF) is unique among other *Citrus* species in terms of taste, odor, and utilities. Most citrus varieties are orange in color, but many GF varieties are ranging from white, yellow, orange to red, yet with the characteristic, so-called, GF flavor. Similar to orange, GF can be consumed fresh or in juice. Among the public, GF is esteemed for vitamins and mineral content similar to other *Citrus* members. However, GF is the only *Citrus* which is linked to slimming and body shape (Chudnovskiy et al. 2014). Similar to other *Citrus*, GF waste is underutilized. The current review explores GF uniqueness by defining the botanical origin of GF and its varieties followed by an updated report on its multifaceted relationship between phytochemicals, sensory characteristics, biological activities, and drug interactions. The review explores postharvest treatments as well as juice production and their impact on the phytochemical composition of fresh GF or its juice. Finally, the valorization of GF waste is presented. The review aims to present to the reader a comprehensive and global overview of the different aspects

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Figure 1. Tree of Grapefruit (X = 0.007), leaves (x = 0.17), flower (X = 0.34), and cluster of fruits (X = 0.05).

of GF so that better and sustainable programs could be drawn for GF production and further its waste.

Botanical description

GF tree was an accidental hybrid between two Asian varieties, namely, *C. sinensis* (sweet orange) and *C. maxima* (pomelo or shaddock). GF tree attains 4.5–6 m in height and 15 cm in diameter (Figure 1), while old trees can attain 13 m in height 2.4 m in circumference. Its twigs have short and supple thorns, leaves are dorsiventral and ovate and are dotted with oil glands. Flowers have four white petals (5 m) and are grown singly or in clusters in the leaf's axil. Fruits are nearly spherical to slightly pear-shaped. The pericarp is pale yellow or orange with a smooth surface that is dotted by fine oil glands. The juice is acidic to sweet-acid when it is fully ripe. Fruits could be seedless or to encompass white elliptical pointed seeds (Morton and Dowling 1987). The fruit's color is yellow with either yellow or red juicy pulp, with size-dependent upon the variety and growing conditions.

World production of fruits attained over 9.4 million tons in 2018 (Fao.org/faostat), with China as the largest producer (50% of the world production), followed by Vietnam, USA, and Mexico (Fao.org/faostat). Several varieties were introduced which are seedless or of fewer seeds (Morton and Dowling 1987), with differences in their metabolites composition (Zheng et al. 2016) and their karyotypes (de Moraes, dos Santos Soares Filho, and Guerra 2007). The warm subtropical climate is the most suitable for its cultivation (Morton and Dowling 1987).

Grapefruit cultivars (redder & seedless)

Although that most economically important *Citrus* species are native to Southeast Asia, GF originated in the Caribbean and evolved in the USA. Since its introduction in Florida, new GF cultivars were continuously developed to improve fruit traits. Developing seedless fruit with red pulp was the principal goal for introducing new cultivars (Table 1 and Figure 2). All the developed varieties are traced back to one ancestor that is the "Duncan" variety, the oldest GF cultivar, with most of the descendant cultivars derived from somatic mutation or vegetative propagation. Several reviews have traced the development of the different GF cultivars in Florida and Texas (Da Graca, Louzada, and Sauls 2004; Gmitter 1995; Rouse, Wutscher, and Youtsey 2001). Table 1 summarizes the most important information about the different varieties. The development of new varieties is still ongoing utilizing different techniques, namely, the examination of new budsports, irradiation of budwood, and tissue culture (Da Graca, Louzada, and Sauls 2004). Noteworthy, other local varieties in different countries do exist but they are less common in the global market and thus their description is beyond the scope of this review. A recent study revealed that red GF juice was more preferable than yellow juice and fruits, with low bitter/high sweet taste are more favored (Gous et al. 2019).

Grapefruit composition & biological actions

Soluble acids

No comprehensive report could be traced regarding the total sugar and acid content across all GF varieties. Six organic acids were quantified in the pulp of 6 GF cultivars, namely, Marsh, Oroblanco, Cocktail, Thompson, Red Blush, and Rio Red (Zheng et al. 2016). Citric acid was the main acid to account for 39–64% of the total organic acid content (12–27 mg/g FW), followed by quinic, malic, tartaric, oxalic, and aconitic acid (<3%, 1 mg/g FW). The total acid content was highest in Red Blush cultivar (47 mg/g FW) versus the

Table 1. History and characters of different varieties of grapefruit.

White varieties	Duncan	Walters	Marsh
Year of introduction	1809	1887	1860
Seed/fruit	50-60	Seedy	Seedless (2–3 seeds/fruit)
Main Characters	Firm, widely used for juice production	Minor differences to Duncan in terms of fruit morphology and quality	Similar to Duncan variety but the aroma and flavor are less pronounced, however, segments are more tender
Notes	The oldest cultivar and considered as the reference standard for flavor and aroma of grapefruit	Abandoned because of many seeds. However, it is the parent of "Star Ruby" cultivar	The most commercially available white GF variety.

Red varieties	**Foster**	**Thompson**	**Ruby Red**	**Star Ruby**	**Ray Ruby**	**Rio Red**	**Flame**
Year of introduction	1907	1913	1929	1970	1977	1984	1987
Seed/fruit	50	Seedless	seedless	Seedless	Seedless	seedless	Seedless
Main Characters	Pigmented flesh, albedo and rind	Red pulp but white albedo and segment membrane. Pigment of the pulp fades quickly.	External red blush and uniform red flesh color. Red Blush or Ruby Red are synonyms.	Most red cultivar either internally or externally. It retains the red color throughout the season and has a thinner rind	The pigmentation is intermediate between Ruby Red and Star Ruby cultivars. However, it suffers from (haloing), red color is not uniform it fades exterior to interior of fruit segments.	Redder than Ruby red but equivalent to Star Ruby	Redder than Ruby and more persistent
Origin	Budsport mutation on Walters tree.	Sport limb on Marsh tree.	Budsport mutation on Thompson tree.	Irradiated seed of Hudson, a dark red seedy variety from the budsport of Foster tree. However, it is cold and pests sensitive.	Mutation of budwood of "Ruby Red" tree.	Budsport of the noncommercial A&I 1–48 variety. A&I 1–48 was originally developed from Ruby Red.	Bud sport of Thompson to give "Henderson" whose nucellar seedling was selected to develop the Flame variety.

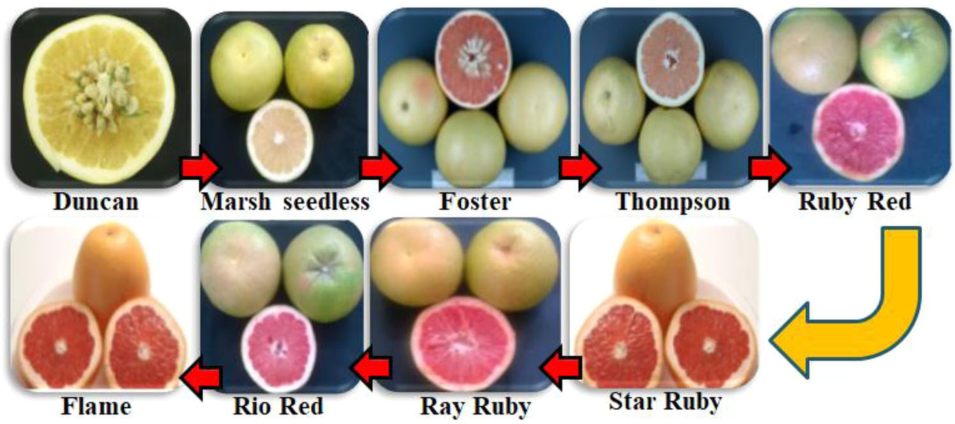


Figure 2. Grapefruit cultivars. Sources: Duncan photo from Orbović, Dutt, and Grosser (2013); Thompson photo: shorturl.at/bjkEO; other cultivars' photos from Ahmed, Rattanpal, and Singh (2018). Photos of cultivars are arranged in order of development.

lowest level in Cocktail (29 mg/g FW). Citric and malic acid contents in GF were 3 times higher than that of sweet orange, while quinic acid was 10 times higher than that of sweet orange (Zheng et al. 2016). Similar to other fruits, acidity decreased significantly during ripening, with acid value to attain its highest level at the early harvest season in June and to reach its lowest level at the late harvest season in April as exemplified in Rio Red cultivar (Chaudhary, Jayaprakasha, and Patil 2018).

Soluble sugars

Fructose, sucrose, and glucose represented the main sugars of the pulp accounting for ca. 80% of the total soluble solids (TSS) with sucrose as the main sugar, representing up to 59% of the total sugars (Zheng et al. 2016). The Cocktail variety showed the highest sugar content (120 mg/g FW) versus lowest in Marsh (57.7 mg/g FW). The legal average ^{0}Brix value for GF juice traded in the USA is 10.2 (https://www.law.cornell.edu/cfr/text/19/151.91). ^{0}Brix value is defined as the sugar content in g/100 g of juice. No significant difference in that value was observed in Rio Red fruit at different harvest times, though with a decrease in acidity from early to late harvest leading to an increase in the ripening ratio (TSS value/Acidity) (Chaudhary, Jayaprakasha, and Patil 2018). Different ratios of Brix/acid were prepared by reconstituting concentrated GF juice using sucrose and citric acid, with the most optimum values between 8.4 and 11.1. However, regardless of how sweet was the GF juice, the bitter or tart taste was more pronouncing (Fellers, Carter, & de Jager, 1988).

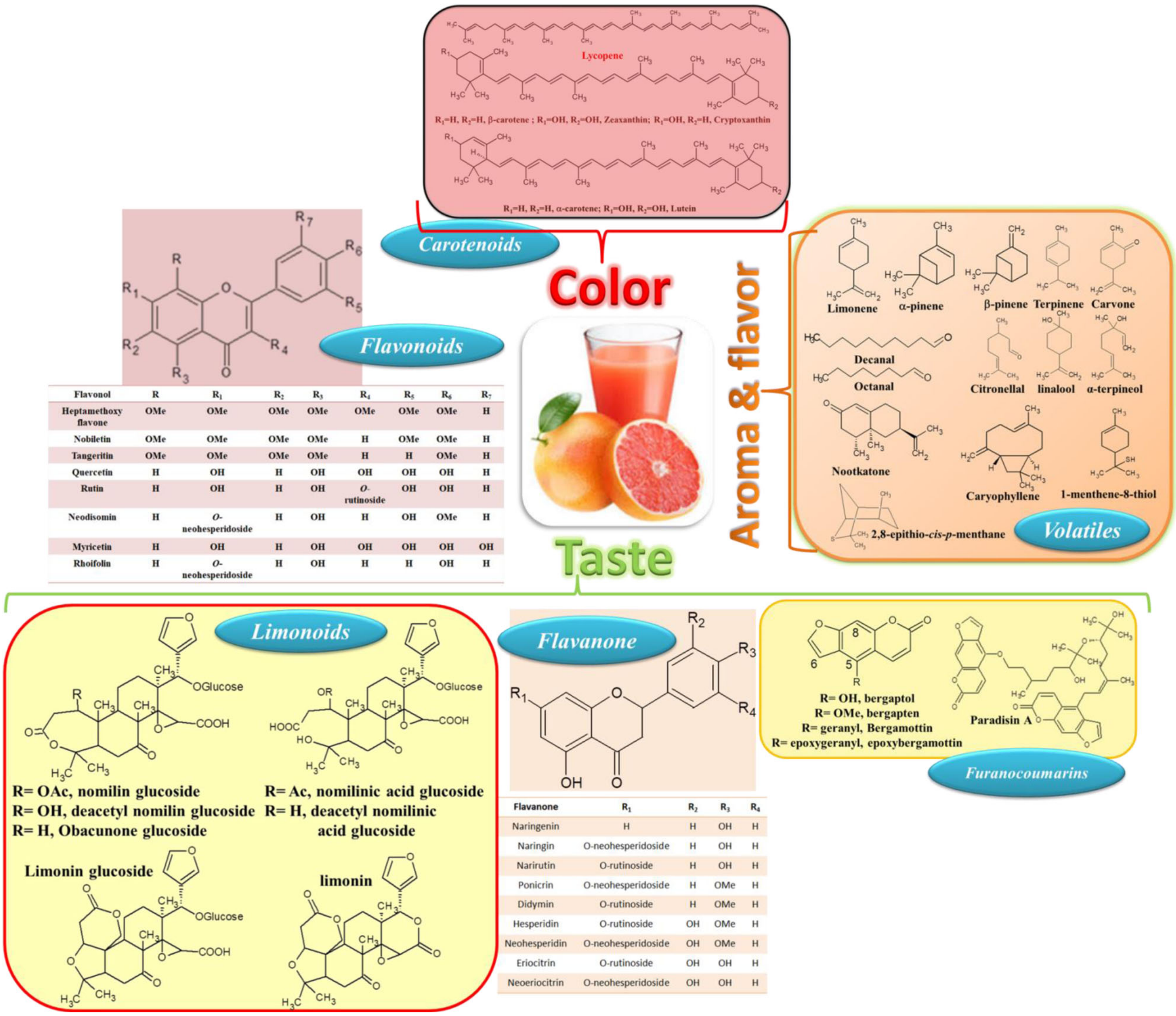
Carotenoids, color determinant of GF pulp

Zheng et al. (2016) identified 6 carotenoids in pulps of white, orange, and red varieties of GF represented by β-/α-carotene, β-cryptoxanthin, zeaxanthin, lutein, and lycopene (Figure 3). β-carotene was the most abundant followed by lutein ranging from 18.4–87.2%, and to amount for 14.4–81.6% of the total carotenoids. Red varieties were rich in lycopene, albeit at levels lower than β-carotene. In contrast, orange-colored GF varieties encompassed higher zeaxanthin and β-cryptoxanthin levels than yellow and red varieties. Nevertheless, it was the ratio between zeaxanthin (yellow), β-cryptoxanthin and lycopene (red carotene) that determined pulp color *viz.*, yellow, orange, or red. In contrast to β-carotene in GF, violaxanthin was the main carotenoid in orange while β-cryptoxanthin was the major carotenoid in mandarin. A comparative transcriptional study of carotenoid biosynthesis between Marsh (white variety) and Star Ruby (red variety) was conducted (Alquezar et al. 2013), revealing for no differences in transcript levels between the two varieties except for the downregulation of the chromoplast-specific lycopene cyclase 2 (β-*LCY2*), the enzyme catalyzing the conversion of lycopene into β-carotene, in the pulp of the red variety (Alquezar et al. 2013). Shading was found to promote lycopene accumulation in Star Ruby peels where β-lycopene cyclase and β-carotene synthase showed downregulation (Joanna et al. 2015). Among the three red GF varieties Star Ruby, Ray, and Flame (Rouseff et al. 1992), Star ruby exhibited the highest lycopene content 33 µg/g, followed by Ray (21 µg/g) and finally Flame (7.9 µg/g). A similar pattern was observed in β-carotene, though at lower levels compared to lycopene (Rouseff et al. 1992).

Several reviews have explored the health benefits of carotenoids (Cooperstone and Schwartz 2016; Eggersdorfer and Wyss 2018; Rodriguez-Concepcion et al. 2018) and especially lycopene for its well-recognized anticancer effect in prostate and mammary cancer (Rao and Agarwal 2000).

Mineral & vitamin content

Regarding the nutritional value, GF showed moderate vitamin C content equal to lemon but less than orange. Raw GF juice (per 100 g) contains niacin (0.2 mg), ascorbic acid (36–40 mg), vitamin A (10–440 IU), riboflavin (0.02 mg), thiamin (0.04 mg), potassium (162 mg), phosphorus (15 mg), calcium (9 mg), iron (0.2 mg), sodium (1.0 mg), carbohydrate (8.8–10.2 g), protein (0.4–0.5 g) and fat (0.1 g) (Morton and Dowling 1987). Peel had higher mineral content than pulp in red, white, and green Turkish varieties of GF (Czech et al. 2020). No recent study was found estimating similar



Flavonol	R	R1	R2	R3	R4	R5	R6	R7
Heptamethoxy flavone	OMe	OMe	OMe	OMe	OMe	OMe	OMe	H
Nobiletin	OMe	OMe	OMe	OMe	H	OMe	OMe	H
Tangeritin	OMe	OMe	OMe	OMe	H	H	OMe	H
Quercetin	H	OH	H	OH	OH	OH	OH	H
Rutin	H	OH	H	OH	O-rutinoside	OH	OH	H
Neodisomin	H	O-neohesperidoside	H	OH	H	OH	OMe	H
Myricetin	H	OH	H	OH	OH	OH	OH	OH
Rhoifolin	H	O-neohesperidoside	H	OH	H	H	OH	H

Flavanone	R1	R2	R3	R4
Naringenin	H	H	OH	H
Naringin	O-neohesperidoside	H	OH	H
Narirutin	O-rutinoside	H	OH	H
Ponicrin	O-neohesperidoside	H	OMe	H
Didymin	O-rutinoside	H	OMe	H
Hesperidin	O-rutinoside	OH	OMe	H
Neohesperidin	O-neohesperidoside	OH	OMe	H
Eriocitrin	O-rutinoside	OH	OH	H
Neoeriocitrin	O-neohesperidoside	OH	OH	H

Figure 3. Chemical structures of major secondary metabolites in GF and its contribution to GF sensory characteristics viz., taste, color, and aroma.

parameters in new GF varieties, e.g., red varieties, please refer to (https://fdc.nal.usda.gov/fdc-app.html#/food-details/174676/nutrients). Compared to lemon, orange, and tangerine, GF exhibited a moderate and balanced blend of vitamins C, A, folate to reach 31–61 mg, 58 µg, 13 µg/100 g FW, respectively (Turner and Burri 2013).

GF peel and pulp aroma & flavor

Several studies were performed to characterize GF aroma specifically in peel and pulp. These studies have used different techniques spanning from hydrodistillation, solvent extraction to headspace volatiles analysis as discussed below.

Peel aroma composition

Peel was the richest part in volatile oil as detected using cold and hot methods, being composed mostly of monoterpene hydrocarbons (>99%) with limonene as the major component (> 95%) followed by α-/β-pinene and terpinene (Figure 3) (Manaila et al. 2016). GF Peels from different geographical origins or of different varieties showed comparable composition, except in case of minor components, e.g., sabinene (Feger, Brandauer, and Ziegler 2001), myrcene (González et al. 2002). Oxygenated hydrocarbons though present at much lower levels (∼ 4%) played a role in GF aroma and as an indicator for its quality, whereas sesquiterpene hydrocarbons showed no taxonomical significance. Aldehydes/ketones were the major oxygenated compounds represented by decanal, citronellal, octanal, (*Z*/*E*)-carvone, and nootkatone (Ng et al. 2016; Njoroge et al. 2005). Nootkatone was common in all types of GF from Japan (Sawamura 2000), detected in pummelo (pomelo) and all GF types (Ortuno et al. 1995). Nootkatone contributed significantly to GF flavor where it leaches to its juice during juicing (Ortuno et al. 1995; Ren et al. 2015), with its levels found to increase upon storage temperature and to serve as an indicator of oil quality (Ng et al. 2016). Based on the published results, a recent review applied hierarchical cluster analysis on citrus species based on their volatiles composition. Bitter orange peel oil was the most similar oil to GFO. GFO was clustered with *C. grandis* (pomelo) *C. sinesnsis* (sweet orange), *C. aurantium* (bitter orange), and *C. reticulata* (mandarin) away from other clusters occupied by other citrus species in a hierarchical cluster analysis (HCA). Such clusters segregation was due to the abundance of non-terpenoid ester and aldehyde, e.g., octanal, decanal, hexenyl, and octenyl acetate (González-Mas et al. 2019).

Effect of storage temperature on fresh fruit aroma. Noteworthy, volatile emission of the fruit is affected by storage temperature and to affect its aroma perception to the consumer. Cold storage at 2 °C caused cold damage to oil glands in the flavedo part, causing emission of monoterpenes, mainly, limonene, linalool, and α-terpineol. In contrast, storage at 12 °C led to higher emission of cyclic sesquiterpenes, e.g., β–caryophyllene, valencene, and aliphatic esters (Lado et al. 2019). Nootakatone was considered as a senescence indicator of GF, where its level was found to significantly increase in Rouge LaToma variety peel subjected to non-chilling storage (Biolatto et al. 2002).

Pulp & juice aroma composition

Minor compounds' role in GF aroma & flavor. VOCs detected in GF juice were higher in number than in peel oil, though likely attributed to the different methods used for its analysis. Hydrodistillation followed by GC-MS is the most common method for peel oil aroma analysis, whereas HS-SPME-GC was more employed for GF juice analysis.

170 Volatiles were detected in 6 GF pulp varieties using solid phase microextraction (SPME)-GC technique (Zheng et al. 2016), with D-limonene as the major component (74–95% of total monoterpenes and 30–67% of the total volatiles) followed by β-pinene. Sesquiterpenes amounted for 11–45% of volatiles composition, with β-caryophyllene as the major component. Nootkatone was detected in juice at levels more or equal to its effective odor or taste thresholds confirming its key role in GF juice aroma (Stevens, Guadagni, and Stern 1970) (Figure 3).

Chaudhary, Jayaprakasha, and Patil (2018) assessed changes in Rio Red fruit juice aroma at different ripening stages. Although limonene and β-caryophyllene were the major volatiles at all stages, their levels decreased significantly during ripening, whereas nootkatone showed an opposite pattern. Such an aroma profile confirmed that nootkatone is an indicator of GF ripening and quality (Chaudhary, Jayaprakasha, and Patil 2018).

Aroma extract dilution method revealed for 37 odor active compounds in fresh, hand-squeezed juice, with the most odor active constituents identified as ethyl butanoate, *1-p*-menthene-8-thiol, (*Z*)-3-hexenal, 4,5-epoxy-(*E*)-2-decenal, 4-mercapto-4-methylpentane-2-one, 1-heptene-3-one, and wine lactone, though present at trace levels (Figure 3) (Buettner and Schieberle 1999). The aroma of hand-squeezed GFJ appeared to be determined by its *1-p*-menthene-8-thiol and 4-mercapto-4-methylpentane-2-one. Similar results were observed in White Marsh GFJ (Buettner and Schieberle 2001), with 4-mercapto-4-methylpentan-2-one and 1-*p*-menthene-8-thiol as key contributors to GF sulfurous odor.

Considering the interest in sulfur compounds as major influencers of GF pulp aroma, further targeted analysis for this class using GC-olfactometry and sulfur chemiluminescence led to the detection of 13 sulfur volatiles, e.g., hydrogen sulfide, sulfur dioxide, methanethiol, and 1-*p*-menthene-8-thiol, with 1-*p*-menthene-8-thiol as the most potent aroma compound in nature (Jabalpurwala, Gurbuz, and Rouseff 2010), commonly called as GF mercaptan. Interestingly, canned reconstituted GFJ encompassed more sulfur volatiles than fresh unpasteurized white Marsh GFJ attributed to thermal processing and concentration of canned juice. Dimethyl sulfide (58%), methanethiol (17%), and 1-*p*-menthene-8-thiol (7%) were the major sulfur volatiles in canned GFJ (Jabalpurwala, Gurbuz, and Rouseff 2010). GFJ pasteurization led to a reduction in nonvolatile sulfur content concurrent with an increase in sulfur volatile components likely derived from sulfur-containing amino acids, e.g., cysteine, methionine, or glutathione (Lin et al. 2002).

Analysis of sulfur volatiles is still one of the intricate processes due to its thermal instability, high volatility. A comprehensive study about sulfur volatiles across the different GF varieties and juice preparations is still needed. Finally, it can be concluded that nootakatone, minor oxygenated terpenoids, and sulfur components serve as key determinants of GF peel oil or juice aroma (Rouseff, Ruiz Perez-Cacho, and Jabalpurwala 2009; Shaw and Wilson 1981).

GF bitter principles

Flavonoids

Similar to other citrus species, GF is rich in flavonoids (Figure 3). Several studies have reported on GF flavonoids composition across different cultivars, geographical source, maturity stages, and different fruit parts as summarized in the review of Zhang (2007). Flavonoids of GF belong to different classes, namely, flavanone, flavones, flavonol, and polymethoxylated flavones, with flavanones amounting to 98% of total flavonoids present mainly as –*O*-glycosides i.e., –rutinoside or –neohespridoside. Glycosides with neohespridoside are generally bitterer than rutinosides, among which naringin was the major form followed by narirutin, and poncirin (Ross et al. 2000; Zhang 2007). Albedo was found to be the richest in flavonoids followed by flavedo, pulp, and seeds (De Castro et al. 2006; Maurer, Burdick, and Waibel 1950). GF Red varieties exhibited lower naringin levels than lightly colored varieties, whereas immature fruit showed higher naringin, hesperidin, and neohesperidin levels than mature ones (Del Rio et al. 1997). Flavanones constituted ca. 98% of the total flavonoids with naringin and poncirin as the most bitter followed by neohesperidin and neoeriocitrin (Zhang 2007). Polymethoxylated flavonoids were detected in GF albedo and flavedo parts only, whereas flavonols were detected in juice and peel (Zhang 2007). The application of modern LC-MS has tremendously aided to profile GF flavonoid subclasses (Diaconu et al. 2017; Sicari et al. 2018; Tong et al. 2018). Flavonoids content of GF were more versatile compared to other citrus fruits i.e., lemon or clementine (Nakajima, Macedo, and Macedo 2014). Flavonoids and limonoids showed similar patterns found at the highest levels in fruits collected in the early season (August) than those collected in mid-season (January) or late season (April) (Chaudhary et al. 2016).

Regarding GF flavonoids biological effects, naringin major flavanone in GF was extensively examined for its effects on metabolic syndrome components, namely, hyperglycemia, hypertension, insulin resistance, obesity (Alam et al. 2014; Chen et al. 2016; Raja Kumar et al. 2019; Razavi and Hosseinzadeh 2019; Singh, Sharma, and Kaur 2018; Wang, Li, and Du 2018). Preclinical and clinical trials of naringin were also recently reviewed (Bharti et al. 2014; Salehi et al. 2019). Hesperidin another major flavonoid in citrus fruits exhibited diverse activities (Montanari, Chen, and Widmer 1998), among which neuronal and skin protection effects were reviewed (Hajialyani et al. 2019), whereas its clinical and preclinical trials were reviewed in Li and Schluesener (2017).

Furanocoumarins

Furanocoumarins, a phenylpropanoid derived class in citrus fruits showed quantitative differences among GF varieties (De Castro et al. 2006; Girennavar et al. 2008). Major furanocoumarins included bergaptol, bergapten, bergamottin, epoxybergamottin, and 6′,7′-dihydroxybergamottin besides dimeric furanocoumarins i.e., paradisin A, B, C (Hung, Suh, and Wang 2017) (Figure 3). Juice derived from white varieties encompassed higher furanocoumarins than red varieties (Widmer and Haun 2006). Likewise, in flavonoids, fruit peel showed higher furanocoumarin monomers than fruit flesh and juice (Lee et al. 2016), whereas furanocoumarin dimers were higher in fruit than in peel (Fukuda et al. 2000). Aside from furanocoumarins' biological activities such as anti-cancer, anti-oxidant, and anti-inflammatory effects (Hung, Suh, and Wang 2017), they showed drugs interaction by interfering with hepatic and intestinal cytochrome P450 as in case of St. John's wort molecule i.e., hypericin.

Limonoids

Limonoids are polycyclic terpenoids present as aglycones especially in seeds or as glycosides in mature fruit. They are derived from the polymerization of isoprene units followed by cyclization, aromatization, or rearrangements. Limonin glucoside was the major limonoid in Ruby Red GF followed by nomilinic acid & nomilin glucoside (Breksa, King, and Vilches 2015), found at the highest levels in segment membranes followed by juice, albedo and finally flavedo. Limonoids content of GF was lower than in lemon, but higher than that of sweet orange (Wang, Tu, et al. 2016). Limonin, obacunone, deacetyl nomilin, nomilin, and nomilin glucoside were isolated from the seed of Red Mexican GF (Mandadi et al. 2007) and suggestive that seed as a fruit waste is a rich source of limonoids (Figure 3). The aglycone part in limonoids is responsible for the quinine-like bitter taste in GF and to decrease upon glycosylation. Several reviews on limonoids chemistry and pharmacology were published (Arora, Mohanpuria, and Sidhu 2018; Gualdani et al. 2016; Zhang and Xu 2017). Asides from limonoids biological effects, limonin serves as a promising lead compound for the synthesis of anticancer molecules (Gualdani et al. 2016).

Determinants of GF juice bitterness

As mentioned earlier, GF juice is characterized by a low ^{0}Brix/acid ratio especially in the early season; however, it is the sweet-tart and slightly bitter taste which makes GF juice unique from other varieties (Rouseff, Ruiz Perez-Cacho, and Jabalpurwala 2009). Bitter flavonoids along with limonoids mediate for the juice bitter taste, and with such bitterness being affected by harvest date and juicing process. Limonoids declined significantly during fruit maturation, therefore bitter flavonoids, i.e., flavanones remain as the key determinant of fresh fully ripe GF bitter taste. Subjects who are not sensitive to 6-n-propylthiouracil, a genetic bitterness taste marker, found GF juice as unacceptable (Drewnowski, Henderson, and Shore 1997). Mechanical extraction of GF juice increases limonoids content in the juice by leaching from segment membrane, core, and seeds and to account for why commercial juice is more bitter than fresh juice, i.e., higher content of limonoids compared to hand-squeezed GFJ (Rouseff, Ruiz Perez-Cacho, and Jabalpurwala 2009).

Supplementary Table S1 summarizes the major differences between GF and other citrus species in terms of chemical composition.

Biological activity of GF and GFJ

Several studies have explored the health benefits of GF pulp or juice as summarized in Table 2. The effect of GF on obesity and weight reduction was the most studied. Clinical and *in vivo* studies confirmed that GFJ and pulp were protective against obesity complications by reducing insulin resistance, lipid accumulation, hypertension, and ameliorating oxidative stress (Table 2). Aside from bitterness and rich fiber content, the anti-obesity activity was verified for the phenolic content (Chudnovskiy et al. 2014; Gamboa-Gomez et al. 2014). Nevertheless, clinical studies on GF and its products on obese patients are still scarce and contradictory as in other citrus species (Nakajima, Macedo, and Macedo 2014). There are no conclusive results that GF ingestion could reduce body weight and waist circumference. However, all studies confirmed its protective effects against obesity complications and cardiovascular diseases. As it will be discussed later, GF flavor and aroma also play a role in weight loss and reduced food intake.

GFJ and fruit exhibited many positive effects on bone health and management of osteoporosis as evidenced by several *in vivo* models (Table 2). GF rich content in polyphenols and dietary fibers represent a perfect remedy for ulcerative colitis. Unprocessed GFJ was more effective than bioprocessed juice (Mendes et al. 2019), suggestive that juice processing to decrease its pectin and bitterness level could lead to an attenuation of GFJ biological effects. A recent review on GFJ, seed, and peel anticancer, chemopreventive,

Table 2. Various biological activities of GF, GFJ, and GFO.

Biological activity	Tested material	Model	Main results	comments	References
Anti-obesity	Sweetened and clarified juice	C57Bl/6 mice fed on low or high-fat diet	-Reduced blood glucose - Reduced liver triglycerides - Reduced fasting serum insulin.	GF beneficial effects are not confined to its bitterness or insoluble fibers	Chudnovskiy et al. (2014)
	Infusion of oven-dried GF slices	Rats fed on high fructose, high saturated fat diet	- Downregulation of genes responsible for lipogenesis - Increased lipid β-oxidation - Ameliorated of oxidative stress		(Gamboa-Gomez et al. 2014)
	Naringin (10 mg/kg/day)	Rats fed on high carbohydrates, high fat diet	- Improved glucose intolerance - Ameliorated of liver and cardiovascular dysfunction	Flavanone was a key player in GF activities.	(Alam, Kauter, and Brown 2013)
	Naringin (0.72 mg/day in water)	C57Bl/6 mice fed on low or high-fat diet	- Reduced blood glucose - Improved insulin tolerance.	No effect of weight gain	Chudnovskiy et al. (2014)
	GF pulp ingestion Or GFJ	Obese volunteers for 12 weeks	- Improved serum lipid profile.	No significant weight reduction	Silver, Dietrich, and Niswender (2011)
	Ingestion of half of Rio Red GF before meals (3x daily -6 weeks)	Healthy overweight volunteers	- Moderate weight reduction compared to baseline values. - reduced serum LDL and cholesterol	No significant reduction in body weight compared to the control group. - GF could be preventive against obesity complications.	Dow et al. (2012)
	Fresh GF, GFJ, capsule (500 mg fruit including peel)	Obese patients	- Fresh GF reduced body weight significantly. - GF products improved insulin resistance	GF should be included in weight reduction diet	Fujioka et al. (2006)
Osteoporosis	Lyophilized powder of red GF pulp Drinking GFJ	Orchidectomized Sprague-Dawley rats (90 days old)	- Increased bone mineral deposition. - Reduced bone turn-over	Ingestion of GF or GFJ was effective as a therapy.	Deyhim, Mandadi, Faraji et al. (2008) Deyhim, Mandadi, Patil et al. (2008)
	GFJ	prednisolone-induced osteoporosis a rat femoral fracture	GF counteract osteoporosis via RANKL/OPG axis (receptor activator of nuclear factor kappa-B ligand/ osteoprotegerin expression)	GF have both protective and therapeutic effects	Bastawy et al. (2019)
Ulcerative colitis	Unprocessed and bioprocessed GFJ (processed by co-encapsulated pectinase and rhamnopyranosidase in hydrogels)	Ulcerative colitis model in mice induced by ethanol and TNBS (2,4,6-Trinitrobenzenesulfonic acid)	- Reduction in lesion size. - Reduction in inflammatory and oxidative stress linked enzymes.	unprocessed GFJ was more active than the clarified and less bitter one (bioprocessed)	Mendes et al. (2019)
Anticancer	GFJ, seed, and peel	Review article	anticancer, chemopreventive, and antigenotoxic		Cristóbal-Luna et al. (2018)
Antimicrobial	Cold-pressed oil	Agar disk diffusion method against food spoilage bacteria	**Tested against** *Lactobacillus curvatus,* *L. sakei,* *S. carnosus* *S. xylosus* *Enterobacter gergoviae* *E. amnigenus*	- Among other citrus oils, GFO was potent against *S. xylosus, L. curvatus, L. sakei* - More active than orange and mandarin oil.	Viuda-Martos et al. (2008)
	Cold-pressed oil	Agar dilution method against food spoilage molds	**Tested against** *Penicillium chrysogenum* *P. verrucosum* *Aspergillus niger* *A. flavus*	- Among other citrus oils, GFO was the most active against *P. chrysogenum and P. verrucosum*	Viuda-Martos et al. (2008)
					(Okunowo et al. 2013)

	Oil obtained by hydrodistillation	Agar well diffusion method against clinical bacterial isolates and fungal isolates	**Active against** *Bacillus cereus, Enterococcus faecalis,* *E. coli,* *E. coli ATCC 25292, Klebsellia pneumonia, Pseudococcus sp., Salmonella typhmurium,* *Shigella flexneri,* *S. aureus* *A. niger,* *Candida albican,* *P.chrysogenum*		
	Oil prepared by solvent-free microwave extraction or hydrodistillation.	Disk diffusion method against several bacteria	**Active against** *S. aureus,* *E. faecalis,* *S. epidermidis,* *E. coli,* *S. typhimurium,* *S. marcescens,* *Proteus vulgaris*	No significant difference in antibacterial activity between oils prepared by hydrodistillation or solvent-free microwave extraction.	Uysal et al. (2011)
	Cold-pressed oil and cold-pressed followed by hydrodistillation	Several assays related to quorum sensing	- Reduced biofilm production. - Reduced viability in biofilm. - Reduced production of signal molecules.	- Limonene was less active than the oil	Luciardi et al. (2020)
	Commercial GFO	Antibacterial assay of 3 coumarins isolated from the oil alone or in combination with other antibacterials against methicillin-resistant *S. aureus*	The coumarin isolate modulates the efflux pump and could act as an adjuvant to other antimicrobials.		Abulrob et al. (2004)
Skin anti-aging, antiwrinkle	Commercial oil	In vitro enzyme inhibition assay against elastase	GFO along with lemon and juniper oils were the most active tested oils	The oil was more active than limonene or α-pinene	Mori et al. 2002)
Insecticidal, insect repellent	Hydrodistilled oil	Fumigant toxicity against cowpea seed beetle	It was lethal against adult beetles	- It was more active than bitter orange and lemon oils	Moravvej and Abbar (2008)
	Commercial GFO	Repellent activity using T-tube olfactometer	Among the potent oils repellent for the three cockroach species *Blattella germanica* *Periplaneta americana* *P. fuliginosa*	Limonene and minor constituents of the oil contribute to the overall repellent activity	Yoon et al. (2009)
	Oil obtained by hydrodistillation	Determination of ovicidal and larvicidal activities of the oil against yellow fever mosquito *Aedes aegypti*	Exposure time was inversely proportional to oil concentration.	- Potent persistent larvicidal	Ivoke et al., 2013
	Commercial GFO	Repellent activity using T-tube olfactometer	Strong repellent against rice weevil *Sitophilus oryzae*	- it was suggested that caraway and GF mixture or carvone/limonene mixtures could be utilized for insect control owing to its strong repellent activity.	Yoon et al. (2007)

and antigenotoxic ought to be consulted (Cristóbal-Luna et al. 2018) (Table 2).

Asides from GFJ biological effects, it exhibits some potential in drug delivery. GF nanovectors prepared from GFJ (Wang et al. 2013) were evaluated for the delivery of anticancer drugs, e.g., delivering miRNA by the nasal route to reduce brain tumors (Zhuang et al. 2016). These particles could be directed to inflammatory or tumor sites if the nanoparticles were coated by inflammatory-related receptors (Wang, Ren et al., 2015) or loaded by an aptamer (Tang et al. 2020).

Grapefruit-drug interaction

GF drug interaction studies are increasingly growing since the first discovery of an interaction between GF and felodipine, a calcium channel blocker (Bailey et al. 1991). A review of GF interaction with 85 drugs of different classes revealed that the interaction was drug-specific rather than class-specific (Bailey, Dresser, and Arnold 2013; Sarah 2016). GF affected the pharmacokinetics of the concomitant orally administered drugs by inhibiting its metabolism or absorption (Bailey, Dresser, and Arnold 2013; Sarah 2016). Sources of interaction occur through several mechanisms including the irreversible inhibition of cytochrome P450 3A4, CYP3A4 by furanocoumarins. This irreversible inhibition is effective and pronouncing just from drinking one cup of GF juice (200 ml) and for 3 days relapse for *de novo* synthesis of the enzyme (Kiani and Imam 2007; Sarah 2016). Two new GF cultivars were developed with lowered furanocoumarins level to prevent such negative effects (Fidel et al. 2016).

A second mechanism is mediated *via* the inhibition of P-glycoprotein (P-gp) responsible for the excretion of drugs. Inhibition of P-gp will lead to increased bioavailability (Wang et al. 2001), whereas the third mechanism is *via* the inhibition of organic anion-transport polypeptide (OATP) affecting intestinal absorption. Naringin in GF is an inhibitor for OATP and to increase the bioavailability of fexofenadine (Bailey 2010). Prolonging the interval between GF intake and drug administration can help to blunt the interaction but with a certain degree; the interval could though extend from 3 to 24 h (Takanaga et al. 2000). The interaction is more pronounced when drugs are (i) orally administered, (ii) have limited bioavailability or extensively metabolized through the first pass effect (Bailey, Dresser, and Arnold 2013). A concise list of the harmful adverse effects due to GF drug interactions was presented in the review by Bailey, Dresser, and Arnold (2013).

GF peel dietary fibers

Dietary fibers comprise a type of carbohydrate that cannot be digested by our bodies' enzymes, found in fruit rind and grouped by its physical properties into soluble, insoluble, or resistant starch. Time of collection had a clear impact on the yield of sugars constituting soluble dietary fibers. Generally, the more mature the fruit, the greater the solubility and depolymerization of soluble dietary fibers. In contrast, insoluble dietary fibers composition showed no change throughout the harvest season (Larrauri et al. 1997) as revealed from water holding capacity and glucose dialysis retardation index. Both activities showed a decrease in parallel to the decrease in soluble fibers level (Larrauri et al. 1997).

Citrus and apple are two major sources of commercial pectin, a class of soluble dietary fiber (DF) that is a polymer of galacturonan, which is partially methyl esterified at C-6 or acetyl esterified at *O*-2 or *O*-3 (Kaya et al. 2014). Neutral sugars characterized from GF pectin were arabinose, galactose, rhamnose, glucose, mannose, and xylose (Kaya et al. 2014; Mohamed 2016). Pectin prepared from white and red varieties of GF showed comparable composition except that acetyl content was lower in the red variety (Mohamed 2016). Pectin prepared from white and red varieties was found superior to commercial citrus pectin attributed to its higher methoxy content posing it as a good thickening agent. Moreover, both varieties were classified as high ester pectin showing the rapid formation of a stable gel (Mohamed 2016).

Compared to cereals DF, DF of GF exhibited higher soluble/insoluble DF, making it more active in lowering the absorption of sugars and lipids. GF pomace exhibited the highest SDF/total DF (0.76) followed by peels (0.15) and finally seeds (0.09) (Garcia-Amezquita et al. 2018). Compared to lemon and pomegranate DF, grapefruit DF showed the highest total DF and protein levels, though with the low fat and moderate free sugar content (López-Marcos et al. 2015). Compared to lemon peel and apple pomace, GF DF exhibited the highest water holding, fat adsorption and swelling capacities (Figuerola et al. 2005) posing it as a good source of DF. Indeed, compared to other citrus peels, GFP showed a moderate and balanced blend of free sugars, cellulose, hemicellulose, and lignin (Mamma and Christakopoulos 2014; Rivas-Cantu, Jones, and Mills 2013).

Incorporating GF fibers in muffins backing showed a reduced amount of fat indicating its suitability for preparing low-calorie cakes (Koshali, Ghotbi, and Nasiriyah 2019).

Valorization of GF peel

Worldwide trade of GFP is estimated to grow globally (Walia 2019) owing to its increased recognized value. In the GF juice industry, fruit waste represents 50% of its fruit wet mass, with the waste comprised of peel, segment membranes, juice sacs, and seeds. The waste is typically dried and pelleted to be commercialized as low-value cattle feed (GF peel waste, GPW). This process is though not cost-effective owing to the energy expenditure of the citrus pulp pellets (CPP) mills besides low revenue of CPP (Braddock 1999; Wilkins et al. 2007). Such waste can present a burden to the manufacturers and the environment (Mamma and Christakopoulos 2014), warranting for implementing better waste management into a value-added product. The waste can also serve as a source for limonene, pectin, biosorbents for wastewater treatment or lignocellulose source for

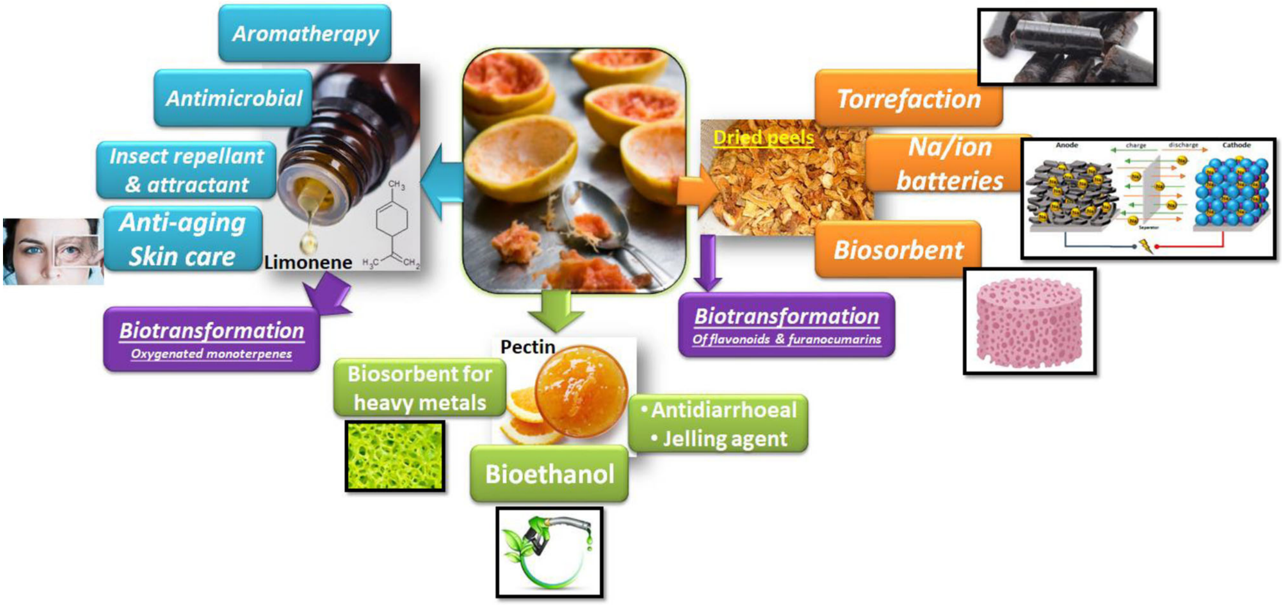


Figure 4. Valorization of GF waste concerning the whole dried peel, isolated volatile oil and polysaccharides into other value-added products.

bioethanol production and to be discussed in detail over the next sections (Figure 4).

Applications of peel oil

Antimicrobial activity

Grapefruit oil (GFO) peel exhibits great potential as an antimicrobial agent (Figure 4, Table 2). GFO could be used as a preservative to control food-spoiling bacteria and molds. Furthermore, GFO demonstrated moderate antibacterial and antifungal activities against human and clinical microbes (Table 2). The activity was attributed mostly to limonene content, albeit minor constituents also promote limonene activity. Indeed, owing to the potent antimicrobial activity of limonene, it must be removed from the peel waste before its fermentation for bioethanol production (John, Muthukumar, and Arunagiri 2017).

GFP oil & cosmetics

GFP oil can be incorporated in cosmetics to fight against aging *via* the inhibition of elastase enzyme, with oil found more active than its isolates, limonene, and α-pinene (Mori et al. 2002) (Figure 4, Table 2). Although the oil is incorporated in many cosmetics formulae for many claims, relevant literature to these claims was not found and urging for more studies to prove its efficacy in the future.

Aromatherapy

The inhalation of GFO was suggested to contribute to weight loss (Figure 4). Olfactory stimulation in rats or mice with GFO scent stimulated the autonomic nerve endings innervating white and brown adipose tissues and the adrenal gland, and concurrent with a reduction in gastric vagal nerve. Such physiological effects led ultimately to increased lipolysis and thermogenesis while food intake and appetite were decreased (Niijima and Nagai 2003; Shen et al. 2005). Rats exposed to GF scent for 5 weeks showed reduced food intake and body weight associated with increasing salivary amylase secretion (Suda et al. 2010). Compared to sibutramine, olfactory stimulation with GFO was not associated with an elevation in the brain noradrenaline level. Consequently, GFO was considered safer than sibutramine in suppressing appetite (Farouk et al. 2012). GFO was combined with other oils as an aromatherapy massage to reduce subcutaneous fat and waist circumference in post-menopausal women (Kim 2007). GFO halted adipogenesis and accumulation of triglycerides in subcutaneous adipocytes and preadipocytes (Haze et al. 2010).

However, these aforementioned effects were coupled with the stimulation of renal sympathetic nerve activity and an increase in blood pressure (Tanida et al. 2005). Elevation in diastolic blood pressure in healthy men by the inhalation of GFO for 10 min was mediated by an increment in muscle sympathetic nerve activity and decrease in cortisol level (Kawai et al. 2020), and with a family history of hypertension leading to the increased response of human vascular system to GF fragrance (Kawai et al. 2019). The same effects were observed when limonene was used for olfactory stimulation suggestive it is a key molecule mediating for GFO aromatherapy. Appetite suppression and elevation in blood pressure were mediated through central histaminergic nerves (Shen et al. 2005; Tanida et al. 2005). From our point of view, the effect of GF olfactory stimulation on blood pressure needs further studies with a larger sample size to be more conclusive as previous studies were performed on a limited number of subjects or in rats.

On the other hand, GFO inhalation was found to increase salivary IgA in healthy subjects *via* immune and autonomic nervous systems, thereby reducing stress. Compared to lavender oil, the GFO effect was slower but persistent, suggesting that it is suited for aromatherapy in patients receiving chemotherapy (Takagi et al. 2019). GFO was further effective in reducing the abdominal discomfort of anxious patients during colonoscopy (Hozumi et al. 2017).

GFO as agro- & semiochemical

GFO could serve as an eco-friendly and safe pesticide or insect repellent due to its strong repellent activity against several insects, e.g., cockroach, cowpea beetle, rice weevil and yellow fever mosquito (Figure 4 and Table 2). GFO could be utilized to enhance the attraction of Mexican flies to a bait of synthetic food-odor lure (Robacker and Rios 2005). Limonene and methyl anthranilate in natural and synthetic GF blend could be used to lure *Diaphorina citri* in traps (Amorós et al. 2019). However, GFO promotes the male matting of Mediterranean fruit fly (Shelly 2009). Consequently, massive utilization of GFO as a bait or insect repellent should be monitored in the field to avoid the attraction of harmful pests or fungi.

Limonene & nootkatone as precursors for added value chemicals

Limonene, the principal component of the peel oil, can be transformed into many other volatile oil isolates which are more expensive or of higher market demand. An interesting review explored the different biotransformation products of limonene by bacteria and yeast to include limonene-1,2-diol, α-terpineol (8-hydroxylimonene), isopiperitenol (3-hydroxylimonene), carveol and carvone (oxygenation at C-6), perillylalcohol, perillylaldehyde and perillic acid (oxygenation at C-7) (Duetz et al. 2003). Recently, yeast *Yarrowia lipolytica* and *Mortierella minutissima* were utilized to convert *R*-(+)-limonene to perillic acid which is utilized as a flavoring and antimicrobial agent (Ferrara et al. 2013). Noteworthy, culture condition, and media composition affected the type and relative amounts of compounds produced during biotransformation of limonene by *Aspergillus niger* (García-Carnelli et al. 2014). Surface response methodology was thus applied to optimize the biotransformation production of *R*-(+)-limonene to *R*-(+)-alpha-terpineol by *Fusarium oxysporum*, and leading to 6 times higher yield (Bicas et al. 2008).

Transformation of nootkatone key aroma in GFO by several fungi i.e., *Botrytis*, *Didymosphaeria*, *Aspergillus*, *Chaetomium*, and *Fusarium* led to either C11/C13 epoxidation or C9/C13 hydroxylation of nootkatone or oxidation of the double bond of the 9-hydroxynootkatone. All the resulted molecules showed better anticancer activity compared to the hydroxylated nootkatone (Gliszczyńska et al. 2011).

GF peel pectin as biosrobent and biofuel

Modern green techniques for the extraction of GF pectin were investigated and compared to conventional heating, e.g., to include ultrasound and microwave-assisted extraction. In one study, ultrasound-assisted heat extraction (UAHE) provided a higher pectin yield in a shorter time and at a lower temperature, with no difference in chemical composition, albeit with differences in physicochemical properties, and microstructure (Wang, Ma, et al. 2015). Ultrasound and heat acted synergistically to improve extractability, dissolution, and degradation of pectin (Xu et al. 2014). Ultrasound was found to affect the rheological properties of GF pectin likely attributed to its lower degree of methoxylation, a higher degree of acetylation, and the presence of more branched side chains (Wang, Ma, et al. 2016).

Pectin is conventionally utilized in the food and pharmaceutical industries as a thickening and jelling agent as well as anti-diarrheal and antidiabetic, and more recently in wastewater remediation (Figure 4). In this aspect, GF pectin serves as a cheaper adsorbent substitute and its richness in hydroxyl and carboxyl functional groups may further bind cationic dyes in industrial wastewater (Saeed, Sharif, and Iqbal 2010). GF pectin as well as other citrus pectin were found superior to apple and grape pectin as biosorbents for heavy metals removal owing to their higher uptake capacity, rapid kinetics, lower cost, and higher stability (Schiewer and Patil 2008). Recently, GFP waste was used in preparing biochar and low esterified pectin, both incorporated in a novel biochar/pectin/alginate hydrogel used for Cu^{2+} removal from waste aqueous solutions (Zhang et al. 2020).

Citrus peel represents an attractive biomass for bioethanol production owing to its low lignin content, and richness in fermentable sugars (hydrolyzable cellulose, hemicellulose, and pectin) (John, Muthukumar, and Arunagiri 2017). However, prior to bioethanol production, *d*-limonene must be removed due to its antibacterial action against yeast or bacteria used in fermentation to produce ethanol. Then, GF polysaccharides were hydrolyzed using pectinase and cellulase to avoid viscosity imparted by pectin (Wilkins et al. 2007).

Valorization of the whole peel as biosorbent and in torrefaction

Apart from pectin, dried and grounded GFP was considered as a promising biosrobent for wastewater remediation from nickel and cadmium owing to its carboxyl and hydroxyl groups in the peel (Torab-Mostaedi et al. 2013). Moreover, native GF biomass, mass left after isolation of polyphenols was assessed as biosorbent for Cd(II) removal from aqueous solution (Bayo, Esteban, and Castillo 2012) or treated urban effluent even in the presence of other heavy metals i.e., Pb, Ni, and Cu (Bayo 2012). Recently, the whole dried peel was dried and incorporated into an ecofriendly and economical magnetic composite, namely, Fe_3O_4/GF used in removal of Congo red, humic acid, and phosphate (Inkoua et al. 2020). GFP was utilized as a bio-template for the detection of Cu ions in water using electrochemical detection, with GFP functionalized to act as an electrode (Romero-Cano et al. 2019) (Figure 4).

Another alternative was developed by Romero-Cano et al. (2019) for GFP to serve as a sustainable anode material for energy storage in Na/ion batteries. Alternatively, GFP could be converted to an energy source by torrefaction similar to orange peel (Tamelová, Malaťák, and Velebil 2018) (Figure 4).

Table 3. Transformation of GF peel major constituents, its products and applications (Amor et al. 2010) (Céliz et al. 2011) (Frydman et al. 2005) (Liu et al. 2013) (Marumoto and Miyazawa 2010) (Okuno and Miyazawa 2004) (Özyürek et al. 2014) (Ruberto et al. 2002) (Wang et al. 2014)

Substrate	Means of transformation	Product	Outcome	Reference
Naringin	Chemical reaction	Naringin oxime	Higher antioxidant	(Özyürek et al. 2014)
Naringin	Two enzymatic steps I) hydrolysis to monoglycoside prunin II) acylation using lipase and vinyl esters or fatty acids	Acylated prunin	Stronger antibacterial, antilisterial and antistaphylococcal	(Celiz, Daz, and Audisio 2011)
Naringenin	3′-Hydroxylation by enzyme flavonoid-3′-hydroxylase	Eriodictyol	Higher antioxidant	(Amor et al. 2010)
Tangeretin	Chemical demethylation of 5-OH then acetylation	5-acetyloxy-6,7,8,4′-tetramethoxyflavone	More potent anticancer and has better solubility and bioavailability	(Wang et al. 2014)
Nobiletin	Biotransformation by *Aspergillus. niger*	*4′-hydroxy-5,6,7,8,3′-pentamethoxyflavone*	Antimutagenic	(Okuno and Miyazawa 2004)
Hesperidin	Metabolic engineering tobacco or carrot cell culture expressing a flavanone-7-*O*-glucoside-2-*O*-rhamnosyltransferase	Neohesperidin Dihydrochalcone	Sweetening and flavoring agent	(Frydman et al. 2005)
Eriodictyol	Transmethylation using flavone 3'-*O*-methyltransferase ROMT-9, which was expressed and isolated from the fungus *Yarrowia lipolytica*	Homoeriodictyol	Bitter masking flavanone, antioxidant	(Liu et al. 2013)
limonin	Chemical modification	Limonol, limonein-7-oxime, limonin-7-oxime acetate.	The antifeedant activity of the new compounds were lower than limonin	(Ruberto, Renda, Tringali, Napoli, and Simmonds 2002)
Bergapten	Biotransformation by the fungus *Glomerella cingulate*	6,7-Furano-5-methoxy hydrocoumaric acid	The methyl ether and ester of the product wereactive as β-Secretase inhibitor, so, it can act as anti-Alzheimer.	(Marumoto and Miyazawa 2010)

Chemical & biotransformation of GF phenolics to added-value products

As previously mentioned, GFP encompasses high flavonoids, furanocoumarins, and limonoids, even higher than the juice itself after processing. Therefore, constituents of peels can be isolated, then biotransformed to other valuable constituents. Possible biotransformation to GF peel constituents are presented in (Table 3).

GF quality enhancement *via* cultivation and or processing

Two studies compared organic and conventionally grown GF Rio Red reporting that conventionally grown GF exhibited better color, higher carotenoid content, less tart with less naringin content, and with improved sensory characters. In contrast, organic fruit encompassed higher nomilin content (Chebrolu et al. 2012; Lester, Manthey, and Buslig 2007). Further, fruits MS fingerprinting demonstrated that the farming mode (organic *vs.* conventional), growing year, and harvest time affect GF composition without providing a detailed information about the source of variation (Chen, Harnly, and Lester 2010). The application of metabolomics as a large scale analytical technologies has yet to be capitalized for answering such questions in GF pertaining, cultivation, pre- and post-harvesting effects on fruit quality.

Postharvest treatments & storage

Postharvest treatments aim to reduce microbial loading, preserve fruit quality, and extend its shelf life (Figure 5).

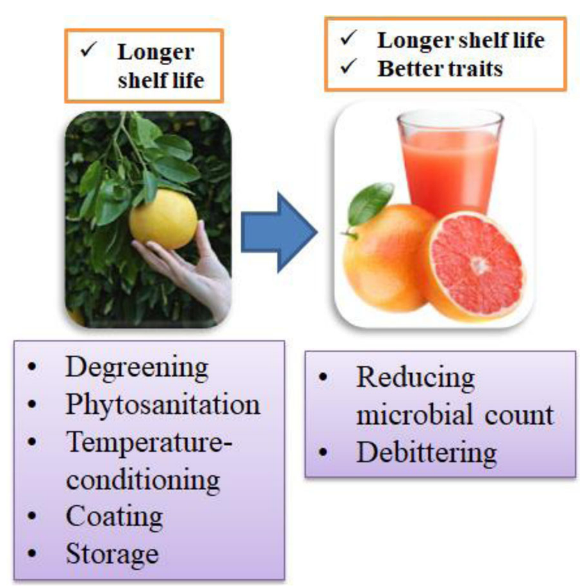


Figure 5. Post-processing steps applied to GF.

Several treatments were proposed and studied. No study has compared the different postharvest treatments to determine the best one. After collection, fruit was subjected to short hot water brushing (SHWB) to remove fungal spores and mud. The process involves pressurized hot water (60 °C) for 20–60 sec, it was found preferable to hot water dipping (HWD) which detrimentally affected fruit constituents (Sala et al. 2004). GF was sensitive to low-temperature storage, storage temperature below 9 °C leading to chilling injury, and blackening of the seed suggestive that the optimum storage temp was at 12–14 °C and relative humidity of 90–95% (Arpaia and Kader 1999).

An approach to reduce chilling injury to fruit rind was through curing or high-temperature pre-storage (24–48 h at 37 °C, 90% relative humidity) resulting in reducing chilling injury and increasing fruit ripening (Vázquez, Meier, and Ponte 2005) (Figure 5). At the molecular level, it was found that combining hot water spray (a rinse at 62 °C for 20 sec) and pre-conditioning (storage at 16 °C for 7 d) aided in priming genes responsible for chilling resistance (storing at 2 °C) (Sapitnitskaya et al. 2006). Similarly, a transcriptome study revealed that pre-storage conditioning enhanced chilling adaptation processes related to hormone biosynthesis, stress stimuli, and primary metabolism (Maul et al. 2008).

A single study evaluated the effects of postharvest treatments, namely, temperature conditioning, low storage temperature, and storage period on ascorbic acid content in GF cultivars, Rouge La Toma, and Ruby Red. Low storage temperature storage did not affect ascorbic acid level compared to control, whereas temperature conditioning affected ascorbic acid level in Rouge La Toma variety, albeit not in Ruby Red (Biolatto et al. 2005), suggestive for variety type effect. Fruits storage at 13 °C increased color index and lycopene content of the peel, whereas storage at lower temperature 2 °C showed no effect on peel color (Aispuro-Hernández et al. 2019).

Recently, the application of grafted copolymer of chitosan and salicylic acid on the fruit, depressed infection of green mold and delayed fruit softening by inhibiting the activity of cell wall solubilizing enzymes (Shi et al. 2019) (Figure 5). Alternatively, treatment of harvested fruit with salicylic acid and chitosan enhanced GF resistance against green mold infection mediated by activating defense responses and enzymes involved in polyphenol biosynthesis. Chemical treatments did not though affect total soluble acids or ascorbic acid levels (Shi et al. 2018). Similarly, a combination of carboxymethyl chitosan and *Cryptococcus laurentii* induced resistance in the fruit by boosting polyphenols biosynthesis and without affecting fruit quality i.e., total soluble acids, weight loss, and acidity (Wang, Deng, et al. 2019).

As a method for controlling microbial growth during storage, controlled release chlorine dioxide (ClO_2) packets were placed in GF boxes, found effective till certain limits without affecting fruit color (Sun et al. 2017).

Phytosanitation can be applied to GF using e-beam before cold storage at 4 °C for 20 d without compromising fruit sensory characters and juice content (Ramakrishnan et al. 2019).

Irradiation with gamma rays to extend GF shelf life, increased flavonoid content concurrent with a decrease in lycopene, limonene, and *p*-myrcene content. However, the effect of irradiation on fruit secondary metabolites content (Vanamala et al. 2005) has yet to be reported. UV-C irradiation of fruit was likewise applied to reduce microbial load and to extend Star Ruby fruit shelf life at a dosage of 0.5 $kJ \cdot m^{-2}$. This treatment reduced decay development without causing peel browning, necrosis nor affecting TSS and fruits acidity, though concurrent with an increase in phytoalexins, *viz.*, scopoletin, and scoparone (D'Hallewin et al. 2000).

Degreening using ethylene oxide is commonly used as a postharvest treatment when fruits are harvested in the early season (October-November) and to convert peel green color to orange/red. Degreening coupled to low-temperature storage resulted in enhancing fruits' esthetic quality with minimal effect on the nutritional quality of Star Ruby cultivar (Chaudhary et al. 2012). Ethylene treatment yielded fruit with better color, albeit without affecting organoleptic characters. In another study, Ruby Red fruit was degreened by exposure to ethylene oxide 3.5 μl/l at 21 °C followed by storage for 5 weeks (Chaudhary, Jayaprakasha, and Patil 2015). The peel color of degreened fruits was more uniform and attractive than untreated fruits (Chaudhary, Jayaprakasha, and Patil 2015), without affecting TSS, acidity, and ripening ratio. However, and contrary to results reported in Chaudhary et al. (2012), degreened fruits showed an increase in flavonoids level, concurrent with a decline in carotenoids, nomilin, and 6′,7′-dihydroxybergamottin. It was concluded that degreening treatment was beneficial for the fruit appearance and phytochemical content of Rio Red fruits (Chaudhary, Jayaprakasha, and Patil 2015).

Juice processing

Regarding household preparation of GFJ, it was found that mechanical blending yielded higher levels of flavonoids, limonoids, and furanocoumarins, except for dihydroxybergamottin, compared to juicing or hand squeezing (Uckoo et al. 2012).

After juice production, several approaches were reported to prolong the juice shelf life and stability by controlling the activity of enzymes and microbial load to include: high-temperature treatment, pasteurization, sonication, high-pressure treatment, and UV irradiation (Figure 5). No comparative study has compared the efficacy of these different techniques. Although heat treatment is disfavored due to sugars caramelization and darkening of the juice (Guerrero-Beltrán, Welti-Chanes, and Barbosa-Cánovas 2009), it is still used owing to its cost-effectiveness. In that aspect, UV-C irradiation offered a cost-effective alternative with minimal effect on fruit constituents (Guerrero-Beltrán, Welti-Chanes, and Barbosa-Cánovas 2009), and without affecting flavonoids, organic acid contents nor the juice color though with less antioxidant capacity (La Cava and Sgroppo 2015). The identification of how UV light irradiation interacts with the GF phenolic matrix in preservation has though yet to be reported. Combination of UV-C light irradiation and mild heat application (65 °C) was more effective in reducing microbial growth in GFJ and extending its shelf life without affecting its physicochemical properties, though with a decrease in antioxidant capacity (La Cava and Sgroppo 2019).

To minimize the loss of flavonoids composition, microwave pasteurization was found superior to conventional pasteurization in maintaining GF flavonoids (M. Igual et al. 2011). High-pressure processing (HPP) represents another non-thermal treatment process that showed likewise no effect on GFJ bioactives in Rio Red variety. The juice was pressurized at a temperature of 31.8 °C which led to an effective control of microbial growth and a higher L^* and b^* values (Uckoo et al. 2013). High-pressure treatment was also effective in pectinesterase enzyme inhibition, where the amplitude and duration of the applied pressure yielded different effects on enzyme isoforms (Goodner, Braddock, and Parish 1998). Effects of high-pressure processing on white GFJ were compared to those of thermal pasteurization (Chang et al. 2017), and to show no significant differences from fresh juice in terms of acidity, TSS albeit with lower antioxidant capacity posing it as a better method than thermal pasteurization. Conclusively, the authors concluded that HPP GFJ was more similar to fresh juice than thermal pasteurized one.

Sonication was also examined in GF preparation and to provide better cloud value, ascorbic acid, total phenolics, DPPH scavenging activity, acidity, or TSS values (Aadil et al. 2013). Sonication for 90 min produced more stable juice and preserved total phenolics, flavonoids, and antioxidant activities likely attributed to improved metabolite extraction from fruit material. Optimization of parameters *viz*. power, frequency, and time should be considered (Aadil, Zeng, Abbasi, et al. 2015). The pulsed electric field strength did not affect color, pH, Brix, acidity, and total anthocyanins, though at higher strength significant decrease in antioxidant capacity, total flavonoids, total carotenoids, nonenzymatic browning occurred (Aadil, Zeng, Ali, et al. 2015).

GFJ debittering

Debittering was performed to increase consumer appeal (Figure 5) (Sami et al. 1997), with naringin, the main bitter constituent being the target of these processes. Debittering was performed either by (i) adsorption using different ion exchange resin or by (ii) enzyme hydrolysis of naringin (bitter glycoside) to naringenin (tasteless aglycone). Narnoliya and Jadaun (2019) presented an up-to-date review on recent biotechnological advances in the debittering of fruit juices.

Several ion exchange resins were evaluated, e.g., XAD-16, polystyrene divinylbenzene adsorbents, ultrafiltration and adsorption, XAD-7HP, β-cyclodextrin, and γ-cyclodextrin for the removal of bergamotin and its dihydroxy derivative. Adsorption removed not only naringin and/or limonin but also other beneficial bioactive constituents, negatively affecting juice health benefits. Debittering of GFJ using naringinase enzyme was more preferable than adsorption using Amberilte® IRA-400 in terms of preserving juice antioxidant and free radical scavenging properties of the juice. Enzyme-treated juice performed better than resin-treated juice in all *in vitro* antioxidant assays (Cavia-Saiz et al. 2011), and posing such method as being superior for GFJ production.

Enzymatic hydrolysis could be performed using a single enzyme, naringinase, isolated from *Penicillium species* or *Aspergillus niger*. Alternatively, hydrolysis can be performed by two enzymes, namely, L-rhamnosidase and glucosidase. Rhamonisdase removes the rhamnose unit to yield the monoglycoside prunin which is further hydrolyzed using β-glucosidase (Busto et al. 2014). A drawback of employing enzymes in GF juice production is that soluble enzymes are rather costly and enzymes get inactivated by juice low pH. Enzyme immobilization offered more enzyme stability and cost-effectiveness compared to soluble enzymes (Bodakowska-Boczniewicz and Garncarek 2019; Busto et al. 2014). Several polymers were used in enzyme immobilization (Busto et al. 2014; Narnoliya and Jadaun 2019). Debittering using whole-cell, i.e., microorganisms containing these enzymes, is a potential approach (Busto et al. 2014). Low alcoholic carbonated beverage was produced by simultaneous debittering and fermentation of GFJ using a yeast strain (Pandove, Sahota, and Gupta 2016).

Kore et al. (2018) presented a collection of low-cost techniques which could be applied pre- and post-harvesting to lower the bitterness of citrus fruits to include: the selection of rootstock, manipulation of plant hormones, harvest time, soft expression of fruit, increasing pH, blending with non-bitter juice, lye peeling and use of packaging films. Delayed bitterness develops from the conversion of limonoate A-ring lactone (LARL) (non-bitter) to limonin (bitter) as catalyzed by the acidic pH of the juice. Consequently, LARL was either glycosylated by limonoid glucosyltransferase or oxidized by limonoate dehydrogenase to 17-dehydrolimonoate; both metabolites are non-bitter and would not be converted to limonin under acidic pH (Busto et al. 2014). Nevertheless, removal of naringin is the most targeted to reduce GF juice bitterness, but if this is accompanied by limonin removal as well would represent an added value.

GF seed byproducts

Although that new GF varieties encompass fewer seeds, some local varieties still encompass a considerable amount of seeds to be utilized in reasonable ways. The Turkish Beyaz GF variety was presented as a model for the valorization of GFS (Yilmaz et al. 2019). Seeds were debittered using naringinase and hesperidinase then cold-pressed. The oil is rich in linoleic acid, tocopherol, and sterols and could be used as an additive in combination with other oils though with a bitter taste. GFS extract combined with geranium oil was effective against methicillin-resistant *S. aureus* (Edwards-Jones et al. 2004). GFS extract was incorporated in oral care preparations, e.g., toothpaste and mouthwash. When combined with fluoride salts, GF seed extract synergistically inhibited the growth ad metabolism of bacterial plaque (Finnegan and Pan 2003).

Recently, GFS extract was incorporated in different biodegradable fibers and films to be used in food packaging owing to its inherent antibacterial action (Alonso et al. 2010; Bof et al. 2016; Oun and Rhim 2020; Wang, Lim, et al. 2019). Alternatively, GFS extract could be incorporated as food preservatives against heat-tolerant *Listeria monocytogenes* (Haskaraca et al. 2019). The antibacterial activities of GFS extract were employed by being incorporated in a hydrogel film used for wound healing (Koneru, Dharmalingam, and Anandalakshmi 2020). A wound-healing hydrogel film based on carrageenan was formulated with chitosan capped sulfur nanoparticles and GFS extract, found effective to treat full-thickness wounds (Jaiswal, Shankar, and Rhim 2019).

Novel trends for GF cultivation, production, and uses (2019–2020)

In pursuit of introducing new GF varieties with better traits and stress-tolerant, different reports were traced. A new variety of GF with low furanocoumarin composition was introduced as a mean to reduce the interaction of GF with drugs and to overcome limitations of the debittering processes (Guttman et al. 2020). Historically, GF breeding approaches were to improve fruit pulp red color with higher lycopene content. A recent variety was patented and termed TR-1 from Rio Red that exhibited pink-colored peel, mild flavor, and reduced bitterness. No more information about its detailed chemical composition is available (Louzada and del Rio 2019). Similar to other fruits, improvement in aroma and taste come at the expense of pest tolerance. Enhancing the resistance against citrus canker has experimented in 3 GF cultivars through cybridization. Cybrids comprising of GF nucleus and chloroplast of the resistant Kumquat (*Citrus japonica*) were found to be disease resistant to that disease (Murata et al. 2018).

Freeze drying or spray drying were recently optimized to serve as a tool for fruit drying or juice production. Freeze drying of GF could be improved and enhanced by using additives, e.g., bamboo fibers and gum to avoid losses in phenolics and antioxidant capacity. Moreover, lyophilization could be optimized by a pretreatment with mild drying in a microwave (Marta Igual et al., 2019). Reconstituted juice from spray- or freeze-dried samples showed inferior properties than commercial or natural juices owing to the higher content of fruit pulp (Martínez-Navarrete et al. 2019).

Modern technologies are being investigated regarding nutraceuticals development from GF. Nutraceutical powder could be prepared by spray drying and encapsulation (González et al. 2019) to replace the heating process during the preparation of juice concentrate (dewatering). The GF lycopene could be encapsulated in alginate-based beads to improve its stability and shelf life (Calvo and Santagapita 2019a, 2019b). Green extraction of GF polyphenol was investigated utilizing eutectic solvents and aqueous glycerol (El Kantar et al. 2019), a hot topic in functional food extraction that has potential in the future and to be more applied for GF production.

Conclusion & future trends

The current review capitalizes on the uniqueness and versatility of GF and its constituents as a prelude for sustainable production and valorization of its waste products. Not only does GF among citrus fruits exhibit a characteristic bitter taste due to flavanones, furanocoumarins, and limonoids, but a unique aroma imparted from limonene, nootkatone, and sulfur volatiles. The color of fruit pulp is determined by the ratio of its different carotenoids. The aforementioned metabolites have a characteristic accumulation pattern throughout ripening stages. This versatility made GF or GFJ a favorable healthy component in different diet programs, especially in alleviating chronic diseases, e.g., metabolic syndrome, osteoporosis. To minimize GF drug interactions and concurrently maintaining GF health benefits, new varieties are continually introduced and different pre- and postharvest techniques are also applied. An overview of these modern technologies included those to prolong the storage of fruit, increase the efficiency of juice production, debitter the juice, and to prolong the expiration date by controlling microbial content.

Versatility is propagated toward the applications of GF waste. Being richer than pulp in phytoconstituents, phytochemicals of the peel could be transformed into other high-value chemicals by chemical or biological means. Peel oil, rich in limonene has also many applications as safe antimicrobial, agrochemical disinfectant, skin anti-aging. Apart from being utilized in food, modified and/or unmodified pectin is an excellent source for biosorbents utilized in water remediation. The carbon content of GF peel is a source of energy either by torrefaction, bioethanol production, or as an anode in new batteries, whereas its seeds can be utilized in the manufacture of valuable green chemicals. It can be thus concluded that GF waste products can be utilized by high-tech or simple technologies in the fields of energy, material science, water remediation, and chemical industries. Hence, every community can tailor how this waste could be utilized according to their priorities and the available facilities.

Despite the plethora of researches about GF, several scientific questions have yet to be answered regarding a full genomic sequencing for GF varieties to understand genetic or epigenetic factors affecting the expression of the uique traits across varieties. RNA-sequencing and expression analysis across different ripening stages could contribute to better control of desirable or undesirable traits. Large metabolomics and *in vitro* biological studies should compare between old and new varieties to better assess if improvement in consumer appeal was accompanied by improvement in health-promoting constituents, e.g., antioxidant capacity. Finally, the correlation between genomics, transcriptomics, and metabolomics data of these varieties would reveal several insights into the dynamic process of fruit ripening and budsports selection. From such holistic data, models could be designed to predict the quality and biological activities of new varieties. Such versatility in metabolites and production processes is seldom found in industrial crops and offers an opportunity to decipher a lot of clues about citrus fruit metabolism. Finally, a more holistic scheme should be designed and adopted in each community to achieve better sustainable exploitation of GP and its waste products.

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Conflict of interest

The authors proclaim no conflict of interest.

Abbreviations

GA	Gibberellic acid
GF	grapefruit
GFJ	grapefruit juice
GFO	grapefruit oil
GFP	grapefruit peel
GFS	grapefruit seed **SPME** Solid Phase Microextraction
VOC	volatile organic compounds

References

Aadil, R. M., X.-A. Zeng, A. M. Abbasi, M. S. Khan, S. Khalid, S. Jabbar, and M. Abid. 2015. Influence of power ultrasound on the quality parameters of grapefruit juice during storage. *Science Letters* 3:6–12.

Aadil, R. M., X.-A. Zeng, A. Ali, F. Zeng, M. A. Farooq, Z. Han, S. Khalid, and S. Jabbar. 2015. Influence of different pulsed electric field strengths on the quality of the grapefruit juice. *International Journal of Food Science & Technology* 50 (10):2290–6. doi: 10.1111/ijfs.12891.

Aadil, R. M., X.-A. Zeng, Z. Han, and D.-W. Sun. 2013. Effects of ultrasound treatments on quality of grapefruit juice. *Food Chemistry* 141 (3):3201–6. doi: 10.1016/j.foodchem.2013.06.008.

Ahmed, S., H. S. Rattanpal, and G. Singh. 2018. Diversity assessment of grapefruit (Citrus x paradisi) and tangelo (Citrus X tangelo) under Indian conditions using physico-chemical parameters and SSR markers. *Applied Ecology and Environmental Research* 16 (5): 5343–58. doi: 10.15666/aeer/1605_53435358.

Aispuro-Hernández, E., A. M. Vera-Guzmán, I. Vargas-Arispuro, and M. Á. Martínez-Téllez. 2019. Low-temperature storage regulates the expression of genes related to peel pigments of grapefruit. *Scientia Horticulturae* 254:208–14. doi: 10.1016/j.scienta.2019.04.085.

Alam, M. A., K. Kathleen, and L. Brown. 2013. Naringin improves diet-induced cardiovascular dysfunction and obesity in high carbohydrate, high fat diet-fed rats. *Nutrients* 5 (3):637–50. doi: 10.3390/nu5030637.

Alam, M. A., N. Subhan, M. M. Rahman, S. J. Uddin, H. M. Reza, and S. D. Sarker. 2014. Effect of citrus flavonoids, naringin and naringenin, on metabolic syndrome and their mechanisms of action. *Advances in Nutrition* 5 (4):404–17. doi: 10.3945/an.113.005603.

Alonso, D., M. Gimeno, J. D. Sepúlveda-Sánchez, and K. Shirai. 2010. Chitosan-based microcapsules containing grapefruit seed extract grafted onto cellulose fibers by a non-toxic procedure. *Carbohydrate Research* 345 (6):854–9. doi: 10.1016/j.carres.2010.01.018.

Alquezar, B., M. J. Rodrigo, J. Lado, and L. Zacarías. 2013. A comparative physiological and transcriptional study of carotenoid biosynthesis in white and red grapefruit (Citrus paradisi Macf). *Tree Genetics & Genomes* 9 (5):1257–69. doi: 10.1007/s11295-013-0635-7.

Amor, L.-B., A. Hehn, E. Guedon, K. Ghedira, J.-M. Engasser, L. Chekir-Ghedrira, and M. Ghoul. 2010. Biotransformation of naringenin to eriodictyol by saccharomyces cerevisiea functionally expressing flavonoid 3′ hydroxylase. *Natural Product Communications* 5 (12):1934578X1000501 doi:10.1177/1934578X1000501211.

Amorós, M. E., V. P. d. Neves, F. Rivas, J. Buenahora, X. Martini, L. L. Stelinski, and C. Rossini. 2019. Response of Diaphorina citri (Hemiptera: Liviidae) to volatiles characteristic of preferred citrus hosts. *Arthropod-Plant Interactions* 13 (3):367–74. doi: 10.1007/s11829-018-9651-8.

Arora, S., P. Mohanpuria, and G. S. Sidhu. 2018. Citrus limonoids: Mechanism, function and its metabolic engineering for human health. *Fruits* 73 (3):158–73. doi: 10.17660/th2018/73.3.3.

Bailey, D. G. 2010. Fruit juice inhibition of uptake transport: A new type of food-drug interaction. *British Journal of Clinical Pharmacology* 70 (5):645–55. doi: 10.1111/j.1365-2125.2010.03722.x.

Bailey, D. G., G. Dresser, and J. M. O. Arnold. 2013. Grapefruit-medication interactions: Forbidden fruit or avoidable consequences? *CMAJ: Canadian Medical Association Journal = Journal de L'Association Medicale Canadienne* 185 (4):309–16. doi: 10.1503/cmaj.120951.

Bailey, D. G., J. D. Spence, C. Munoz, and J. M. Arnold. 1991. Interaction of citrus juices with felodipine and nifedipine. The *Lancet* 337 (8736):268–9. doi: 10.1016/0140-6736(91)90872-M.

Bayo, J. 2012. Kinetic studies for Cd(II) biosorption from treated urban effluents by native grapefruit biomass (Citrus paradisi L.): The competitive effect of Pb(II), Cu(II) and Ni(II). *Chemical Engineering Journal* 191:278–87. doi: 10.1016/j.cej.2012.03.016.

Bayo, J., G. Esteban, and J. Castillo. 2012. The use of native and protonated grapefruit biomass (Citrus paradisi L.) for cadmium(II) biosorption: Equilibrium and kinetic modelling. *Environmental Technology* 33 (7-9):761–72. doi: 10.1080/09593330.2011.592227.

Bharti, S., N. Rani, B. Krishnamurthy, and D. S. Arya. 2014. Preclinical evidence for the pharmacological actions of naringin: A review. *Planta Medica* 80 (6):437–51. doi: 10.1055/s-0034-1368351.

Bicas, J. L., F. F. C. Barros, R. Wagner, H. T. Godoy, and G. M. Pastore. 2008. Optimization of R-(+)-alpha-terpineol production by the biotransformation of R-(+)-limonene. *Journal of Industrial Microbiology & Biotechnology* 35 (9):1061–70. doi: 10.1007/s10295-008-0383-0.

Biolatto, A., V. Salitto, R. J. C. Cantet, and N. A. Pensel. 2005. Influence of different postharvest treatments on nutritional quality of grapefruits. *Lwt - Food Science and Technology* 38 (2):131–4. doi: 10.1016/j.lwt.2004.03.016.

Biolatto, A., A. M. Sancho, R. J. C. Cantet, D. R. Güemes, and N. A. Pensel. 2002. Use of Nootkatone as a senescence indicator for Rouge La Toma Cv. Grapefruit (Citrus paradisi Macf.). *Journal of Agricultural and Food Chemistry* 50 (17):4816–9. doi: 10.1021/jf011674b.

Bodakowska-Boczniewicz, J., and Z. Garncarek. 2019. Immobilization of naringinase from Penicillium decumbens on chitosan microspheres for debittering grapefruit juice. *Molecules* 24 (23):4234. doi: 10.3390/molecules24234234.

Bof, M. J., A. Jiménez, D. E. Locaso, M. A. García, and A. Chiralt. 2016. Grapefruit seed extract and lemon essential oil as active agents in corn starch–chitosan blend films. *Food and Bioprocess Technology* 9 (12):2033–45. doi: 10.1007/s11947-016-1789-8.

Braddock, R. J. 1999. *Handbook of citrus by-products and processing technology*. New York: Wiley.

Breksa, A. P., D. E. King, and A. M. Vilches. 2015. Determination of citrus limonoid glucosides by high performance liquid chromatography coupled to post-column reaction with Ehrlich's reagent. *Beverages* 1 (2):70–81. doi: 10.3390/beverages1020070.

Buettner, A., and P. Schieberle. 1999. Characterization of the most odor-active volatiles in fresh, hand-squeezed juice of grapefruit (Citrus paradisi Macfayden). *Journal of Agricultural and Food Chemistry* 47 (12):5189–93. doi: 10.1021/jf990071l.

Busto, M. D., M. Cavia-Saiz, N. Ortega, and P. Muñiz. 2014. Chapter 20—Enzymatic debittering on antioxidant capacity of grapefruit juice. In *Processing and impact on antioxidants in beverages*, ed. V. Preedy, 195–202. San Diego: Academic Press.

Calvo, T. R. A., and P. R. Santagapita. 2019a. Freezing and drying of pink grapefruit-lycopene encapsulated in Ca (II)-alginate beads containing galactomannans. *Journal of Food Science and Technology* 56 (7):3264–71.

Calvo, T. R. A., and P. R. Santagapita. 2019b. Pink grapefruit lycopene encapsulated in alginate-based beads: Stability towards freezing and drying. *International Journal of Food Science & Technology* 54 (2): 368–75. doi: 10.1111/ijfs.13946.

Cavia-Saiz, M., P. Muñiz, N. Ortega, and M. D. Busto. 2011. Effect of enzymatic debittering on antioxidant capacity and protective role against oxidative stress of grapefruit juice in comparison with adsorption on exchange resin. *Food Chemistry* 125 (1):158–63. doi: 10.1016/j.foodchem.2010.08.054.

Céliz, G., M. Daz, and M. C. Audisio. 2011. Antibacterial activity of naringin derivatives against pathogenic strains. *Journal of Applied Microbiology* 111 (3):731–8. doi:10.1111/j.1365-2672.2011.05070.x.

Chang, Y.-H., S.-J. Wu, B.-Y. Chen, H.-W. Huang, and C.-Y. Wang. 2017. Effect of high-pressure processing and thermal pasteurization on overall quality parameters of white grape juice. *Journal of the Science of Food and Agriculture* 97 (10):3166–72. doi: 10.1002/jsfa.8160.

Chaudhary, P., G. K. Jayaprakasha, R. Porat, and B. S. Patil. 2012. Degreening and postharvest storage influences 'Star Ruby' grapefruit (Citrus paradisi Macf.) bioactive compounds. *Food Chemistry* 135 (3):1667–75. doi: 10.1016/j.foodchem.2012.05.095.

Chaudhary, P. R., H. Bang, G. K. Jayaprakasha, and B. S. Patil. 2016. Variation in key flavonoid biosynthetic enzymes and phytochemicals in 'Rio Red' grapefruit (Citrus paradisi Macf.) during fruit development. *Journal of Agricultural and Food Chemistry* 64 (47):9022–32. doi: 10.1021/acs.jafc.6b02975.

Chaudhary, P. R., G. K. Jayaprakasha, and B. S. Patil. 2015. Ethylene degreening modulates health promoting phytochemicals in Rio Red grapefruit. *Food Chemistry* 188:77–83. doi: 10.1016/j.foodchem.2015.04.044.

Chaudhary, P. R., G. K. Jayaprakasha, and B. S. Patil. 2018. Identification of volatile profiles of Rio Red grapefruit at various developmental to maturity stages. *Journal of Essential Oil Research* 30 (2):77–83. doi: 10.1080/10412905.2017.1386131.

Chebrolu, K. K., G. K. Jayaprakasha, J. Jifon, and B. S. Patil. 2012. Production system and storage temperature influence grapefruit vitamin C, limonoids, and carotenoids. *Journal of Agricultural and Food Chemistry* 60 (29):7096–103. doi: 10.1021/jf301681p.

Chen, P., J. M. Harnly, and G. E. Lester. 2010. Flow injection mass spectral fingerprints demonstrate chemical differences in Rio Red grapefruit with respect to year, harvest time, and conventional versus organic farming. *Journal of Agricultural and Food Chemistry* 58 (8):4545–53. doi: 10.1021/jf904324c.

Chen, R., Q. L. Qi, M. T. Wang, and Q. Y. Li. 2016. Therapeutic potential of naringin: An overview. *Pharmaceutical Biology* 54 (12): 3203–10. doi: 10.1080/13880209.2016.1216131.

Chudnovskiy, R., A. Thompson, K. Tharp, M. Hellerstein, J. L. Napoli, and A. Stahl. 2014. Consumption of clarified grapefruit juice ameliorates high-fat diet induced insulin resistance and weight gain in mice. *PLoS One* 9 (10):e108408. doi: 10.1371/journal.pone.0108408.

Cooperstone, J. L., and S. J. Schwartz. 2016. Recent insights into health benefits of carotenoids. In *Handbook on natural pigments in food and beverages*, eds. Reinhold Carle and R. Schweiggert, 473–97. Elsevier.

Cristóbal-Luna, J. M., I. Álvarez-González, E. Madrigal-Bujaidar, and G. Chamorro-Cevallos. 2018. Grapefruit and its biomedical, antigenotoxic and chemopreventive properties. *Food and Chemical Toxicology* 112:224–34. doi: 10.1016/j.fct.2017.12.038.

Czech, A., E. Zarycka, D. Yanovych, Z. Zasadna, I. Grzegorczyk, and S. Kłys. 2020. Mineral content of the pulp and peel of various citrus fruit cultivars. *Biological Trace Element Research* 193 (2):555–63. doi: 10.1007/s12011-019-01727-1.

D'Hallewin, G., M. Schirra, M. Pala, and S. Ben-Yehoshua. 2000. Ultraviolet C irradiation at 0.5 kJ·m-2 reduces decay without causing damage or affecting postharvest quality of star ruby grapefruit (C. paradisi Macf.). *Journal of Agricultural and Food Chemistry* 48 (10): 4571–5. doi: 10.1021/jf000559i.

Da Graca, J. V., E. S. Louzada, and J. W. Sauls. 2004. The origins of red pigmented grapefruits and the development of new varieties. Paper presented at the Proceedings of the International Society of Citriculture. Morocco: Agadir.

De Castro, W. V., S. Mertens-Talcott, A. Rubner, V. Butterweck, and H. Derendorf. 2006. Variation of flavonoids and furanocoumarins in grapefruit juices: A potential source of variability in grapefruit juice-drug interaction studies. *Journal of Agricultural and Food Chemistry* 54 (1):249–55. doi: 10.1021/jf0516944.

de Moraes, A. P., W. dos Santos Soares Filho, and M. Guerra. 2007. Karyotype diversity and the origin of grapefruit. *Chromosome Research* 15 (1):115–21. doi: 10.1007/s10577-006-1101-2.

Del Rio, J. A., M. D. Fuster, F. Sabater, I. Porras, A. García-Lidón, and A. Ortuno. 1997. Selection of citrus varieties highly productive for the neohesperidin dihydrochalcone precursor. *Food Chemistry* 59 (3):433–7.

Diaconu, C., L. Vlase, M. Cuciureanu, and L. Filip. 2017. Assessment of flavonoids content in citrus juices using a LC/MS method. *Farmacia* 65 (1):92–6.

Drewnowski, A., S. A. Henderson, and A. B. Shore. 1997. Taste responses to naringin, a flavonoid, and the acceptance of grapefruit juice are related to genetic sensitivity to 6-n-propylthiouracil. *The American Journal of Clinical Nutrition* 66 (2):391–7. doi: 10.1093/ajcn/66.2.391.

Duetz, W. A., H. Bouwmeester, J. B. van Beilen, and B. Witholt. 2003. Biotransformation of limonene by bacteria, fungi, yeasts, and plants. *Applied Microbiology and Biotechnology* 61 (4):269–77. doi: 10.1007/s00253-003-1221-y.

Edwards-Jones, V., R. Buck, S. G. Shawcross, M. M. Dawson, and K. Dunn. 2004. The effect of essential oils on methicillin-resistant *Staphylococcus aureus* using a dressing model. *Burns* 30 (8):772–7. doi: 10.1016/j.burns.2004.06.006.

Eggersdorfer, M., and A. Wyss. 2018. Carotenoids in human nutrition and health. *Archives of Biochemistry and Biophysics* 652:18–26. doi: 10.1016/j.abb.2018.06.001.

El Kantar, S., H. N. Rajha, N. Boussetta, E. Vorobiev, R. G. Maroun, and N. Louka. 2019. Green extraction of polyphenols from grapefruit peels using high voltage electrical discharges, deep eutectic solvents and aqueous glycerol. *Food Chemistry* 295:165–71. doi: 10.1016/j.foodchem.2019.05.111.

Farouk, H., B. A. El-Sayeh, S. S. Mahmoud, and O. A. Sharaf. 2012. Effect of olfactory stimulation with grapefruit oil and sibutramine in obese rats. *Journal of Pakistan Medical Association* 2 (1):3–10.

Feger, W., H. Brandauer, and H. Ziegler. 2001. Analytical investigation of sweetie peel oil. *Journal of Essential Oil Research* 13 (5):309–13. doi: 10.1080/10412905.2001.9712221.

Fellers, P. J., R. D. Carter, and G. Jager. 1988. Influence of the ratio of degrees brix to percent acid on consumer acceptance of processed modified grapefruit juice. *Journal of Food Science* 53 (2):513–5. doi: 10.1111/j.1365-2621.1988.tb07744.x.

Ferrara, M. A., D. S. Almeida, A. C. Siani, L. Lucchetti, P. S. B. Lacerda, A. Freitas, M. R. R. Tappin, and E. P. S. Bon. 2013. Bioconversion of R-(+)-limonene to perillic acid by the yeast Yarrowia lipolytica. *Brazilian Journal of Microbiology* 44 (4): 1075–80. doi: 10.1590/S1517-83822014005000008.

Fidel, L., M. Carmeli-Weissberg, Y. Yaniv, F. Shaya, N. Dai, E. Raveh, Y. Eyal, R. Porat, and N. Carmi. 2016. Breeding and analysis of two new grapefruit-like varieties with low furanocoumarin content. *Food and Nutrition Sciences* 07 (02):90–101. doi: 10.4236/fns.2016.72011.

Figuerola, F., M. L. Hurtado, A. M. Estévez, I. Chiffelle, and F. Asenjo. 2005. Fibre concentrates from apple pomace and citrus peel as potential fibre sources for food enrichment. *Food Chemistry* 91 (3): 395–401. doi: 10.1016/j.foodchem.2004.04.036.

Finnegan, M., and P. Pan. 2003. Oral care compositions containing grapefruit seed extract: Google Patents.

Frydman, A., O. Weisshaus, D. V. Huhman, L. W. Sumner, M. Bar-Peled, E. Lewinsohn, R. Fluhr, J. Gressel, and Y. Eyal. 2005. Metabolic engineering of plant cells for biotransformation of hesperedin into neohesperidin, a substrate for production of the low-calorie sweetener and flavor enhancer NHDC. *Journal of Agricultural and Food Chemistry* 53 (25):9708–12. doi:10.1021/jf051509m.

Fukuda, K., L. Guo, N. Ohashi, M. Yoshikawa, and Y. Yamazoe. 2000. Amounts and variation in grapefruit juice of the main components causing grapefruit-drug interaction. *Journal of Chromatography. B, Biomedical Sciences and Applications* 741 (2):195–203. doi: 10.1016/s0378-4347(00)00104-3.

Gamboa-Gomez, C., L. M. Salgado, A. Gonzalez-Gallardo, M. Ramos-Gomez, G. Loarca-Pina, and R. Reynoso-Camacho. 2014. Consumption of Ocimum sanctum L. and Citrus paradisi infusions modulates lipid metabolism and insulin resistance in obese rats. *Food & Function* 5 (5):927–35. doi: 10.1039/c3fo60604j.

Garcia-Amezquita, L. E., V. Tejada-Ortigoza, S. O. Serna-Saldivar, and J. Welti-Chanes. 2018. Dietary fiber concentrates from fruit and vegetable by-products: Processing, modification, and application as functional ingredients. *Food and Bioprocess Technology* 11 (8): 1439–63. doi: 10.1007/s11947-018-2117-2.

García-Carnelli, C., P. Rodríguez, H. Heinzen, and P. Menéndez. 2014. Influence of culture conditions on the biotransformation of (+)-limonene by Aspergillus niger. *Zeitschrift fur Naturforschung C: Journal of Biosciences* 69 (1-2):61–7. doi: 10.5560/znc.2013-0048.

Girennavar, B., G. K. Jayaprakasha, J. L. Jifon, and B. S. Patil. 2008. Variation of bioactive furocoumarins and flavonoids in different varieties of grapefruits and pummelo. *European Food Research and Technology* 226 (6):1269–75. doi: 10.1007/s00217-007-0654-4.

Gliszczyńska, A., A. Łysek, T. Janeczko, M. Świtalska, J. Wietrzyk, and C. Wawrzeńczyk. 2011. Microbial transformation of (+)-nootkatone and the antiproliferative activity of its metabolites. *Bioorganic & Medicinal Chemistry* 19 (7):2464–9. doi: 10.1016/j.bmc.2011.01.062.

Gmitter, F. G., Jr. 1995. Origin, evolution, and breeding of the grapefruit. In *Plant breeding reviews*, ed. J. Janick, 345–363. New York: Wiley.

González, C. N., F. Sánchez, A. Quintero, and A. Usubillaga. 2002. Chemotaxonomic value of essential oil compounds in citrus species. *Acta Horticulturae* 576:49–51.

González, F., E. García-Martínez, M. Del Mar Camacho, N. Martínez-Navarrete, B. Sarmento, I. Fernandes, V. Freitas, F. Rodrigues, and B. Oliveira. 2019. Insights into the development of grapefruit nutraceutical powder by spray drying: Physical characterization, chemical composition and 3D intestinal permeability. *Journal of the Science of Food and Agriculture* 99 (10):4686–94. doi: 10.1002/jsfa.9709.

González-Mas, M. C., J. L. Rambla, M. P. López-Gresa, M. A. Blázquez, and A. Granell. 2019. Volatile compounds in citrus essential oils: A comprehensive review. *Frontiers in Plant Science* 10:12. doi: 10.3389/fpls.2019.00012.

Goodner, J. K., R. J. Braddock, and M. E. Parish. 1998. Inactivation of pectinesterase in orange and grapefruit juices by high pressure. *Journal of Agricultural and Food Chemistry* 46 (5):1997–2000. doi: 10.1021/jf9709111.

Gous, A. G. S., V. L. Almli, V. Coetzee, and H. L. de Kock. 2019. Effects of varying the color, aroma, bitter, and sweet levels of a grapefruit-like model beverage on the sensory properties and liking of the consumer. *Nutrients* 11 (2):464. doi: 10.3390/nu11020464.

Gualdani, R., M. M. Cavalluzzi, G. Lentini, and S. Habtemariam. 2016. The chemistry and pharmacology of citrus limonoids. *Molecules* 21 (11):1530. doi: 10.3390/molecules21111530.

Guerrero-Beltrán, J., J. Welti-Chanes, and G. V. Barbosa-Cánovas. 2009. Ultraviolet-C light processing of grape, cranberry and grapefruit juices to inactivate Saccharomyces cerevisiae. *Journal of Food Process Engineering* 32 (6):916–32. doi: 10.1111/j.1745-4530.2008.00253.x.

Guttman, Y., I. Yedidia, A. Nudel, Y. Zhmykhova, Z. Kerem, and N. Carmi. 2020. New grapefruit cultivars exhibit low cytochrome P4503A4-Inhibition activity. *Food and Chemical Toxicology* 137: 111135. doi: 10.1016/j.fct.2020.111135.

Hajialyani, M., M. Hosein Farzaei, J. Echeverria, S. M. Nabavi, E. Uriarte, and E. Sobarzo-Sanchez. 2019. Hesperidin as a neuroprotective agent: A review of animal and clinical evidence. *Molecules* 24 (3):648. doi: 10.3390/molecules24030648.

Haskaraca, G., V. K. Juneja, S. Mukhopadhyay, and N. Kolsarici. 2019. The effects of grapefruit seed extract on the thermal inactivation of Listeria monocytogenes in sous-vide processed döner kebabs. *Food Control* 95:71–6. doi: 10.1016/j.foodcont.2018.07.006.

Haze, S., K. Sakai, Y. Gozu, and M. Moriyama. 2010. Grapefruit oil attenuates adipogenesis in cultured subcutaneous adipocytes. *Planta Medica* 76 (10):950–5. doi: 10.1055/s-0029-1240870.

Hozumi, H., S. Hasegawa, T. Tsunenari, N. Sanpei, Y. Arashina, K. Takahashi, A. Konnno, E. Chida, and S. Tomimatsu. 2017. Aromatherapies using Osmanthus fragrans oil and grapefruit oil are effective complementary treatments for anxious patients undergoing colonoscopy: A randomized controlled study. *Complementary Therapies in Medicine* 34:165–9. doi: 10.1016/j.ctim.2017.08.012.

Hung, W. L., J. H. Suh, and Y. Wang. 2017. Chemistry and health effects of furanocoumarins in grapefruit. *Journal of Food and Drug Analysis* 25 (1):71–83. doi: 10.1016/j.jfda.2016.11.008.

Igual, M., L. Cebadera, R. M. Cámara, C. Agudelo, N. Martínez-Navarrete, and M. Cámara. 2019. Novel ingredients based on grapefruit freeze-dried formulations: Nutritional and bioactive value. *Foods* 8 (10):506. doi: 10.3390/foods8100506.

Igual, M., E. García-Martínez, M. M. Camacho, and N. Martínez-Navarrete. 2011. Changes in flavonoid content of grapefruit juice caused by thermal treatment and storage. *Innovative Food Science & Emerging Technologies* 12 (2):153–62. 10.1016/j.ifset.2010.12.010.

Inkoua, S., H. L. Maloko, M. M. Koko, and L. Yan. 2020. Facile solvothermal synthesis of Fe_3O_4/magnetic grapefruit peel for adsorptive removal of Congo red, humic acid and phosphate from aqueous solutions. *Materials Express* 10 (1):37–44. doi: 10.1166/mex.2020.1610.

Jabalpurwala, F., O. Gurbuz, and R. Rouseff. 2010. Analysis of grapefruit sulphur volatiles using SPME and pulsed flame photometric detection. *Food Chemistry* 120 (1):296–303. doi: 10.1016/j.foodchem.2009.09.079.

Jaiswal, L., S. Shankar, and J.-W. Rhim. 2019. Carrageenan-based functional hydrogel film reinforced with sulfur nanoparticles and grapefruit seed extract for wound healing application. *Carbohydrate Polymers* 224:115191. doi: 10.1016/j.carbpol.2019.115191.

Joanna, L., J. R. Paul, M. Cronje, J. Rodrigo, and Z. Lorenzo. 2015. Fruit shading enhances red color and carotenoid accumulation in 'Star Ruby' grapefruit. *Acta Hortic* 1065:1521–27. doi:10.17660/ActaHortic.2015.1065.193.

John, I., K. Muthukumar, and A. Arunagiri. 2017. A review on the potential of citrus waste for D-Limonene, pectin, and bioethanol production. *International Journal of Green Energy* 14 (7):599–612. doi: 10.1080/15435075.2017.1307753.

Kawai, E., R. Takeda, A. Ota, E. Morita, D. Imai, Y. Suzuki, H. Yokoyama, S.-Y. Ueda, H. Nakahara, T. Miyamoto, et al. 2020. Increase in diastolic blood pressure induced by fragrance inhalation of grapefruit essential oil is positively correlated with muscle sympathetic nerve activity. *The Journal of Physiological Sciences* 70 (1):2. doi: 10.1186/s12576-020-00733-6.

Kawai, E., R. Takeda, K. Saho, A. Ota, E. Morita, D. Imai, Y. Suzuki, H. Yokoyama, and K. Okazaki. 2019. Effect of fragrance inhalation of grapefruit essential oil on blood pressure and baroreflex sensitivity in human with, and without, family history of hypertension. *The FASEB Journal* 33 (1_supplement):533.3. doi: 10.1096/fasebj.2019.33.1_supplement.533.3.

Kaya, M., A. G. Sousa, M.-J. Crépeau, S. O. Sørensen, and M.-C. Ralet. 2014. Characterization of citrus pectin samples extracted under different conditions: Influence of acid type and pH of extraction. *Annals of Botany* 114 (6):1319–26. doi: 10.1093/aob/mcu150.

Kiani, J., and S. Z. Imam. 2007. Medicinal importance of grapefruit juice and its interaction with various drugs. *Nutrition Journal* 6 (1): 33. doi: 10.1186/1475-2891-6-33.

Kim, H. J. 2007. [Effect of aromatherapy massage on abdominal fat and body image in post-menopausal women]. Taehan *Kanho Hakhoe Chi* 37 (4):603–12. doi: 10.4040/jkan.2007.37.4.603.

Koneru, A., K. Dharmalingam, and R. Anandalakshmi. 2020. Cellulose based nanocomposite hydrogel films consisting of sodium carboxymethylcellulose-grapefruit seed extract nanoparticles for potential wound healing applications. *International Journal of Biological Macromolecules* 148:833–42. doi: 10.1016/j.ijbiomac.2020.01.018.

Kore, V. T., S. S. Tawade, L. H. Devi, and I. Chakraborty. 2018. Use of pre and post harvest low cost techniques to control/minimize citrus juice bitterness. *American Research Journal of Food and Nutrition* 1: 11–21.

Koshali, Z. S., M. Ghotbi, and L. R. Nasiriyah. 2019. Study of the effect of flour replacement with grapefruit fibers on the chemistry and sensory properties of muffins. *Journal of Innovation in Food Science and Technology* 11 (4):37–49.

La Cava, E. L. M., and S. C. Sgroppo. 2015. Evolution during refrigerated storage of bioactive compounds and quality characteristics of grapefruit [Citrus paradisi (Macf.)] juice treated with UV-C light. *LWT - Food Science and Technology* 63 (2):1325–33. 10.1016/j.lwt.2015.04.013.

La Cava, E. L. M., and S. C. Sgroppo. 2019. Combined effect of UV-C light and mild heat on microbial quality and antioxidant capacity of grapefruit juice by flow continuous reactor. *Food and Bioprocess Technology* 12 (4):645–53. doi: 10.1007/s11947-019-2239-1.

Lado, J., A. Gurrea, L. Zacarías, and M. J. Rodrigo. 2019. Influence of the storage temperature on volatile emission, carotenoid content and chilling injury development in Star Ruby red grapefruit. *Food Chemistry* 295:72–81. doi: 10.1016/j.foodchem.2019.05.108.

Larrauri, J. A., P. Rupérez, B. Borroto, and F. Saura-Calixto. 1997. Seasonal changes in the composition and properties of a high dietary fibre powder from grapefruit peel. *Journal of the Science of Food and Agriculture* 74 (3):308–12. doi: 10.1002/(sici)1097-0010(199707)74:3 < 308::aid-jsfa803 > 3.0.co;2-n.

Lee, S. G., K. Kim, T. M. Vance, C. Perkins, A. Provatas, S. Wu, A. Qureshi, E. Cho, and O. K. Chun. 2016. Development of a comprehensive analytical method for furanocoumarins in grapefruit and their metabolites in plasma and urine using UPLC-MS/MS: A preliminary study. *International Journal of Food Sciences and Nutrition* 67 (8):881–7. doi: 10.1080/09637486.2016.1207157.

Lester, G. E., J. A. Manthey, and B. S. Buslig. 2007. Organic vs conventionally grown Rio Red whole grapefruit and juice: Comparison of production inputs, market quality, consumer acceptance, and human health-bioactive compounds. *Journal of Agricultural and Food Chemistry* 55 (11):4474–80. doi: 10.1021/jf070901s.

Li, C., and H. Schluesener. 2017. Health-promoting effects of the citrus flavanone hesperidin. *Critical Reviews in Food Science and Nutrition* 57 (3):613–31. doi: 10.1080/10408398.2014.906382.

Liu, Q., L. Liu, J. Zhou, H-d. Shin, R. R. Chen, C. Madzak, J. Li, G. Du, and J. Chen. 2013. Biosynthesis of homoeriodictyol from eriodictyol by flavone 3′-O-methyltransferase from recombinant Yarrowia lioplytica: Heterologous expression, biochemical characterization, and optimal transformation. *Journal of Biotechnology* 167 (4):472–8. doi:10.1016/j.jbiotec.2013.07.025.

López-Marcos, M. C., C. Bailina, M. Viuda-Martos, J. A. Pérez-Alvarez, and J. Fernández-López. 2015. Properties of dietary fibers from agroindustrial coproducts as source for fiber-enriched foods. *Food and Bioprocess Technology* 8 (12):2400–8. doi: 10.1007/s11947-015-1591-z.

Mamma, D., and P. Christakopoulos. 2014. Biotransformation of citrus by-products into value added products. *Waste and Biomass Valorization* 5 (4):529–49. doi: 10.1007/s12649-013-9250-y.

Manaila, E., M. Berechet, M. Stelescu, G. Craciun, D. E. Mihaiescu, B. Purcareanu, I. Calinescu, A. Fudulu, and M. Radu. 2016. Comparation between chemical compositions of some essential oils obtained by hydrodistillation from citrus peels. *Revista de Chimie (Bucharest)* 67:106–12.

Mandadi, K. K., G. K. Jayaprakasha, N. G. Bhat, and B. S. Patil. 2007. Red Mexican grapefruit: A novel source for bioactive limonoids and their antioxidant activity. *Zeitschrift fur Naturforschung C: Journal of Biosciences* 62 (3-4):179–88. doi: 10.1515/znc-2007-3-405.

Martínez-Navarrete, N., M. M. Camacho, C. Agudelo, and A. Salvador. 2019. Sensory characterization of juice obtained via rehydration of freeze-dried and spray-dried grapefruit. *Journal of the Science of Food and Agriculture* 99 (1):244–52. doi: 10.1002/jsfa.9166.

Marumoto, S., and M. Miyazawa. 2010. Biotransformation of bergapten and xanthotoxin by glomerella cingulata. *Journal of Agricultural and Food Chemistry* 58 (13):7777–81. doi:10.1021/jf101064v.

Maul, P., G. T. McCollum, M. Popp, C. L. Guy, and R. Porat. 2008. Transcriptome profiling of grapefruit flavedo following exposure to low temperature and conditioning treatments uncovers principal molecular components involved in chilling tolerance and susceptibility. *Plant, Cell & Environment* 31 (6):752–68. doi: 10.1111/j.1365-3040.2008.01793.x.

Maurer, R. H., E. M. Burdick, and C. W. Waibel. 1950. Distribution of naringin in Texas grapefruit. Proceedings 4th Annual Rio Grande Valley Horticultural Society. 147–51. Texas, US.

Mohamed, H. 2016. Extraction and characterization of pectin from grapefruit peels. *MOJ Food Processing & Technology* 2 (1):31–8.

Montanari, A., J. Chen, and W. Widmer. 1998. Citrus flavonoids: A review of past biological activity against disease. In *Flavonoids in the living system*, ed. J. A. Manthey and B. S. Buslig, 103–16. Boston, MA: Springer US.

Mori, M., N. Ikeda, Y. Kato, M. Minamino, and K. Watabe. 2002. Inhibition of elastase activity by essential oils in vitro. *Journal of Cosmetic Dermatology* 1 (4):183–7. doi: 10.1111/j.1473-2165.2002.00059.x.

Morton, J. F., and C. F. Dowling. 1987. *Fruits of warm climates*, vol. 20534. Miami, FL: Morton JF.

Murata, M. M., A. A. Omar, Z. Mou, C. D. Chase, J. W. Grosser, and J. H. Graham. 2018. Novel plastid-nuclear genome combinations enhance resistance to citrus canker in cybrid grapefruit. *Frontiers in Plant Science* 9:1858. doi: 10.3389/fpls.2018.01858.

Nakajima, V. M., G. A. Macedo, and J. A. Macedo. 2014. Citrus bioactive phenolics: Role in the obesity treatment. *LWT - Food Science and Technology* 59 (2):1205–12. doi: 10.1016/j.lwt.2014.02.060.

Narnoliya, L. K., and J. S. Jadaun. 2019. Biotechnological avenues for fruit juices debittering. In *Green bio-processes: Enzymes in industrial food processing*, ed. B. Parameswaran, S. Varjani, and S. Raveendran, 119–49. Singapore: Springer Singapore.

Ng, T. B., A. E.-D A. Bekhit, E. F. Fang, X. Li, Q. Lu, H. Guo, and J. H. Wong. 2016. Chapter 52 Grapefruit (Citrus paradisii) oils. In *Essential Oils in Food Preservation, Flavor and Safety,* ed. R. Preedy, 463–470. London: Elsevier Science.

Niijima, A., and K. Nagai. 2003. Effect of olfactory stimulation with flavor of grapefruit oil and lemon oil on the activity of sympathetic branch in the white adipose tissue of the epididymis. *Experimental Biology and Medicine (Maywood)* 228 (10):1190–2. doi: 10.1177/153537020322801014.

Njoroge, S. M., H. Koaze, P. N. Karanja, and M. Sawamura. 2005. Volatile constituents of redblush grapefruit (Citrus paradisi) and pummelo (Citrus grandis) peel essential oils from Kenya. *Journal of Agricultural and Food Chemistry* 53 (25):9790–4. doi: 10.1021/jf051373s.

Okuno, Y., and M. Miyazawa. 2004. Biotransformation of nobiletin by aspergillusniger and the antimutagenic activity of a metabolite, 4′-hydroxy-5,6,7,8,3′-pentamethoxyflavone. *Journal of Natural Products* 67 (11):1876–8. doi:10.1021/np034007g.

Okunowo, W. O., O. Oyedeji, L. O. Afolabi, and E. Matanmi. 2013. Essential oil of grape fruit (Citrus paradisi) peels and its antimicrobial activities. *American Journal of Plant Sciences* 04 (07):1–9. doi: 10.4236/ajps.2013.47A2001.

Orbović, V., M. Dutt, and J. W. Grosser. 2013. Evaluation of the germination potential of citrus seeds during the harvesting season. *HortScience* 48 (9):1197–9. doi: 10.21273/HORTSCI.48.9.1197.

Ortuno, A., D. Garcia-Puig, M. D. Fuster, M. L. Perez, F. Sabater, I. Porras, A. Garcia-Lidon, and J. A. Del Rio. 1995. Flavanone and nootkatone levels in different varieties of grapefruit and pummelo. *Journal of Agricultural and Food Chemistry* 43 (1):1–5. doi: 10.1021/jf00049a001.

Oun, A. A., and J.-W. Rhim. 2020. Preparation of multifunctional carboxymethyl cellulose-based films incorporated with chitin nanocrystal and grapefruit seed extract. *International Journal of Biological Macromolecules* 152:1038–46. doi: 10.1016/j.ijbiomac.2019.10.191.

Özyürek, M., D. Akpınar, M. Bener, B. Türkkan, K. Güçlü, and R. Apak. 2014. Novel oxime based flavanone, naringin-oxime: Synthesis, characterization and screening for antioxidant activity. *Chemico-Biological Interactions* 212:40–6. doi:10.1016/j.cbi.2014.01.017.

Pandove, G., P. Sahota, and N. Gupta. 2016. Development of low alcoholic naturally carbonated fermented debittered beverage from grapefruit (Citrus paradisi). *Journal of Applied and Natural Science* 8 (3):1649–53. doi: 10.31018/jans.v8i3.1017.

Raja Kumar, S., E. S. Mohd Ramli, N. A. Abdul Nasir, N. H. M. Ismail, and N. A. Mohd Fahami. 2019. Preventive effect of naringin on metabolic syndrome and its mechanism of action: A systematic review. *Evidence-Based Complementary and Alternative Medicine* 2019:9752826. doi: 10.1155/2019/9752826.

Ramakrishnan, S. R., Y. Jo, H.-A. Nam, S.-Y. Gu, M.-E. Baek, and J.-H. Kwon. 2019. Implications of low-dose e-beam irradiation as a phytosanitary treatment on physicochemical and sensory qualities of grapefruit and lemons during postharvest cold storage. *Scientia Horticulturae* 245:1–6. doi: 10.1016/j.scienta.2018.09.058.

Rao, A. V., and S. Agarwal. 2000. Role of antioxidant lycopene in cancer and heart disease. Journal *of the American College of Nutrition* 19 (5):563–9. doi: 10.1080/07315724.2000.10718953.

Razavi, B. M., and H. Hosseinzadeh. 2019. Chapter 34—A review of the effects of Citrus paradisi (grapefruit) and its flavonoids, naringin, and naringenin in metabolic syndrome. In *Bioactive food as dietary interventions for diabetes*, ed. R. R. Watson and V. R. Preedy, 2nd ed., 515–43. San Diego: Academic Press.

Ren, J.-N., Y.-N. Tai, M. Dong, J.-H. Shao, S.-Z. Yang, S.-Y. Pan, and G. Fan. 2015. Characterisation of free and bound volatile compounds from six different varieties of citrus fruits. *Food Chemistry* 185:25–32. doi: 10.1016/j.foodchem.2015.03.142.

Rivas-Cantu, R. C., K. D. Jones, and P. L. Mills. 2013. A citrus waste-based biorefinery as a source of renewable energy: Technical advances and analysis of engineering challenges. *Waste Management & Research* 31 (4):413–20. doi: 10.1177/0734242x13479432.

Robacker, D. C., and C. Rios. 2005. Grapefruit oil enhances attraction of Mexican fruit flies to a synthetic food-odor lure. *Journal of Chemical Ecology* 31 (5):1039–49. doi: 10.1007/s10886-005-4246-0.

Rodriguez-Concepcion, M., J. Avalos, M. L. Bonet, A. Boronat, L. Gomez-Gomez, D. Hornero-Mendez, M. C. Limon, A. J. Meléndez-Martínez, B. Olmedilla-Alonso, A. Palou, et al. 2018. A global perspective on carotenoids: Metabolism, biotechnology, and benefits for nutrition and health. *Progress in Lipid Research* 70:62–93. doi: 10.1016/j.plipres.2018.04.004.

Romero-Cano, L. A., H. García-Rosero, F. Carrasco-Marín, A. F. Pérez-Cadenas, L. V. González-Gutiérrez, A. I. Zárate-Guzmán, and G. Ramos-Sánchez. 2019. Surface functionalization to abate the irreversible capacity of hard carbons derived from grapefruit peels for sodium-ion batteries. *Electrochimica Acta* 326:134973. doi: 10.1016/j.electacta.2019.134973.

Ross, S. A., D. S. Ziska, K. Zhao, and M. A. ElSohly. 2000. Variance of common flavonoids by brand of grapefruit juice. *Fitoterapia* 71 (2):154–61. doi: 10.1016/s0367-326x(99)00131-8.

Rouse, R. E., H. K. Wutscher, and C. O. Youtsey. 2001. Tracing the development of currently planted grapefruit cultivars. *Subtropical Plant Science* 53:1–3.

Rouseff, R. L., P. Ruiz Perez-Cacho, and F. Jabalpurwala. 2009. Historical review of citrus flavor research during the past 100 years. *Journal of Agricultural and Food Chemistry* 57 (18):8115–24. doi: 10.1021/jf900112y.

Rouseff, R. L., G. D. Sadler, T. J. Putnam, and J. E. Davis. 1992. Determination of.beta.-carotene and other hydrocarbon carotenoids in red grapefruit cultivars. *Journal of Agricultural and Food Chemistry* 40 (1):47–51. doi: 10.1021/jf00013a009.

Ruberto, G., A. Renda, C. Tringali, E. M. Napoli, and M. S. J. Simmonds. 2002. Citrus limonoids and their semisynthetic derivatives as antifeedant agents against spodoptera frugiperda larvae. a structure−activity relationship study †. *Journal of Agricultural and Food Chemistry* 50 (23):6766–74. doi:10.1021/jf020607u.

Sabiiti, E. N. 2011. Utilising agricultural waste to enhance food security and conserve the environment. *African Journal of Food, Agriculture, Nutrition and Development* 11 (6):1–9.

Saeed, A., M. Sharif, and M. Iqbal. 2010. Application potential of grapefruit peel as dye sorbent: Kinetics, equilibrium and mechanism of crystal violet adsorption. *Journal of Hazardous Materials* 179 (1-3):564–72. doi: 10.1016/j.jhazmat.2010.03.041.

Sala, J. M., M. T. Sánchez-Ballesta, M. J. Gosalbes, J. F. Marcos, L. González-Candelas, Y. Lluch, A. Granell, M. T. Lafuente, and L. Zacarias. 2004. Understanding the basis of chilling injury in citrus fruit. Paper presented at the V International Postharvest Symposium 682, Verona, Italy.

Salehi, B., P. V. T. Fokou, M. Sharifi-Rad, P. Zucca, R. Pezzani, N. Martins, and J. Sharifi-Rad. 2019. The therapeutic potential of naringenin: A review of clinical trials. *Pharmaceuticals* 12 (1):11. doi: 10.3390/ph12010011.

Sami, P. S., R. B. Toma, D. B. Nelson, and G. C. Frank. 1997. Effects of debittering on grapefruit juice acceptance. *International Journal of Food Sciences and Nutrition* 48 (4):237–42. doi: 10.3109/09637489709028567.

Sapitnitskaya, M., P. Maul, G. T. McCollum, C. L. Guy, B. Weiss, A. Samach, and R. Porat. 2006. Postharvest heat and conditioning treatments activate different molecular responses and reduce chilling injuries in grapefruit. *Journal of Experimental Botany* 57 (12):2943–53. doi: 10.1093/jxb/erl055.

Sarah, B. C. 2016. Grapefruit juice-drug iteractions: A practical review for clinicians. *Natural Medicine Journal* 8 (6).

Sawamura, M. 2000. Volatile components of essential oils of the citrus genus. *Recent Research Developments in Agricultural & Food Chemistry* 4 (1):131–64.

Schiewer, S., and S. B. Patil. 2008. Pectin-rich fruit wastes as biosorbents for heavy metal removal: Equilibrium and kinetics. *Bioresource Technology* 99 (6):1896–903. doi: 10.1016/j.biortech.2007.03.060.

Shaw, P. E., and C. W. Wilson. 1981. Importance of nootkatone to the aroma of grapefruit oil and the flavor of grapefruit juice. *Journal of Agricultural and Food Chemistry* 29 (3):677–9. doi: 10.1021/jf00105a063.

Shelly, T. F. 2009. Exposure to grapefruits and grapefruit oil increases male mating success in the Mediterranean fruit fly (Diptera: Tephritidae). *Proceedings of the Hawaiian Entomological Society* 2009: (41): 31–36.

Shen, J., A. Niijima, M. Tanida, Y. Horii, K. Maeda, and K. Nagai. 2005. Olfactory stimulation with scent of grapefruit oil affects autonomic nerves, lipolysis and appetite in rats. *Neuroscience Letters* 380 (3):289–94. doi: 10.1016/j.neulet.2005.01.058.

Shi, Z., F. Wang, Y. Lu, and J. Deng. 2018. Combination of chitosan and salicylic acid to control postharvest green mold caused by Penicillium digitatum in grapefruit fruit. *Scientia Horticulturae* 233:54–60. doi: 10.1016/j.scienta.2018.01.039.

Shi, Z., H. Yang, J. Jiao, F. Wang, Y. Lu, and J. Deng. 2019. Effects of graft copolymer of chitosan and salicylic acid on reducing rot of postharvest fruit and retarding cell wall degradation in grapefruit during storage. *Food Chemistry* 283:92–100. doi: 10.1016/j.foodchem.2018.12.078.

Sicari, V., T. M. Pellicanò, A. M. Giuffrè, C. Zappia, M. Capocasale, and M. Poiana. 2018. Physical chemical properties and antioxidant capacities of grapefruit juice (Citrus paradisi) extracted from two different varieties. *International Food Research Journal* 25 (5):1978–84.

Silver, H. J., M. S. Dietrich, and K. D. Niswender. 2011. Effects of grapefruit, grapefruit juice and water preloads on energy balance, weight loss, body composition, and cardiometabolic risk in free-living obese adults. *Nutrition & Metabolism* 8 (1):8. doi: 10.1186/1743-7075-8-8.

Singh, Z., S. Sharma, and A. Kaur. 2018. Antitoxic effects of naringin: A flavonoid with diverse biological activities. *World Journal of Pharmaceutical Research* 7:484–9.

Stevens, K. L., D. G. Guadagni, and D. J. Stern. 1970. Odour character and threshold values of nootkatone and related compounds. *Journal of the Science of Food and Agriculture* 21 (11):590–3. doi: 10.1002/jsfa.2740211112.

Suda, K., Y. Takahashi, M. Matsuki-Fukushima, and K. Satoh. 2010. Effect of the scent from grapefruit oil on salivary secretion in rats. *International Journal of Oral-Medical Sciences* 9 (1):31–5. doi: 10.5466/ijoms.9.31.

Sun, X., E. Baldwin, C. Ference, J. Narciso, A. Plotto, M. Ritenour, K. Harrison, D. Gangemi, and J. Bai. 2017. The effect of controlled-release chlorine dioxide on the preservation of grapefruit. *HortScience* 52 (1):122–6. doi: 10.21273/HORTSCI11363-16.

Takagi, C., S. Nakagawa, N. Hirata, S. Ohta, and S. Shimoeda. 2019. Evaluating the effect of aromatherapy on a stress marker in healthy subjects. *Journal of Pharmaceutical Health Care and Sciences* 5 (1):18 doi: 10.1186/s40780-019-0148-0.

Takanaga, H., A. Ohnishi, H. Murakami, H. Matsuo, S. Higuchi, A. Urae, S. Irie, H. Furuie, K. Matsukuma, M. Kimura, et al. 2000.

Relationship between time after intake of grapefruit juice and the effect on pharmacokinetics and pharmacodynamics of nisoldipine in healthy subjects. *Clinical Pharmacology & Therapeutics* 67 (3): 201–14. doi: 10.1067/mcp.2000.104215.

Tamelová, B., J. Malaťák, and J. Velebil. 2018. Energy valorisation of citrus peel waste by torrefaction treatment. *Agronomy Research* 16 (1):276–85.

Tang, Z., Y. Jun, Y. Lv, Y. Li, Z. Zhang, M. Tao, X. Chen, J. He, L. Zhang, and Q.-L. Wang. 2020. Aptamer-conjugated and doxorubicin-loaded grapefruit-derived nanovectors for targeted therapy against HER2+ breast cancer. *Journal of Drug Targeting* 28 (2): 186–94. doi: 10.1080/1061186X.2019.1624970.

Tanida, M., A. Niijima, J. Shen, T. Nakamura, and K. Nagai. 2005. Olfactory stimulation with scent of essential oil of grapefruit affects autonomic neurotransmission and blood pressure. *Brain Research* 1058 (1-2):44–55. doi: 10.1016/j.brainres.2005.07.048.

Tong, C., M. Peng, R. Tong, R. Ma, K. Guo, and S. Shi. 2018. Use of an online extraction liquid chromatography quadrupole time-of-flight tandem mass spectrometry method for the characterization of polyphenols in Citrus paradisi cv. Changshanhuyu peel. *Journal of Chromatography A* 1533:87–93. doi: 10.1016/j.chroma.2017.12.022.

Torab-Mostaedi, M., M. Asadollahzadeh, A. Hemmati, and A. Khosravi. 2013. Equilibrium, kinetic, and thermodynamic studies for biosorption of cadmium and nickel on grapefruit peel. *Journal of the Taiwan Institute of Chemical Engineers* 44 (2):295–302. doi: 10.1016/j.jtice.2012.11.001.

Turner, T., and J. B. Burri. 2013. Potential nutritional benefits of current citrus consumption. *Agriculture* 3 (1):170–87. doi: 10.3390/agriculture3010170.

Uckoo, R. M., G. K. Jayaprakasha, V. M. Balasubramaniam, and B. S. Patil. 2012. Grapefruit (Citrus paradisi Macfad) phytochemicals composition is modulated by household processing techniques. *Journal of Food Science* 77 (9):C921–6. doi: 10.1111/j.1750-3841.2012.02865.x.

Uckoo, R. M., G. K. Jayaprakasha, J. A. Somerville, V. M. Balasubramaniam, M. Pinarte, and B. S. Patil. 2013. High pressure processing controls microbial growth and minimally alters the levels of health promoting compounds in grapefruit (Citrus paradisi Macfad) juice. *Innovative Food Science & Emerging Technologies* 18: 7–14. 10.1016/j.ifset.2012.11.010.

Vanamala, J., G. Cobb, N. D. Turner, J. R. Lupton, K. S. Yoo, L. M. Pike, and B. S. Patil. 2005. Bioactive compounds of grapefruit (Citrus paradisi Cv. Rio Red) respond differently to postharvest irradiation, storage, and freeze drying. *Journal of Agricultural and Food Chemistry* 53 (10):3980–5. doi: 10.1021/jf048167p.

Vázquez, D. E., G. E. Meier, and M. Ponte. 2005. Influence of postharvest curing on 'marsh' grapefruit quality during long-term storage. *Acta Horticulturae* 682:1257–1264.

Walia, K. 2019. Grapefruit peel market analysis, share, size and forecast report upto 2026. Berkeley: bepress.

Wang, J., Y. Duan, D. Zhi, G. Li, L. Wang, H. Zhang, L. Gu, H. Ruan, K. Zhang, Q. Liu, et al. 2014. Pro-apoptotic effects of the novel tangeretin derivate 5-acetyl-6,7,8,4′-tetramethylnortangeretin on MCF-7 breast cancer cells. *Cell Biochemistry and Biophysics* 70 (2):1255–63. doi:10.1007/s12013-014-0049-7.

Wang, E. J., C. N. Casciano, R. P. Clement, and W. W. Johnson. 2001. Inhibition of P-glycoprotein transport function by grapefruit juice psoralen. *Pharmaceutical Research* 18 (4):432–8. doi: 10.1023/A:1011089924099.

Wang, F., J. Deng, J. Jiao, Y. Lu, L. Yang, and Z. Shi. 2019. The combined effects of Carboxymethyl chitosan and Cryptococcus laurentii treatment on postharvest blue mold caused by Penicillium italicum in grapefruit fruit. *Scientia Horticulturae* 253:35–41. doi: 10.1016/j.scienta.2019.04.031.

Wang, K., P. N. Lim, S. Y. Tong, and E. San Thian. 2019. Development of grapefruit seed extract-loaded poly (ε-caprolactone)/chitosan films for antimicrobial food packaging. *Food Packaging and Shelf Life* 22:100396. doi: 10.1016/j.fpsl.2019.100396.

Wang, Q., Y. Ren, J. Mu, N. K. Egilmez, X. Zhuang, Z. Deng, L. Zhang, J. Yan, D. Miller, and H.-G. Zhang. 2015. Grapefruit-derived nanovectors use an activated leukocyte trafficking pathway to deliver therapeutic agents to inflammatory tumor sites. *Cancer Research* 75 (12):2520–9. doi: 10.1158/0008-5472.can-14-3095.

Wang, Q., X. Zhuang, J. Mu, Z.-B. Deng, H. Jiang, L. Zhang, X. Xiang, B. Wang, J. Yan, D. Miller, et al. 2013. Delivery of therapeutic agents by nanoparticles made of grapefruit-derived lipids. *Nature Communications* 4:1867. doi: 10.1038/ncomms2886.

Wang, S., H. Tu, J. Wan, W. Chen, X. Liu, J. Luo, J. Xu, and H. Zhang. 2016. Spatio-temporal distribution and natural variation of metabolites in citrus fruits. *Food Chemistry* 199:8–17. doi: 10.1016/j.foodchem.2015.11.113.

Wang, W., X. Ma, P. Jiang, L. Hu, Z. Zhi, J. Chen, T. Ding, X. Ye, and D. Liu. 2016. Characterization of pectin from grapefruit peel: A comparison of ultrasound-assisted and conventional heating extractions. *Food Hydrocolloids* 61:730–739. doi: 10.1016/j.foodhyd.2016.06.019.

Wang, W., X. Ma, Y. Xu, Y. Cao, Z. Jiang, T. Ding, X. Ye, and D. Liu. 2015. Ultrasound-assisted heating extraction of pectin from grapefruit peel: Optimization and comparison with the conventional method. *Food Chemistry* 178:106–114. doi: 10.1016/j.foodchem.2015.01.080.

Wang, Y.-H., W.-H. Li, and G.-H. Du. 2018. *Naringin natural small molecule drugs from plants*, 595–600. Singapore: Springer.

Widmer, W., and C. Haun. 2006. Variation in furanocoumarin content and new furanocoumarin dimers in commercial grapefruit (Citrus paradisi Macf.) juices. *Journal of Food Science* 70 (4):C307–12. doi: 10.1111/j.1365-2621.2005.tb07178.x.

Wilkins, M. R., W. W. Widmer, K. Grohmann, and R. G. Cameron. 2007. Hydrolysis of grapefruit peel waste with cellulase and pectinase enzymes. *Bioresource Technology* 98 (8):1596–1601. doi: 10.1016/j.biortech.2006.06.022.

Xu, Y., L. Zhang, Y. Bailina, Z. Ge, T. Ding, X. Ye, and D. Liu. 2014. Effects of ultrasound and/or heating on the extraction of pectin from grapefruit peel. *Journal of Food Engineering* 126:72–81. doi: 10.1016/j.jfoodeng.2013.11.004.

Yoon, C., S.-H. Kang, S.-A. Jang, Y.-J. Kim, and G.-H. Kim. 2007. repellent efficacy of caraway and grapefruit oils for *Sitophilus oryzae* (Coleoptera: Curculionidae). *Journal of Asia-Pacific Entomology* 10 (3):263–267. doi: 10.1016/S1226-8615(08)60361-1.

Zhang, J. 2007. Flavonoids in grapefruit and commercial grapefruit juices: Concentration, distribution, and potential health benefits. *Proceedings of the Florida State Horticultural Society* 120:288–94.

Zhang, W., J. Song, Q. He, H. Wang, W. Lyu, H. Feng, W. Xiong, W. Guo, J. Wu, and L. Chen. 2020. Novel pectin based composite hydrogel derived from grapefruit peel for enhanced Cu(II) removal. *Journal of Hazardous Materials* 384:121445. doi: 10.1016/j.jhazmat.2019.121445.

Zhang, Y., and H. Xu. 2017. Recent progress in the chemistry and biology of limonoids. *RSC Advances* 7 (56):35191–220.

Zheng, H., Q. Zhang, J. Quan, Q. Zheng, and W. Xi. 2016. Determination of sugars, organic acids, aroma components, and carotenoids in grapefruit pulps. *Food Chemistry* 205:112–21. doi: 10.1016/j.foodchem.2016.03.007.

Zhuang, X., Y. Teng, A. Samykutty, J. Mu, Z. Deng, L. Zhang, P. Cao, Y. Rong, J. Yan, D. Miller, et al. 2016. Grapefruit-derived nanovectors delivering therapeutic miR17 through an intranasal route inhibit brain tumor progression. *Molecular Therapy* 24 (1):96–105. doi: 10.1038/mt.2015.188.