Hesperidin from citrus peel waste: extraction and its health implications

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REVIEW ARTICLE

Abstract

Hesperidin is abundantly present as a flavanone glycoside in citrus fruits. The citrus peels, seeds, pulp, and cell and membrane residues contain a high amount of hesperidin. It has received scientific momentum lately as it offers several health benefits upon consumption, as it possesses antioxidant, anti-hypocholesteric, antitumor, anticancer, antimicrobial, antibacterial, anti-inflammatory, anti-diabetic properties, and so on. It is used in the treatment of various diseases and disorders such as type-II diabetes, cancer, cardiovascular diseases, and neurological and psychiatric disorders. Various extraction methods such as solvent extraction, cold extraction, microwave-assisted extraction (MAE), ultrasound-assisted extraction (UAE), and supercritical fluid extraction have been employed globally to obtain the maximum yield of hesperidin, which is also environment-friendly and cost-effective. The food industries produce a huge amount of citrus residue after the preparation of juices, jellies, jams, etc. These byproduct wastes are used to extract hesperidin. This review aims at highlighting the updated and scientific information about the nutritional, phytochemical, and biological activities of hesperidin; various classical and modern extraction methods; and their impact on the yield of hesperidin and health implications of hesperidin.

Keywords: anti-inflammatory; antioxidant; antitumor; bioactive compounds; health implications; citrus peel; citrus waste utilization; hesperidin extraction

Introduction

The processing of fruits plays an essential role in the agro-industrial system, as it reduces wastage of perishable products with an increase in the shelf life and adds value to farmers' lives by increasing employment opportunities and eventually enhancing their source of income. Citrus is widely grown globally and is the third-largest crop produced in India. The total world production of various citrus species (oranges, mandarins, tangerines, lemons, limes, grapefruit, etc.) stood at 143755.6 thousand tones in 2019 (Citrus fruit fresh and processed, Statistical bulletin, Food and Agriculture Organization, 2020). The different varieties of citrus fruits are known to possess the natural source of bioflavonoids Sentkowska and Pyrzynska, 2022).

As per the reports of FAO, about one-third of the citrus fruit produced worldwide is used for processing-by-processing industries with the main focus on making juices, jams, jellies, and other fruit preparations. While preparing these products, 50–70% of citrus residue (basically peels, pulp, and seeds) is generated from the whole fruit mass yielding a considerable amount of waste (Ellouze, 2022). Most of them are discarded, fed to animals, and disposed of by burning, which potentially causes environmental pollution (Londoño *et al.*, 2010; Suri *et al.*, 2022). The leftover citrus biomass has a huge potential for valorization by processing into functional foods to be served as a dietary supplement for human consumption. It can also be utilized in biorefineries, in essential oil preparation, and as a gelling agent for making various emulsified products. It is extensively used in the cosmetic (Nath *et al.*, 2022; Pinto *et al.*, 2021) and pharmaceutical industries as a food additive (Sharma *et al.*, 2018).

Extraction and production of various bioactive compounds like pectin, flavonoids, and other phenolic compounds from citrus peel have gained momentum as there is increased demand for herbal products globally. This is because they are safe, possess various biological activities as compared to synthetic formulations, and are cost-effective. Citrus peel is rich in one of the main flavonoids: Hesperidin (A flavanone glycoside). Lately, hesperidin has been immensely employed in the treatment of various diseases and disorders such as type-II diabetes, cancer, cardiovascular diseases, and neurological and psychiatric disorders (Dukare *et al.*, 2022a, 2022b; Sentkowska and Pyrzynska, 2022; Singh *et al.*, 2022). Other flavonoids present in citrus are neo-hesperidin, eriocitrin, naringin, narirtin, didymin, sinenstin, tangeretin, nobiletin, etc. (M'hiri *et al.*, 2016). The total phenol content in the peel varies from 0.67 to 7.30 g/100 g of dry weight (M'hiri *et al.*, 2014). Flavonoid content in the fresh lime tissue is 197 mg/100 g of dry weight. The presence of various hydroxyl groups in different position rings in flavonoids defines their chemical activity. Considering the typical use of raw material/peel residue, this paper aimed at describing the various extraction techniques to extract hesperidin and highlighting the potential benefits of Hesperidin in combating health implications.

Hesperidin—History of Emergence, Structure, and Its Importance

Hesperidin (3', 5, 7-trihydroxy-4'-methoxy-flavanone-7-rhamnoglucoside) is abundantly present as a flavanone glycoside (bio-flavonoid) in citrus peels and tissues. The first isolation of hesperidin dates back to 1828 by Leverton from the inner spongy portion called albedo of the orange peel of the family *Hesperides* (Evans, 2009). Later on, in 1874, its presence was found in lemons by Pheffer and has been isolated with neo-hesperidin, which is an isomer of hesperidin from other citrus fruits (Ikan, 1991). Thus, the name hesperidin came into existence from the term "Hesperidium," meaning citrus fruits (Ladaniya, 2008; Pao and Fellers, 2003; Zubrick, 1997). It is also named hesperetin-7-rutinoside and was also given the name Vitamin P owing to its wound-healing characteristics. Hesperidin (3',5,7-trihydroxy-4'-methoxy-flavanone-7-o-β-rutinoside) is a bioflavonoid found in the citrus family and is a major constituent of tangerine (*Citrus reticulata*) and sweet orange (*Citrus sinensis*) peel. Hesperidin is the prodrug for hesperetin, which is the main molecule in the structure of hesperidin in the same manner as G-hesperidin is the prodrug of hesperidin. Both hesperetin and hesperidin can act as S and R isomers. Hesperetin-7-o-rhamnosyl-(1-6) glucoside, an aglycone of hesperidin, has no sugar moiety (Pietta *et al.*, 2003; Yamamoto *et al.*, 2013), whereas another form has sugar moiety and is known as 5, 7, 3'-trihydroxy-4'-methoxyflavanone (Gattuso *et al.*, 2007; Sharma *et al.*, 2013). Pure hesperidin has a white color with needle-like powder when recrystallized at the melting point between 252 and 254°C. The molecular weight of hesperidin is 610.6 and the chemical formula is $C_{28}H_{34}O_{15}$ (Lanza, 2003; Zubrick, 1997).

Several variants of hesperidin have been developed and these have improved solubility properties in water and thus are absorbed better in the gut. Among the synthetic modified variants, G-Hesperidin, hesperidin-7, 3'-o-dimethylether (HDME), hesperidin methyl chalcone, daflon, and phosphorylated hesperidin are few to name. G-hesperidin is also termed alpha glucosyl hesperidin and is a synthetic prodrug of hesperidin. Also, the diglycoside group has been converted to trigycoside group thereby retaining the hesperetin structure (Miwa *et al.*, 2006). G-hesperidin after ingestion into the body gets converted into hesperidin which then releases hesperetin, thereby imparting therapeutic and curative properties. Also, hesperetin has higher pharmacological activity. Kometani *et al.* (2008) have reported higher bioavailability of G-hesperidin in rats with a more rapid appearance in blood plasma. G-hesperidin is utilized as a skin tonic and has been shown to increase blood circulation. Another synthetic hesperidin variation that is lipid-soluble is HDME, which has a changed hydroxyl into methoxy group on the B ring. It has phosphodiesterase inhibitory potential than hesperetin (Ko *et al.*, 2004; Yang *et al.*, 2011b). Methyl chalcone is a water-soluble semi-synthetic variant of hesperidin, which is widely used in medicinal preparations. Several methyl groups are substituted in open rings, contributing to higher water solubility and better metabolic stability (Chanal *et al.*, 1981; Walle, 2009). By combining 10% hesperidin and 90% Diosmin, a patented synthetic variant named

Daflon has been developed to treat chronic venous insufficiency (CVI) and various venous disorders and varicose veins (Cospite, 1994; Godeberge, 1994; Ibegbuna *et al.*, 1997). Phosphorylated hesperidin is a salt variant of hesperidin and is found to possess contraceptive properties and thus help in the inhibition of fertilization (Hajialyani *et al*., 2019).

Hesperidin has several intact health benefits upon consumption and helps in preventing several diseases. Many researchers have found that it exhibits anti-inflammatory, analgesic, antihypertensive, anti-hypocholesteric, neuroprotective, diuretic, and cytotoxic properties against cancer cells (Bok *et al.*, 1999; Chen *et al.*, 2010b; Galati *et al.*, 1994; Raza *et al.*, 2011). Hesperidin is also used to treat fever and other allergic conditions by controlling the release of histamine from mast cells (Chaudhry *et al*., 2016). It helps in maintaining cholesterol levels by inhibiting the activity of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (Lahmer *et al.*, 2015). It also helps in curing edema or swelling in the legs due to the accumulation of fluids. It is also associated with the enhancement of the activity of Vitamin C in the body.

Extraction of Hesperidin

Several methods have been proposed by researchers for the extraction of hesperidin from the citrus peel (both albedo and flavedo). The methods vary from the very primitive extraction methods known as cold extraction and other modern methods like hot extraction or Soxhlet extraction method. The primitive methods are cumbersome and time-consuming with less sensitivity and accuracy. Nowadays the focus is shifting toward the invention of advanced methods, which could overcome the drawbacks of existing methods, thereby developing higher degrees of automation to meet the faster and greater need for accuracy. Various factors affect the extraction yield such as characteristics of food material, that is., shape and size, type of solvent utilized, volume and temperature of food sample, and several repeated extractions made (Liu *et al*., 2017; Tak *et al*., 2022; Samota *et al*., 2022; Sharma *et al*., 2022).

Cold Extraction Method

This is one of the most traditional methods employed for the extraction of hesperidin. Different researchers have proposed different methods. The method reported by Bassam *et al*. (2018) involved maceration of orange peel powder with petroleum ether. Another method involves alkaline extraction, where the orange peel was macerated with 10% KOH solution with pH varying from 8 to 9 (Sharma *et al.*, 2013).

Di Giacomo and Dugo (2002) and Padilla de la Rosa *et al.* (2018) suggested an alkaline extraction technique where the ground peel is blended with water and an alkaline solution of NaOH with pH –11 to 11.5. Later, the pH was adjusted to 4.2 to 4.5 by the addition of mineral acids to the filtered product. The prepared solution is subjected to heating at 40–45°C for 12–24 h. Finally, the solution is dried to get separated hesperidin crystals. The major disadvantage of this primitive method is that the flavonoid complex formed by this technique has lower hesperidin content, that is, from 60 to 70%. To get higher hesperidin content in the range of >90%, there is a need for repeated crystallization (Di Giacomo and Dugo, 2002). This process is time-consuming with the adequate requirement of different acids and basic compounds ultimately resulting in the reduction of purity and efficiency of hesperidin. Furthermore, Saini *et al*. (2019) carried out a study to evaluate the effectiveness of the maceration process for the extraction of polyphenols from citrus peels, namely, the kinnow mandarin and mosambi peels. Using maceration of kinnow mandarin and Mosambi cpeels, respectively, the mean yield of acetone extract was 12.20 and 5.20%. These findings were closely consistent with the research done by Safdar *et al*. (2017) to determine the best method for extracting polyphenols from the peel of kinnow (Citrus reticulate L.) by maceration using various solvents, including ethanol, methanol, acetone, and ethyl acetate, at three different solvent concentrations (50, 80, and 100%), with a ratio of 1:15 sample to solvent and an extraction temperature of 40°C. Briefly, 20 h were spent extracting 5-g samples of kinnow peel powder. The extracts were centrifuged for 10 min at 5000 rpm with a filter. The extract was created by collecting the supernatant and evaporating the solvent in a rotary evaporator under vacuum at 45°C. The extract was then passed through a 0.45-mm membrane filter before being collected in amber glass bottles and kept at cold temperature. The extract was produced by collecting the supernatant and evaporating the solvent in a rotary evaporator at 45°C under vacuum to create the supernatant. The extract was then further filtered through a 0.45-mm membrane filter, collected in amber glass bottles, and kept at refrigerator temperature. A green extraction technique was created by Phucharoenrak *et al*. in 2022 to obtain the maximum yield of limonin and hesperidin from lime peel powder (*Citrus aurantifolia*). Ethanol concentrations, solvent pH levels, and extraction temperature were all variable components in the study procedure, which included ethanolic-aqueous extraction. A green extraction process using food waste, such as lime peel, as an energy-saving source and ethanol as a biosolvent to achieve the highest amount of double bioactive compounds was demonstrated. These conditions yielded the highest amounts of limonin and hesperidin, yielding 2.072 and 3.353 mg/g of limonin and hesperidin, respectively.

Deep eutectic solvents (DESs) were investigated as a green solvent for improved extraction of narirutin, naringin, hesperidin, and neohesperidin from *Aurantii Fructus* by Yongjing Liu *et al.* (2018). The composition of the DESs, the concentration of added water, the solid-to-liquid ratio, and the effects of time, temperature, and stirring speed on the extraction yield and composition of extracted flavonoids have all been studied. DESs are used to extract flavonoids from a variety of fruits, vegetables, spices, and orange (*Citrus sinensis*) peels. The extraction yields of narirutin, naringin, hesperidin, and neohesperidin were improved under the optimal extraction conditions of 40% water in betaine/ethanediol (1:4) at 60°C heated for 30 min and were found to be 8.39 ± 0.61, 83.98 ± 1.92, 3.03 ± 0.35, and 35.94 ± 0.63 mg/g, respectively, which were much higher than those of methanol as an extraction solvent (5.5 ± 0.48, 64.23 ± 1.51, 2.16 ± 0.15 and 30.14 ± 0.62 mg/g). Joki'c *et al*. (2019) extracted hesperidin from a subset of Croatian mandarin peels using a sustainable green method. 15 different choline chloride-based DESs were used for the extraction, which was carried out at 50°C for 30 minutes. with the addition of 20% water. According to the screening results, the solvent combination of choline chloride and acetamide (1:2) produced the highest yield of hesperidin (112.14 mg/g of plant), whereas the solvent combination of choline chloride and citric acid (1:1) produced the lowest yield (1.44 mg/g of plant).

Hot Extraction or Soxhlet/Solvent Extraction

The extraction is named after its inventor, Franz Ritter Von Soxhlet (1848–1926), a German chemist who worked on the issues of milk chemistry. The solvent extraction technique has been considered an important method to extract various bioactive compounds from foods (Luengo *et al.*, 2013). However, there are various parameters affecting the solvent extraction process such as temperature, pH, ionic strength of the solution, the concentration of solutes or solvent-to-feed ratio present, and the time for which the extraction is being carried out (Contini *et al.*, 2008).

Extraction with Petroleum Ether

Many researchers have proposed various Soxhlet extraction techniques for obtaining crude hesperidin. As discussed by Sharma *et al.* (2013), the dried orange peel was taken in powder form in the Soxhlet extractor and was filled with petroleum ether and heated for 4 h at 40–60 °C with pH ranging from 3–4. The concentrated residue was then kept in the refrigerator at 4°C and solid crystals appeared overnight. Again, filtration was done, and crude hesperidin was obtained on a Buchner funnel in the form of an amorphous powder. The results reported indicated that maceration yielded 1.8 g and the Soxhlet method yielded 2.35 g of hesperidin, respectively. Similar results were reported by Chaudhry *et al*. (2016) for the extraction of crude hesperidin using the above method and the crude hesperidin obtained was yellowish brown with a yield of 1.75 g with a melting point of 242–244°C. A study conducted by Belboukhari *et al.* (2015) employed three different citrus species, namely, tangerine, clementine, and sweet orange to extract hesperidin from the peel waste. The dried citrus powder from each species was taken and refluxed for 1.5 h after adding petroleum ether and the mixture was left to dry at room temperature. Similarly, methanol was added and again refluxing was performed for 2 h followed by filtration of the hot mixture. The filtrate leaves crystallized syrup residue upon concentration from dilute acetic acid (6%), thereby yielding orange-colored needles called crude hesperidin with a melting point of 268°C. Results indicated that crude hesperidin yielded from different species weighed 1.75% from tangerine and 2.45% from clementine and sweet orange.

Extraction with Methanol

Methanolic extraction is another method followed for the extraction of hesperidin from citrus peels. Al-Ashaal and El-Sheltawy (2011) carried out the experiments using two different methanolic and alkaline extraction methods. In the first extract, the dried orange peel was macerated with MeOH-1% HCl at room temperature and kept overnight. In preparation for the second extract, the dried sample (at 50°C) was defatted by maceration in petroleum ether (60–80°C) for 2 h. The residue was filtered and was subjected to extraction by Soxhlet extraction using methanol at 65°C for 4 h. Results indicated that hesperidin obtained by these extraction methods had a yellow amorphous powder with a purity index of 97.3% and a melting point of 250–252°C. The extracts obtained from orange peel were 18.5 and 18.7 g, respectively, by the former two methods. The concentration of hesperidin at room temperature using a 1% HCl methanol mixture was 3.95%. On the other hand, 4.65% of hesperidin was obtained after defatting and Soxhlet extraction using hot methanol. With regard to weight, the yields of hesperidin were 0.73 and 0.87 g, respectively, for the first and second extractions. Also, the antioxidant capacity of hesperidin was found to be comparatively active in this study (Garg *et al.*, 2001).

Victor *et al.* (2018) isolated hesperidin from dry and fresh albedos using methanol extraction at room temperature. In the first method, the dry albedo was extracted using ethanol. The slurry was filtered after 3 days, methanol

was distilled at 45°C under reduced pressure, and the mixture was stirred for 30 min at 60–70°C. The prepared mixture was left for 4 days at room temperature and the organic layer was obtained by filtration and subsequent drying. The second extraction method was performed by adding methanol to dry albedo followed by heating at 55°C for 3 h. Decantation of the organic layer was performed, and additional methanol was added for hot extraction (30 min). In the third method of extraction, the methanol was added to fresh albedo and heated for 3 h at 55°C and later additional methanol was added to obtain two combined phases and subjected to drying at 45°C. The results showed that the first, second, and third extraction methods yielded 1% (0.2980 g), 2.5% (0.3373 g), and 2.8% (0.5184 g) of hesperidin, respectively. Kim and Lim (2020) determined the flavonoid content of mature and immature citrus whole fruits. The ground sample of fruits was added to methanol for 30 min at room temperature. The supernatant was separated by centrifugation and the residue was extracted more than four times until the complete flavonoids were recovered. Results reported that mature fruit contained 21,898 µg/g, immature fruit contained 50,822 µg/g, and immature pomace contained 49,731 µg/g dry sample of hesperidin.

Extraction with Ethanol

Although being less expensive and more time-consuming than traditional maceration and refluxing methods, solvent extraction techniques eventually replaced them, resulting in lower yields of flavonoids. Primitive maceration and refluxing techniques were overtaken by solvent extraction techniques even though these were inexpensive but at the same time, it was time-consuming ultimately leading to lower yields of flavonoids obtained (Yaqoob *et al*., 2020). Among the solvents extracted, methanol was the most used solvent, resulting in higher yields of flavonoids from citrus fruits (Garcia-Castello *et al*., 2015; Iglesias-Carres *et al*., 2019; Khan *et al*., 2018). However, nowadays, the usage of methanol is avoided because of its toxic limits. Therefore, methanol is avoided in food industry applications; instead, ethanol is declared a safe solvent and is used as a substitute for methanol. It is also considered as a bio-solvent as it is generally produced from renewable sources (Capello, 2007). It is also named a "Generally Recognized as Safe" (GRAS) solvent by the US Food and Drug Administration (Yaqoob *et al*., 2020).

Li (2006) carried out the experiments to extract total phenolic compounds from the peels of lemons, grapefruit, sweet orange, and mandarin using ethanol at concentrations of 20, 50, 72, 85, and 95%, and at temperatures of 19, 37, 50, 65, and 80°C with single (3 h) and double (2*1.5 h) extractions. Results indicated that the yield of total phenolic content increased with an increase in ethanol concentration of up to 85%. Also, single extraction gave a higher yield as compared to double extraction with an increase in extraction temperature except for 37°C. Inoue *et al.* (2010) performed a study to isolate hesperidin using an ethanol solvent extraction procedure from immature thinned and mature *Citrus unshiu* fruits. Different aqueous ethanol concentrations were chosen as 0, 10, 20, 30, 40, 50, 60, 70, 80, 90, and 100% at room temperature (20°C). Results revealed that the flavonoid present in the highest amount was narirutin followed by hesperidin, and nobiletin was present in the lowest concentration. The maximum yield of flavonoids was obtained at 70% (v/v) aqueous ethanol reaching 7.6 mg/g out of which narirutin accounts for 5.2 mg/g, hesperidin 2.2 mg/g, and nobiletin 0.2 mg/g. Also, by elongating the extraction time from 0.5 to 2 h, the yields of narirutin and hesperidin were enhanced. In another study conducted by M'hiri *et al*. (2015b), ethanol extraction was done from the orange peel with 80% ethanol followed by shaking at 200 rpm with a mechanical stirrer for 30 min at 35°C. It has been reported in the literature that ethanol concentration in the range of 70–80% is most commonly used for extracting flavonoids from the orange peel (Cheigh *et al*., 2012). The extraction temperature was maintained at 35°C to prevent the thermal degradation of antioxidants. It was observed that the total phenol content from orange peel powder after three successive extractions obtained was 18.88 ± 0.18 g/kg and 19.69 ± 0.03 g/kg at 70 and 80% ethanol concentration, respectively. At equilibrium conditions, it was reported that three extraction steps are sufficient to extract the phenolic compounds to the maximum limit, that is, 96.15% with an extraction time of 30 min.

Later a study was conducted by Boudhrioua *et al*. (2016) on the extraction of total phenols and flavonoids from citrus peel powder using a conventional extraction method, as optimized by M'hiri *et al*. (2015b). The total phenolic content obtained was 1.968 ± 0.003 g GAE /100 g of citrus peel powder. Similar results were also reported by Kammoun Bejar *et al*. (2011), but the values reported were a little lower (1.130 ± 0.040 g) at its commercial ripening stage. It could be attributed to different extraction conditions used as the latter have applied single-stage extraction with filtering the extract followed by the evaporation of solvent and lyophilization of the residue. Hassan *et al*. (2018) conducted a study based on hot extraction to isolate flavonoids and glycosides, with 90% ethanol at 40–60°C for 3 h, and the pH was adjusted in the range of 3–4 by adding 6% acetic acid. This study produced 2.9 g of hesperidin. Kim and Lim (2020) developed an optimized extraction method for enhancing the recovery of flavonoids such as hesperidin and narirutin from immature *C. unshiu* pomace (ICUP). Various parameters were studied such as ethanol

concentration, extraction temperature, solvent-to-fruit ratio, and extraction time on the yield of hesperidin and narirutin while applying single-factor experiments at the varied concentrations of ethanol, that is, 20, 40, 60, 80, and 100% (v/v), temperatures of 25, 35, 45, 60, 75, 85, and 90°C, with solvent to fruit ratios of 20, 30, 40, 50, 60, and 70 mL/g dry sample, and extraction time of 10, 20, 30, 40, 50, and 60 min. Also, the yield of hesperidin and narirutin increased with an increase in ethanol concentration up to 60% and thereafter decreased. With the increase in temperature from 25 to 75°C, hesperidin yield increased significantly and then slightly decreased at 90°C. It could be attributed to the fact that high temperature increases the extraction yields of flavonoids due to increased solubility. Upon obtaining optimum conditions for ethanol (80.3°C, 58.4%, and 40 mL/g dry samples for 30 min), hesperidin and narirutin yields obtained were 66.6 and 82.3%, respectively. Using the optimum conditions obtained from ethanol, the effect of different extraction solvents was also studied using methanol and acetone. It was found that the concentration of hesperidin and narirutin in methanol was 25–100 and 10–89 mg/mL, respectively. Ethanol was found to be more effective than methanol and acetone.

Other Extraction Methods

Al-Ashaal and El-Sheltawy (2011) carried out the alkaline extraction of orange peel dried at 50°C after adding 0.2 N of NaOH adjusted to a pH of 10–11, followed by heating at 40–50°C for 1 h. The prepared solution was later acidified using 2N HCl to attain a pH of 4–4.5 and was kept overnight for precipitation. It was found that the yield of hesperidin obtained was 1.008 g; even though the crude extract obtained by alkaline extraction was the lowest, yields are higher with this method. These studies are also per those carried out by Balbaa *et al.* (1976) illustrating the methods of application of heated alkaline extraction to accelerate the process of extraction of hesperidin from orange peels. Chaudhry *et al.* (2016) proposed a method for the extraction of hesperidin from dried orange peel using an aqueous solution of Ca $(OH)_2$ by allowing the precipitation of calcium precipitates from colloidal pectin, which can interfere with the subsequent phases of adsorption and thus allow the separation of hesperidin. Another method was proposed by Chaudhry *et al*. (2016) to isolate hesperidin using $Ca(OH)_2$ and then recycle extracted liquor ultimately leading to an increase in yields of hesperidin and naringin. Results revealed that with this method, the highest yields of hesperidin and naringin were obtained, that is, 15.5 g/2 kg peel and 12 g/2 kg peel, respectively. Also, the maturity of the crop affects the hesperidin yield. Padilla de la Rosa *et al*. (2018) have mentioned the alkaline extraction method in their studies as one of the traditional methods to extract hesperidin from the citrus peel with NaOH solution with a pH of 11–11.5 at room temperature. Later, the pH was adjusted to 4.2–4.5 while heating the solution at 40–45°C for 12–24 h. This method allows for the formation of flavonoids with 60–70% hesperidin content. Furthermore, to achieve a higher percentage (>95%) of hesperidin, there is a need for repeated crystallizations. It was attributed to the conformation change of hesperidin into anionic form with basic pH conditions into anion poly-phenolate (Di Mauro *et al*., 1999). Earlier studies were carried out by Di Mauro *et al*. (1999) to see the effect of the amount of $Ca(OH)_2$ on the extraction efficiency of hesperidin from orange peels where the extracts were purified with resin Kastell D-112 giving recovery of more than 90% with 0.5 N NaOH and 10% ethanol solutions. Table 1 summarized the different studies conducted on Soxhlet/solvent extraction of hesperidin from citrus.

Advanced Extraction Techniques

As discussed above, various extraction techniques are in use for the extraction of flavonoids and phenolic compounds from the citrus peel such as traditional maceration as well as modern Soxhlet extraction and chromatographic techniques. Even though these methods have been modernized, they are still characterized by low efficiency causing potential damage to the environment by using large volumes of organic solvents. These methods also cause deterioration of bioactive compounds, especially phenols and flavonoids, because of exposure to high temperature for a longer duration of time. Considering the drawbacks of these methods, several scientists are exploring different advanced processing and extraction techniques, which could help in the extraction process, thereby enhancing the yields of bioactive compounds. These techniques, to name a few, are microwave-assisted extraction (MAE), ultrasound-assisted extraction (UAE), high-pressure extraction, ohmic heating– assisted extraction, supercritical fluid extraction or subcritical water extraction, etc. (Ayinzat *et al*., 2021; M'hiri *et al*., 2016). Some researchers have also been shifting focus on using a combination of several technologies such as controlled pressure drop technology and ultrasound assisted extraction (DIC-UAE) to enhance extraction kinetics and yields of bioactive compounds (M'hiri *et al*., 2014). A combination of microwave and ultrasound-assisted techniques has been used by Boukroufa *et al*. (2015) to isolate the phenolic compounds from waste orange peel using recycled water. Also, different scientists have worked on individual advanced extraction methods and have compared the extraction efficiencies (Hayat *et al*., 2009; Khan *et al*., 2010; Li *et al*., 2012c). These methods are also more sensitive, accurate, rapid, and efficient.

Microwave-Assisted Extraction

MAE is an advanced method with much more efficiency in extracting bioactive compounds with lesser extraction time and is more environmentally friendly (Wang and Weller, 2006). The basic principle underlying MAE is that dipolar compounds are directly heated by microwaves, causing changes in structural characteristics of plant tissues thereby increasing the capillary porous properties, water absorption capacity of plant cells, and allowing better penetration of solvent through the matrix (Kratchanova *et al*., 2004), which ultimately enhances the extraction efficiency of flavonoids from flavedo. Also, during microwave heating, disruption of weak hydrogen bonds occurs due to dipolar rotation of molecules. It accelerates the rupture of cells leading to a sudden rise in temperature and buildup of internal pressure inside the cell walls of plant tissue (Ahmad and Langrish, 2012; Ookushi *et al*., 2006, 2008a, 2008b; Tsubaki *et al*., 2009, 2010; Xiao *et al*., 2009). Sun *et al*. (2007) have employed a MAE process for extracting hesperidin from *Pericarpium citri reticulate* (dried pericarp of the ripe fruit of *C. reticulate*) using 70% aqueous methanol as a solvent and the results showed that MAE is an efficient, fast, and energy-saving method.

Inoue *et al*. (2010) carried out the closed system MAE of *C. unshiu* peel powder with 70% ethanol and was subjected to homogenization for 5 min followed by microwave irradiation at 60–180°C for about 2–12 min. Later, the cooled liquor was kept in the refrigerator at 5°C for 24 h to obtain hesperidin. It was found that MAE was much more effective for extracting hesperidin with 70% aqueous ethanol under pressurized conditions above 100°C. By using microwave irradiation, the yield of hesperidin reached 58.6 mg/g, which is 27 times higher than that obtained by a conventional method. Another laboratory scale study was carried out by M'hiri *et al*. (2015a) for microwave extraction of flavonoids and phenols under high pressure and temperature. The powdered peel of *C. sinensis* was extracted with 80% ethanol. Samples were heated at different wattages of 100, 200, 300, and 400 W for 180 s, and corresponding temperatures are measured as 67, 76, 92, and 108°C, respectively. It was concluded that MAE at 100 W power leads to a total phenol content of 23.40 ± 0.12 g GAE/kg, whereas the conventional method gave 22.13 ±0.36 g GAE/kg. Also, with an increase in microwave power, the amount of flavonoids like hesperidin, neo-hesperidin, naringin, and didymin increases with an increase in microwave power up to 200 W. The content of hesperidin reached 6.904 at 100 W, 9.289 at 200 W, and then decreased to 7.655 g/kg of orange peel at 30 W. The results are also per those reported by Hayat *et al*. (2010) that microwave increases extraction efficiency and yields of phenolics from mandarin peel up to 160 W. From the above-cited literature, lower power of microwaves is recommended to obtain optimized flavonoid content. M'hiri *et al*. (2016) conducted a study to extract antioxidants from orange peel using 80% ethanol by heating it in a microwave oven for 10 s at 35°C at 170 W with three successive extractions. It was found that the total hesperidin content obtained was higher with MAE (0.781 ± 0.074 g/100 g of orange peel) as compared to the conventional solvent extraction (CSE) system (0.551 ± 0.001 g/100 g of orange peel). Another study was conducted by Tran *et al*. (2021) on pomelo flavedo extract (PFE) to study the influence of extraction techniques on the yield of polyphenols, flavonoids, and antioxidant capacity. MAE was carried out with pomelo powder in absolute ethanol by applying different power levels of 150, 300, 450, and 600 W and corresponding extraction times were varied as 15, 20, 25, and 30 min. The results showed that applied power at 150 W resulted in the highest yield of polyphenols and flavonoids, that is, 84.12 and 92.83%, respectively. Similar results were also reported by Ghanem *et al*. (2012) for a 33.6% enhancement in the yield of phenolic content from citrus peel at a power level 450 W. Contradictory to this, flavonoid content decreased with an increase in microwave power level due to an increase in electric field strength and faster electric heating within the sample, leading to the deterioration of flavonoids (Hayat *et al*., 2010).

Ultrasound-Assisted Extraction

Ultrasound is a form of energy generated by sound waves of frequencies that are too high to be detected by the human ear, that is, above 16 kHz. It minimizes the processing time and maximizes the quality and safety of food. The basic principle behind ultrasonication is that the propagation through a biological structure induces compressions and depressions of the particles and high energy is imparted. The application of ultrasound in the food industry can be classified into two categories, that is, Low energy (low power/intensity) with frequencies >100 kHz and intensities <1 W/cm^2. These are employed as a nondestructive analytical technique for the food industry. Low intensity does not alter the chemical or physical properties of the material through which it propagates (McClements, 1995). The other category is High energy (high power/intensity) with frequencies – 18–100 kHz and intensities – 10–1000 W/cm^2. It is used for enzyme inactivation, enhanced drying, extraction, and filtration. It can produce physical, chemical, and other mechanical effects as high-intensity ultrasonic waves cause intense pressure, shear, and temperature gradient to build up due to bubble cavitation (Mason *et al*., 1996). Also, the effect of high-intensity ultrasound waves depends upon many factors such as ultrasonic parameters, ultrasonic generator, the reaction medium characteristics, treatment tank geometry, etc. (Henglein, 1995; Raso *et al*., 1999).

Table 1. Soxhlet/solvent extraction of hesperidin from citrus.

Plant material	Analytes	Solvent	Methodology	Inference	References
Dried orange peel	Hesperidin	Petroleum ether	250 g dried orange peel + 800 mL of petroleum ether at about 40–60°C. Heating for 4 h. Placed in extraction sleeve with 800 mL of methanol until the leaving solvent is colorless.	Maceration yielded 1.8 g and Soxhlet method yielded 2.35 g of hesperidin, respectively.	Sharma *et al*. (2013)
Dried orange peel	Hesperidin	Petroleum ether	250 g dried orange peel + 800 mL of petroleum ether at about 40–60°C. Heating for 4 h. Placed in extraction sleeve with 800 mL of methanol until the leaving solvent is colorless.	Crude yellowish-brown in color hesperidin was obtained with yield of 1.75 g and melting point in the range of 242–244°C.	Chaudhry *et al*. (2016)
Citrus peel waste from the tangerine, clementine, and sweet varieties	Hesperidin	Petroleum ether	80 g of dried citrus powder. Refluxed for 1.5 h after adding 600 mL of petroleum ether. 600 mL of methanol was added and again refluxing was performed for 2 h.	Crude hesperidin yielded from different species weighed 1.75% from tangerine and 2.45% from Clementine and sweet orange with a melting point of 268°C.	Belboukhari *et al*. (2015)
Dried orange peel	Hesperidin	Methanol	First extract—50 g dried orange peel was macerated with 200 mL MeOH-1% HCl. Extraction by Soxhlet extraction using 200 mL of methanol at 65°C for 4 h. Second extract—same amount of sample dried at 50°C, was defatted by maceration in 150 mL of petroleum ether (60–80°C) for 2 h.	Hesperidin obtained by these extractions had yellow amorphous powder with purity index of 97.3% and melting point of 250–252°C. On weight basis, the yields of hesperidin were 0.73 and 0.87 g, respectively, for first and second extractions.	Al-Ashaal and El-Sheltawy (2011)
Dry and fresh albedos	Hesperidin	Methanol/Hot methanol	First method—30 g dry albedo was extracted using 190 mL of ethanol. 20 mL distilled methanol was added while stirring the mixture for 30 min at 60–70°C in the prepared slurry. Second method—600 mL of hot methanol was added to 13.4 g of dry albedo followed by heating at 55°C for 3 h. Third method—fresh albedo (55 g) was taken instead of dry and 330 mL of methanol was added. The prepared mixture was heated for 3 h at 55°C and later 100 mL of additional methanol was added to obtain two combined phases.	First extraction yielded 1% (0.2980 g) hesperidin crystals with weight 298 mg. The second hot extraction method yielded 2.5% (0.3373 g) of hesperidin crystals with 337 mg weight. The third extraction resulted in 2.8% (0.5184 g) of hesperidin with weight of 518 mg.	Victor *et al*. (2018)
Mature and immature citrus whole fruits	Hesperidin	Methanol	700 g ground sample was added to 30 mL of methanol	Results reported that mature fruit contained 21,898, immature contained 50,822, and immature pomace contained 49,731 µg/g dry sample of hesperidin.	Kim and Lim (2020)
Peels of lemons, grapefruit, sweet orange, and mandarin	Total phenolic compounds	Ethanol	2 g/16 mL with ethanol concentration of 20, 50, 72, 85, and 95%, temperatures of 19, 37, 50, 65, and 80°C with single (3 h) and double (2*1.5 h) extraction.	Yield of total phenolic content increased with increase in ethanol concentration up to 85%.	Li *et al*. (2006)

Citrus *unshiu* (C. *unshiu*) (Immature thinned and mature)	Hesperidin	Ethanol	2 g powdered peels of C. *unshiu* were dipped in 20 mL of ethanol concentrations (0, 10, 20, 30, 40, 50, 60, 70, 80, 90, and 100%).	Maximum yield of flavonoids was obtained at 70% (v/v) aqueous ethanol reaching 7.6 mg/g out of which narirutin accounts for 5.2 mg/g, hesperidin, 2.2 mg/g, and nobiletin 0.2 mg/g. By increasing the extraction time from 0.5 to 2 h, the yields of narirutin and hesperidin were enhanced.	Inoue *et al.* (2010)
Orange peel powder	Total phenolic content	Ethanol	Orange peel powder was extracted with 50 mL of 70 and 80% ethanol, followed by shaking at 200 rpm with a mechanical stirrer for 30 min at 35°C.	Total phenol content from orange peel powder after three successive extractions obtained was 18.88 ± 0.18 g/kg and 19.69 ± 0.03 g/kg at 70 and 80% ethanol concentration, respectively.	M'hiri *et al.* (2015a)
Citrus peel powder	Total phenols and flavonoids	Ethanol	The extraction conditions were: ethanol (80%), m/v: 5 g 50 mL, 30 min, 35°C, followed by mechanical stirring.	The total phenolic content obtained was 1.968 ± 0.003 g GAE /100 g of citrus peel powder.	Boudhrioua *et al.* (2016)
Citrus	Flavonoids and glycosides	Ethanol	Extraction was carried out using 300 mL of 90% ethanol at 40–60°C.	Upon concentration, filtration and successive acidification, 2.9 g of hesperidin was obtained.	Hassan *et al.* (2018)
Immature *Citrus unshiu* pomace (ICUP)	Flavonoids such as hesperidin and narirutin	Ethanol	Concentration of ethanol was varied at 20, 40, 60, 80, and 100% (v/v); temperatures of 25, 35, 45, 60, 75, 85, and 90°C, with solvent-to-fruit ratios of 20, 30, 40, 50, 60, and 70 mL/g dry sample and extraction times of 10, 20, 30, 40, 50, and 60 min.	At optimum conditions for ethanol (80.3°C, 58.4%, and 40 mL/g dry sample for 30 min), hesperidin and narirutin yields obtained were 66.6 and 82.3%, respectively.	Kim and Lim (2020)
Orange peel dried	Hesperidin	Alkaline extraction	200 mL of alkaline 0.2 N of NaOH adjusted to pH of 10–11, followed by heating at 40–50°C for 1 h.	Yield of hesperidin obtained was 1.008 g; even though the crude extract obtained by alkaline extraction was the lowest, yields were higher with this method.	Al-Ashaal and El-Sheltawy (2011)
Dried orange peel	Hesperidin and naringin	Aqueous solution of Ca $(OH)_2$	Ca $(OH)_2$ allows the precipitation of calcium precipitates from colloidal pectin, which can interfere in the subsequent phases of adsorption and thus allow the separation of hesperidin and naringin.	The highest yields of hesperidin and naringin were found to be 15.5 g/2 kg peel and 12 g/2 kg peel, respectively.	Chaudhry *et al.* (2016)
Citrus peel	Hesperidin	Alkaline extraction	The peel is crushed and ground for the removal of soluble solids and blended in water and NaOH solution with pH of 11–11.5.	This method allows the formation of flavonoids with 60–70% hesperidin content.	Padilla de la Rosa *et al.* (2018)

Therefore, the application of ultrasound waves can significantly increase the enhancement of organic and bioactive compounds from the plant tissues by the induction of mechanical effects, which could provide a higher penetration of solvent into the cellular matrix of plant or vegetable material (Toma *et al*., 2001; Vinatoru, 2001).

One of the major factors affecting the extraction process is the type of extraction solvent used. In the case of UAE, the type of solvent should be selected based on target compounds based upon their selectivity, price, availability, and as well as safety. Aqueous ethanol and ethanol are widely recognized solvents used in the extraction of bioactive compounds. As reported by Lapornik *et al*. (2005), pure ethanol being utilized as a solvent reduces the extraction efficiency of phenols due to the presence of hydroxyl groups in phenols (such as flavonoids, especially with sugars in molecules), is hydrophilic, and is more soluble in water–ethanol solutions as compared to pure alcohol. Enzymes are inactive in alcoholic media. The studies conducted by M'hiri *et al*. (2015b), and Londoño *et al*. (2010) showed that ethanol has been recognized as one of the most suitable solvents to attain better yields of hesperidin. ŠicŽlabur *et al*. (2015) have claimed in their studies that ultrasonic extraction using ethanol as a solvent to extract carbonic acid from *Rosmarinus officinalis* was much more effective in giving higher yields with less extraction time. The use of ultrasound energy (20–100 kHz) for the extraction of bioactive compounds is one of the emerging extraction techniques that can give high reproducibility with reduced solvent consumption, extraction times, temperature, and lower power consumption (Chemat *et al*., 2008; Da Porto *et al*., 2013; Romdhane, 2002; Sun and Tomkinson, 2002; Tian *et al*., 2013). Many other scientists worked on UAE to isolate hesperidin from citrus peel (Ma *et al*., 2008b), flavanone, glycosides, and phenolics from Satsuma Mandarin peel (Ma *et al*., 2008a, 2009). They have used methanol as an extraction solvent. Chaudhry *et al*. (2016) have optimized the conditions for UAE of hesperidin from *Citrus reticulate* as per the following conditions: Extraction solvent: methanol, frequency of ultrasound waves: 60 kHz, extraction time: 60 min, and extraction temperature: 40°C. Dahmoune *et al*. (2013) have compared three extraction techniques, namely, CSE, MAE, and UAE on the extraction of phenolic compounds from the lemon peel. They have reported that plant cells are disrupted by cavitation caused by ultrasonication. It has been found that particles of lemon peel were resistant to ultrasound energy. Similar studies have been supported by Guo *et al*. (2014) and Zhang *et al*. (2011) who have stated that the application of ultrasound energy at high ultrasonic intensity and power degrades some bioactive compounds, especially phenols. Zhao *et al*. (2006) reported that the increase in the treatment time and ultrasonication power (higher than 100 W) led to the degradation of all E-astaxanthins. The influence of enzymatic as well as UAE has been explained by Anh *et al*. (2021) that the abovesaid treatments enhanced the extraction yields of naringin and hesperidin by 5.70 and 1.20%, respectively.

Ma *et al*. (2008b) conducted an experiment to extract hesperidin from fresh Pengann (*C. reticulata*) using ultrasonic extraction with 20 kHz, 60 kHz, and 100 kHz frequencies for 20 min at operating temperatures of 30, 40, and 50°C using ethanol, methanol, and isopropanol as solvents. Another experiment was performed by using only methanol at 40°C with extraction time from 20 to 160 min. The results indicated that yields of hesperidin from all the combinations of ultrasonic frequencies were higher than those obtained by the Soxhlet method. The type of solvent, application frequency, and processing temperature are the most important factors reported in this study affecting the yields of hesperidin. At the same temperature and similar time conditions using all three frequencies, methanol was found to be more effective for enhancing yields as compared to ethanol and isopropanol. Based on these results, optimum conditions obtained for the highest yields of hesperidin were: solvent: methanol, frequency: 60 kHz, extraction time: 60 min, and extraction temperature: 40°C. Another study was conducted by Khan in 2010 for the extraction of flavanone from the orange peel with ethanol using an UAE method. The optimized conditions for ultrasonication obtained were temperature of 40°C, operating power of 150 W, with a 4:1(v/v) to ethanol:water ratio. Results indicated that flavanone concentration in terms of naringin and hesperidin obtained was higher compared to the conventional method, that is, 70.3 mg and 205.2 mg/100 g FW, respectively. The extraction yield (10.9%) was also the highest under optimized conditions. As such no evidence of flavanone degradation was observed. *C. sinensis* peel powder was treated with 80% ethanol in an ultrasound sonicator with power levels of 100, 125, 150, and 200 W. By the use of ultrasonic energy, there was an enhancement in the phenolic content to 21.40 g/kg from 19.68 g/kg in the CSE method. For the yield of hesperidin, no significant difference was observed for ultrasound extraction.

M'hiri *et al*. (2015) evaluated different operating conditions for the extraction of phenolic compounds in orange peel with ultrasonic power levels of 100, 125, 150, and 200 W for 30 min at 35°C. It was found that the use of ultrasound enhanced the total phenol content from 19.68 ± 0.03 g/kg to 21.40 ± 0.05 g/kg. M'hiri *et al*. (2016) compared the efficiency of different extraction techniques like CSE, MAE, and UAE on the total phenol and flavonoid contents from Maltese Orange peel. UAE was carried out by using 80% of ethanol and was subjected to

sonication at 125 W at 35°C for 30 min. Results indicated that the efficiency of UAE was higher in isolating the hesperidin from the orange peel, that is, 0.836 ± 0.029 g/100 g as compared to CSE, that is, 0.551 ± 0.001 g/100 g. It was also reported that the efficiency of extraction using a particular method depends upon the structure of the flavonoid. Nipornram *et al.* (2018) conducted a study to optimize the extraction parameters using UAE by setting various power levels, that is, Level-1 (30.34 W), Level-4 (44.85 W), and Level-7 (59.36 W), with temperatures of 30, 40, and 50°C and times of 20, 30, and 40 min. A significant effect of selected parameters was found on the extraction yield of hesperidin and total phenolic contents. The maximum yield of 26.52% was obtained at optimized conditions, that is, 56.71 W at 48°C for 40 min for UAE. At optimum conditions, the total hesperidin and phenol contents were found to be 6435.53 mg/100 g DW and 15263.32 mg Eq gallic acid/100 g DW, respectively. Taking into account similar extraction conditions, UAE was much more efficient in providing higher extraction yields as compared to MAE (1.77 times higher).

Limitations of UAE

Physical characteristics are attributed to both the extraction apparatus and the ultrasound waves employed during ultrasound-aided extraction. In this sense, the parameters connected to ultrasound equipment are extraction time, form, and size of ultrasonic reactors, while those related to ultrasound waves include power, frequency, and ultrasound intensity. Practically speaking, increasing power boosts ultrasound intensity up to a point when higher acoustic pressures might cause liquid agitation, halting the propagation of ultrasonic waves and lowering cavitation efficiency. Another physical aspect of UAE that depends on the characteristics of the matrix is the extraction time. Increased extraction times result in higher extraction yields, but prolonged extraction times may overexpose the extracted compounds to ultrasonic waves, which could result in undesired modifications to the derived compounds. To maximize the extraction, solvent selection is crucial. As can be observed, UAE typically outperforms traditional extraction, and the majority of techniques adhere to green chemistry principles. However, it can also be argued that in order to create appropriate methods and achieve the highest extraction efficiency, operating conditions and techniques must be optimized based on the chosen matrix and target chemicals. In many laboratories throughout the world that specialize in analytical chemistry and food analysis, ultrasound probe and bath are the most popular ultrasound tools. The position of the container holding the matrix and solvent inside the bath is a common flaw in all ultrasound baths since the effect of the ultrasound waves vary based on position (Carreira-Casais *et al*., 2021). Lack of bath T and proper power control, which results in inefficient energy transmission within the extract-containing vessel, is another crucial factor to take into account. It should also be investigated as to how to increase the production of bubbles when using cavitation-based techniques through inventive reactor design and uniform cavitation energy distribution throughout the extraction solution. Consequently, the application of the cavitation-based extraction approach could result in a promising, innovative, and environmentally friendly extraction method for the recovery of important natural compounds (Carreira-Casais *et al*., 2021).

Supercritical Fluid (SC-Co_2) Extraction

Nowadays, solvents that are toxic and ecologically unacceptable are replaced by supercritical solvents like supercritical Co_2 being the extracts rich in slightly polar or nonpolar compounds. Extraction of flavones from citrus peel was found to be rich in polar compounds than the nonpolar ones (poly-methoxylated flavones). Thus, supercritical Co_2 extraction is favorable for isolating nonpolar bioactive compounds and essential oil compounds, whereas other techniques are suitable for extracting polar compounds, such as phenolics (Berna *et al*., 2000; Budich *et al*., 1999; Diaz *et al*., 2005; Sato *et al*., 1998). Jokić *et al.* (2019) studied the combined effect of SC-Co_2 and UAE to extract the volatiles and hesperidin from the byproducts, that is, orange peel. Citrus peel was subjected to supercritical extraction and limonene-rich extracts to obtain up to 89% hesperidin. Further UAE was carried out for the treatment of the residual material to obtain 3.3–23 µg/mL of hesperidin. M'hiri *et al.* (2016) carried out SC-CO_2 using 80% ethanol at 22 MPa. Table 2 summarized the different studies conducted on advanced extraction techniques of hesperidin from citrus.

Limitations of Supercritical Fluid Extraction

Its inability to dissolve polar analytes, even at very high densities, is the only drawback of using supercritical CO_2 in supercritical fluid extraction. As a result, it is best suited for lipid, greasy, and nonpolar substances (such as carotenoids, aromas, and volatile compounds), but not for polar flavonoids. Chemical modifiers or co-solvents, such as methanol, water, acetone, ethanol, and acetonitrile, have been effective in overcoming the restriction of the low polarity of CO_2. These co-solvents can make the supercritical fluid combination more polar, which affects how well the target bioactive chemicals dissolve in it (Chaves *et al*., 2020).

Health Implications

Antioxidant properties

The antioxidant activities of hesperidin were addressed previously. Recently, the studies have aimed primarily at defending properties against various oxidants and toxins that are responsible for tissue damage (Garg *et al*., 2001; Kalpana *et al*., 2009; Kamaraj *et al*., 2010; Kawaguchi *et al*., 2004; Kim *et al*., 2004; Shrivastava *et al*., 2013). Kalpana *et al*. (2009) studied hesperidin effects on RBCs' (Red blood corpuscles) damage induced by H_2O_2 and they observed that hesperidin had radical scavenging activity and inhibited the damage of RBCs membranes (Kalpana *et al*., 2008). Many studies reported that hesperidin neutralized nitric oxide (NO) radicals, hydroxyl radicals, peroxynitrite, and superoxide anions (Garg *et al*., 2001; Kim *et al*., 2004; Wilmsen *et al*., 2005). The scavenging capability of hesperidin shows a critical role in damage protection of tissues, DNA, and proteins that are stimulated by intrinsic and extrinsic factors. Hesperidin could attenuate the tissue damage that was induced by various compounds such as nicotine, acrylonitrile, peroxynitrite, gamma radiation, cadmium, hydrogen peroxide, lipopolysaccharide, and technetium (Ahmad *et al*., 2012; Arafa *et al*., 2009; Balakrishnan and Menon, 2007a, 2007b; Chen *et al*., 2010a, 2010b; El-Sayed *et al*., 2008; Hosseinimehr *et al*., 2009; Kamaraj *et al*., 2011; Kumar *et al*., 2003; Pradeep *et al*., 2012; Sahu *et al*., 2013).

Previous studies reported that hesperidin treatment increases the activity of antioxidant enzymes to nearly normal levels during tissue damage caused by intrinsic and extrinsic factors (Ahmad *et al*., 2012; Arafa *et al*., 2009; Balakrishnan and Menon, 2007a, 2007b; Chen *et al*., 2010a, 2010b; El-Sayed *et al*., 2008; Hosseinimehr *et al*., 2009; Kamaraj *et al*., 2011; Kumar *et al*., 2003; Pradeep *et al*., 2012; Sahu *et al*., 2013). In addition, various studies showed that hesperidin upregulated the gene expression of Nrf2, ERK1/2, and cellular defenses to attenuate cell damage (Elavarasan *et al*., 2012; Martínez *et al*., 2009). In addition to the mentioned studies, hesperidin showed an inhibitory effect on the formation of advanced glycation end products that are associated with aging, chronic renal failure, and diabetic complications. In 2012, Li *et al*. reported that hesperidin showed activity against advanced glycation end-product formation (Li *et al*., 2012a, 2012b). In addition, Shi *et al*. (2012) demonstrated that hesperidin (100 & 200 mg/kg) provided to diabetic rats for 12 weeks decreased the accumulation of advanced glycation end products (Shi *et al*., 2012). According to Figure 1: (1) Hesperidin increases antioxidant levels via the ERK/Nrf2 pathway, resulting in a decrease in oxidative stress and lipid peroxidation, resulting in the protection of cellular elements, DNA, proteins, and lipids. It reduces the levels of inflammatory markers that had been elevated due to heavy metal toxicity, causing a downregulation in MAPK activation and ERK phosphorylation; (2) the flavonoid promotes apoptosis by increasing the activity of caspase-3, p53, and Bax, while it inhibits apoptosis by increasing the levels of caspase-3 and caspase-9 and decreasing the levels of Bcl-2; (3) hesperidin, through the ERK/Nrf2 pathway, increases the levels of HO-1, GSH, SOD, CAT, GPx, and downregulates MDA, resulting in a reduction in oxidative stress. It protects against inflammation by downregulating inflammatory markers such as COX-2, iNOS, CD45, and TNF-, which had been elevated due to heavy metal toxicity; (4) it promotes apoptosis by upregulating Bad and Bax and downregulating Bcl-2, and NF-k inhibition causes apoptosis; and (5) it also counteracts the effect of neuronal apoptosis by increasing Bcl-2 and Bax levels while decreasing caspase-3 levels and inhibits the NF-k pathway, which protects against inflammation in cardiac tissue.

Antitumor properties

Among the newest trends in pharmaceutical products are the use of sustainable resources and preferably agricultural waste. Pharmaceutical companies are attracted to fruit waste, especially orange peel, because of its affordability and availability as a source of active ingredient. Citrus fruits and their products have been relied upon for thousands of years to treat a wide array of ailments in humans (Falsafi *et al*., 2022; Kumar *et al*., 2021; Radha *et al.*, 2021; Zaidun *et al*., 2018). Numerous studies have found that swilling citrus juices reduce the expression of pro-inflammatory cytokines and inflammatory enzymes in the colon, consequently reducing the risk of colon cancer (Jiang *et al*., 2019). In this sense, flavonoids are considered the largest group of dietary polyphenols (Grosso *et al*., 2017; Kaur *et al*., 2021; Pandey *et al*., 2022; Prakash *et al*., 2021a, 2021b). There are numerous flavonoids but hesperidin (3, 5, 7 – trihydroxy flavanone 7-rhamnoglucoside), a flavanone glycoside, is commonly found in lemons, sweet oranges, also in some other fruits and vegetables (Tejada *et al*., 2018). It can be isolated from species of the genus citrus such as *C. unshiu, C. aurantium*, and *C. sinensis* (Garg *et al*., 2001). According to scientific research, hesperidin is a potent phytocompound with many health benefits such as anti-inflammatory, antifungal, antioxidant, anticancer, and antidiabetic properties (Ali *et al*., 2020). It has been found to have both chemopreventive and chemotherapeutic properties (Chikara *et al*., 2018). Devi *et al*. (2015) discovered that hesperidin increases wild-type p53 levels in colon cancer cell lines, lung cancer, leukemia cell lines, and breast cancer as a result of its modulation of cell cycles regulatory proteins such as CDK inhibitors, cyclins, and cyclin-dependent kinases. Hong

Table 2. Advanced extraction techniques of hesperidin from citrus.

Plant material	Analytes	Extraction technique	Methodology	Inference	References
Pomelo flavedo extract	Polyphenols, flavonoids, and antioxidant capacity	Microwave	5 g of pomelo powder was extracted with 150 mL of absolute ethanol by applying different power levels of 150, 300, 450, and 600 W and corresponding extraction times were 15, 20, 25, and 30 min.	Applying power at 150 W resulted in the highest yield of polyphenols and flavonoids at 84.12 and 92.83%	Tran *et al*. (2022)
Citrus peel	Volatiles and hesperidin	SC-CO_2 and ultrasound-assisted extraction (UAE)	Supercritical extraction and limonene-rich extracts (up to 89%) were obtained.	UAE was carried out for the treatment of the residual material to obtain 3.3–23 µg/mL of hesperidin.	Jokić *et al*. (2019)
Citrus	Hesperidin	Ultrasonication	Optimized the extraction parameters by setting the power levels as level 1 (30.34 W), level 4 (44.85 W), and level 7 (59.36 W), with temperature variation of 30, 40, and 50°C and times of 20, 30 and, 40 min.	A maximum yield of 26.52% was obtained at optimized conditions of 56.71 W at 48°C for 40 min for UAE. At optimum conditions, total hesperidin and phenol contents were found to be at 6435.53 mg/100 g DW and 15263.32 mg Eq gallic /100 g DW.	Nipornram *et al*. (2018)
C. unshiu peel	Hesperidin	Microwave	1–6 g powder was mixed with 20 mL of 70% ethanol and was subjected to homogenization for 5 min followed by microwave irradiation at 60–180°C for about 2–12 min.	It was found that microwave-assisted extraction (MAE) was much more effective for extracting hesperidin with 70% aqueous ethanol under pressurized conditions above 100 °C. By using microwave irradiation, yield of hesperidin reached 58.6 mg/g being 27 times higher than that obtained by the conventional method.	Inoue *et al*. (2010)
C. sinensis powdered peel	Flavonoids and phenols	Microwave	Extraction was done with 50 mL using 80% ethanol and was heated at different wattages of 100, 200, 300, and 400 W for 180 s and corresponding temperatures are measured as 67, 76, 92, and 108°C, respectively.	MAE at 100 W power leads to a total phenol content of 23.40 ± 0.12 g GAE/kg, whereas the conventional method gave 22.13 ± 0.36 g GAE/kg. Also, with an increase in microwave power, the amount of flavonoids like hesperidin, neo-hesperidin, naringin, and didymin increases with an increase in microwave power up to 200 W.	M'hiri *et al*. (2015a)
Orange peel	Total phenol and total flavonoid contents	Microwave	Extraction was done with 80% ethanol; m/v: 5 g: 50 mL heating in microwave oven for 10 s at 35°C at 170 W with three successive extractions.	Total hesperidin content by MAE was found to be 0.781 ± 0.074 g/100 of orange peel, whereas conventional solvent extraction (CSE) yielded 0.551 ± 0.001 g/100 of orange peel.	M'hiri *et al*. (2016)
Pengann (*C. reticulata*)	Hesperidin	Ultrasonication	Ultrasonic extraction with 20 kHz, 60 kHz, and 100 kHz frequencies for 20 min at operating temperatures of 30, 40, and 50°C using ethanol, methanol, and isopropanol as solvents.	Yields of hesperidin from all the combinations of ultrasonic frequencies are higher than those obtained by the Soxhlet method. The type of solvent, application frequency, and processing temperature are the most important factors reported in this study affecting the hesperidin yield.	Ma *et al*. (2008b)

(continues)

Table 2. Continued.

Plant material	Analytes	Extraction technique	Methodology	Inference	References
Orange peel	Flavanones	Ultrasonication	Optimized conditions for ultrasonication obtained were temperature of 40°C, the operating power of 150 W with 4:1 (v/v) to ethanol: water ratio.	Flavanone concentration in terms of naringin and hesperidin obtained was higher compared to conventional method (70.3 mg and 205.2 mg/100 g FW respectively). The extraction yield was also highest at optimized conditions at 10.9%.	Khan *et al*. (2010)
Orange peel	Phenol content	Ultrasonication	Ultrasonic power levels of 100, 125, 150, and 200 W for 30 min at 35°C were applied.	Ultrasound enhances the total phenol content from 19.68 ± 0.03 g/kg to 21.40 ± 0.05 g/kg.	M'hiri *et al*. (2015b)
Maltese Orange peel	Hesperidin	Ultrasonication	Extraction was carried out by using 80% of ethanol with m/v ratio as 5:50 mL and was subjected to sonication at 125 W at 35°C for 30 min.	Results indicated that efficiency of UAE was higher in isolating the hesperidin from the orange peel being 0.836 ± 0.029 g/100 g compared to CSE being 0.551 ± 0.001 g/100 g.	M'hiri *et al*. (2016)

and Zhang (2020) discovered that hesperidin has the potential to promote the differentiation of human alveolar osteoblasts by activating the Wnt/catenin signaling pathway. It has also shown significant anticancer potential by placing the focus on apoptosis-mediated cell death pathways and inducing apoptosis through a variety of mechanisms, including increased nuclear condensation and DNA fragmentation. Furthermore, hesperidin induces apoptosis by activating caspase-3 and -9, inhibiting cell cycle progression, resulting the Bcl-2 family proteins, decreasing levels of nuclear factor-B, and increasing ROS (reactive oxygen species) levels (Ahmad *et al*., 2012). A combination of PPAR* and Nrf2/HO-1/ARE pathways activated by hesperidin inhibited hepatocarcinogenesis and suppressed oxidative stress, cell proliferation, collagen deposition, and inflammation (Heo *et al*., 2020). Analogs, nanoformulations, and metabolites of hesperidin are effective in treating cancer as many drug delivery methods are available to enhance its targeted delivery, solubility, and bioavailability to improve its anticancer and biological activity, including microencapsulation, enzyme modification, and complexation (Roberts *et al*., 2020). Using modified nano-hesperidin, Ali *et al*. (2019) showed that it modulated the apoptotic pathway of caspase-3 and p53 in breast cancer cells to produce greater growth inhibitory effects. A study conducted by Balakrishnan *et al*. showed that nanoparticles of hesperidin were more effective than native hesperidin in Hep-2 cells (Balakrishnan *et al*., 2020). As a result of Hesperidin's actions, breast cancer cells contracted, vacuolated, and formed blebs in their plasma membranes, which were indicative of apoptosis. In addition to this, it has other apoptotic characteristics, including an increase in the level of LDH (lactate dehydrogenase), depletion of glutathione levels, DNA fragmentation, and activation of caspase 3 (Natarajan *et al*., 2011). Several studies have shown that hesperidin is an effective natural flavonoid that is effective against breast cancer. Besides inhibiting cancer cell proliferation, migration, invasion, and viability, it also promotes DNA damage and apoptosis. Being a promising anticancer agent, Hesperidin (100 *M) inhibited mammosphere formation, colony formation, and migration of MCF-7 breast cancer cells by elevating the expression of mRNAs of p53, NOTCH1, and PPARG and by reducing the level of catenin, causing cell cycle arrest in the G0/G1 phase (Hermawan *et al*., 2020). Research by Tan *et al*. (2018) demonstrated that hesperidin (1-20 *M) inhibited the Ahr (Aryl hydrocarbon receptor) and decreased CYP1A1, 1A2, and 1B1 expression in MCF-7 breast cancer cells. The Synergistic interaction of hesperidin with different compounds is shown in Table 3. According to Figure 2: (1) Hesperidin-mediated cell cycle arrest is associated with the modulation of cell cycle regulatory proteins such as CDK inhibitors, cyclin-dependent kinases, and cyclins. EGFR (receptor tyrosine kinase) is activated by its ligands, which further promotes the phosphorylation of PI3K (phosphoinositide 3-kinase) and MAPK signaling, playing an important role in cell survival; (2) it inhibited tumor proliferation and migration via targeting UDP-glucuronosyltransferase (UGT) family 1 member A3 (UGT1A3); (3) hesperidin can reduce the level of inflammatory factors such as IL-4, IL-6, iNOS, and NO_2, and can stimulate TNF secretion in a variety of cancer cells.

Antitumor efficacy *in vitro*

Several types of cancer are inhibited by hesperidin in vitro, including breast, prostate, glioma, pancreas,

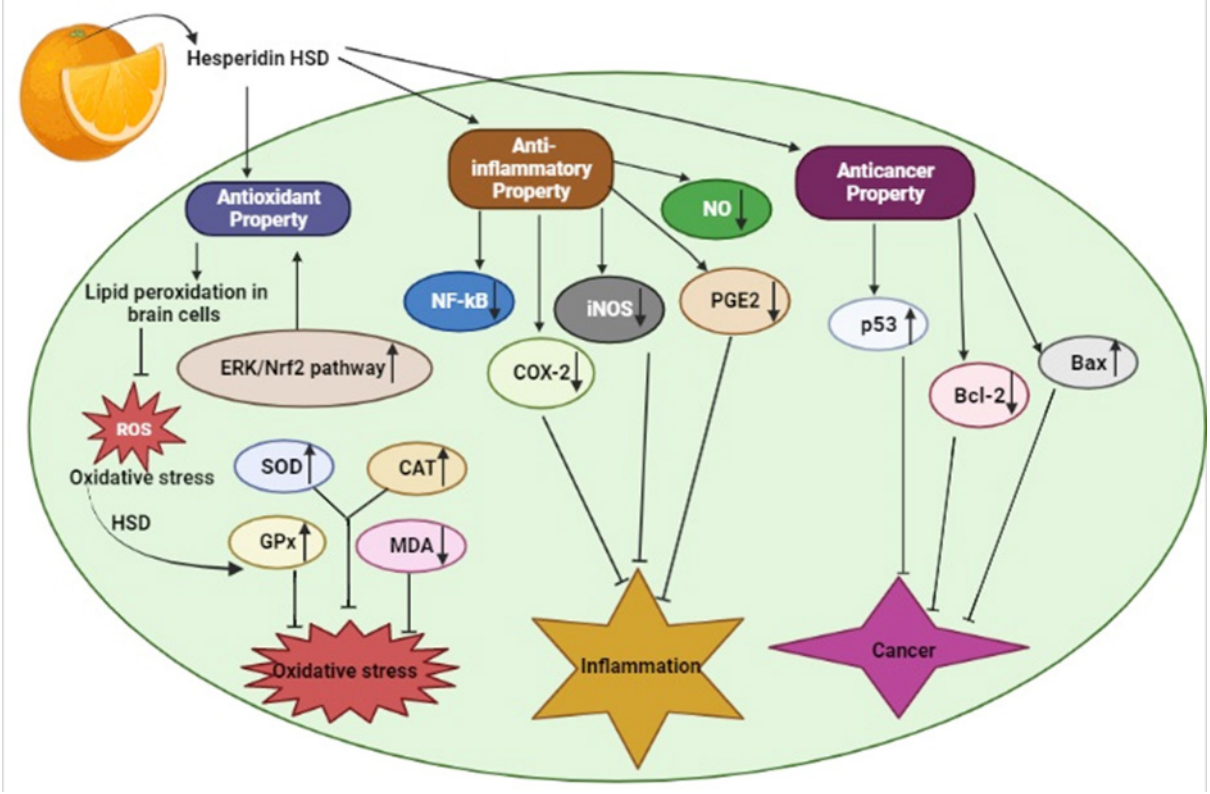

Figure 1. Hesperidin increases antioxidant levels via the ERK/Nrf2 pathway, resulting in a decrease in oxidative stress and lipid peroxidation that leads to the protection of cellular elements, DNA, proteins, and lipids; (1) it reduces the levels of inflammatory markers that had been elevated due to heavy metal toxicity, causing a downregulation in MAPK activation and ERK phosphorylation; (2) the flavonoid promotes apoptosis by increasing the activity of caspase-3, p53, and Bax, while it inhibits apoptosis by increasing the levels of caspase-3 and caspase-9 and decreasing the levels of Bcl-2. (3) Hesperedin, through the ERK/Nrf2 pathway, increases the levels of HO-1, GSH, SOD, CAT, GPx, and downregulates MDA, resulting in a reduction in oxidative stress; it protects against inflammation by downregulating inflammatory markers such as COX-2, iNOS, CD45, and TNF-, which had been elevated due to heavy metal toxicity. (4) Hesperidin promotes apoptosis by inhibiting NF-k and upregulating Bad and Bax while downregulating Bcl-2. (5) It also counteracts the effect of neuronal apoptosis by increasing Bcl-2 and Bax levels while decreasing caspase-3 levels and inhibits the NF-k pathway, which protects against inflammation in cardiac tissue.

lung, ovarian, colon, skin, and liver cancers (Vijayvergia *et al*., 2020). Among its numerous anticancer properties, hesperidin inhibits the metastasis, invasion, migration, angiogenesis and proliferation of cancer cells along with stimulating apoptosis and autophagy. When combined with chemotherapeutic drugs, hesperidin inhibits tumor growth either by itself or by combining with doxorubicin, paclitaxel, oxaliplatin, tamoxifen, methotrexate, cyclophosphamide, pirarubicin, etc. Yunita *et al*. (2020) in their study demonstrated that by inducing G2/M phase cell cycle arrest and apoptosis, hesperidin has the potential to be used as a Dox (Doxorubicin) co-chemotherapy against 4T1 cells. More importantly, it inhibits Dox-induced migration and MMP-9 (Matrix Metallopeptidase-9) expression. Several studies show that hesperidin suppresses cyclin D1, aromatase activity, CDK4, pS2, Bcl-Xl, and induces p57Kip2, CCAAT/C/EBP, Perk-1 &2 expressions, which reduce tumor growth in female athymic mice model and MCF-7 breast cancer cells both in vitro and in vivo (Li *et al*., 2011; Ye *et al*., 2012). Moreover, Abdallah and his colleagues found that the presence of hesperidin enhances the expression of miR-486-5P, which is known to reduce the viability, clonogenicity, and metastatic potential of MDA-MB-231 breast cancer cells. A study demonstrated by Chandrika *et al*. (2016) showed that 50–500 μM of hesperidin reduces cell growth and apoptosis in SKBR3 and MDA-MB-231 breast cancer cells. As a result, flavonoids inhibit HER2-TK activity, lead to MMP loss and chromatin condensation, and activate caspase-8 and -3 to arrest the cell cycle at the G2/M phase, decreasing the growth of MDA-MB-231 breast cancer cells (Chandrika *et al*., 2016). So, from the above discussion, it is summarized that by upregulating tumor suppressor gene expression, hesperidin controls cell cycle progression; this phytoestrogen also leads to increased estrogen metabolism, which can cause breast

cancer and apoptosis through both extrinsic and intrinsic pathways. In addition to treating lung cancer, hesperidin stimulates several targets. Upon treatment with hesperidin, H522 lung cancer cells exhibited induction of the Fas death receptor and intrinsic pathway. This resulted in dose-dependent activation of Bax, caspase-3, and caspase-9 expression (Elango *et al*., 2017). A similar study showed that HSP inhibited the expression of the glucose transporter in cancer cells and reduced the uptake of glucose by transforming growth factor * in H441 lung cancer cells (Wolfram *et al*., 2016). It was reported that hesperetin treatment could prevent the growth of tumors in Swiss albino mice by alleviating LPO and modulating antioxidant enzymes like NF-kB, PCNA, and CYP1A1 (Bodduluru *et al*., 2015).

Antitumor efficacy *in vivo*

Hesperidin has demonstrated anticancer potential against a wide array of cancer types in vivo, including colon, prostate, lymphoma, and breast. Research studies of hesperidin's chemotherapeutic potential are commonly conducted using Wistar rats, Balb/c nude mice, and Swiss albino mice (Memariani *et al*., 2021). There have been several studies examining hesperidin administration through either oral or intraperitoneal routes with varying doses and treatments based on the experimental setup (Birsu Cincin *et al*., 2015; Nurhayati *et al*., 2020). As a tumor growth inhibitor, hesperidin mainly inhibits tumor growth by inducing apoptosis, inhibiting angiogenesis, suppressing metastasis, and regulating associated cell signaling pathways (Birsu Cincin *et al*., 2015). To study how hesperidin affects human epidermal growth factor receptor 2 (HER2) production, scientists studied standard breast cancer cells (MCF-7/HER2) and MCF-7/EV cells and observed that, at 95 μM concentration, hesperidin suppresses HER2, Rac1, MMP-9 expression, lamellipodia formation, and arrests the cell cycle at G2/M phase, resulting in decreased cell viability, migration, invasion, and apoptosis (Nurhayati *et al*., 2020). According to Palit *et al*., hesperetin (20-200*M) has been found to enhance ROS production release Bax/Bcl-2 ratio, JNK, caspase-9, -3, -7, cyto-c, PARP cleavage,

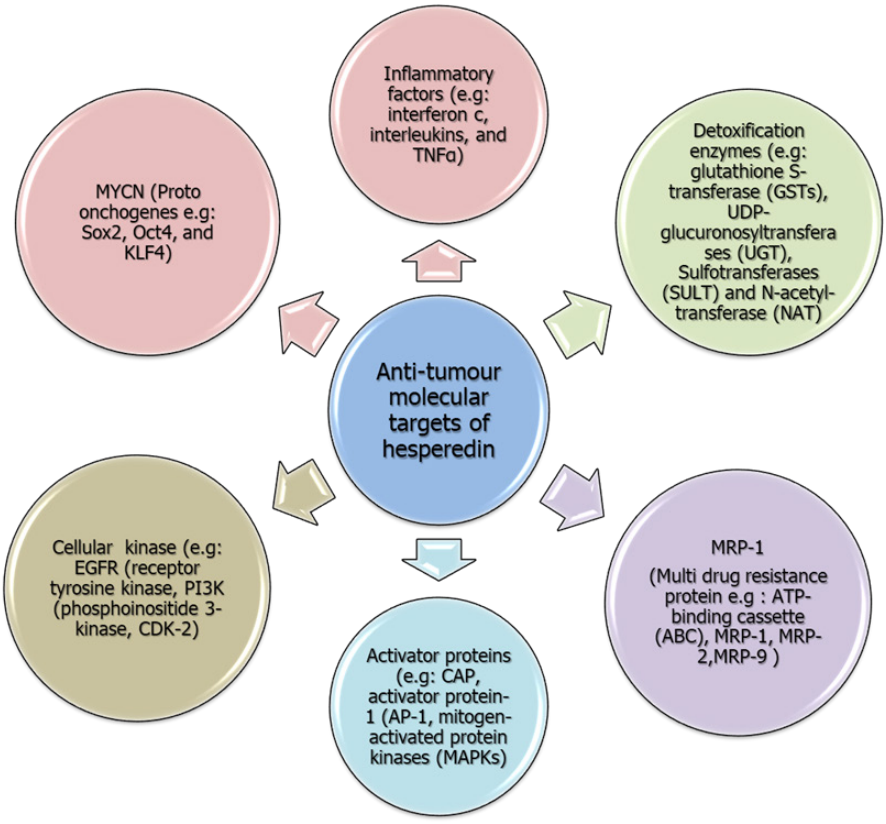

Figure 2. Hesperidin-mediated cell cycle arrest is associated with the modulation of cell cycle regulatory proteins such as CDK inhibitors, cyclin-dependent kinases, and cyclins. EGFR (receptor tyrosine kinase) that are activated by its ligands, which further promotes the phosphorylation of PI3K (phosphoinositide 3-kinase) and MAPK signalling, playing an important role in cell survival. 2) It inhibited tumor proliferation and migration via targeting UDP-glucuronosyltransferase (UGT) family 1 member A3 (UGT1A3). 3). Hesperidin can reduce the level of inflammatory factors such as IL-4, IL-6, iNOS, and NO_2, and can stimulate TNF secretion in a variety of cancer cells.

and SK1 activation, and activate the ASK1/JNK pathway in MCF-7, MCF-10A, HMEC, and MDA-MB 231 breast cancer cells (Palit *et al*., 2015).

Anti-inflammatory properties

Inflammation is a natural biological response of body tissues to potentially harmful irritants, pathogenic attack, and potentially harmful stimuli. Inflammation causes pain, redness, swelling, and warmth. Oxidative stress and inflammation have been linked to a variety of life-threatening conditions, including cardiovascular diseases (Cottone *et al*., 2008), cancer (Oztanir *et al*., 2014), and neurodegenerative diseases (Donato *et al*., 2014). Lebreton, in 1827, discovered hesperidin, a naturally occurring flavonoid found in citrus fruits, which has been shown to protect against infection, inflammation, apoptosis, oxidative stress, nitric oxide (NO) synthase inhibition, and hypotension (Chen *et al*., 2010a). Febriansah *et al*. (2014) evaluated hesperidin's analgesic and anti-inflammatory activities in mice using standard procedures such as acetic acid, hot plate, tail immersion, formalin-induced edema tests, and xylene. Hesperidin induced anti-inflammatory and analgesic activities in mice in a dose-dependent manner, as evidenced by reduced inflammation and pain inhibition. Because macrophages produce pro-inflammatory mediators, their activation contributes to inflammation (Kang *et al*., 2011; Walsh, 2003). As a result, macrophages have seemed to be one of the best cellular models for studying inflammatory mechanisms. Some studies in mouse macrophage cell lines using LPS as an immune activator discovered that hesperidin has inhibitory effects on the inducible enzymes COX-2 (cyclooxygenase) and iNOS (an isoform of NO synthase) (Lawrence *et al*., 2001; Sakata *et al*., 2003). Hesperidin rehabilitation might suppress NOS and COX-2 activity in a dose-dependent way, reducing the levels of iNOS proteins as well as the release of NO_2 and PGE2 (Prostaglandin E2) to the medium.. Inhibiting iNOS and COX-2 activity in macrophage cells may result in anti-inflammatory action (Tejada *et al*., 2018). Yet, in another similar cellular model, a flavonoid fraction (Naringin, nobiletin, and HD) from Korean *Citrus aurantium* L. inhibited significantly COX-2, the pro-inflammatory enzyme, at the protein, mRNA levels, and the pro-inflammatory cytokines (Kang *et al*., 2011). Jeon *et al*. (2014) also reported a significant reduction in LPS-induced NO production in RAW264.7. Cells treated with *Gelidium elegans* extract *G. elegans* is an edible red alga from Asia's Intertidal Zone that contains the antioxidants rutin and hesperidin. Yang *et al*. (2012) investigated ex vivo that hesperidin from citrus fruit is converted into hesperetin by gut microflora and then conjugated mostly into glucuronides. Researchers have collected the pretreated serum of rats with hesperetin, which was considered the source of hesperetin metabolites like Hst glucuronides and Hst sulfate, and concluded that LPS-induced COX-2 and iNOS protein expressions were significantly downregulated by hesperetin metabolites. Numerous studies have also looked into hesperidin's anti-inflammatory effects in other immune cells such as monocytes, microglial cells, mast cells, and polymorphonuclear neutrophils.

Antidiabetic properties

Diabetes mellitus is a hormonal and chronic metabolic disorder that has eluded clinical researchers for decades. According to the International Diabetes Federation (IDF), 415 million adults worldwide have diabetes (one in every 11 adults in 2015), and 642 million (20% of all adults) may develop diabetes by 2040 (Atlas, 2015). Citrus flavonoids have been thoroughly researched in vitro and in vivo to see if they have any effect on chronic degenerative disorders such as cancer, cardiovascular diseases, and diabetes. According to Figure 3: (1) Hesperidin reduces systolic blood pressure (SBP) and diastolic blood pressure (DBP), increases vascular NO, and leads to antihypertensive effect that protects endothelial function from ROS; (2) hesperidin improved the reported oxidative stress observed under hypertensive conditions as a consequence of overexpression of NADPH oxidase via suppression of this enzyme, which results in enhanced NO bioavailability; (3) hesperidin increases glucose consumption in the hepatocyte cell line HepG2, which was associated with increased phosphorylation levels of adenosine monophosphate (AMP)-activated protein kinase (AMPK); (4) it increases glucose uptake in lipopolysaccharide (LPS)-induced insulin-resistant HepG2 cells treated with hesperidin. These changes seemed to be associated with the regulation of the insulin receptor substrate 1 (IRS1)-glucose transporter (GLUT)-2 pathway via toll-like receptor (TLR)-4; and (5) it is effective in lowering the plasma free fatty acids (FFAs) and plasma and hepatic triglyceride levels, reducing the hepatic fatty acid oxidation and carnitine palmitoyltransferase activity. It leads to the suppression of hepatic fatty acid synthase, glucose-6-phosphate dehydrogenase, and phosphatidate phosphohydrolase activities, and to an increase in the fecal triglycerides. It led to a decrease in plasma and hepatic cholesterol levels through downregulation of the hepatic 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase and acyl CoA: cholesterol acyltransferase (ACAT) activities.

In addition, citrus flavonoids have been shown to lower blood sugar levels and improve insulin sensitivity and secretion. Citrus polyphenols affect type-II diabetes markers in different tissues, according to in vitro and animal studies, primarily by affecting hepatic glucose

Table 3. Analytical studies of chemotherapeutic drug/irradiation combinations with hesperidin for anticancer potential.

Cancer cells	Type of cancer	Treatments in combination	Efficiencies synergistic	References
MCF-7 (Michigan Cancer Foundation-7) and T47D (Human breast cancer cells)		Tamoxifen + hesperidin + piperine	Vehicle for tamoxifen and enhanced the anticancerous properties Can be used as an adjuvant	Khamis *et al*. (2018)
Breast cancer MCF-7 cell line	Breast cancer	Hesperidin + doxorubicin	Pgp (P-glycoprotein) expression in MCF-7/Dox cells was inhibited by a combination of hesperidin and doxorubicin treatment	Febriansah *et al*. (2014)
Breast cancer 4T1 metastatic cells	Breast cancer	Hesperidin + doxorubicin	Apoptosis and cell cycle arrest in the G2/M phase were induced by the combined treatment. In 4T1 cells, the combined treatment inhibited migration and MMP-9 expression	Yunita *et al*. (2020)
Acute Myeloid Leukemia (AML) cells	Blood cancer	Cytarabine + hesperidin	Lowering IC50 values of Cytarabine	Desai *et al*. (2015)
MCF7 breast cancer cell lines	Breast cancer	Apigenin + hesperidin	Altered the expression levels of glycolytic pathway genes—HK2 (hexokinase 2) and LDHA (lactate dehydrogenase A), which possess a major role in the Warburg effect	Aggarwal *et al*. (2020)
AML cells	Blood cancer	Silibinin + hesperidin	Showed 50% cell inhibition	Desai *et al*. (2015)
HepG2 cells	Liver cancer	Doxorubicin + hesperidin	Alterations in the expression levels of HK2 and LDHA	Korga *et al*. (2019)
DMBA (7,12-Dimethyl benzanthracene), treated Sprague female Dawley rats		Hesperidin	Suppress the gluconeogenesis key enzymes and ATPases Quenching free radicals ameliorated lipid profile and carbohydrates metabolism and ATPases activity	Nandakumar *et al*. (2013)
MCF-7 cells	Breast cancer	Hesperidin	Proliferation and inhibition of MCF-7-GFP Tubulin cells	Lee *et al*. (2010a)
AOM (Azoxymethane), treated Swiss albino male mice	Colon cancer	Hesperidin	Exerts chemopreventive effect against colon carcinogenesis	Saiprasad *et al*. (2013)
LNCaP cells	Prostate cancer	Hesperidin	In LNCaP cells, inhibits testosterone and basal-induced proliferation	Lee *et al*. (2010b)
Benzo(a)pyrene-treated Swiss albino male mice	Lung cancer	Hesperidin	Reduces mitochondrial dysfunction and restores cellular normalcy	Kamaraj *et al*. (2011)
Malignant pleural mesothelioma (MPM)	MSTO-211H cells	Hesperidin	Inhibited the Sp1 (Specificity protein 1) and mesothelioma cell growth	Lee *et al*. (2012)
Hematopoietic malignancies	NALM-6 cells	Hesperidin	Exerts antiproliferative and proapoptotic effects via both PPARc-independent and PPARγ-dependent pathways	Ghorbani *et al*. (2011)

MCF-7, Michigan cancer foundation-7; Dox, Doxorubicin; MMP-9, matrix metallopeptidase 9; T47D, human breast cancer cells; 4T1, breast cancer cell line derived from the mammary gland tissue of a mouse Pgp, P-glycoprotein.

metabolism, increasing insulin secretion in the pancreas, and promoting insulin sensitivity in insulin target tissues (Visvanathan and Williamson, 2021). In rodents with type-I and type-II diabetes, hesperidin normalized glucose metabolism by altering the activities of glucose-metabolizing enzymes and reduced lipid levels in four preclinical trials (Akiyama *et al*., 2010; Jung *et al*., 2006; Liu *et al*., 2017). The antidiabetic effect of citrus fruits was found to enhance glucose uptake in C_2C_{12} myotubes by modulating the AMPK and peroxisome proliferator-activated receptor-gamma (PPAR-γ) pathways, and reducing insulin resistance in mice with a high-fat diet (HFD) (Kim *et al*., 2013). A study by Kappel *et al*. (2013) demonstrated that flavone glycosides enhance intracellular Ca^{2+} concentration and inhibit the ionization of ATP-sensitive K^+ channels in pancreatic islets, a precursor to insulin synthesis. Long-term (11-week) consumption of growth hormone (GH) reduced body weight, fasting blood glucose concentration, glucose intolerance, and insulin resistance in mice fed an HFD (Yoshida *et al*., 2021). Furthermore, GH reduced macrophage infiltration into adipose tissue despite not affecting fat pad weight. On the other hand, the short-term consumption of GH (twice per week) did not alleviate obesity or high fasting blood glucose caused

by HFD, nor did it mitigate glucose intolerance or insulin resistance. In contrast, short-term intake had a beneficial effect on reducing macrophage infiltration in adipose tissue as well as monocyte chemotactic protein 1-expression. Jung *et al*. (2006) studied the impacts of hesperidin on glucose and lipid regulation in C57BL/KsJ-db/db mice and discovered that it significantly increased the glucokinase mRNA level in the liver, as well as effectively lowered plasma FFA and plasma and hepatic triglyceride levels, while simultaneously decreasing hepatic fatty acid oxidation and carnitine palmitoyltransferase activity As a result, the changes appeared to be due to a suppression of hepatic fatty acid synthase, glucose-6-phosphate dehydrogenase, and phosphatidate phosphohydrolase activities, as well as an increase in fecal triglycerides. As a result of these findings, hesperidin appears to be beneficial for improving hyperlipidemia and hyperglycemia in type-II diabetic animals. According to Figure 4, hesperidin significantly increased phosphorylation of IRS-1 in adipose tissues that further enhanced phosphorylation of PDK1, which is a critical kinase responsible to transduce the signal from IR to AKT, thereby suggesting that hesperidin may prevent diabetes by activating the IR/PKB pathway.

Conclusion and future perspectives

Hesperidin has emerged as a potent natural bioflavonoid found in citrus fruits as it offers various health benefits to

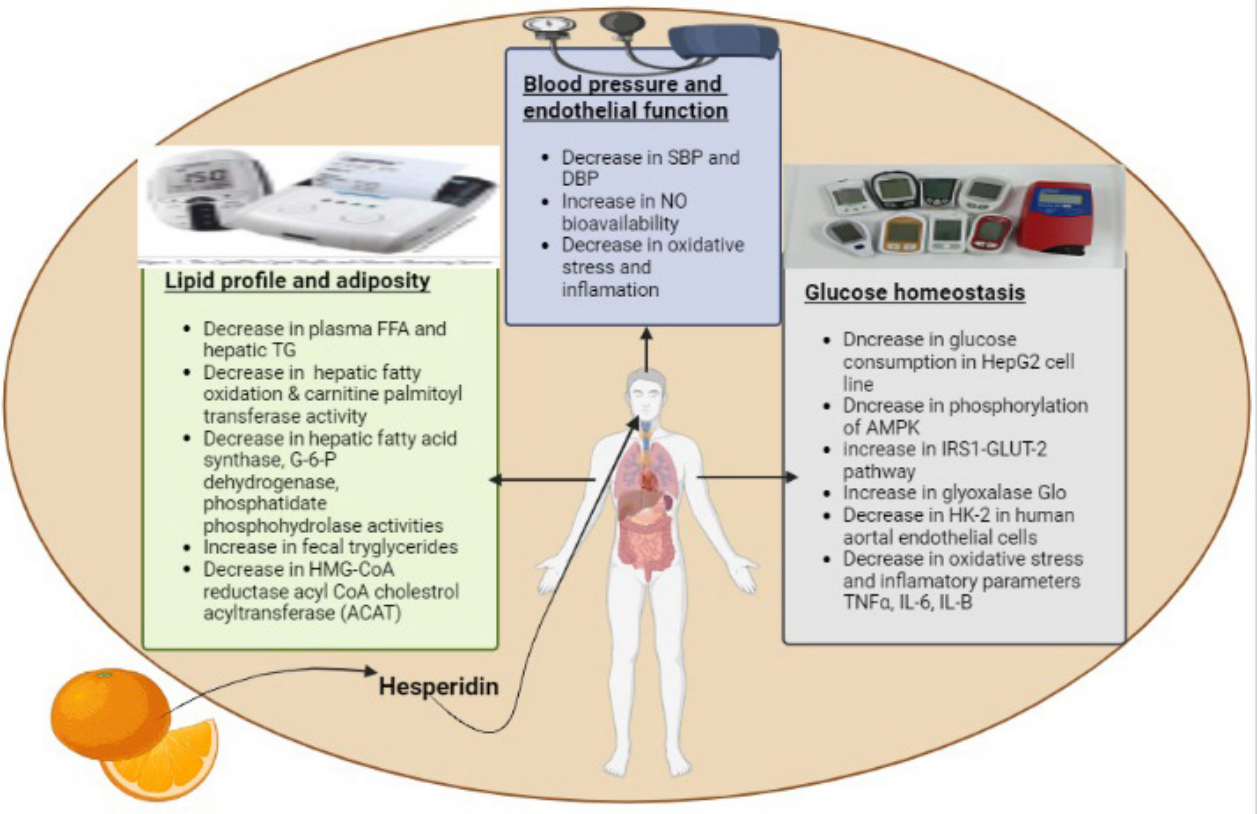

Figure 3. Hesperidin reduces SBP and DBP, increases vascular NO, and leads to antihypertensive effects that protect endothelial function from ROS; (2) hesperidin improved the reported oxidative stress observed under hypertensive conditions as a consequence of overexpression of NADPH oxidase via suppression of this enzyme, which results in enhanced NO bioavailability; (3) hesperidin increases glucose consumption in the hepatocyte cell line HepG2, which was associated with increased phosphorylation levels of adenosine monophosphate AMPK; (4) it increases glucose uptake in lipopolysaccharide (LPS)-induced insulin-resistant HepG2 cells treated with hesperidin. These changes seemed to be associated with the regulation of the IRS1-GLUT-2 pathway via TLR-4; (5) it is effective in lowering the plasma FFAs and plasma and hepatic triglyceride levels, reducing the hepatic fatty acid oxidation and carnitine palmitoyltransferase activity. It leads to the suppression of hepatic fatty acid synthase, glucose-6-phosphate dehydrogenase, and phosphatidate phosphohydrolase activities, and to an increase in the fecal triglycerides. It led to a decrease in plasma and hepatic cholesterol levels through downregulation of the hepatic 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase and acyl CoA: cholesterol acyltransferase (ACAT) activities. Here SBP: systolic blood pressure; DBP: diastolic blood pressure; NO: nitric oxide; FFA: free fatty acids; TG: triglycerides; Chol: cholesterol; IRS1: insulin receptor substrate 1.

human beings due to its immense pharmacological activities. Citrus fruits and their products are extensively consumed globally as they contain hesperidin and have a wide range of therapeutic properties, high nutraceutical potential that is beneficial to human health, and can be used against various diseases and disorders. Hesperidin is used in cosmetics, pharmaceutical industries, biorefineries, essential oil preparation, and as a gelling agent for making various emulsified products. Various extraction methods have been employed to extract hesperidin using different solvents at optimum conditions to obtain the maximum yield. The traditional methods possessed more demerits due to the long extraction times required, the consumption of large amounts of organic solvents, and the high temperatures employed, which may have adverse effects and deteriorate the quality of hesperidin. Nonetheless, new and innovative techniques have been developed allowing the effective extraction of hesperidin while preserving its properties.

Despite various promising health and other benefits of hesperidin, further research is still needed to investigate the exact effect of hesperidin to treat various ailments. A lot of information and data already exist, but a translation into clinical or intervention studies is still necessary to validate the biological activities reported in this review. We highly suggest that future studies should focus on finding the precise molecular mechanisms of anticancer effects of hesperidin, finding out the most effective doses for future clinical trials on hesperidin, evaluating the anticancer effects of hesperidin in patients who suffered from cancer, and increasing the bioavailability and absorption of hesperidin and/or its aglycone form, hesperetin. Based on the scientific evidence, it can be concluded that citrus fruits are a rich source of hesperidin along with various bioactive compounds and their biomass can be used as a source of valuable biologically active compounds for the creation of preparations for the food industry, nutraceuticals, and cosmetics.

Authorship Contribution Statement

MKS was involved in conceptualization, writing the original draft, and writing the review. MK and MS wrote the original draft. S, VK, JT, MR, and GPN wrote the review, and edited and validated the manuscript.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that influence the work reported in this paper.

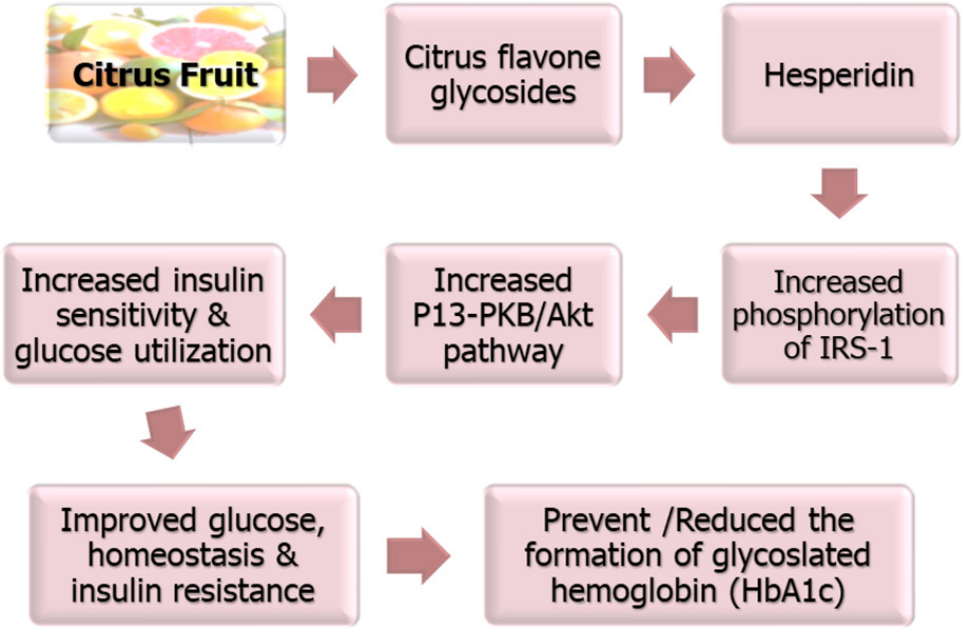

Figure 4. Efficacy of hesperidin on blood glucose in the diabetic state. Hesperidin significantly increased phosphorylation of IRS-1 in adipose tissues that further enhanced phosphorylation of PDK1, which is a critical kinase responsible to transduce the signal from IR to AKT, thereby suggesting that hesperidin may prevent diabetes by activating the IR/PKB pathway. IRS: insulin receptor substrate; PI3K: phosphatidylinositol-3-Kinase; AKT: v-akt murine thymoma viral oncogene homology.

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