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Fig "*Ficus carica* L." and its by-products: A decade evidence of their health-promoting benefits towards the development of novel food formulations

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ABSTRACT

Background: The food industry constantly searches for natural derived bioactive molecules with preventive and therapeutic effects using innovative and sustainable strategies. Fig production and processing generate a considerable amount of by-products (leaves, pulp, peels, seeds, and latex) with limited commercial exploitation and negative impact on the environment. These by-products are important sources of high value-added ingredients, including anthocyanins and pectins that can be of particular interest to the food industry as functional colourants, emulsifiers, and additives.

Scope and approach: This review curates recent advances in the valorisation of fig by-products as valuable sources of bioactive molecules for functional food development. Special attention was given to widely used extraction processes, main bioactive compounds, relevant biological properties, and the application of recovered bioactives for functional food development.

Key findings and conclusions: Fig by-products are essential sources of structurally diverse bioactive molecules with unique antidiabetic, anti-inflammatory, anti-tumour, immunomodulatory and cardioprotective properties. Owing to these health-promoting potentials, an integral valorisation approach involving sustainable technologies to recover these high value-added ingredients and its utilisation in novel food formulation development should be further stimulated.

1. Introduction: current state of Fig and Fig by-products

Ficus is one of the largest genera of angiosperm with more than 800 species worldwide. This genus belongs to the Moraceae family, rich in edible species with milky latex and aggregated drupes or achenes as fruit. *Ficus carica* is the most important commercial species within the genus due to its fruits, which are enclosed inflorescence with a hollow succulent receptacle (Mawa et al., 2013). This species may generate two crops per year: the main fruit, figs, which are produced during the concurrent growing year and are picked up at the end of the harvest and the breba crops, that are formed in the previous growing year and remain dormant during the winter producing an early harvest crop (Aradhya et al., 2010). *F. carica* is native to the Middle East, domesticated from a group of fig trees in the Mediterranean region, associated with grape and olive fruit trees in the beginning of this region's horticulture. Its domestication history and expansion worldwide have strongly influenced its current distribution, fruit morphology, and genetic diversity. The above-mentioned together with poor documentation of germplasm passport data, synonymous with local and regional names for the same clonal cultivars, and the modifications within cultivars,

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make proper identification of *F. carica* cultivars difficult (Ferrara et al., 2016). However, based on their reproduction biology and pollination, every fig variety can be classified into four types: Caprifig, Smyrna, San Pedro, and common fig. Figs trees are gynodioecious with two majors sex types: the caprifig and fig types. The caprifig type has male and female flowers (hermaphroditic) but functionally is a male fig plant because it is the only type that produces pollen and doesn't produce edible fruits. Still, they are necessary to pollinate some of the fig type varieties via caprification, which is carried out through wasps or manually. The female fig may produce two crops per year, the brebas during spring and the figs in summer. The female fig is classified into three groups according to their pollination: the common fig, which is parthenocarpic and not needs caprification; the San Pedro type, which produces parthenocarpy brebas and figs by caprification; and the Smyrna type, which is non-parthenocarpic (Ikegami et al., 2013).

F. carica is an important crop that appears on the market more often in its fresh or dry form, being consumed directly or as part of culinary dishes. In the last ten years (data available from 2010 to 2019), Turkey, Egypt, and Algeria have been the largest fig producers in the world. According to FAOSTAT, only Spain appeared in the top 10 fig producers in Europe. The consumption of this fruit has grown worldwide, and it is estimated to grow significantly in the coming years. This growth is attributed to the increased utilisation of these fruits in developing functional foods and beverages, contributing to a healthier diet. They are rich sources of vitamins (mainly thiamin and riboflavin), sugars, carbohydrates, minerals, and organic acids. In addition, the fresh and dry figs are a good source of fibre and phenolic compounds, mainly proanthocyanidins, furanocoumarins, and phenolic acids (Badgujar et al., 2014). The demand for fresh figs has attracted lots of attention due to the growing awareness of consumers of the potential health-promoting benefits of figs. The leaves and fruits also have been processed as ingredients of juices, jams, jellies, infusions, and alcoholic beverages (Badgujar et al., 2014; Barolo et al., 2014; Mawa et al., 2013). *F. carica* also presents many biological activities related to their phytochemicals, and is used in folk medicine for its endocrine, cardiovascular, respiratory, antispasmodic, and anti-inflammatory benefits (Mawa et al., 2013; Wang, Wu, et al., 2017).

The fig processing industry produces many by-products from fresh fig discarded because of spoilage, size, texture, low quality as table fruit, inadequate ripening, and over-ripening. These bio-residues constitute a real economic loss due to their richness in bioactive compounds, which can be extracted and used as value-added ingredients (Barolo et al., 2014). Hence, integral approaches for the sustainable valorisation of fig by-products to further improve the economic performance of the Mediterranean region and promote a circular economy in line with current consumer preferences towards sustainability still need to be adopted.

2. Main by-products from Fig processing

In recent years, there has been great concern in the food industry about a large amount of waste generated and new solutions have been proposed. Food waste is essential to global food security because it can cause serious environmental, economic, and social concerns. According to Directive 2006/12/EC 'waste' shall mean any substance or object which the holder discards or intends or is required to discard. However, according to FUSIONS, food removed from the food supply chain to be valorised for animal feed, non-food products, and fuel are considered food wastes that are not designated as fit for human consumption. Moreover, raw materials recovered from the processing, distribution, and consumption of food, represent food surplus that could be recycled for value addition. Hence, several integral strategies are needed to obtain value addition from food by-products using emerging technologies to obtain novel foods with additional functionalities with minimal contamination risks (Lavelli, 2021).

According to FAOSTAT, fig world production is increasing in the last years (1,142,611 tons in 2009; 1,148,211 tons in 2014; and 1,315,588 tons in 2019). Due to the high perishability of figs, the whole fruit is mainly consumed in dried form. In addition, the food industry also applies this methodology to produce paste, concentrate and powder (Bey et al., 2013). According to the International Nut and Dried Fruit Council Foundation, the consumption of dried figs in 2020/2021 reached 148, 400 tons, and the largest consumers were Iran, the United States of America, Germany, France, India, and Italy.

The different parts of *F. carica*, leaves, pulp, peels, seeds, and latex, can be used for distinct applications (Palmeira et al., 2019). In general, potential functional food ingredients can be generated during the primary production, processing, manufacturing, distribution, retail, and final consumption of figs (Comunian et al., 2021). In the example of fig at primary production, the main by-products are the leaves but also the "imperfect" foods that do not meet the quality criteria to be commercialized. On the other hand, the main by-product from the processing and manufacturing of fresh figs, including juices, syrups, and jams, are fig peels.

Therefore, the leaves and peels represent the main by-products resulting from fig production that can be valorised due to their richness in bioactive molecules and potential nutritional value. Considering that peels represent approximately 27% of the total weight of the fig fruit, 366,928 tons of fig peels can be produced from this raw product, generally discarded as industrial waste (Mahmoudi et al., 2018). Fig peels and leaves characterization presents structurally diverse metabolites, including organic acids, phenolic acids, triterpenoids, flavonoids, tocopherols, and fatty acids. In Table 1, a summary of the most common bioactive compounds identified in fig by-products is shown.

To our best knowledge, the phytochemical composition and biological properties of *F. carica* by-products have been well documented. Still, there is a lack in their unique application as sources of functional ingredients in novel foods (Barolo et al., 2014; Mawa et al., 2013). Furthermore, they revealed that fig by-products exhibit higher phytochemical properties than the pulp of the fruit, fully justifying its valorisation and application (Ammar et al., 2015; Mahmoudi et al., 2018; Palmeira et al., 2019).

3. Extraction, separation, and refinement of Fig biomolecules

The use of Fig and Fig by-products as a source of food or pharmacological agents to improve human health dates back thousands of years. Figs are an excellent source of different biologically active biomolecules and are responsible for a wide range of bioactive effects: antioxidant, anti-inflammatory, anticancer, antimicrobial, anti-ageing, and wound healing effects (Abdel-Rahman et al., 2021; Boyacıoğlu et al., 2021). The main bioactive molecules present in various fig and fig by-products are terpenoids, carotenoids, phytosterols, volatile organic compounds, phenolic acids, and flavonoids, including anthocyanins, flavonols, flavan-3-ols, and flavanones (Pereira et al., 2017). The presence of these high value-added metabolites with attractive applications in food, cosmeceutical, and nutraceutical fields has reinforced the potential valorisation of these by-products. The use of fig as a low-cost source of bioactive compounds as ingredients for new products and/or nutraceuticals, or as raw materials for secondary processes, greatly depends on the availability of adequate extraction technology of these bioactive compounds (Alexandre et al., 2017; Bey et al., 2013). These vital extraction procedures, achieved through several conventional extraction methodologies, including soxhlet, maceration (M), and hydrodistillation, usually require organic solvents, a large volume of solvents, long extraction time, and high energy consumption (Taofiq et al., 2019). Some of these conventional methodologies have been traditionally applied to recover different high-value compounds from fig by-products using solvents, such as ethanol, methanol, acetone, or ethyl acetate either alone or in combination with water, as shown in Table 2.

There is a renewed effort to efficiently extract different bioactive compounds from plant biomass using sustainable and environmentally friendly technologies. These methodologies offer several advantages,

Table 1
Summary of the common bioactive compounds identified in fig by-products.

Group	Compounds	References
Leaves		
Flavonoids	Quercetin, luteolin, biochanin-A, luteolin-6C-hexose-8Cpentose, apigenin rutinoside, kaempferol rutinoside, quercetin rutinoside, quercetin glucoside, quercetin acetilglucoside, catechin, epicatechin	(Ammar et al., 2015; Pande & Akoh, 2010)
Organic acids	Oxalic, citric, malic, quinic, shikimic, ascorbic, succinic and fumaric acids	Pande and Akoh (2010)
Phenolic compounds	3-O-caffeoylquinic, 5-O-caffeoylquinic, ferulic, quercetin 3-O-glucoside, quercetin 3-O-rutinoside, psoralen, bergapten, pyrogallic, phenol, 3–5-dimethoxy, p-coumaric, phenolptethlin, pinocembrine, chysin, galangin, protocetchol, vinallin, cinnamic, quercetin, pinostrobin, pyrogallol, quinol, p-hydroxybenzoic acid, caftaric acid, gallic acid, ellagic scid, oleuropein, quercitin, rosmarinic acid, ligstroside, kampherol and caffeic acid	(Ammar et al., 2015; El Abdel-Aziz et al., 2020; Pande & Akoh, 2010)
Tocopherols	α-tocopherol	(Konyalioğ;lu et al., 2005)
Peels		
Organic acids	Oxalic, citric, malic, shikimic, fumaric, ascorbic, succinic, tartaric	(Palmeira et al., 2019; Pande & Akoh, 2010)
Phenolic acids	Gallic, ellagic, chlorogenic, syringic, 1,2,2′-Triferuloylgentiobiose, hydroxycaffeic, scopoletin, 3-feruloylquinic acid, p-coumaric, vanillic deoxyhexoside, vanillic di-deoxyhexoside, 5-*p*-coumaroylquinic, vanillic acid malonyl di-deoxyhexoside	(Ammar et al., 2015; Palmeira et al., 2019; Pande & Akoh, 2010)
Flavonoids	Catechin, epicatechin, luteolin-7-*O*-glucoside, apigenin, luteolin, rutin, cyanidin 3-rutinoside dimer, (epi) catechin-(4–8)-cyanidin 3-glucoside, (epi)catechin-(4–8)-cyanidin 3-rutinoside, cyanidin 3,5-diglucoside, (epi) catechin-(4–8)-cyanidin 3-rutinoside, (epi)catechin-(4–8)-Pg 3-rutinoside, (epi)catechin-(4–8)-Pg 3-rutinoside, Carboxypyrano-cyanidin 3-rutinoside, cyanidin 3-malonylglycosyl-5-glucoside, cyanidin 3-glucoside, cyanidin 3-rutinoside, Pg 3-glucoside, Pg 3-rutinoside, Pn 3-rutinoside, cyanidin 3-malonylglucoside, quercetin-*O*-hexoside-*O*-acetylhexoside, quercetin-3-*O*-rutinoside, quercetin-*O*-acetylhexoside, apigenin-C-hexoside-C-pentoside, taxifolin-*O*-hexoside, kaempherol-O-deoxyhexosyl-hexoside, apigenin-C-hexoside-C-pentoside, apigenin-2″-*O*-rhamnose-C-acetylhexoside, luteolin-6C-hexose-8Cpentose, kaempferol rutinoside, quercetin rutinoside, quercetin glucoside, quercetin acetilglucoside	(Palmeira et al., 2019; Pande & Akoh, 2010)
Other polyphenols	Syringaldehyde, scopoletin	Palmeira et al. (2019)
Tocopherols	α-tocopherol; β-tocopherol; γ-tocopherol; δ-tocopherol	Palmeira et al. (2019)

including high extraction efficiency in the shortest period and minimal energy consumption (Taofiq et al., 2019). Some common green and sustainable extraction methods utilised to obtain phenolic acids, anthocyanins, and furanocoumarins from Fig by-products, include ultrasound-assisted (UAE), microwave-assisted (MAE), pressurized liquid, supercritical fluid, and subcritical water extraction (Backes et al., 2018; Wang, Wu, et al., 2017; Yu et al., 2020). More emphasis has been made on these green extraction processes that are environmentally friendly and sustainable for sample preparation in recent years. In this regard, many researchers have explored green solvents such as ionic liquids (ILs), deep eutectic solvents (DESs), and natural deep eutectic solvents (NADESs) as substitutes to traditional toxic and volatile organic solvents that present serious environmental and human concerns to extract bioactive molecules from Fig by-products (Wang, Wu, et al., 2017). These solvents also offer many excellent advantages: cheapness, sustainability, biocompatibility, environmental friendliness, favourable thermal and chemical stabilities, high solubilizing capacity, and non-flammability (Wang, Wu, et al., 2017). However, the use of these green solvents at the industrial scale is still faced with some challenges. Hence, more work is needed in life cycle assessment to select the most environmentally favourable alternative solvent mixtures that effectively recover target biomolecules from different fig by-products.

3.1. Furanocoumarin

Furanocoumarins are tricyclic aromatic compounds containing the α-benzopyrone fused furan ring system. Psoralen, isopsoralen, and bergapten are the main furanocoumarin compounds found predominantly in the leaves and unripe fruit of *F. carica*. Furanocoumarins have also been recovered in whole fig fruit and fig latex, and have been reported to display anti-inflammatory, antipyretic, anticancer, and antibacterial properties (Belguith-Hadriche et al., 2017; Irudayaraj et al., 2016). They have also been used with UV radiation to treat autoimmune skin diseases such as psoriasis, vitiligo, and eczema via multiple pathways (Son et al., 2017). However, DNA damage and hepatoxicity have been associated with these low-polar compounds (Gaaliche et al., 2017). This phototoxic property is associated with their ability to react with nucleobases in DNA under the influence of UVA radiation, leading to a higher incidence of skin cancer (Son et al., 2017). Several research findings report a high incidence of furanocoumarins in Ficus leaves compared to other plant parts (Belguith-Hadriche et al., 2017; Wang, Wu, et al., 2017). Oxypeucedanin hydrate, psoralen, methoxypsoralen, and prenyl methoxypsoralen are the main furanocoumarins detected in the hydroethanolic leaves extract of two different cultivars from Tunisia prepared by dynamic maceration using HPLC-DAD-QTOF-MS (Belguith-Hadriche et al., 2017). A tailor-made DES made up of glycerol, xylitol, and D-Fructose was utilised to recover phenolic compounds and furanocoumarins from fig leaves. The UAE-DES system at the optimized condition (Temp: 64.46 °C, liquid-solid ratio:17.53%, and ultrasonic time: 24.43 min) yielded three major furanocoumarins, namely, psoralic acid-glucoside (16.34 mg/g), psoralen (15.22 mg/g) and bergapten (2.475 mg/g), accounting for more than 74% of the extract. The use of ionic liquids as extraction solvents in the recovery of phenolic compounds has also gained increasing attention in recent years, mainly due to their excellent solubilizing properties. Eight different pH-dependent ionic liquids were employed in a UAE system to recover psoralen (Wang et al., 2018) from the leaves of *F. carica*. Among all the tested solvents, [1-butyl-3-methylimidazolium bromide ([Bmim]Br)-citric acid mixture yielded 31.22 mg/g of psoralen (96.32%), being 1.45, 2.45 and 3.68 times more efficient than [Bmim]Br-water, ethanol-critic acid, and ethanol, respectively. This finding showed that the recovery of furanocoumarins is highly dependent on the solvent used.

3.2. Anthocyanins

Anthocyanins are phytochemicals from the flavonoid group that have garnered interest due to their extensive array of colours, typically ranging from bright red, purple and blue. This colouring potential, in addition to the numerous multifunctional health-promoting properties associated with anthocyanins, makes them potential natural food colourants (Lama et al., 2020). The amount of these compounds in *F. carica* is dependent on colour, fruit variety, harvest season, and drying processes employed (Pereira et al., 2017). Cyanidin-3-*O*-rutinoside and cyanidin-3-*O*-glucoside represent the two major cyanidins in ripened Fig fruits. They have been successfully recovered from Fig peel and other *F. carica* plant parts using M, heat-assisted extraction (HAE), UAE, and MAE techniques (Backes et al., 2018, 2020; Lama et al., 2020; Sedaghat & Rahemi, 2018). The recovery of anthocyanin pigments from Fig

Table 2
Recovered bioactive compounds from different by-products of *F. carica*.

Plant Part	Extraction Technique	Process Conditions	Class of compounds	Main compounds	References
Infructescences	UAE	*S*: 100% ethanol, *t*: 21 min, *P*: 310 W	Anthocyanins	Cyanidin-3-*O*-rutinoside, cyanidin-3-*O*-glucoside	Backes et al. (2018)
	HAE	*S*: 100% ethanol, *t*: 13.74 min, *T*: 35.64 °C			
	MAE	*S*:100% ethanol, *t*: 5 min, *T*:62.41 °C			
Latex	M	*S:* 80% methanol, *T*: 30 °C	Phenolic acids, flavones, and flavonols	Protochatechuic acid, catechin, chlorogenic acid, vanillic acid, caffeic acid, ferulic acid, sinapic acid, rutin, *p*-coumaric acid, cinnamic acid, quercetin, and apigenin	(Abdel-Aty et al., 2019b)
	M	*S/L*: 30 mg/mL, *T*: 37 °C, *t*: 24 h, *S*: 70% ethanol	Phenolic acids, flavones, flavonols, and furanocoumarins	Caffeoylquinic acid, dihydroxybenzoic acid, luteolin C-hexoside C-pentoside I, apigenin C-hexoside C pentoside, rutin, psoralen, methoxypsoralen and oxypeudacin hydrate	Belguith-Hadriche et al. (2017)
Leaves	M	*S/L*: 30 g/L, *T*: 37 °C, *t*: 24 h, *S*: 70% ethanol	Phenolic acids, flavones, flavonols, anthocyanins, flavan-3-ols, and furanocoumarins	Dihydroxybenzoic acid hexoside I, vanillic acid glucoside, dihydroxybenzoic acid hexoside II, gallic acid di-pentoside II, dihydrocaffeic acid hexose, caffeoylquinic acid hexoside III, luteolin C-hexoside C pentoside I, quercetin 3-*O*-glucoside, quercetin 3-*O*-(6″-malonyl) glucoside, quercetin, naringenin, (+)-catechin, genistein, 7-hydroxycoumarin, methoxypsoralen, psoralen	Ammar et al. (2015)
	M	*S/L*: 0.3 kg/L, *S*: hexane, ethyl acetate and methanol, *t*: 72hr	Furanocoumarins	Psoralen	Irudayaraj et al. (2016)
	MAE	*S/L*:19.95 mL/g, *T*: 40 °C, *t*: 10.27 min	Phenolic acids, flavonols, furanocoumarins	Caffeoylmalic acid, psoralic acid-glucoside, rutin, psoralen and bergapten	Yu et al. (2020)
	DES-MAE	*S/L*:17.53 mL/g, *T*: 64.46 °C, *t*: 24.43 min	Phenolic acids, flavonols, furanocoumarins	Caffeoylmalic acid, psoralic acid-glucoside, rutin, psoralen and bergapten	Wang, Wu, et al. (2017)
	M	*S*: 100% Methanol, *T*: 40 °C	Phenolic acids, flavonols, furanocoumarins	5-*O*-caffeoylquinic acid, ferulic acid, Quercetin 3-*O*-rutinoside, Psoralen, and Bergapten	Oliveira et al. (2012)
	IL-UAE	*T*: 60 °C, *t*: 30min, and *P*: 450 W	Furanocoumarins	Psoralic acid-glucoside and psoralen	Wang et al. (2018)
	M	*S*: Water, *S/L*: 50 g/L	Phenolic acids, flavan-3-ols, flavonols, s	Chlorogenic acid, 5-*O*-caffeoylquinic acid, dihydroxybenzoic acid, catechin, caffeoylmalic acid, rutin, isoquercetin, and kaempferol 3-*O*-glucoside	Ladhari et al. (2020)
Peel and Pulp	M	*T*: 25 °C, *t*: 60min	Phenolic acids, flavanonols, and flavonols	Caffeic acid hexoside, taxifolin-*O*-hexoside, 5-*O*-caffeoylquinic acid, vanillic acid di-deoxyhexoside, 5-*p*-coumaroylquinic acid, apigenin-C-hexoside-C-pentoside, Vanillic acid malonyl di-deoxyhexoside, Quercetin-3-*O*-rutinoside, quercetin-*O*-acetylhexoside, apigenin-2″-*O*-rhamnose-C-acetylhexoside	Palmeira et al. (2019)
	UAE	*S:* metanol (1%BHT), *t*:1h, *S/L:* 0.2 g/mL	Phenolic acids, flavan-3-ols, flavonols, and anthocyanidins	(+) Catechin, luteolin-8-glucoside, chlorogenic acid, rutin, methylGallate, cyanidin-3-malonyl-glucoside, (−) epicatechin, quercetin-3-*O*-glucoside, cyanidin 3-*O* rutinoside, kaempferol-3-*O*-glucoside, cyanidin-3-glucoside, cinamoyl glucoside, pelargonidin-3-glucoside	Sedaghat and Rahemi (2018)
	M	*S/L*:30 g/L, *T: 37°C, t:* 24 h, *S:70% ethanol*	Phenolic acids, flavones, flavonols, flavanonols, anthocyanins, flavan-3-ols, and furanocoumarins	Vanillic acid glucoside, gallic acid di-pentoside II, vanillic acid, dihydrocaffeic acid hexose, ferulic acid hexoside I, caffeic acid, apigenin C-hexoside C pentoside II, quercetin 3-*O*-glucoside, quercetin 3-*O*-(6″-malonyl) glucoside, quercetin, naringenin, (+)-catechin, taxifolin, prenylhydroxygenistein III, 7-hydroxycoumarin, cyanidin 3,5-diglucoside, cyanidin 3-malonylglucosyl-5-glucoside, cyanidin rutinoside III, methoxypsoralen, and psoralen	Ammar et al. (2015)
	UAE	*S*:100% ethanol, *S/L*: 180 g/L, *t*: 21 min, *P*:310 W	Anthocyanins	Cyanidin-3-*O*-rutinoside and cyanidin-3-*O*-glucoside	Backes et al. (2020)
	UMAE	*P*: 580.9W, *t*: 21.35 min, *S/L*: 24.66 mL/g	Pectin	Low-methoxyl pectin	Gharibzahedi et al. (2019b)
	M	*S*: 80% ethanol containing 1% conc. HCl, *t*: 20 min, *T*:25 °C	Flavonoids and phenolic acids	Quercitin-3-*O*-rutinoside, quercitin-3-acetylglucoside chlorogenic acid, ellagic acid, epicatechin, catechin, cyanidin-3-*O*-glucoside, cyanidin-3-*O*-rutinoside, and pelargonidin-3-O-rutinoside	Pereira et al. (2017)
Receptacle	M	*S*: cold methanol:water: acetic acid, (11:5:1 *v/v*), *S/L*: 0.1 g/mL	Anthocyanins	cyanidin 3-*O*-glucoside and cyanidin 3-*O*-rutinoside	Lama et al. (2020)
Stem bark	M	*S*: 80% methanol, *S/L*: 100 g/L, *T*: 40 °C	Flavonoids, phenolic acids, and oligosaccharides	Protocatechuic acid-*O*-arabinose, chlorogenic acid, vanillic acid-*O*-(rhamnose)3, rutin, and glucopyranoside oligomer	Raafat and Wurglics (2019)
Whole Fruit	UAE		Phenolic acid and flavonoid	Coumaric acid, methyl vanillate glucoside	Zhao et al. (2020)

(*continued on next page*)

Table 2 (*continued*)

Plant Part	Extraction Technique	Process Conditions	Class of compounds	Main compounds	References
		S/L: 0.76 g/mL, *S*: 95% ethyl alcohol, *F*: 40 kHz, *P*: 400 W, *t*: 30 min, *T*: 40 °C,			
	M	*S/L*: 60 g/L, *S*: 70% ethanol, *t*: 48h,	Furanocoumarins	Psoralen, 8-methoxypsoralen, angelicin, bergapten, rutaretin and pimpinellin	Marrelli et al. (2012)

BHT: 2.6-di-tert-butyl- 4-methylphenol, DES: Deep eutectic solvents, F: Frequency, HAE: Heat assisted extraction, IL: Ionic liquid, M: Maceration; MAE: Microwave assisted extraction; P-Power, S/L: Solid liquid ratio, S: Solvent, t-Time, T-Temperature, UAE: Ultrasound assisted extraction; UMAE: Ultrasound microwave assisted extraction.

infructescence was first reported by Backes et al. (2018), who optimized the interaction of several extraction variables using a circumscribed central composite design in HAE, UAE, and MAE. Overall, a high anthocyanin yield was obtained in the UAE system (9.01 ± 0.76 mg of cyanidin 3-rutinoside in dry weight extract residue) which was 1.5 and 1.2 times better than the MAE and HAE systems. Exogenous application

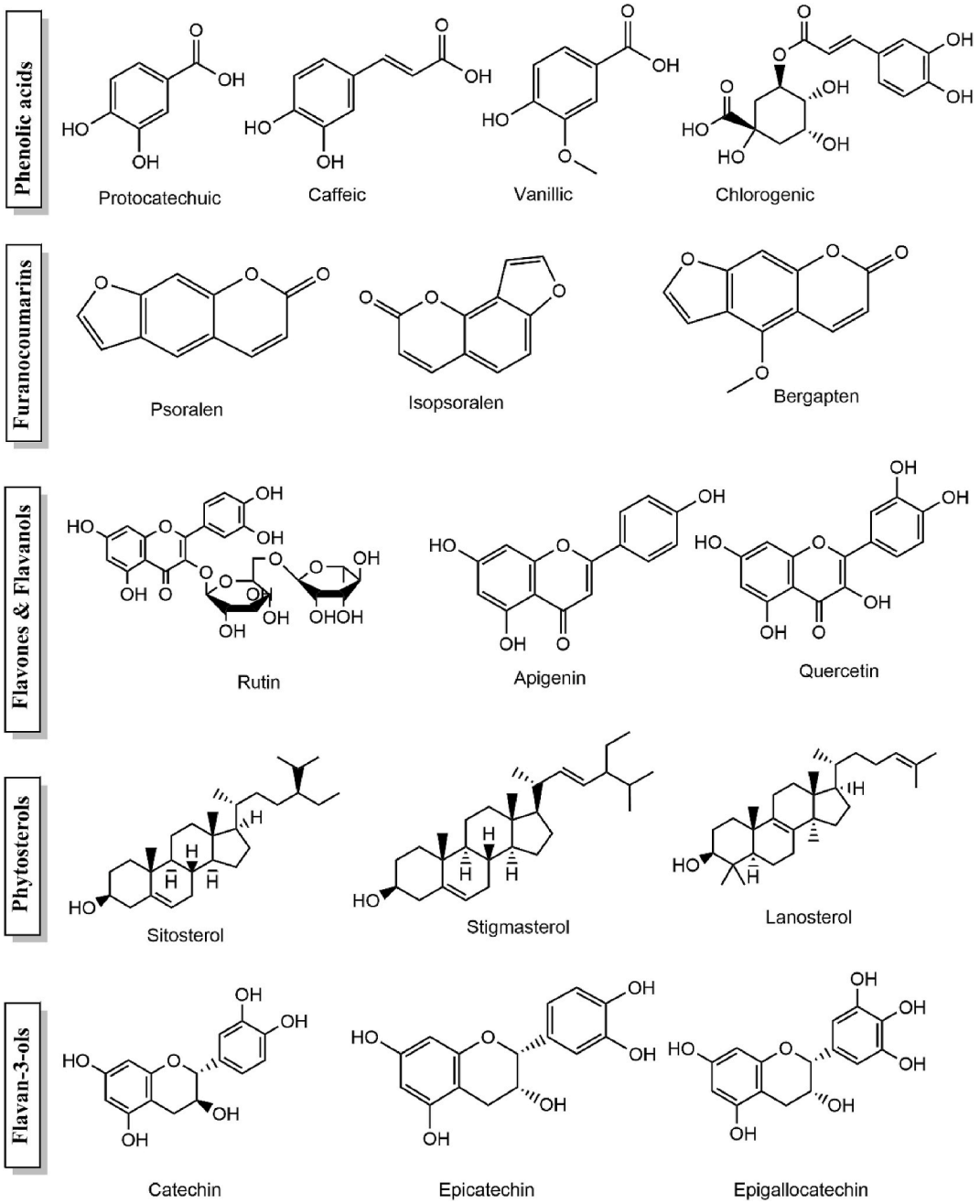

Fig. 1. Structures of the most common bioactive compounds found in *F. carica* by-products.

of phytohormones could increase phenolic content during postharvest ripening (Tao et al., 2020). Fresh fig receptacle subjected to exogenous application of abscisic acid enhanced the levels of cyanidin 3-*O*-glucoside (31.66 ± 4.24 μg/g fresh weight) and cyanidin 3-*O*-rutinoside (10.39 ± 3.2 μg/g fresh weight) after 72hr treatment, presenting significantly higher anthocyanin content in comparison with control fruits (Lama et al., 2020). Other anthocyanins and derivatives, including Cyanidin-3 malonyl-glucoside, Cyanidin 3,5-diglucoside, Cyanidin 3-rutinoside hexose, pelargonidin-3-glucoside, pelargonidin-3-*O*-rutinoside have also been quantified in fig peels, pulp, and whole fruits, as shown in Table 2. Overall, figs have shown to be important sources of anthocyanins currently being utilised in the food industry as a sustainable source of natural food colourants, with additional health-promoting benefits that might effectively prevent cardiovascular diseases, inflammation, cancers, diabetes, obesity, and other health challenges. Nevertheless, more work still needs to be conducted on the chemical stability and kinetics of anthocyanin colour degradation over time to obtain functional colourants with improved stability for the food industry.

3.3. Other phenolic compounds

Other phenolic compounds found in *F. carica* by-products include phenolic acids, flavonols, flavones, flavanones, flavanols, and flavanonols. These compounds have been the most important contributors to several health benefits associated with fig by-product extracts due to their multifunctional biological properties (Ammar et al., 2015; Raafat & Wurglics, 2019; Sedaghat & Rahemi, 2018). *F. carica* by-products have shown to be interesting sources of phenolic acids belonging to both subclasses (hydroxycinnamic acids and hydroxybenzoic acids derivatives). These derivatives (caffeic acid hexoside, caffeoylmalic, 5-*O*-caffeoylquinic, vanillic acid di-deoxyhexoside, 5-*p*-coumaroylquinic, vanillic acid malonyl di-deoxyhexoside, ferulic, sinapic, and *p*-coumaric acids) have been identified in the peel, and pulp extract obtained by maceration (Ammar et al., 2015; Palmeira et al., 2019), in the leaves extract using a surfactant-based microwave-assisted extraction (Yu et al., 2020) and deep eutectic solvents based-MAE (Wang, Wu, et al., 2017), and in the latex extract obtained by maceration (Abdel-Aty et al., 2019; Belguith-Hadriche et al., 2017). Quercetin represents the major flavonols founds in *F. carica* latex, leaves, peel and pulp extract (Abdel-Aty et al., 2019; Ammar et al., 2015; Palmeira et al., 2019; Sedaghat & Rahemi, 2018), while (+)-Catechin and (−) epicatechin, are the main flavan-3-ols found in the leaves, latex, and pulp extract (Pereira et al., 2017). These by-products, as shown in Table 2, are interesting sources of structurally diverse phenolic compounds (Fig. 1). However, more in-depth studies still need to be conducted to exhaustively describe all the compounds in these by-products and their related biological properties to foster their application in the food, pharmaceutical, and cosmetic industries, promoting a circular economy.

3.4. Pectin

Pectin is a complex polysaccharide consisting mainly of galacturonic acid units. It is predominant in the cell wall of fig peels, possessing unique chemical, physical, and biological properties. It is applied as a high value-added functional thickener, colourant, emulsifier, gelling, and stabilizing agent (Gharibzahedi et al., 2019a). Standard extraction methods used to recover pectin include hot acidic extraction, which is energy consuming, requiring chemicals with high corrosivity and negative environmental impacts (Çavdaroğlu et al., 2020). More sustainable systems such as UAE have been utilised to recover a high pectin yield from fig. Gharibzahedi et al. (2019b) obtained a pectin-rich extract from fig peels using a hybrid ultrasound-microwave assisted extraction (UMAE) system. They yielded 14.0% pectin with an average molecular mass of 6.89×10^3 kDa. The pectin rich extract also presented antioxidant and cytotoxic effects against Human non-small cell lung cancer (A549) and human hepatocellular carcinoma (HepG2) cells. Gharibzahedi et al. (2019a) also compared the best method to recover pectin from fig peels using hot water (HWE), UAE, MAE, and UMAE systems. The UMAE-pectin presented the highest galacturonic acid content (76.85%), the best emulsifying capacity, and emulsion stability at different storage conditions. Enzyme-assisted extraction is also promising in the recovery of bioactive compounds from various plant matrices on a large scale (Wang, Wu, et al., 2017). Chen et al. (2015) used a complex enzyme extraction (CEE) to obtain polysaccharide-rich extracts from dried figs. Response surface methodology (RSM) was employed and at the optimal condition, two heteropolysaccharides (FPs-1-1 and FPs-2-1) were fractionated by DEAE-Sepharose and Sephadex G-200 column chromatography, with a molecular weight of 1.52×10^6 and 4.75×10^5Da, respectively. Hence finding industrially scalable methods based on innovative technologies to recover and process pectin from Fig by-products remains the major bottlenecks. Some of these challenges are still responsible for the high, non-competitive market price, and low supply of pectin.

3.5. Ficin

F. carica typically exudes a milky juice (latex) from the various plant parts, including its fruits, stems, and seeds, containing diverse secondary metabolites, including terpenoids, organic acids, alkaloids, fatty acids, tannins, sterols, enzymes, and amino acids (Barolo et al., 2014). This juice is secreted in an appreciable amount, and its principal activity is the protection and self-healing of plants from external assaults. These diverse metabolites present in the latex are responsible for the biological properties of latex extracts, namely, antioxidant, cytotoxic and wound healing effects (Abdel-Aty et al., 2019; Boyacıoğlu et al., 2021). Ficin (EC:3.4.22.3), a cysteine endopeptidase enzyme, represents an essential component of Ficus latex. These enzymes are involved in triggering, regulating, and executing all sorts of biological and physiological processes such as protein degradation, cell maintenance, signalling, differentiation, growth, development, apoptosis, ripening, germination, senescence, and necrosis (Baeyens-Volant et al., 2015; Baidamshina et al., 2020; Zare et al., 2013). Several isoforms designated as A, B, C, D1, D2, and unnamed isoforms have been obtained from Ficus latex suspension (Hamed et al., 2020). A novel ficin, termed ficin E, was purified from fig latex using a combination of cation-exchange chromatography on SP-Sepharose Fast Flow, Thiopropyl Sepharose 4B and Fast Protein Liquid-gel filtration chromatography (Baeyens-Volant et al., 2015). Detailed characterization showed a molecular weight of 24,294 ± 10 Da, an optimum activity at pH 6.0 and 50 °C, and at 10 mM, the enzyme activity was not affected by divalent cations (Mg^{2+}, Mn^{2+}, and Ca^{2+}). One major obstacle regarding ficin recovery is its autolytic effect, using neighbouring native proteolytic proteins as substrate. Some studies showed that the rate of autolysis was significantly increased with increasing storage time, irrespective of the storage temperature (Zare et al., 2013). Nevertheless, the successful utilisation of ficin for several applications is still faced with certain drawbacks, including low stability during storage and thermal degradation. A three-phase partitioning (TPP) purification step was first reported by Gagaoua et al. (2014) as a simple, effective, and inexpensive procedure for the efficient recovery of ficin from Ficus latex. This method involves the salting-out, isoionic precipitation, and co-solvent precipitation process of the protein. The authors reported a 167% recovery of ficin from Ficus latex, with the enzyme presenting a molecular weight of 23.4 kDa and thermal stability between 40 and 70 °C for 1 h. Hence, Ficus latex is an important matrix to obtain a purified fraction of ficin for its widespread usage in biotechnological, food, pharmaceutical, and biomedical applications (Hamed et al., 2020).

3.6. Phytosterols

Phytosterols are triterpenes analogues of cholesterol naturally occurring in plants. They are well known for reducing intestinal

cholesterol absorption, contribute to cancer prevention, and lower the risk of cardiovascular and metabolic diseases (Bai et al., 2021). GC–MS analysis of the derivatised extract obtained from the leaves of two *F. carica* cultivars from Tunisia revealed the presence of campesterol, stigmasterol trimethylsilyl ether, β-sitosterol trimethylsilyl ether, α-amyrin, trimethylsilyl ether, lupeol, and β-amyrin (Gaaliche et al., 2017). β-sitosterol trimethylsilyl ether (1158 and 373 μg/g/DW) was the most abundant phytosterol in both the Bidhi and Hemri cultivar, respectively. Few studies have been conducted on the phytosterol composition in the unsaponifiable extract of figs and fig by-products (fruit, bark, stem, pith). Jeong and Lachance (2001) identified campesterol, stigmasterol, sitosterol, psi-taraxasterol as the principal phytosterols in the various fig tree components. The above authors reported that the phytosterol content was more abundant in the stem and bark components of the Fig tree. The latex of *F. carica* is considered an important source of several metabolites. Its phytochemical profile studied by Oliveira et al. (2010) identified six different phytosterols (betulol, lupeol, lanosterol, β-amyrin, β-sitosterol, and R-amyrin), being β-sitosterol (10564.3 ± 251.8 mg/kg) the most abundant. A Fig fruit latex bioactive extract obtained using trichloromethane and petroleum ether contains steroidal compounds designated as fatty acid glycosides-6-O-acyl-β-D-glucosyl-β-sitosterols, lupeol acetate, stigmasterol, and oleandiene (Ghanbari et al., 2019). These findings show that fig by-products (whole fruit, bark, latex, and leaves) are interesting sources of phytosterols; however, the role of these phytosterol rich extracts in several biological activities still need to be conducted.

3.7. Volatile compounds

Volatile organic compounds (VOCs) constitute multiple organic compounds, ubiquitous and effused from flowers, roots, stems, leaves, seeds, barks, fruits, and other unique storage parts of plants (Nawade, Shaltiel-Harpaz, Yahyaa, Kabaha, et al., 2020). They are utilised by different insects to locate resources for survival, including food, mates, prey, and predators from a very complex chemical environment, and in recent years they have become vital biomarkers for quality assessment in medicine, agriculture, pharmaceutics and environmental fields (Tiwari et al., 2020). Nawade, Shaltiel-Harpaz, Yahyaa, Kabaha, et al. (2020) showed that the volatile profile determined by SPME-GC–MS analysis of different pollinated and unpollinated fig were mainly fatty acid-derived volatiles, monoterpenes, sesquiterpenes, and phenylpropanoids. Among all the tested samples, six weeks pollinated figs presented the most abundant amount of VOCs (867.76 ng/g FW) being E−2-hexenal (160.84 ± 22.2 ng/g FW), benzaldehyde (361.06 ± 55.3 ng/g FW), 3-ethyl-4-methylpentan-1-ol (85.19 ± 11.26 ng/g FW), benzyl alcohol (68.94 ± 11.59 ng/g FW). The blend of VOCs specific for each week after pollination (WAP) were geranyl acetone, hydrocinnamaldehyde, α-thujene, terpinen-4-ol, δ-elemene, and α-terpineol common in unpollinated fruits; p-cymene at 0 WAP, farnesene at 1 WAP, styrene (6 WAP and 7WAP), and γ-cuprenene (0 WAP and 1 WAP). Three apocarotenoid volatiles 6-methyl-5-hepten-2-ol (MHOL), β-cyclogeraniol, and β-ionone were detected in pollinated and parthenocarpic fig fruits harvested at different time intervals, being MHOL and β-cyclogeraniol presenting remarkable levels after two weeks of pollination (Nawade, Shaltiel-Harpaz, Yahyaa, Bosamia, et al., 2020). The aroma of fresh figs has been attributed mainly to volatile compounds belonging to aldehydes, monoterpenes, ethers, and ketone groups. Villalobos et al. (2018) studied the changes in volatile compounds along time under different passive modified atmospheric conditions. Forty-eight compounds were identified, being aldehydes (14), esters (6), hydrocarbons (5), furans (5), alcohols (5), ketones (4) most widely represented.

4. Biological properties of Fig and Fig by-products

4.1. Antidiabetic activity

Nowadays, diabetes has become the most frequent endocrine illness. It is considered a metabolic disorder characterized by an imbalance of carbohydrate and lipid metabolism, giving rise to high glucose levels (Tripathy et al., 2021). Diabetes incidence is continuously growing, and synthetic antidiabetic drugs are the most widely used therapeutic intervention to treat the disease. There is a preference for natural-derived pharmaceutical formulations compared to their synthetic counter paths due to minimal efficacy and safety concerns associated with the latter. In this context, several plants have been demonstrated to exert antidiabetic activity, among which *Ficus* sp. is included (Deepa et al., 2018).

Fig extracts show antidiabetic activity through different mechanisms: 1) inhibiting glucose absorption in the intestinal tract through α-glucosidase and α-amylase inhibition, 2) enhancing glucose uptake via Glucose transporter type 4 (GLUT4) - phosphatidylinositol-3 kinase (PI3K)- serine/threonine-protein kinase, and 3) regulating glucose homeostasis via protein kinase (AMPK) activation (Fig. 2) (Deepa et al., 2018). On the other hand, they also show a strong connection with antioxidant activity. A study showed that IC_{50} of the leave extract was 5.50 μM (ascorbic acid = 4.8 μM). This activity was attributed to flavonoids (quercetin, kaempferol, and chrysin) and was also correlated with low levels of transaminases and protective effects in the case of diabetic neuropathy (Khan Dureshahwar, Mohammed Mubashir et al., 2019). In the same perspective, oral ingestion of ficusin, a known furanocoumarin, increased the expression of related antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (Gpx) in rat model (Irudayaraj et al., 2016, 2017). In general, most studies about the antidiabetic activity of *Ficus carica* L. extracts have been conducted in leaves (Deepa et al., 2018) (Table 3).

4.2. Anti-inflammatory activity

The term inflammation is somehow an old-fashioned concept. Traditionally, it is characterized by several symptoms (redness, warmth, pain and swelling) produced by the organism in response to external stimulus and the initialization of an elimination process mediated by defence cells and proinflammatory mediators. This process is implicated in the pathophysiology of several diseases, including atherosclerosis, obesity, depression, Alzheimer's, asthma, type 2 diabetes, and several cancer types (Netea et al., 2017). Moreover, even though it is not clear yet, there is evidence that diet and inflammation are connected (Pansarasa et al., 2019).

During this decade, several by-products of *F. carica,* including fruits, barks, leaves or latex, have been proved to exert anti-inflammatory properties (Lansky et al., 2008). However, these findings have been assessed *in vitro* mostly by measuring the inhibitory effect of the extracts on nitric oxide (NO) production in RAW 264.7 cells. In a recent study, ficucaricone A was shown as the most effective compound recovered from fig fruits extract, exerting an IC_{50} of 0.89 μM, presenting a better inhibitory effect than hydrocortisone (3.68 ± 0.16 μM) used as positive control (Liu et al., 2019) (Table 3). Furthermore, the inhibition of tumour necrosis factor-α (TNF-α) has also been tested on *F. carica* branches ethanolic extract showing inhibition of 70% at 12.5 μg/mL (Park et al., 2013) (Table 3).

Evaluating percentage reduction of carrageenan-induced paw oedema volume is the most widely utilised model to assess inflammatory effects *in vivo*. Oral treatment of rats with 100–200 mg/kg of *F. carica* ethanolic leaves extracts presented 18–76% inhibition of paw oedema volume (Ali et al., 2012; Patil & Patil, 2011) (Table 3). Similar percentages were obtained when treated with indomethacin intraperitoneally (79%) but administrated in a much lower dose (10 mg/kg) (Patil & Patil, 2011). In the same studies, the hydroalcoholic extract of

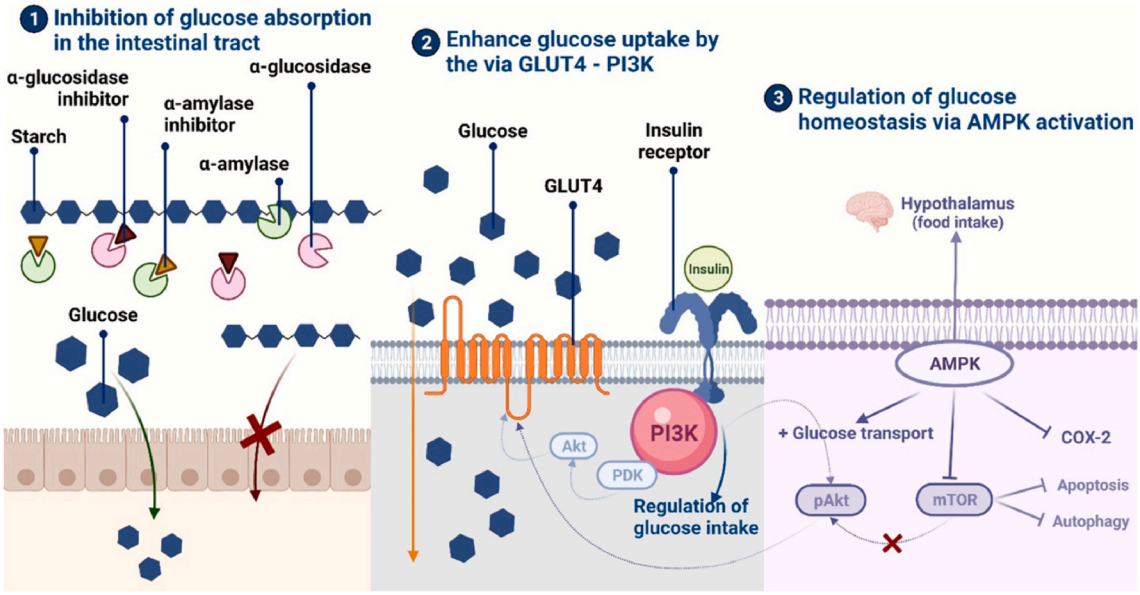

Fig. 2. Mechanism of action of fig extracts antidiabetic activity. Created with BioRender.com.

F. carica leaves showed related antioxidant activity with a superoxide radical scavenging activity of IC_{50} = 10 mg/mL, hydroxyl radical scavenging activity of IC_{50} = 52.5 mg/mL, and lipid peroxide scavenging activity of IC_{50} = 136 mg/mL (Ali et al., 2012). Also, the anti-angiogenic effect was observed using haemoglobin content reduction up to 56% when ethanolic extract of *F. carica* leaves was administered in a mouse model, displaying a similar effect to diclofenac sodium (Eter-af-Oskouei et al., 2015).

4.3. Anti-tumor and immunomodulatory properties

Cancer is one of the diseases with the highest mortality in the world. The side effects of chemotherapy and radiotherapy have prompted the search for novel, safe, and effective cancer therapeutic biomolecules from natural sources (Garcia-Oliveira et al., 2021). *F. carica* has been suggested as a possible candidate since ancient knowledge gathered different preparations of this plant indicated for tumours treatment (Lansky et al., 2008).

Latex has been highlighted as a potential inhibitor of cell proliferation (Abdel-Aty et al., 2019; AlGhalban et al., 2021; Boyacıoğlu et al., 2021) (Table 3). The cytotoxic effect of *F. carica* leaf latex assessed in breast cancer cells (MDA-MB-231) showed a higher cytotoxic effect and involved different molecular mechanisms of action in comparison to *F. salicifolia* (AlGhalban et al., 2021). On the contrary, *F. carica* latex extract showed no cytotoxic effect on human normal melanocyte cells (HFB4) in comparison to doxorubicin (86.20 ± 8.88), a known chemotherapeutic agent (Abdel-Aty et al., 2019). In human prostate (PC3) and colon (HT-29) cancer cell lines, good inhibition results were achieved, although it was suggested that ficin peroxidase-like activity was not sufficient to explain all the results (Boyacıoğlu et al., 2021). Recently, *F. carica* extracts have been administered *in vivo* to suppress the side effects associated with the use of specific drugs in cancer therapies, including 5-fluorouracil and cisplatin, by taking advantage of its synergistic effect with extra virgin olive oil (Elghareeb et al., 2021).

The ethanolic and acetone extract of the leaves from *F. carica* showed inhibition of the viability of different cell lines (Abdel-Rahman et al., 2021; Mustafa et al., 2021). These results also demonstrated a relation between anti-tumour properties and antioxidant activity, which is in turn caused by the inhibition of certain enzymes, including tyrosinase and α-glucosidase (Meziant et al., 2021). Regarding the mechanism of action, *F. carica* caused inhibition of mRNA expression of ERK1/2, CREB, GSK-3a/B, and AMPKa1 and confirmed downregulation of ERK, CREB and Akt gene expression. ERK and CREB biomarkers play key roles in cellular proliferation, whereas ERK and Akt indicate acute toxicity and their pathways are related to anoikis programmed cell death (AlGhalban et al., 2021). Furthermore, another study reported down-regulation of the expression of Bcl-2, TP53, and cyclin-dependent kinases (CDK1, CDL5, CDK9 and CDK10) when cells were treated with *F. carica* leaves extract (Mustafa et al., 2021) (Table 3).

In recent years the correlation between bioactive compounds and immunomodulatory activity has been established, which is especially related to anti-tumour and anti-inflammatory properties. Du et al. (2018) isolated a polysaccharide able to modulate the immune response and stimulate the production of TNF-α, interleukin-6 (IL-6) and NO in macrophages by upregulating the expression of p-p38, p-ERK, p-JNK, IκB-α, and p65, through the mitogen-activated protein kinase (MAPK) and the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signalling pathways (Table 3). On this basis, a recent study tested a fermented fig extract in immunosuppressed mice treated with cyclophosphamide and showed an increased production of interferon-γ (IFN-γ), IL-4, IL-6, and TNF-α compared to control animals, consistent with previous results (Zhao et al., 2020).

4.4. Cardioprotective and neuroprotective activity

Cardioprotection is a general term used to group all the mechanisms that are related to the prevention of myocardial damage. However, this definition can be extended to all cardiovascular diseases and those factors that can improve the risk, such as hypertension or diabetes and the conjunction of three of them, the metabolic syndrome (Gonzalez-Chávez et al., 2018).

In this sense, different plants from the genus *Ficus* spp. have shown their potential as anti-hypertensive agents (Alamgeer et al., 2017). *F. carica* methanolic extract from ripe fruits reduced blood pressure levels in normal and hypertensive rats and a reduction of the contraction force and heart rate on the *in vitro* experiments. These effects were related to the antioxidant properties of its phenolic compounds (Alamgeer et al., 2017) (Table 3). In addition, thrombosis is one of the pathologies hidden behind cardiovascular diseases, including anti-coagulation, fibrinolysis, and platelet activity (Shore-Lesserson, 2002). For this purpose, different properties, including anticoagulant, procoagulant, and antiplatelet activity, have been assessed in *F. carica* latex and

Table 3
Biological properties of fig and fig by-products.

By-product	Compound	Assay	Dose	Results	Ref
Antidiabetic activity					
Leaves	Ficusin	*In vivo* diabetic rats: FBG levels, BW, PI level, TC, TG, HG, carbohydrate metabolizing enzymes	250 and 500 mg/kg	Decreased FBG and PI levels, BW, TC, TG, HG, PI, enzymes	Irudayaraj et al. (2017)
Leaves	Ficusin	*In vivo* diabetic rats: BW, PI level, HG, TC, TG, FFA, liver markers	20 and 40 mg/kg	Decreased PI levels, BW, AST, ALP, ALP, HG, TC, TG, FFA	Irudayaraj et al. (2016)
Leaves	Nd	HepG2: MTT, WB, q-PCR (hepatic gluconeogenic enzymes)	–	IC_{50} = 82.29 μg/mL. Reduced expression levels via AMPK.	Zhang et al. (2019)
		In vivo diabetic mice: FBG levels, PI level, TC, TG,	1000 mg/kg	Decreased FBG levels and TG. No effect on TC, PI levels	
Leaves	Quercetin, kaempferol, and chrysin	*In vivo* diabetic rats: BGL and neuropathy, liver, kidney markers	25–100 mg/kg	Decreased BGL. Increased PWL and SGOT, SGPT, BUN expression	(Khan Dureshahwar, Mohammed Mubashir et al., 2019)
Anti-inflammatory activity					
Leaves	Steroids	*In vivo* rats: PEV	100 and 200 mg/kg	Inhibition % = 48–57%	Ali et al. (2012)
Leaves	Nd	*In vivo* rats: PEV, CPG	300–600 mg/kg	Inhibition % = 18–76% (PEV), 21–72% (CPG)	Patil and Patil (2011)
Branches	Nd	RAW 264.7: NO production, TNF-α inhibition	50 μg/mL	Inhibition % = 100% (NO), 70% (TNF-α)	Park et al. (2013)
Fruits	Ficucaricone A	RAW 264.7: NO production	–	IC_{50} = 0.89 μM	Liu et al. (2019)
Immunomodulatory and anti-tumour activity					
Leaves latex	nd	MDA-MB-231 cells: MTT assay	0.1–1%	Inhibition % = 60–85%	AlGhalban et al. (2021)
Latex	Ficin	HT-29 and PC3 cells, 72 h	–	IC_{50} = 23–38 μg/mL (HT-29), 14–24 μg/mL (PC3)	(Boyacıoğlu et al., 2021)
Latex	PC (rutin, chlorogenic)	HepG2, MCF7, A549, HL-60 and HCT116 cells	–	IC_{50} = 30–40 μg/mL (HepG2, MCF7, HCT116)	Abdel-Aty et al. (2019)
Leaves and stems	PC (gallic acid, quercetin)	HepG2 cells	–	IC_{50} = 0.179 mg/mL	Mustafa et al. (2021)
Leaves	Ethanolic extract	MCF7, HepG2, CaCo-2, Hep-2 cells	1,250–5,000 mg/mL	Inhibition % = 60–80%	Abdel-Rahman et al. (2021)
Fruits	Polysaccharide	RAW 264.7 macrophages	10–40 μg/mL	Increased phagocytosis	Du et al. (2018)
Cardioprotective and neuroprotective activity					
Fruits	PC	*In vivo* rats: Antihypertensive effect	1,000 mg/kg	SBP, MBP, DBP <100 mmHg	Alamgeer et al. (2017)
		In vitro perfused rabbit heart: cardiac parameters	10^{-9}-10^{-2} mg/mL	Reduced contraction force and heart rate	
Latex	Ficin	APTT and PT	13–65 mg	APTT 70–134%, PT 50–200%	Hamed et al. (2020)
Fruits	H_2O-ethanolic extract	*Ex vivo* model of human platelets	0.6–0.12 mg/mL	Antiplatelet effect against adrenaline	Gilani et al. (2008)
Peels	Flavonoids	Tyrosinase and α-glucosidase inhibition	10 mg/mL	IC_{50} = 0.09–0.45 mg/mL (tyrosinase), 1.18–3.38 mg/mL (α-glucosidase)	Meziant et al. (2021)

Abbreviations: Fasting Blood Glucose (FBG), Plasma Insulin (PI), Body Weight (BW), Total Cholesterol (TC), Triglycerides (TG), Free Fatty Acids (FFA), Hepatic Glycogen (HG), Not determined (nd), Blood Glucose Level (BGL), Serum glutamic oxaloacetic (SGOT), Serum glutamic pyruvic transaminase (SGPT), Blood urea nitrogen (BUN), Paw withdrawal latency (PWL), Paw Oedema Volume (PEV), Cotton Pellet Granuloma (CPG), Phenolic compounds (PC), Human glioblastoma (U87), systolic blood pressure (SBP), mean blood pressure (MBP), diastolic blood pressure (DBP), Activated partial thromboplastin time (APTT), Prothrombin time (PT).

fruits (Gilani et al., 2008; Hamed et al., 2020) (Table 3). A more recent study evaluated the effects of *F. carica* on the activity of enzymes related to metabolic syndrome such as α-amylase, α-glucosidase, and lipase, associated with diabetes and obesity (Mopuri et al., 2018).

Neurodegenerative disorders are a major concern for public health. *F. carica* active metabolites from the mesocarp showed a protective effect on the neuroblastoma (SHSY5Y) cell line (Khojah & Edrada-Ebel, 2017). In another study, fig peels extract caused the inhibition of enzymes related to neuroprotection (tyrosinase and α-glucosidase) with IC_{50} levels ranging from 0.1 to 3.5 mg/mL (Meziant et al., 2021).

4.5. Anti-ageing, wound healing, and antimicrobial properties

Ageing is a natural process that can be intrinsic and associated with specific genes, signalling pathways, and certain antioxidant mechanisms (Cătană et al., 2018). In this sense, even though there are no specific studies on this property for *F. carica*, the wide variety of reports about the antioxidant potential and related properties makes it feasible to extrapolate that its by-products could be a source of potential anti-ageing metabolicompounds (Abdel-Rahman et al., 2021; Ali et al., 2012; Irudayaraj et al., 2016, 2017; Meziant et al., 2021; Mustafa et al., 2021). In the case of wound healing, a recent study showed a reduced dose-dependent migration in cells treated with *F. carica* latex, showing an anti-metastatic effect (AlGhalban et al., 2021). Also, ficin, extracted from *F. carica* latex, improved the infected wound healing on rats acting as a biofilm (Baidamshina et al., 2020).

Fig by-products have also been tested for other properties such as antimicrobial activity (Souhila Mahmoudi et al., 2016). The hexane extract of latex from unripe fruits showed antimicrobial activity against *Staphylococcus aureus, S. saprophyticus* and *S. epidermidis*, showing low minimal inhibitory concentration (MIC) values between 19 and 39 μg/mL (Lazreg-Aref et al., 2012). More recently, the peels from *F. carica* were tested against nine bacteria; the best results were MIC values of 2,5 μg/mL for *Escherichia coli*, methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-sensitive *Staphylococcus aureus* (MSSA) (Backes et al., 2020). Another study screened 13 species of *Ficus* spp. and found that three were effective antimicrobials against foodborne pathogens (Elhawary et al., 2018). Therefore, the antimicrobial potential of fig and its by-products needs to be further explored.

5. Development of novel functional foods: recent advancements and challenges

There are newly emerging consumer demands for food formulations with enhanced nutritional values, enriched with health-promoting biomolecules, and improved functional and physical food properties (Gemechu, 2020). However, with the growing population, natural resources are faced with continuous depletion, and as such, there is a renewed interest to sustainably mobilize food by-products as sources of functional ingredients, thereby preventing biodiversity loss and sustainable use of the terrestrial ecosystem.

Food additives and colourants are critical components in the food industry to enhance food quality and safety, appearance during processing, storage, and packaging (Sun et al., 2021). There is a current increasing consumer demand for colourants derived from natural sources to enhance the nutritional and biological efficacies such as antioxidant, anticancer, anti-obesity of the food formulation. *F. carica* contains anthocyanins and carotenoids with a bright red, purple, and blue colouration. There is a renewed interest to explore these anthocyanin-rich bioresidues as sustainable sources of potential natural food colourants. In this regard, anthocyanin-rich extracts were obtained from the peels of *F. carica* using a UAE (Backes et al., 2020). The bioactive extract presented antioxidant, antimicrobial, and no cytotoxic effect in a normal cell line model followed by incorporating two dairy confectionery products (doughnut icings and "beijinho" pastry). The anthocyanin-rich extract maintained the colouring effect and improved the texture properties of the final food formulation for at least 24 h without influencing its nutritional properties (moisture content, ashes, proteins, fat, and carbohydrates). The preservative potential of aqueous extract from fig leaves, olive leaves, and their mixture was conducted by Abdel-Aziz et al. (2020). The results showed that 0.6% of these extracts extended the shelf life of pasteurized buffalo milk for 5–16 days, without influencing its sensorial properties. The strong catalytic effect of ficin has enhanced its utilisation in the dairy industry to develop milk protein hydrolysates with improved bioavailability and as a clotting ingredient in cheese production (Aider, 2021).

Hence, extracts obtained from *F. carica* either solely or in combination with other extracts can contribute further to developing new functional food additives for improved nutrition and health benefits. Despite these promising possibilities, there are some drawbacks associated with the chemical instability of numerous naturally derived food colorants and additives, and as such, more studies still need to be conducted to improve these challenges.

Despite the enormous health effects of natural extracts and their related metabolites, their utilisation either directly as food or their incorporation into food formulations are faced with several challenges during storage and food processing, thereby rendering these bioactive ingredients physically, chemically, and/or enzymatically unstable. This instability leads to the degradation and loss of functionality of the bioactive extracts (Dias et al., 2015). Microencapsulation techniques have been adopted in recent times to improve the retention time of these bioactive in the food, allow for their controlled release, preserve the stability of the bioactive compounds during processing and storage, prevent undesirable interactions with other food matrices, mask unpleasant taste, and increase bioavailability while maintaining the functional properties of the bioactive ingredient and ensuring their efficient absorption in the human digestive system (Ye et al., 2018). A nutritious fruit snack formulation based on dried fig powder and coated with a hydrocolloid solution containing Persian gum and xanthan gum, and chocolate as the outer shell was developed by Yeganehzad et al. (2020). The results showed that the hydrocolloid coatings were effective in lowering the hardness and adhesiveness of the coated samples. Sensory properties of the formulations in terms of appearance, flavour, texture, and total acceptance by 35 panellists considering ethical regulations and international standards showed Total acceptance as the concentration of hydrocolloid coating increase; with the snack formulated with 1.5% Persian gum being the best.

Current food engineering and packaging research has been focused on the development of a new generation of sustainable bio-based packaging materials that maintain and improve the quality of food products. This is due to the growing consumer interest in consuming fresh food products such as fruits, vegetables, fish, shrimp, and meats with short shelf life (Khezrian & Shahbazi, 2018). An active edible coating with antimicrobial activity against *Listeria innocua* was recently developed using pectin rich extracts obtained from Fig to increase the quality of fresh melon (Çavdaroğlu et al., 2020). Properties such as surface wettability, oxygen permeability, and tensile strength of the coating materials were promising. In addition, melons coated with the developed films gave significantly lower Listeria counts in comparison with uncoated controls. Khezrian and Shahbazi (2018) developed novel antimicrobial packaging films based on nanomontmorillonite-chitosan (MMT-Ch) and nanomontmorillonite-carboxymethyl cellulose (MMT-CMC) incorporated with different concentrations of *Ziziphora clinopodioides* Lam essential oil in combination with *F. carica* extract. The films were found to be very effective in preserving the shelf life of minced camel's meat. The microbial load (*Listeria monocytogenes* and *Escherichia coli*) decreases significantly, and the result confirms the viability of the produced films as promising packaging materials for minced camel's meat. Moreover, sensory parameters such as odour, colour, and overall acceptability were improved significantly in comparison with the untreated control. The authors mentioned that these films formulated with bioactive ingredients constitute a future-oriented direction of food packaging due to their biodegradability, biocompatibility, high-quality film-forming capability, edibility, and non-toxicity. Therefore, they can be explored at the industrial scale to prevent microbial spoilage, lipids peroxidation, and protein oxidation in meats. However, more findings are needed to determine the controlled release of these active ingredients.

The use of fig by-products in food formulation development has shown promising results. However, studies related to factors limiting their use are significantly lacking. In general, allergens are one of the most common limitations in food fortification. Although not very well reported, irritation is an unusual allergic reaction associated with *F. carica*, mainly due to the presence of ficin (Urbani et al., 2020). A 17 kDa allergen homologous to Bet v I allergen was found in fresh and dried figs. Clinical trials in patients with birch pollen allergy revealed a very high prevalence of cross-sensitization (Hemmer et al., 2010). Hence, more work still needs to be conducted to identify and define the structure-activity relationships of potential allergens from fig by-products. Overall, by-products from *F. carica* constitute an essential source of bioactive compounds with interesting health-promoting properties that may be applied in the development of innovative food and pharmaceutical formulations. Therefore, their utilisation along the value chain should be stimulated.

6. Conclusions and future perspectives

Fig by-products, namely leaves, peels, pulp, seeds, and latex, have been explored as a source of bioactive compounds for their application in the food, cosmetic or pharmaceutical industry. However, even though their bioactive and nutritional composition is widely researched, their biological properties are in some cases poorly studied, and few examples of applications have been described. Antidiabetic, anti-inflammatory, anti-tumour, and immunomodulatory properties are the most studied, whereas others such as cardio or neuroprotective properties have been less explored. Despite these promising biological properties, an enormous gap still exists for its exploration using bioassay-guided isolation and fractionation.

Considering the different fig by-products and their specific characteristics, one of the challenges towards valorisation is the correct choice of the extraction technique. Extraction methodologies involving ionic liquids and deep eutectic solvents have been successfully used to recover

furanocoumarins and pectin from Fig leaves and peels, enhancing the drive for a green and sustainable paradigm shift. However, a techno-economic assessment of these novel extraction systems and solvents involving their energy expenses, costs, and carbon dioxide (CO_2) emissions are significantly lacking. Hence, these methods should be applied to assess the economic ramifications of utilising these novel technologies on an industrial scale.

On the other hand, new trends should be considered for the screening of biological properties, such as using microencapsulation and nano-encapsulation technologies to enhance bioavailability and control the release of bioactive ingredients. Nanoparticles have been used as carriers for *F. carica* extracts, demonstrating an antitumoral effect in animal models. Therefore, it is expected that a holistic approach can be adopted that promotes the use of recovered pectin from fig by-products as emulsifying wall material with defined functionalities in the development of these microcapsules and nanoparticles, thereby opening more possibilities for fig by-products valorisation. The utilisation of Fig by-products as functional ingredients in novel food formulation development has shown promise in their use as colourants, texture enhancers, preservatives, and biodegradable coating materials. Although this final stage still needs further research to understand the effectiveness, efficiency, and safety of these fig derived ingredients in a unique product. Overall, more work needs to be done in terms of industrial scale-up and life cycle assessment to design efficient procedures intended at obtaining target biomolecules from fig by-products and developing innovative food formulations based on their health-promoting properties.

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References

Abdel-Aty, A. M., Hamed, M. B., Salama, W. H., Ali, M. M., Fahmy, A. S., & Mohamed, S. A. (2019). Ficus carica, Ficus sycomorus and Euphorbia tirucalli latex extracts: Phytochemical screening, antioxidant and cytotoxic properties. *Biocatalysis and Agricultural Biotechnology, 20*(June), Article 101199. https://doi.org/10.1016/j.bcab.2019.101199

Abdel-Aziz, M., Darwish, M. S., Mohamed, A. H., El-Khateeb, A. Y., & Hamed, S. E. (2020). Potential activity of aqueous fig leaves extract, olive leaves extract and their mixture as natural preservatives to extend the shelf life of pasteurized buffalo milk. *Foods, 9*(5), 1–22. https://doi.org/10.3390/foods9050615

Abdel-Rahman, R., Ghoneimy, E., Abdel-Wahab, A., Eldeeb, N., Salem, M., Salama, E., & Ahmed, T. (2021). The therapeutic effects of Ficus carica extract as antioxidant and anticancer agent. *South African Journal of Botany, 141*, 273–277. https://doi.org/10.1016/j.sajb.2021.04.019

Aider, M. (2021). Potential applications of ficin in the production of traditional cheeses and protein hydrolysates. *JDS Communications, 2*(5), 233–237. https://doi.org/10.3168/jdsc.2020-0073

Alamgeer, Iman, S., Asif, H., & Saleem, M. (2017). Evaluation of antihypertensive potential of Ficus carica fruit. *Pharmaceutical Biology, 55*(1), 1047–1053. https://doi.org/10.1080/13880209.2017.1278611

Alexandre, E. M. C., Araújo, P., Duarte, M. F., de Freitas, V., Pintado, M., & Saraiva, J. A. (2017). High-pressure assisted extraction of bioactive compounds from industrial fermented fig by-product. *Journal of Food Science & Technology, 54*(8), 2519–2531. https://doi.org/10.1007/s13197-017-2697-2

AlGhalban, F. M., Khan, A. A., & Khattak, M. N. K. (2021). Comparative anticancer activities of Ficus carica and Ficus salicifolia latex in MDA-MB-231 cells. *Saudi Journal of Biological Sciences, 28*(6), 3225–3234. https://doi.org/10.1016/j.sjbs.2021.02.061

Ali, B., Mujeeb, M., Aeri, V., Mir, S. R., Faiyazuddin, M., & Shakeel, F. (2012). Anti-inflammatory and antioxidant activity of Ficus carica Linn. leaves. *Natural Product Research, 26*(5), 460–465. https://doi.org/10.1080/14786419.2010.488236

Ammar, S., Del Mar Contreras, M., Belguith-Hadrich, O., Segura-Carretero, A., & Bouaziz, M. (2015). Assessment of the distribution of phenolic compounds and contribution to the antioxidant activity in Tunisian fig leaves, fruits, skins and pulps using mass spectrometry-based analysis. *Food & Function, 6*(12), 3663–3677. https://doi.org/10.1039/c5fo00837a

Aradhya, M. K., Stover, E., Velasco, D., & Koehmstedt, A. (2010). Genetic structure and differentiation in cultivated fig (Ficus carica L.). *Genetica, 138*(6), 681–694. https://doi.org/10.1007/s10709-010-9442-3

Backes, E., Leichtweis, M. G., Pereira, C., Carocho, M., Barreira, J. C. M., Kamal Genena, A., José Baraldi, I., Filomena Barreiro, M., Barros, L., & Ferreira, I, C. F. R. (2020). Ficus carica L. and prunus spinosa L. extracts as new anthocyanin-based food colorants: A thorough study in confectionery products. *Food Chemistry, 333* (February), Article 127457. https://doi.org/10.1016/j.foodchem.2020.127457

Backes, E., Pereira, C., Barros, L., Prieto, M. A. A., Genena, A. K. K., Barreiro, M. F. F., & Ferreira, I. C. F. R. (2018). Recovery of bioactive anthocyanin pigments from Ficus carica L. peel by heat, microwave, and ultrasound based extraction techniques. *Food Research International, 113*, 197–209. https://doi.org/10.1016/j.foodres.2018.07.016

Badgujar, S. B., Patel, V. V., Bandivdekar, A. H., & Mahajan, R. T. (2014). Traditional uses, phytochemistry and pharmacology of Ficus carica: A review. Http://Dx.Doi.Org/10.3109/13880209.2014.892515 https://doi.org/10.3109/13880209.2014.892515, 52, 11, 1487, 1503.

Baeyens-Volant, D., Matagne, A., El Mahyaoui, R., Wattiez, R., & Azarkan, M. (2015). A novel form of ficin from Ficus carica latex: Purification and characterization. *Phytochemistry, 117*, 154–167. https://doi.org/10.1016/j.phytochem.2015.05.019

Baidamshina, D. R., Koroleva, V. A., Trizna, E. Y., Pankova, S. M., Agafonova, M. N., Chirkova, M. N., Vasileva, O. S., Akhmetov, N., Shubina, V. V., Porfiryev, A. G., Semenova, E. V., Sachenkov, O. A., Bogachev, M. I., Artyukhov, V. G., Baltina, T. V., Holyavka, M. G., & Kayumov, A. R. (2020). Anti-biofilm and wound-healing activity of chitosan-immobilized Ficin. *International Journal of Biological Macromolecules, 164*, 4205–4217. https://doi.org/10.1016/j.ijbiomac.2020.09.030

Bai, G., Ma, C., & Chen, X. (2021). Phytosterols in edible oil: Distribution, analysis and variation during processing. *Grain & Oil Science and Technology, 4*(1), 33–44. https://doi.org/10.1016/j.gaost.2020.12.003

Barolo, M. I., Ruiz Mostacero, N., & López, S. N. (2014). Ficus carica L. (Moraceae): An ancient source of food and health. *Food Chemistry, 164*, 119–127. https://doi.org/10.1016/J.FOODCHEM.2014.04.112

Belguith-Hadriche, O., Ammar, S., Contreras, M. del, M., Fetoui, H., Segura-Carretero, A., El Feki, A., & Bouaziz, M. (2017). HPLC-DAD-QTOF-MS profiling of phenolics from leaf extracts of two Tunisian fig cultivars: Potential as a functional food. *Biomedicine & Pharmacotherapy, 89*, 185–193. https://doi.org/10.1016/j.biopha.2017.02.004

Bey, M. B., Louaileche, H., & Zemouri, S. (2013). Optimization of phenolic compound recovery and antioxidant activity of light and dark dried fig (Ficus carica L.) varieties. *Food Science and Biotechnology, 22*(6), 1613–1619. https://doi.org/10.1007/s10068-013-0258-7

Boyacıoğlu, O., Kara, B., Tecimen, S., Kılıç, M., Delibaş, M., Erdoğan, R., Özdemir, E., Bahadır, A., & Örenay-Boyacıoğlu, S. (2021). Antiproliferative effect of Ficus carica latex on cancer cell lines is not solely linked to peroxidase-like activity of ficin. *European Journal of Integrative Medicine, 45*(March). https://doi.org/10.1016/j.eujim.2021.101348

Cătană, C. S., Atanasov, A. G., & Berindan-Neagoe, I. (2018). Natural products with anti-aging potential: Affected targets and molecular mechanisms. *Biotechnology Advances, 36*(6), 1649–1656. https://doi.org/10.1016/j.biotechadv.2018.03.012

Çavdaroğlu, E., Farris, S., & Yemenicioğlu, A. (2020). Development of pectin–eugenol emulsion coatings for inhibition of Listeria on webbed-rind melons: A comparative study with fig and citrus pectins. *International Journal of Food Science and Technology, 55*(4), 1448–1457. https://doi.org/10.1111/ijfs.14458

Chen, R., Li, H., Li, S., Jin, C., & Lu, J. (2015). Extraction optimization, preliminary characterization and immunological activity of polysaccharides from figs.

International Journal of Biological Macromolecules, 72, 185–194. https://doi.org/10.1016/j.ijbiomac.2014.08.021

Comunian, T. A., Silva, M. P., & Souza, C. J. F. (2021). The use of food by-products as a novel for functional foods: Their use as ingredients and for the encapsulation process. *Trends in Food Science & Technology, 108*, 269–280. https://doi.org/10.1016/j.tifs.2021.01.003

Deepa, P., Sowndhararajan, K., Kim, S., & Park, S. J. (2018). A role of Ficus species in the management of diabetes mellitus: A review. *Journal of Ethnopharmacology, 215* (January), 210–232. https://doi.org/10.1016/j.jep.2017.12.045

Dias, M. I., Ferreira, I. C. F. R., & Barreiro, M. F. (2015). Microencapsulation of bioactives for food applications. *Food & Function, 6*(4), 1035–1052. https://doi.org/10.1039/c4fo01175a

Du, J., Li, J., Zhu, J., Huang, C., Bi, S., Song, L., Hu, X., & Yu, R. (2018). Structural characterization and immunomodulatory activity of a novel polysaccharide from Ficus carica. *Food & Function, 9*(7), 3930–3943. https://doi.org/10.1039/c8fo00603b

Dureshahwar, K., Mubashir, M., U, A., Sangshetti, J. N., U, C. D., & Une, H. D. (2019). Quantitative assessment of tactile allodynia and protective effects of flavonoids of Ficus carica Lam. Leaves in diabetic neuropathy. *Pharmacognosy Magazine, 15*(62), 128–134. https://doi.org/10.4103/pm.pm_553_18

El Dessouky Abdel-Aziz, M., Darwish, M. S., Mohamed, A. H., El-Khateeb, A. Y., & Hamed, S. E. (2020). Potential activity of aqueous fig leaves extract, olive leaves extract and their mixture as natural preservatives to extend the shelf life of pasteurized buffalo milk. *Foods, 9*(5), 1–22. https://doi.org/10.3390/foods9050615

Elghareeb, M. M., Elshopakey, G. E., Hendam, B. M., Rezk, S., & Lashen, S. (2021). Synergistic effects of Ficus Carica extract and extra virgin olive oil against oxidative injury, cytokine liberation, and inflammation mediated by 5-Fluorouracil in cardiac and renal tissues of male albino rats. *Environmental Science and Pollution Research, 28* (4), 4558–4572. https://doi.org/10.1007/s11356-020-10778-0

Elhawary, S. S., Younis, I. Y., El Bishbishy, M. H., & Khattab, A. R. (2018). LC–MS/MS-based chemometric analysis of phytochemical diversity in 13 Ficus spp. (Moraceae): Correlation to their in vitro antimicrobial and in silico quorum sensing inhibitory activities. *Industrial Crops and Products, 126*(October), 261–271. https://doi.org/10.1016/j.indcrop.2018.10.017

Eteraf-Oskouei, T., Allahyari, S., Akbarzadeh-Atashkhosrow, A., Delazar, A., Pashaii, M., Gan, S. H., & Najafi, M. (2015). Methanolic extract of Ficus carica Linn. leaves exerts antiangiogenesis effects based on the rat air pouch model of inflammation. *Evidence-based Complementary and Alternative Medicine, 760405*, 1–10. https://doi.org/10.1155/2015/760405

Ferrara, G., Mazzeo, A., Pacucci, C., Matarrese, A. M. S., Tarantino, A., Crisosto, C., Incerti, O., Marcotuli, I., Nigro, D., Blanco, A., & Gadaleta, A. (2016). Characterization of edible fig germplasm from Puglia, southeastern Italy: Is the distinction of three fig types (Smyrna, San Pedro and Common) still valid? *Scientia Horticulturae, 205*, 52–58. https://doi.org/10.1016/J.SCIENTA.2016.04.016

Gaaliche, B., Ladhari, A., de Medeiros, A. G., Ben Mimoun, M., & Hajlaoui, M. R. (2017). Relationship between phytochemical profiles and phytotoxic proprieties of Tunisian fig leaf cultivars. *South African Journal of Botany, 112*, 322–328. https://doi.org/10.1016/j.sajb.2017.06.015

Gagaoua, M., Boucherba, N., Bouanane-Darenfed, A., Ziane, F., Nait-Rabah, S., Hafid, K., & Boudechicha, H. R. (2014). Three-phase partitioning as an efficient method for the purification and recovery of ficin from Mediterranean fig (Ficus carica L.) latex. *Separation and Purification Technology, 132*, 461–467. https://doi.org/10.1016/j.seppur.2014.05.050

Garcia-Oliveira, P., Otero, P., Pereira, A. G., Chamorro, F., Carpena, M., Echave, J., Fraga-Corral, M., Simal-Gandara, J., & Prieto, M. A. (2021). Status and challenges of plant-anticancer compounds in cancer treatment. *Pharmaceuticals, 14*(2), 1–28. https://doi.org/10.3390/ph14020157

Gemechu, F. G. (2020). Embracing nutritional qualities, biological activities and technological properties of coffee byproducts in functional food formulation. *Trends in Food Science & Technology, 104*(June), 235–261. https://doi.org/10.1016/j.tifs.2020.08.005

Ghanbari, A., Le Gresley, A., Naughton, D., Kuhnert, N., Sirbu, D., & Ashrafi, G. H. (2019). Biological activities of Ficus carica latex for potential therapeutics in Human Papillomavirus (HPV) related cervical cancers. *Scientific Reports, 9*(1), 1–11. https://doi.org/10.1038/s41598-018-37665-6

Gharibzahedi, S. M. T., Smith, B., & Guo, Y. (2019a). Pectin extraction from common fig skin by different methods: The physicochemical, rheological, functional, and structural evaluations. *International Journal of Biological Macromolecules, 136*, 275–283. https://doi.org/10.1016/j.ijbiomac.2019.06.040

Gharibzahedi, S. M. T., Smith, B., & Guo, Y. (2019b). Ultrasound-microwave assisted extraction of pectin from fig (Ficus carica L.) skin: Optimization, characterization and bioactivity. *Carbohydrate Polymers, 222*(April), Article 114992. https://doi.org/10.1016/j.carbpol.2019.114992

Gilani, A. H., Mehmood, M. H., Janbaz, K. H., Khan, A. ullah, & Saeed, S. A. (2008). Ethnopharmacological studies on antispasmodic and antiplatelet activities of Ficus carica. *Journal of Ethnopharmacology, 119*(1), 1–5. https://doi.org/10.1016/j.jep.2008.05.040

Gonzalez-Chávez, A., Chávez-Fernández, J. A., Elizondo-Argueta, S., González-Tapia, A., León-Pedroza, J. I., & Ochoa, C. (2018). Metabolic syndrome and cardiovascular disease: A health challenge. *Archives of Medical Research, 49*(8), 516–521. https://doi.org/10.1016/j.arcmed.2018.10.003

Hamed, M. B., El-Badry, M. O., Kandil, E. I., Borai, I. H., & Fahmy, A. S. (2020). A contradictory action of procoagulant ficin by a fibrinolytic serine protease from Egyptian Ficus carica latex. *Biotechnology Reports, 27*, Article e00492. https://doi.org/10.1016/j.btre.2020.e00492

Hemmer, W., Focke, M., Marzban, G., Swoboda, I., Jarisch, R., & Laimer, M. (2010). Identification of Bet v 1-related allergens in fig and other Moraceae fruits. *Clinical and Experimental Allergy, 40*(4), 679–687. https://doi.org/10.1111/j.1365-2222.2010.03486.x

Ikegami, H., Habu, T., Mori, K., Nogata, H., Hirata, C., Hirashima, K., Tashiro, K., & Kuhara, S. (2013). De novo sequencing and comparative analysis of expressed sequence tags from gynodioecious fig (Ficus carica L.) fruits: Caprifig and common fig. *Tree Genetics & Genomes, 9*(4), 1075–1088. https://doi.org/10.1007/S11295-013-0622-Z, 9(4), 2013.

Irudayaraj, S. S., Christudasa, S., Antony, S., Duraipandiyan, V., Abdullah, A. D. N., & Ignacimuthu, S. (2017). 0. *Pharmaceutical Biology, 55*(1), 1074–1081. https://doi.org/10.1080/13880209.2017.1279671

Irudayaraj, S. S., Stalin, A., Sunil, C., Duraipandiyan, V., Al-Dhabi, N. A., & Ignacimuthu, S. (2016). Antioxidant, antilipidemic and antidiabetic effects of ficusin with their effects on GLUT4 translocation and PPARγ expression in type 2 diabetic rats. *Chemico-Biological Interactions, 256*, 85–93. https://doi.org/10.1016/j.cbi.2016.06.023

Jeong, W. S., & Lachance, P. A. (2001). Phytosterols and fatty acids in fig (Ficus carica, var. Mission) fruit and tree components. *Journal of Food Science, 66*(2), 278–281. https://doi.org/10.1111/j.1365-2621.2001.tb11332.x

Khezrian, A., & Shahbazi, Y. (2018). Application of nanocompostie chitosan and carboxymethyl cellulose films containing natural preservative compounds in minced camel's meat. *International Journal of Biological Macromolecules, 106*, 1146–1158. https://doi.org/10.1016/j.ijbiomac.2017.08.117

Khojah, H., & Edrada-Ebel, R. (2017). P43 the isolation and purification of bioactive metabolites from Ficus carica and their neuroprotective effects in alzheimer's disease. *Biochemical Pharmacology, 139*, 140. https://doi.org/10.1016/j.bcp.2017.06.044, 2017.

Konyalioğlu, S., Sağlam, H., & Kivçak, B. (2005). α-tocopherol, flavonoid, and phenol contents and antioxidant activity of Ficus carica leaves. *Pharmaceutical Biology, 43* (8), 683–686. https://doi.org/10.1080/13880200500383538

Ladhari, A., Gaaliche, B., Zarrelli, A., Ghannem, M., & Ben Mimoun, M. (2020). Allelopathic potential and phenolic allelochemicals discrepancies in Ficus carica L. cultivars. *South African Journal of Botany, 130*, 30–44. https://doi.org/10.1016/j.sajb.2019.11.026

Lama, K., Harlev, G., Shafran, H., Peer, R., & Flaishman, M. A. (2020). Anthocyanin accumulation is initiated by abscisic acid to enhance fruit color during fig (Ficus carica L.) ripening. *Journal of Plant Physiology, 251*(September 2019), Article 153192. https://doi.org/10.1016/j.jplph.2020.153192

Lansky, E. P., Paavilainen, H. M., Pawlus, A. D., & Newman, R. A. (2008). Ficus spp. (fig): Ethnobotany and potential as anticancer and anti-inflammatory agents. *Journal of Ethnopharmacology, 119*(2), 195–213. https://doi.org/10.1016/j.jep.2008.06.025

Lavelli, V. (2021). Circular food supply chains – impact on value addition and safety. *Trends in Food Science & Technology, 114*(April), 323–332. https://doi.org/10.1016/j.tifs.2021.06.008

Lazreg-Aref, H., Mars, M., Fekih, A., Aouni, M., & Said, K. (2012). Chemical composition and antibacterial activity of a hexane extract of Tunisian caprifig latex from the unripe fruit of Ficus carica. *Pharmaceutical Biology, 50*(4), 407–412. https://doi.org/10.3109/13880209.2011.608192

Liu, Y. P., Guo, J. M., Yan, G., Zhang, M. M., Zhang, W. H., Qiang, L., & Fu, Y. H. (2019). Anti-inflammatory and antiproliferative prenylated isoflavone derivatives from the fruits of Ficus carica. *Journal of Agricultural and Food Chemistry, 67*(17), 4817–4823. https://doi.org/10.1021/acs.jafc.9b00865

Mahmoudi, S., Khali, M., Benkhaled, A., Benamirouche, K., & Baiti, I. (2016). Phenolic and flavonoid contents, antioxidant and antimicrobial activities of leaf extracts from ten Algerian Ficus carica L. varieties. *Asian Pacific Journal of Tropical Biomedicine, 6* (3), 239–245. https://doi.org/10.1016/j.apjtb.2015.12.010

Mahmoudi, S., Khali, M., Benkhaled, A., Boucetta, I., Dahmani, Y., Attallah, Z., & Belbraouet, S. (2018). Fresh figs (Ficus carica L.): Pomological characteristics, nutritional value, and phytochemical properties. *European Journal of Horticultural Science, 83*(2), 104–113. https://doi.org/10.17660/eJHS.2018/83.2.6

Marrelli, M., Menichini, F., Statti, G. A., Bonesi, M., Duez, P., Menichini, F., & Conforti, F. (2012). Changes in the phenolic and lipophilic composition, in the enzyme inhibition and antiproliferative activity of Ficus carica L. cultivar Dottato fruits during maturation. *Food and Chemical Toxicology, 50*(3–4), 726–733. https://doi.org/10.1016/j.fct.2011.12.025

Mawa, S., Husain, K., & Jantan, I. (2013). Ficus carica L. (Moraceae): Phytochemistry, traditional uses and biological activities. *Evidence-based Complementary and Alternative Medicine*. https://doi.org/10.1155/2013/974256, 2013.

Meziant, L., Bachir-bey, M., Bensouici, C., Saci, F., Boutiche, M., & Louaileche, H. (2021). Assessment of inhibitory properties of flavonoid-rich fig (Ficus carica L.) peel extracts against tyrosinase, α-glucosidase, urease and cholinesterases enzymes, and relationship with antioxidant activity. *European Journal of Integrative Medicine, 43*, Article 101272. https://doi.org/10.1016/j.eujim.2020.101272. December 2020.

Mopuri, R., Ganjayi, M., Meriga, B., Koorbanally, N. A., & Islam, M. S. (2018). The effects of Ficus carica on the activity of enzymes related to metabolic syndrome. *Journal of Food and Drug Analysis, 26*(1), 201–210. https://doi.org/10.1016/j.jfda.2017.03.001

Mustafa, K., Yu, S., Zhang, W., Mohamed, H., Naz, T., Xiao, H., Liu, Y., Nazir, Y., Fazili, A. B. A., Nosheen, S., Bai, X., & Song, Y. (2021). Screening, characterization, and in vitro-ROS dependent cytotoxic potential of extract from Ficus carica against hepatocellular (HepG2) carcinoma cells. *South African Journal of Botany, 138*, 217–226. https://doi.org/10.1016/j.sajb.2020.12.018

Nawade, B., Shaltiel-Harpaz, L., Yahyaa, M., Bosamia, T. C., Kabaha, A., Kedoshim, R., Zohar, M., Isaacson, T., & Ibdah, M. (2020). Analysis of apocarotenoid volatiles during the development of Ficus carica fruits and characterization of carotenoid

cleavage dioxygenase genes. *Plant Science, 290*, Article 110292. https://doi.org/10.1016/j.plantsci.2019.110292. June 2019.
Nawade, B., Shaltiel-Harpaz, L., Yahyaa, M., Kabaha, A., Kedoshim, R., Bosamia, T. C., & Ibdah, M. (2020). Characterization of terpene synthase genes potentially involved in black fig fly (Silba adipata) interactions with Ficus carica. *Plant Science, 298*(June), Article 110549. https://doi.org/10.1016/j.plantsci.2020.110549
Netea, M. G., Balkwill, F., Chonchol, M., Cominelli, F., Donath, M. Y., Giamarellos-Bourboulis, E. J., Golenbock, D., Gresnigt, M. S., Heneka, M. T., Hoffman, H. M., Hotchkiss, R., Joosten, L. A. B., Kastner, D. L., Korte, M., Latz, E., Libby, P., Mandrup-Poulsen, T., Mantovani, A., Mills, K. H. G., … Dinarello, C. A. (2017). A guiding map for inflammation. *Nature Immunology, 18*(8), 826–831. https://doi.org/10.1038/ni.3790
Oliveira, A. P., Baptista, P., Andrade, P. B., Martins, F., Pereira, J. A., Silva, B. M., & Valentão, P. (2012). Characterization of Ficus carica L. cultivars by DNA and secondary metabolite analysis: Is genetic diversity reflected in the chemical composition? *Food Research International, 49*(2), 710–719. https://doi.org/10.1016/j.foodres.2012.09.019
Oliveira, A. P., Silva, L. R., Andrade, P. B., Valentao, P., Silva, B. M., Gonc-Alves, R. F., Pereira, J. A., & De Pinho, P. G. (2010). Further insight into the latex metabolite profile of ficus carica. *Journal of Agricultural and Food Chemistry, 58*(20), 10855–10863. https://doi.org/10.1021/jf1031185
Palmeira, L., Pereira, C., Dias, M. I., Abreu, R. M. V., Corrêa, R. C. G., Pires, T. C. S. P., Alves, M. J., Barros, L., & Ferreira, I. C. F. R. (2019). Nutritional, chemical and bioactive profiles of different parts of a Portuguese common fig (Ficus carica L.) variety. *Food Research International, 126*(June), Article 108572. https://doi.org/10.1016/j.foodres.2019.108572
Pande, G., & Akoh, C. C. (2010). Organic acids, antioxidant capacity, phenolic content and lipid characterisation of Georgia-grown underutilized fruit crops. *Food Chemistry, 120*(4), 1067–1075. https://doi.org/10.1016/j.foodchem.2009.11.054
Pansarasa, O., Pistono, C., Davin, A., Bordoni, M., Mimmi, M. C., Guaita, A., & Cereda, C. (2019). Altered immune system in frailty: Genetics and diet may influence inflammation. *Ageing Research Reviews, 54*(July), Article 100935. https://doi.org/10.1016/j.arr.2019.100935
Park, S., Han, J., Im, K., Whang, W. K., & Min, H. (2013). Antioxidative and anti-inflammatory activities of an ethanol extract from fig (Ficus carica) branches. *Food Science and Biotechnology, 22*(4), 1071–1075. https://doi.org/10.1007/s10068-013-0185-7
Patil, V. V., & Patil, V. R. (2011). Evaluation of anti-inflammatory activity of Ficus carica Linn. leaves. *Indian Journal of Natural Products and Resources, 2*(2), 151–155.
Pereira, C., López-Corrales, M., Serradilla, M. J., Villalobos, M. del, C., Ruiz-Moyano, S., & Martín, A. (2017). Influence of ripening stage on bioactive compounds and antioxidant activity in nine fig (Ficus carica L.) varieties grown in Extremadura, Spain. *Journal of Food Composition and Analysis, 64*(September), 203–212. https://doi.org/10.1016/j.jfca.2017.09.006
Raafat, K., & Wurglics, M. (2019). Phytochemical analysis of Ficus carica L. active compounds possessing anticonvulsant activity. *Journal of Traditional and Complementary Medicine, 9*(4), 263–270. https://doi.org/10.1016/j.jtcme.2018.01.007
Sedaghat, S., & Rahemi, M. (2018). Effects of physio-chemical changes during fruit development on nutritional quality of fig (Ficus carica L. var. 'Sabz') under rain-fed condition. *Scientia Horticulturae, 237*(January), 44–50. https://doi.org/10.1016/j.scienta.2018.04.003
Shore-Lesserson, L. (2002). Point-of-care coagulation monitoring for cardiovascular patients: Past and present. *Journal of Cardiothoracic and Vascular Anesthesia, 16*(1), 99–106. https://doi.org/10.1053/jcan.2002.29692
Son, J. H., Jin, H., You, H. S., Shim, W. H., Kim, J. M., Kim, G. W., Kim, H. S., Ko, H. C., Kim, M. B., & Kim, B. S. (2017). Five cases of phytophotodermatitis caused by fig leaves and relevant literature review. *Annals of Dermatology, 29*(1), 86–90. https://doi.org/10.5021/ad.2017.29.1.86
Sun, L., Xin, F., & Alper, H. S. (2021). Bio-synthesis of food additives and colorants-a growing trend in future food. *Biotechnology Advances, 47*(September 2020), Article 107694. https://doi.org/10.1016/j.biotechadv.2020.107694
Taofiq, O., Corrêa, R. C. G., Barros, L., Prieto, M. A., Bracht, A., Peralta, R. M., González-Paramás, A. M., Barreiro, M. F., & Ferreira, I. C. F. R. (2019). A comparative study between conventional and non-conventional extraction techniques for the recovery of ergosterol from Agaricus blazei Murrill. *Food Research International, 125*, Article 108541. https://doi.org/10.1016/j.foodres.2019.108541. November 2019.
Tao, X., Wu, Q., Aalim, H., Li, L., Mao, L., Luo, Z., & Ying, T. (2020). Effects of exogenous abscisic acid on bioactive components and antioxidant capacity of postharvest tomato during ripening. *Molecules, 25*(6). https://doi.org/10.3390/molecules25061346
Tiwari, S., Kate, A., Mohapatra, D., Tripathi, M. K., Ray, H., Akuli, A., Ghosh, A., & Modhera, B. (2020). Volatile organic compounds (VOCs): Biomarkers for quality management of horticultural commodities during storage through e-sensing. *Trends in Food Science & Technology, 106*(July), 417–433. https://doi.org/10.1016/j.tifs.2020.10.039
Tripathy, B., Sahoo, N., & Sahoo, S. K. (2021). Trends in diabetes care with special emphasis to medicinal plants: Advancement and treatment. *Biocatalysis and Agricultural Biotechnology, 33*(March). https://doi.org/10.1016/j.bcab.2021.102014
Urbani, S., Aruanno, A., & Nucera, E. (2020). Adverse reaction to Ficus Carica: Reported case of a possible cross-reactivity with der p1. *Clinical and Molecular Allergy, 18*(1), 1–4. https://doi.org/10.1186/s12948-020-00125-6
Villalobos, M. C., Serradilla, M. J., Martín, A., Aranda, E., López-Corrales, M., & Córdoba, M. G. (2018). Influence of modified atmosphere packaging (MAP) on aroma quality of figs (Ficus carica L.). *Postharvest Biology and Technology, 136*, 145–151. https://doi.org/10.1016/j.postharvbio.2017.11.001. November 2017.
Wang, T., Gu, C. B., Wang, S. X., Kou, P., Jiao, J., & Fu, Y. J. (2018). Simultaneous extraction, transformation and purification of psoralen from fig leaves using pH-dependent ionic liquid solvent based aqueous two-phase system. *Journal of Cleaner Production, 172*, 827–836. https://doi.org/10.1016/j.jclepro.2017.10.185
Wang, T., Jiao, J., Gai, Q. Y., Wang, P., Guo, N., Niu, L. L., & Fu, Y. J. (2017). Enhanced and green extraction polyphenols and furanocoumarins from Fig (Ficus carica L.) leaves using deep eutectic solvents. *Journal of Pharmaceutical and Biomedical Analysis, 145*, 339–345. https://doi.org/10.1016/J.JPBA.2017.07.002
Wang, L., Wu, Y., Liu, Y., & Wu, Z. (2017). Complex enzyme-assisted extraction releases antioxidative phenolic compositions from guava leaves. *Molecules, 22*(10). https://doi.org/10.3390/molecules22101648
Yeganehzad, S., Kiumarsi, M., Nadali, N., & Rabie Ashkezary, M. (2020). Formulation, development and characterization of a novel functional fruit snack based on fig (Ficus carica L.) coated with sugar-free chocolate. *Heliyon, 6*(7), Article e04350. https://doi.org/10.1016/j.heliyon.2020.e04350
Ye, Q., Georges, N., & Selomulya, C. (2018). Microencapsulation of active ingredients in functional foods: From research stage to commercial food products. *Trends in Food Science & Technology, 78*(May), 167–179. https://doi.org/10.1016/j.tifs.2018.05.025
Yu, L., Meng, Y., Wang, Z., Cao, L., Liu, C., & Gao, M. (2020). Sustainable and efficient surfactant-based microwave-assisted extraction of target polyphenols and furanocoumarins from fig (Ficus carica L .) leaves. *Journal of Molecular Liquids, 318*, Article 114196. https://doi.org/10.1016/j.molliq.2020.114196
Zare, H., Moosavi-Movahedi, A. A., Salami, M., Mirzaei, M., Saboury, A. A., & Sheibani, N. (2013). Purification and autolysis of the ficin isoforms from fig (Ficus carica cv. Sabz) latex. *Phytochemistry, 87*, 16–22. https://doi.org/10.1016/j.phytochem.2012.12.006
Zhang, Y., Chen, J., Zeng, Y., Huang, D., & Xu, Q. (2019). Involvement of AMPK activation in the inhibition of hepatic gluconeogenesis by Ficus carica leaf extract in diabetic mice and HepG2 cells. *Biomedicine & Pharmacotherapy, 109*, 188–194. https://doi.org/10.1016/j.biopha.2018.10.077. October 2018.
Zhao, J., Gong, L., Wu, L., She, S., Liao, Y., Zheng, H., Zhao, Z., Liu, G., & Yan, S. (2020). Immunomodulatory effects of fermented fig (Ficus carica L.) fruit extracts on cyclophosphamide-treated mice. *Journal of Functional Foods, 75*(October), Article 104219. https://doi.org/10.1016/j.jff.2020.104219