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Chapter

Chemical and Biological Characteristics of *Ficus carica* L. Fruits, Leaves, and Derivatives (Wine, Spirit, and Liqueur)

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Abstract

Ficus carica L. is a native plant to Southwest Asia and widely spread from ancient times in the Mediterranean region. Its fruits (figs) and leaves present important nutritional components (vitamins, minerals, sugars, amino acids, etc.) and health-related effects due to their phytochemical composition. Numerous bioactive compounds, such as phenolic compounds (phenolic acids), flavonoids (flavonols, flavones, and anthocyanins), coumarins, sterols, and volatiles (monoterpenes, sesquiterpenes, norisoprenoids, ketones, alcohols, esters, etc.), among others, have been isolated from fruits and leaves of *F. carica* that are the main ingredients used in the production of different alcoholic beverages such as wine, liqueur, and spirit. This chapter aims to review the different chemical and biological characteristics found both in raw materials (fruits and leaves) and in the final product (wine, liqueur, and spirit) that have been consumed and known throughout human history.

Keywords: antioxidant capacity, biological activities, enzyme inhibitory activity, fig fruit, fig leaf, fig liqueur, fig spirit, fig wine, phenolic content, volatiles

1. *Ficus carica* L. fruits, leaves, and derivatives (wine, spirit, and liqueur)

Ficus carica L. is one of the oldest plants cultivated by humans [1]. It is native to the Southwest Asia and spread worldwide in places with typically mild winters and hot dry summers [2]. Fruits and leaves have been widely used as valuable food for people and as folk medicine due to their therapeutic effects [1, 3]. According to the FAO (2013–2017), most of the world's fig production occurs in the Mediterranean basin. The 10 main world producers include countries such as Turkey, Egypt, Morocco, Algeria, Iran, and Syrian Arab Republic. Spain is the only European country included in the list, and the American countries, United States of America and Brazil, are also included [4].

Since ancient times, *F. carica* has been ever present in different cultures. It was the first tree mentioned in the Bible and the figs the first nourishment of human beings according to the Jewish Talmud. Fig tree was linked to the paradise according to the Islamic culture, and in ancient Greece it was considered a gift from Demeter, the earth mother [5].

Figs and leaves are used in their primary and processed form to produce different traditional and industrial products (infusions, jams, wines, spirits, liqueurs, etc.). The fig is a very perishable product, and for this reason it is mainly utilized as dried fruit [6]. Either way, dry or fresh figs are well known for their nutritive value due to the high contents in minerals (mainly calcium and others like copper, manganese, magnesium, potassium, etc.), fats (source of energy), sugars, and other non-nutritive components such as water, fiber, and antioxidants like phenolic compounds [1, 6, 7]. On the other hand, infusions, decoctions, or other preparations

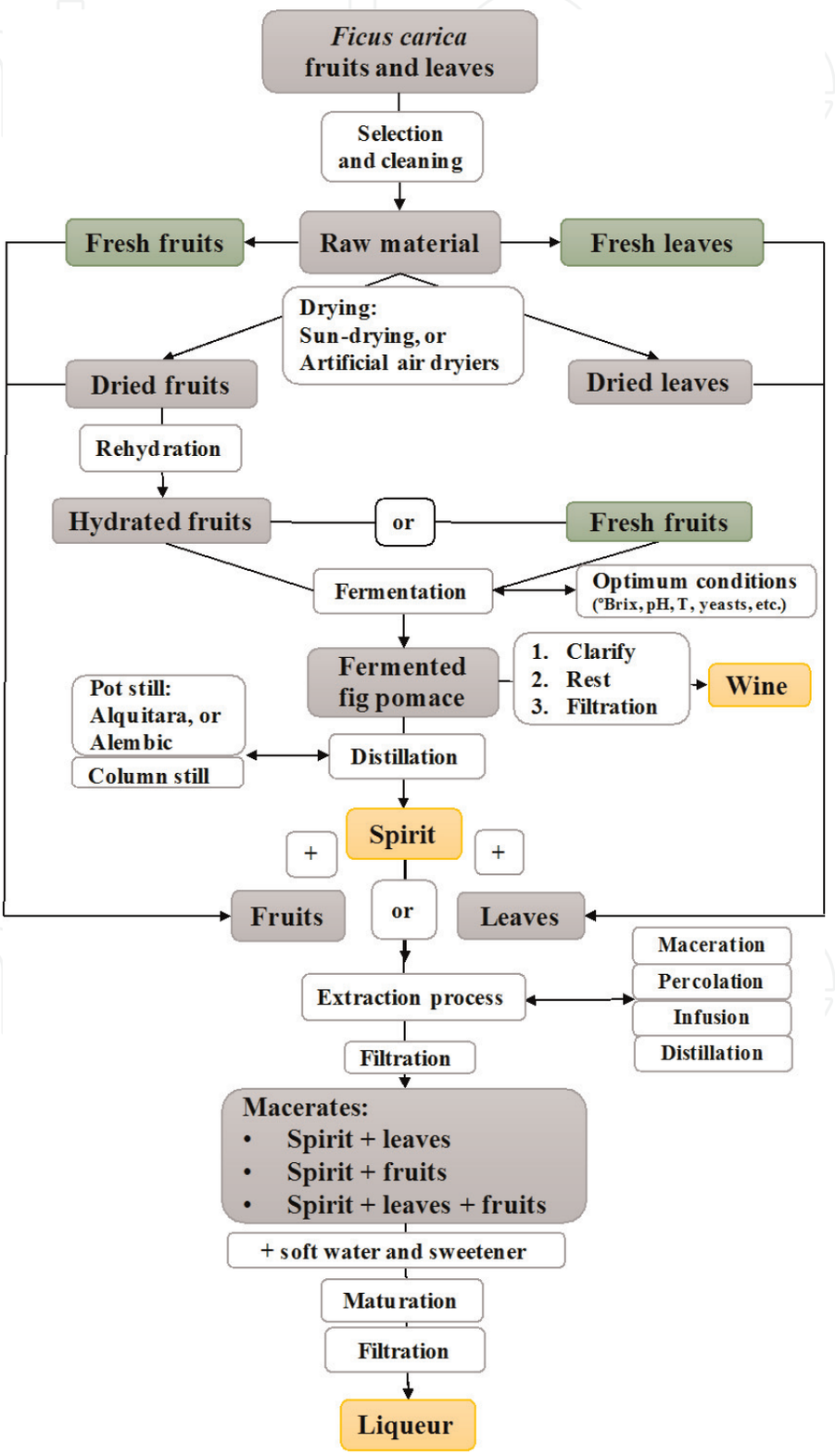

Figure 1.
Manufacturing process of Ficus carica L. wine, liqueur, and spirit from raw materials to the final beverage.

of fig leaves have been traditionally used in the treatment of different diseases due to the therapeutic effects associated with its chemical composition [8]. For all the aforementioned, *F. carica* has been included in occidental pharmacopeias (such as the Spanish and British pharmacopeias) and in therapeutic guides of herbal medicine (including the Physician's Desk Reference (PDR) for herbal medicine) [9].

The study of the extraction of phytochemicals from plants and the use of these compounds as additives has been of great importance as an efficient and safe way to add supplements in foods, to produce what is known as nutraceutical and functional food (food with a relevant effect on health or reduction in disease risk) [10]. More recently, the main objective of *F. carica* phytochemicals extraction has been based not only on finding the best extraction conditions but also the use of green extraction methods such as ionic liquids or deep eutectic solvents, environmentally friendly and sustainable for sample preparation [8]. Despite all the properties and uses found in raw materials, the scarce amount of works related to the chemical composition and biological activities of alcoholic products derived from fig fruits and leaves, specifically, wine [11–13], spirits [14–17], and liqueurs is worth mentioning [18, 19]. Furthermore, despite the mentioned characteristics of the leaves and the great tradition in using this part of the plant in the production of liqueurs [20], this is not reflected in the works cited. An outline of the process followed in the production of these beverages from the raw materials of *F. carica* to the final product can be seen in **Figure 1**. In all these products, the biotechnological step of alcoholic fermentation is required to transform the sugars present in the fruit into alcohol and produce the value-added corresponding alcoholic beverages of commercial importance. The use of yeasts (endogenous or exogenous) and controlled conditions (pH, temperature, etc.) is necessary to obtain a high-quality final product. In addition, during this fermentation process, and other processes taking place such as maceration and maturation of the beverage, new chemical compounds are produced that will contribute to the final profile of the beverages [21, 22].

In the next section, the different chemical compounds (phytochemicals) as well as the biological properties from both *F. carica* raw materials and alcoholic-derived products will be addressed in more detail.

2. Phytochemical composition of fig fruit, leaf, and the alcoholic products, liqueurs, and spirits

Phytochemicals or plant secondary metabolites are non-nutritive plant metabolites which are essential for plant survival and proper growth and reproduction [23]. Many of these components have bioactivities toward animal biochemistry and metabolism with the ability to provide health benefits. *F. carica* plant owns the highest diversity of compounds with the higher quantities of all classes of compounds (except aldehydes and monoterpenes) mainly in leaves, followed by fruits pulps and peels [2, 9, 24].

Phytochemical studies on raw materials (fruits and leaves) and derived products (wine, liqueur, and spirit) of *F. carica* revealed the presence of numerous bioactive compounds including volatiles, organic acids, phytosterols, triterpenoids, fatty acids, phenolic acids, flavonoids, coumarins, and few other classes of secondary metabolites shown in **Figure 2**.

2.1 Volatile compounds

Aroma is an important attribute of the sensory appreciation of a product and is usually used as a criterion for its quality assessment. It is a defining element of the

distinct flavor of individual foods. The ripening period has an important role in the volatile composition, and many volatiles are produced during different developmental stages of plant tissues such as flowering, ripening, or maturation [1]. These volatiles are known as primary aromas, and they are responsible for varietal aromas [25]. These compounds are accumulated in plant storage sites and are released from the surface of the leaf, making this part of the *F. carica* the largest holder of compounds (except aldehydes and monoterpenes, in highest amounts in fruits [9]). On the other hand, in products such as wine, spirits, and liqueurs elaborated from fruits of *F. carica*, other types of aromas come from the different processing steps. Secondary aromas (the greatest pool of volatiles) are mainly produced by yeast as metabolism by-products, while tertiary aromas of finished alcoholic beverages are compounds that illustrate the changes made in the sample matrix during the storage and maturity stages [25].

Fruits [1, 2, 26, 27] and leaves [2, 8] of *F. carica* as well as derived products such as the alcoholic beverages, fig liqueurs [28], and spirits [14, 15, 17] consist of various volatile compounds which are identified and distributed by distinct chemical classes, such as terpenes (monoterpenes and sesquiterpenes), alcohols, aldehydes, ketones, esters, and miscellaneous compounds.

2.1.1 Terpenes

Terpenes, such as monoterpenes (C10) and sesquiterpenes (C15), are the largest class of plant secondary metabolites, as can be seen in **Figure 2**. The high vapor pressures of these compounds, at normal atmospheric conditions, allow their significant release into the air [1]. Monoterpenes such as linalool (1) and epoxylinalool (34) (more important than linalool) are related with their important role in the attraction of specific pollinators, the fig/wasp linkage [1]. Although sesquiterpenes represented just the ~3% of the total volatiles in Tunisian cultivars, it was the main class of compounds identified in leaves, and germacrene D, β-caryophyllene, and τ-elemene are the major compounds detected [9].

α-Pinene (31), one of the main monoterpenes mentioned in different works, has only been found in fruits, while the sesquiterpenes β-elemene (39), β-cubebene (60), α-ylangene (61), β-bourbonene (62), (+)-ledene (viridiflorene) (66), and α-gurjunene (67) are compounds exclusively identified in leaves [1, 2, 9]. The monoterpenes citronellol acetate (7), (E)-geranyl acetone (12), (+)-sylvestrene (16), *p*-mentha-1,3,8-triene (17), cumene (26), *o*- and *p*-cymene (27, 28), and nerol oxide (33) and the sesquiterpenes (E)-nerolidol (35), farnesyl acetate (36), α-curcumene (37), β-bisabolene (38), τ-elemene (40), (−)-δ-cadinol (45), cadina-1 (10),4-diene (48), cadalene (49), α-calacorene (50), valencene (51), acoradiene (53), δ-guaiene (α-bulnesene) (55), α-guaiene (56), isocaryophyllene (57), γ-patchoulene (65), and α-cedrene (68) are compounds only identified in Portuguese monovarietal fig spirits [14]. Linalool acetate (2), geraniol (4), (Z)-8-hydroxylinalool (5), neral (β-citral) (6), geranyl vinyl ether (8), ethyl linalool (9), nerol (10), dihydrocitronellol (11), geranial (α-citral) (13), ocimene (14), *p*-menth-3-ene (19), α-terpinolene (21), α-terpineol (23), pulegone (24), isodihydrocarveol (25), borneol (30), and (Z)- or (E)-linalool oxide (34), as monoterpenes, and cadina-1,4-diene (47) and dihydroactinidiolide (52), as sesquiterpenes, were identified in synthetic liqueurs elaborated from different Greek *F. carica* varieties [28].

On the other hand, common terpenes were found in different *F. carica* parts and/or fig spirits and synthetic liqueurs. Menthol (18), τ-muurolene (44), and τ-cadinene (46) are common compounds found in fruit and leaves [2, 9]. The

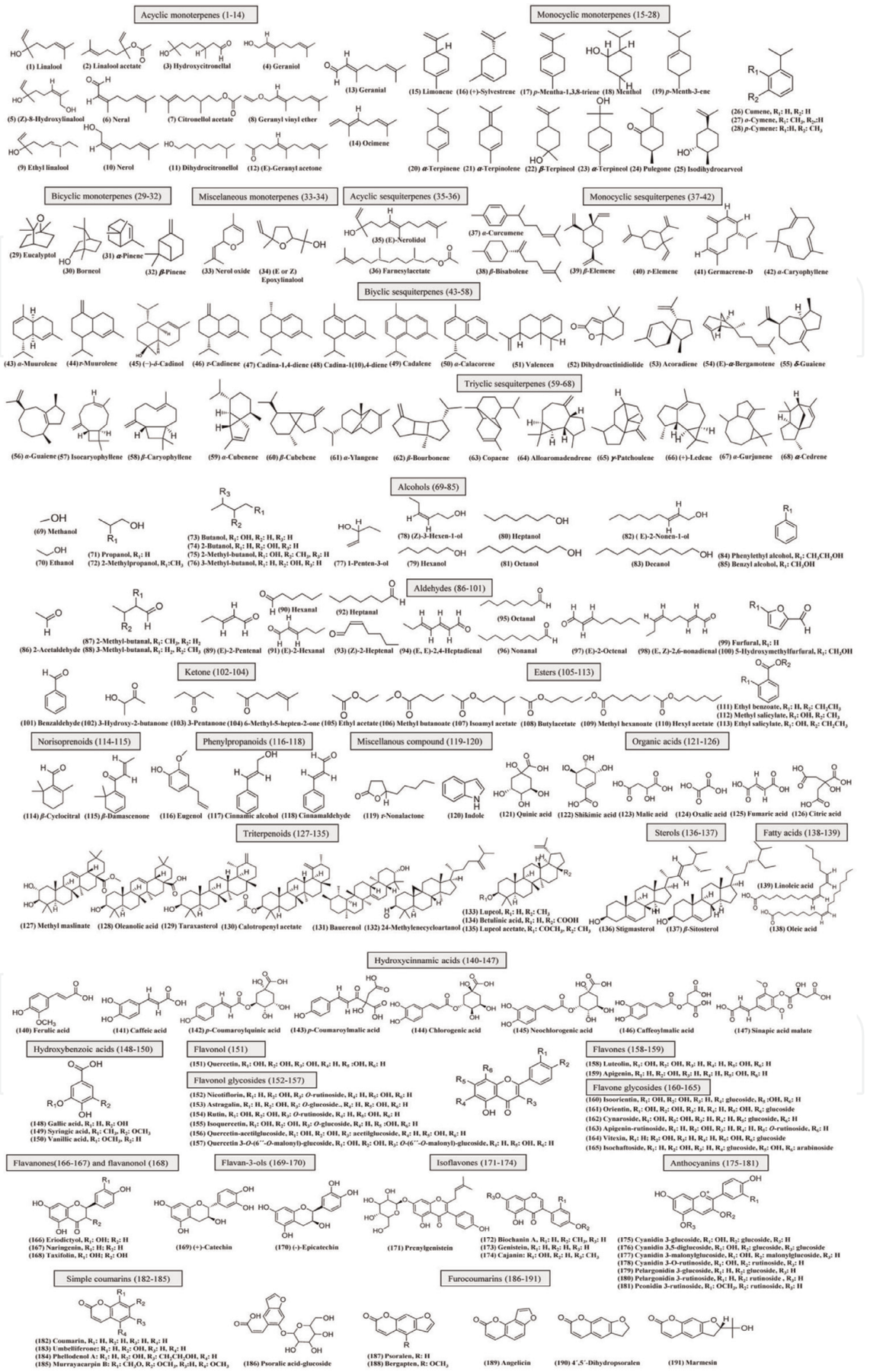

Figure 2.
Chemical structures of different phytochemicals (volatile compounds, organic acids, triterpenoids, sterols, fatty acids, phenolic acids, flavonoids, and coumarins) present in fig fruits, leaves, spirits, and liqueurs.

monoterpenes β-pinene (32) and eucalyptol (29) and the sesquiterpene (E)-α-bergamotene (54) were identified in different fig cultivars from different countries and also in fig liqueurs, while the monoterpenes linalool (1) and linalool oxide (furanoid) (epoxylinalool) (34) were isolated in fig fruits and spirits [2, 9, 28].

Other common terpenes were identified in different fig samples such as α-terpinene (20) in fig spirits and synthetic liqueurs; limonene (15), α-cubenene (59), copaene (63), and germacrene D (41) in fig fruits, leaves, and spirits; α-guaiene (57), aromadendrene (64), and α-muurolene (43) in fig leaves and spirits; and finally, β-caryophyllene (58) in fruit, leaves, spirits, and synthetic liqueurs, while α-caryophyllene (42) in fig leaves, spirits, and synthetic liqueurs [1, 2, 9, 14, 28].

2.1.2 Alcohols, aldehydes, ketones, and esters

Alcohols, ketones, and esters are the more developed compound classes in ripened fruits, representing 41% of total aroma [1].

Different alcohols were identified in fruits [(Z)-3-hexen-1-ol (78)], leaves [2-methyl-1-butanol (76) and 1-heptanol (80)], spirits [methanol (69), ethanol (70), 1-propanol (71), 1-butanol (72), 2-methyl-propanol (isobutyl alcohol) (74), 1-hexanol (79), octanol (81), and decanol (83), among others], in both fruits and leaves [1-penten-3-ol (75), benzyl alcohol (85), and (E)-2-nonen-1-ol (82)] [2, 9], leaves and spirits [1-heptanol (80)] [9, 14], and finally in raw materials and spirits [3-methylbutanol (77), phenylethyl alcohol (84)] [2, 9, 14, 15]. Methanol (69), a toxic compound formed by hydrolytic demethoxylation of esterified methoxyl groups of the pectin polymer by pectic enzymes, with a marked maximum methanol content in fruit spirits of 1500 g/hL of pure alcohol (Regulation (EC) No 110/2008), was present in fresh and dried fig spirits [14]. It should be emphasized that its concentration depends on the technological characteristics of the manufacturing process. Higher quantities were found in spirits prepared from fresh figs because this compound is naturally present in fruits and decreased in spirits prepared using fermentations with immobilized yeast cell technology [15]. In addition, greater amounts of higher alcohols [2-butanol (73) + 1-propanol (71) + 2-methyl-propanol (74) + butanol (72) + 2-methylbutanol (76) + 3-methylbutanol (77)] were also found in samples of spirits made from dried figs (approx. > 350 g/hL absolute alcohol), being indicative of worse quality of these samples [14].

The aldehydes present exclusively in fruits are heptanal (92), octanal (95), nonanal (96), 2-methyl-butanal (87), (Z)-2-heptenal (93), (E, E)-2,4-heptadienal (94), (E)-2-octenal (97), and (E, Z)-2,6-nonadienal (98) [2, 9]. Furfural (99) and 5-hydroxymethylfurfural (100), toxic compounds originated during the fired pot-still distillation process at high temperatures, and acetaldehyde (86) were identified in spirits [14, 15]. Meanwhile, common aldehydes identified in fruits and leaves were 2-methyl-butanal (87), 3-methyl-butanal (88), (E)-2-pentenal (89), hexanal (90), and (E)-2-hexenal (91); benzaldehyde (101) was present in fruits and spirits [2, 9].

The first major compound found in non-pollinated and pollinated figs was the ketone 3-hydroxy-2-butanone (acetoin) (102) [1]. Other ketones, 6-methyl-5-hepten-2-one (104) and 3-pentanone (103), were identified in, respectively, fruits (pulps and peels) and leaves of Portuguese fig varieties [2, 9].

Esters are the major contributors to fruit aroma and are the most important in ripe figs. They are produced through the esterification of alcohols and acyl-CoAs derived from both fatty acid and amino acid metabolism, in a reaction catalyzed by the enzyme alcohol-o-acyltransferase [1]. These compounds are much less developed in non-pollinated fruits, and its content decreases when using immobilized cell application during the fermentation process. In spirits, esters represent the largest

class of volatiles (~95% of total volatiles), particularly the fatty acid ethyl esters such as ethyl decanoate, ethyl octanoate, and ethyl dodecanoate. The second and third major compounds identified in fruits from Tunisian varieties were butyl acetate (108) and isoamyl acetate (107) with banana odor [1]. This last compound was also present in fig spirits [14]. Other ester identified in fruits was ethyl salicylate (113). Methyl butanoate (106), hexyl acetate (110), and ethyl benzoate (111) were found in leaves [2, 9], while methyl hexanoate (109) was a common compound in fruits and leaves and methyl salicylate (113) in fruits, leaves, and spirits [2, 9, 14]. Many methyl and ethyl esters and other esters were identified in fig spirits and are common to other alcoholic beverages. The study comparing dried and fresh fig spirits showed that dried fig spirits presented ethyl acetate (105) in higher proportion than fresh fig spirits. This compound results from the growth of acetic acid bacteria during the fermentation in aerobic conditions [14].

2.1.3 Miscellaneous compounds

The norisoprenoid β-cyclocitral (114) present in leaves and fruits [2, 9] and β-damascenone (115) characteristic of different fig spirits and synthetic fig liqueurs [14, 28] and finally the phenylpropanoids [(eugenol (116), cinnamic alcohol (117), cinnamic aldehyde (118)] and indole (120) in fruits [9] and s-nonalactone (119) [2] in leaves were other volatile compounds detected in different fig samples.

2.2 Organic acids, phytosterols, triterpenoids, and fatty acids

Some organic acids isolated from fruits and leaves of *F. carica* were the shikimic (122), malic (123), oxalic (124), fumaric (125), and citric (126) acids [2, 9, 24, 29], while the quinic acid (121) was reported only in leaves [2, 9].

Phytosterols are found in most plant foods, with the highest concentrations occurring in vegetable oils. Sterols (modified triterpenes) like β-sitosterol (137) [24] and the triterpenoids methyl maslinate (127), oleanolic acid (128), taraxasterol (129), w-taraxasterol ester, calotropenyl acetate (130), bauerenol (131), 24-methylenecycloartanol (132), lupeol (133), and lupeol acetate (135) have been reported in fig leaves [2, 9], and betulinic acid (134) in fruits [3], while stigmasterol (136) was reported in both [29, 30].

Dried and fresh fruits of *F. carica* showed polyunsaturated fatty acids with 84 and 69% of total fatty acids, respectively. Linoleic acid (139), in fresh and dried fruits, was the only polyunsaturated fatty acid identified. With respect to monounsaturated fatty acids, oleic acid (138) is the most abundant in fruits [9].

2.3 Phenolic acids, flavonoids, and coumarins

Among the different chemical structures found in *F. carica*, one of the most important for biological uses is the phenolic compounds. These play many physiological roles in plants and are also favorable to human health [2]. Fruits and leaves presented qualitative differences in phenolic acids. Leaves were richer in phenolic derivatives formed by conjugation with sugars (the hydroxybenzoic derivatives: gallic acid di-pentoside, syringic acid hexoside, vanillic acid hexoside deoxyhexoside, and the dihydroxybenzoic acids hexoside/hexoside pentoside) and organic acids including malic (the hydroxybenzoic derivative, syringic acid malate, and the hydroxycinnamic derivatives, caffeoylmalic acid, coumaroylmalic acid, sinapic acid malate, and ferulic acid malate) and quinic acid (the hydroxycinnamic derivative coumaroylquinic acid) [31, 32]. The signal of hydroxycinnamics was higher in extracts from leaves. On the other hand, in general, free forms of

hydroxycinnamic acids such as caffeic acid (141), and the hydroxybenzoic acids, gallic (148) and syringic (149) acids, were only present in fruits [32]. Also the ferulic acid hexoside and the coumaroyl and ferulic hexosides were present in fruits. Moreover, the following compounds were common to both leaves and fruits: the hydroxybenzoic acids, di-/hydroxybenzoic acids and vanillic acid; the hydroxybenzoic derivatives, dihydroxybenzoic acid attached to hexoside/hexoside pentoside/pentoside/di-pentoside, vanillic acid glucoside, and gallic acid di-pentoside; and the hydroxycinnamic acids, ferulic acid (140) and the chlorogenic (3-O-caffeoylquinic acid) (144) and neochlorogenic (5-O-caffeoylquinic acid) (145) acids. The common hydroxycinnamic derivatives present in fruits and leaves were caffeoylquinic acid hexoside, dihydrocaffeic acid hexose, and the sinapic acid hexoside [2, 9, 24, 32].

Flavonols such as quercetin (151) and glycosylated flavonols such as rutin (quercetin-3-O-rutinoside) (154) (major individual phenolic identified in fruits [2]), isoquercetin (quercetin-3-O-glucoside) (155), quercetin 3-O-(6′-O-malonyl)-glucoside (157), quercetin di-deoxyhexoside hexoside, and quercetin O-di-hexoside were confirmed in fresh and dried figs and leaves [32]. Nicotiflorin (kaempferol-3-O-rutinoside) (152) and quercetin-acetilglucoside (156) were reported in fruits, while astragalin (kaempferol 3-O-glucoside) (153) only in leaves [2, 3, 9, 24, 31, 33].

Free flavones such as luteolin (158) and apigenin (159) are present in fig fruits and leaves. Also, the glycosylated flavones, isoorientin (luteolin 6-C-glucoside) (160), orientin (luteolin 8-C-glucoside) (161), cynaroside (luteolin 7-O-glucoside) (162), vitexin (apigenin 8-C-glucoside) (164), isochaftoside (apigenin 6-C-glucoside 8-C-arabinoside) (165), and apigenin 6-C-hexose-8-C-pentose [which could be identified as schaftoside (apigenin 6-C-glucoside 8-C arabinoside)], were detected in both plant parts. However, apigenin 7-rutinoside (163) and luteolin 6C-hexose-8C-pentose were present in fruits [2, 9, 33].

Another group of flavonoids identified was the flavanones, with the compounds eriodictyol (166) and eriodictyol hexoside in fruits and naringenin (167) in fruits and leaves. The flavanonol taxifolin (dihydroquercetin) (168) was identified in fruits [32]. The flavanols, (+)-catechin (169) in fruits and leaves and (−)-epicatechin (170) in leaves, were also identified [3, 33].

Genistein (173) and hydroxygenistein methyl ether malonylhexoside in leaves and prenylhydroxygenistein, prenylgenistein (171), biochanin A (genistein 4′-methyl ether) (172), and cajanin (7-methoxy 2′-hydroxy genistein) (174), in fruits and leaves, were the isoflavones identified [2, 3, 9, 24, 31, 33].

Different anthocyanin pigments, some of them containing cyanidin or pelargonidin as aglycones, as well as rutinose and glucose substituting sugars and acylation with malonic acid, were found in skin and pulp from different varieties of Iberian fresh figs with different colors (black, red, yellow, and green). These compounds include (epi)-catechin-(4-8)-cyanidin-3-glucoside, (epi)catechin-(4–8)-cyanidin-3-rutinoside,(epi)catechin-(4,8)-pelargonidin 3-rutinoside, 5-carboxypyranocyanidin-3-rutinoside, cyanidin-3-malonylglicosyl-5-glucoside, cyanidin-3-malonylglucoside, cyanidin-3-glucoside (175), cyanidin-3,5-diglucoside (176), cyanidin 3-O-rutinoside (as the main anthocyanin in different commercial fig varieties [2]) (178), pelargonidin-3-glucoside (179), pelargonidin-3-rutinoside (180) and peonidin-3-rutinoside (181). In addition, 5-carboxypyranocyanidin-3-rutinoside, a cyanidin 3-rutinose dimer, and five condensed pigments containing C–C linked anthocyanins and flavanol (catechin and epicatechin) residues were identified [9].

Coumarin (182); the hydroxycoumarins esculetin hexoside, dihydroxy-coumarin, umbelliferone (7-hydroxycoumarin) (183), and prenyl-7-hydroxycoumarin; and the furocoumarins psoralen (187) and bergapten

(5-methoxypsoralen) (188) were isolated from *F. carica* fruits and leaves [32]. Simple coumarins 6-carbaxyl-umbelliferone, phellodenol A (184), and murrayacarpin B (185) and the furocoumarins hydroxypsoralen, hydroxypsoralen hexoside, 4′,5′-dihydropsoralen (190), angelicin (isopsoralen) (189), isopentenoxypsoralen, oxypeucedanin, psoralic acid glucoside and marmesin (191) were isolated from leaves [2, 9, 31, 32].

3. Biological studies in fruit, leaf, and fig spirits and liqueurs

The leaves and fruits of *F. carica* are important in traditional medicine [24]. Many biological activities have been evaluated and confirmed on *F. carica* extracts, and the bioassay-guided fractionation in most cases allowed to assign the chemical structures responsible of such biological effects, thereby ratifying some of its folkloric uses [9]. In this section we analyzed the potential health-promoting constituents of fig fruits, leaves, and derived products, fig liqueurs, and spirits [6].

3.1 Antioxidant capacity

Among the different phytochemicals studied in *F. carica*, phenolic compounds are among the most important with antioxidant capacity (AC). Many of these compounds are able to act as antioxidants by different ways: reducing agents, hydrogen donators, free radical scavengers, singlet oxygen quenchers, and so forth [2].

3.1.1 Fig spirits and liqueurs

The antioxidant capacity (AC) by ABTS [2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonate)] and DPPH (1,1-diphenyl-2-picrylhydrazyl) assays and the total phenolic content (TPC) by Folin–Ciocalteu method were evaluated in different fig spirits and liqueurs [34]. Fig liqueurs showed high values of TPC and AC (ABTS), close to the values of other fruit spirits with highest AC such as green walnut, carob pod, and mulberry. Fig spirits presented high (third value of 15 samples) AC by ABTS assay and among the highest TPC values. However, no DPPH scavenging activity was shown for fig liqueurs and spirits.

3.1.2 Leaf extracts

The maximum total flavonoid content (25.04 mg/g) with marked scavenging activities against hydroxyl and superoxide anion free radicals in a concentration-dependent manner were found in ethanolic (40%) leaf extracts of *F. carica* (solid to liquid ratio 1:60 g/mL, temperature extraction of 60°C, and 50 min of ultrasonic treatment) [6].

3.1.3 Fruit extracts

Several works studied the AC of fruit extracts. Extracts from six commercial fig varieties were evaluated for AC by ferric reducing antioxidant method (FRAP) and also for TPC and total flavonoid content (TFC) and amount and profile of anthocyanins. The extracts exhibiting the highest AC contained the highest levels of TPC and TFC and anthocyanins (cyanidin-3-O-rutinoside as the main compound) [2, 6]. In another work, two fruit extracts [water (WE) and crude hot water-soluble polysaccharide (PS)] were evaluated for AC using the *in vitro* scavenging abilities

on DPPH, superoxide, and hydroxyl radicals and reducing power assays. Both extracts have notable scavenging activities on DPPH [WE (EC50, 0.72 mg/ml) and PS (EC50, 0.61 mg/ml)], while PS showed highest scavenging activity on superoxide radical (EC50, 0.95 mg/ml) and hydroxyl anion radical (43.4% at concentration of 4 mg/ml) [6].

Ethanolic extracts from the white Beni Maouche Algerian figs were compared with carob pods and holm oak acorns [7]. Fig extracts presented lower efficacy to scavenge DPPH (20.54 ± 0.30%) than ABTS radicals (68.98 ± 0.12%) and higher reducing ability in phosphomolybdenum assay (638.23 ± 0.43 mg GAE/100 g). This extract (73.17 ± 0.16%) also inhibited the formation of the complex Fe^{2+}-ferrozine and was also able to scavenge H_2O_2 efficiently. The extracts from the three fruits evaluated (carob, acorns, and figs) showed no significant differences in nitric oxide (NO) radical scavenging activities [7].

3.2 Reactive oxygen species production, xanthine oxidase inhibition assay, and study of oxidative stress

3.2.1 Fruit extracts

The production of reactive oxygen species (ROS) in the presence of ethanolic fig extract was measured by chemiluminescence using lucigenin. This method is widely used to determine the rate of superoxide radicals in human neutrophils. Fig extract inhibited the chemiluminescence of lucigenin and ROS production and differed from each other according to the concentration of the sample and the incubation time. After 15 min of treatment, the extract tested at the highest concentration (250 μg/mL) seemed to reach its higher level of lucigenin inhibition, value 44% below that obtained with diphenylene iodonium (0.2 mM), the standard selective inhibitor of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase tested [7].

Ethanolic fig extracts were able to inhibit the activity of the enzyme xanthine oxidase (XO), an enzyme that generates reactive oxygen species. Different extract concentrations were evaluated (50, 250, and 500 μg/mL), and at 250 μg/mL, ethanolic extracts presented the best inhibition, although its value is much lower (practically half) of that obtained with the positive control allopurinol, a drug clinically used for gout treatment. The extracts tested at 500 μg/mL showed a decrease in the inhibition of XO activity as the result of its prooxidant effect. The strong correlation coefficients between XO inhibition activity and phenolic compounds and flavonoids demonstrate the inhibition activity of XO [7].

3.2.2 Leaf extracts

Oxidative stress is the disturbance in the balance between the production of reactive oxygen species (free radicals) and antioxidant defenses. The role of these free radicals in the production of tissue damage in diabetes mellitus was studied in rats divided into four groups: streptozotocin-induced diabetic rats, diabetic rats that received a single dose of a basic fraction of *F. carica* leaf extract, diabetic rats that received a single dose of a chloroform fraction of the extract, and normal rats. Antioxidant status was affected in the diabetes syndrome, and *F. carica* extracts showed that they normalize it. Diabetic animals exhibited higher values for erythrocyte catalase activity, plasma levels of vitamin E, monounsaturated and polyunsaturated fatty acids, saturated fatty acids and linoleic acid than that of the control group. Both *F. carica* fractions showed that they normalize the values of the diabetic animal's fatty acids and plasma vitamin E values. They showed statistically

significant differences as a function of diabetes with the vitamin E/C 18:2 ratio being normalized by the administration of the chloroform fraction (to 152.1 ± 80.3 μg/mg) and the vitamin A/C 18:2 ratio being raised relative to the untreated diabetic rats by the administration of the basic fraction (91.9 ± 14.5 μg/mg) [2].

3.3 Inhibitory activities of the enzymes α-amylase, α-glucosidase, and pancreatic lipase

3.3.1 Fruit and leaf extracts

The treatment of diabetes and obesity using the inhibition of carbohydrate (α-amylase and α-glucosidase) and lipid (pancreatic lipases)-digesting enzymes is used to reduce the digestion and absorption of carbohydrates and lipids and also to reduce significantly the blood glucose and body fat levels. Ethanolic extracts from fruits and leaves, in relation to hexane, ethyl acetate, and aqueous extracts, presented the higher α-amylase and α-glucosidase and pancreatic lipase inhibitions at the higher concentration tested (500 μg/mL). At this concentration, similar values to that of the standard acarbose were found for α-amylase and α-glucosidase inhibitions in fruit ethanolic extracts [35].

3.4 Antidiabetic, hypocholesterolaemic, and hypolipidemic activities

3.4.1 Leaf extracts

Different works on antidiabetic activity were carried out using methanolic and aqueous leaf extracts [2, 6]. The maximum glucose-lowering effect in induced diabetic rats with alloxan was observed with methanolic extracts at a concentration of 200 mg/kg and after 21 days. At these conditions, results were similar to those obtained with metformin (medication used for the treatment of type 2 diabetes). On the other hand, a clear hypoglycemic effect and reduction of total cholesterol and total cholesterol/HDL cholesterol ratio of the oral or intraperitoneal administration of aqueous leaf extracts in relation to the control group was observed in diabetic rats induced with streptozotocin.

In other work, an 8-week-old rooster's liver with high abdominal fat was used to evaluate the potential of leaf fig extract as food supplement to decrease hepatic triglyceride (TG) content and secretion of TG and cholesterol from the liver. Results showed that the leaf extract reduced the contents to the basal level in a concentration-dependent manner [2]. Another work about the intraperitoneal administration of leaf decoction extracts (50 g dry wt/kg body wt) in hypertriglyceridemia-induced rats with 20% emulsion of long chain triglycerides (LCTG) indicated a decrease in the LCTG content of 84% after 60 min and a reduction of 69% after 2 h. The results suggest the existence of compound/s in fig leaf decoction that influence the lipid catabolism [6].

3.5 Hepatoprotective activity

3.5.1 Leaf extracts

The hepatoprotective activity of methanolic leaf extract in carbon tetrachloride-induced hepatotoxicity in rats was evaluated, and the activity was comparable to that of the known hepatoprotective silymarin [6].

Petroleum ether leaf extract also showed significant reversal of biochemical, histological, and functional changes in oral rifampicin (50 mg/kg)-induced hepatotoxicity in rats [2].

3.6 Anti-herpes simples virus (HSV)

3.6.1 Leaf extracts

Water leaf extract presented low toxicity and directly killing virus effect of HSV on baby hamster kidney fibroblasts (BHK21), primary rat kidney (PRK), and human epithelial (Hep-2) cells with a maximum tolerated concentration (MTC) of 0.5 mg/mL [2]. Ethyl ethanoate and hexane fractions of methanolic extracts also showed anti-HSV-1 effect [24].

3.7 Immunomodulatory activity

3.7.1 Leaf extracts

Administration of ethanolic leaf extract presented immune modulatory activity in cellular and humoral antibody response according to various hematological and serological tests [6].

3.8 Anti-inflammatory activity

3.8.1 Leaf extracts

Different (petroleum ether, ethanolic, and chloroform) leaf extracts showed a significant reduction on carrageenan-induced paw edema in rats and a greater anti-inflammatory effect in relation to indomethacin, a standard nonsteroidal drug used for this effect [6].

3.9 Irritant potential

3.9.1 Leaf extracts

Methanolic leaf extract and isolated triterpenoids [methyl maslinate (127), calotropenyl acetate (130), and lupeol acetate (135)] exhibited irritant potential on open mice ears and were the most potent and persistent irritant effects [2].

3.10 Antimicrobial, nematicidal, and anthelmintic activities

3.10.1 Leaf extracts

Methanolic leaf extracts showed strong antibacterial activities against oral bacteria, *Streptococcus gordonii*, *S. anginosus*, *Prevotella intermedia*, *Actinobacillus actinomycetemcomitans*, and *Porphyromonas gingivalis*, with minimum inhibitory (MIC) and bactericidal (MBC) concentrations of 0.156–0.625 mg/ml and 0.313–0.625 mg/ml, respectively. These antibacterial effects may be related to some phenolic compounds isolated such as flavonoids [6]. Acetone leaf extract possessed antibacterial activity against *Staphylococcus* species and antifungal activity against *Fusarium solani*, *F. lateritium*, *F. roseum*, *Daporuthe nonurai*, and *Bipolaris leersiae* [24]. Leaf extract also showed strongest nematicidal activity against the nematodes

Bursaphelenchus xylophilus, *Panagrellus redivivus*, and *Caenorhabditis elegans* with 74.3, 96.2, and 98.4% mortality, respectively, within 72 h [2].

3.10.2 Fruit extracts

Fruit extract was found useful in protecting from bacterial pathogen attack in tomatoes [6]. Anthelmintics are drugs that either kill or expel infesting helminths living in the gastrointestinal tract or tissues. Helminths cause numerous damages to the host, for example, injury to organs, intestinal or lymphatic obstruction, causing blood loss, depriving it of food, and secreting toxins [36]. The potential of cysteine proteinases extracted from figs as a potential anthelmintic was evaluated. The experiments were carried out *in vitro* using the rodent gastrointestinal nematode *Heligmosomoides polygyrus*. A marked damage was visible within a 2-h incubation period of cysteine proteinases on the cuticle (loss of surface cuticular layers) of adult male and female *H. polygyrus* worms. The results (efficacy and mode of action) proved the potential use of cysteine proteinases as anthelmintics [6].

3.11 Antipyretic activity

3.11.1 Leaf extracts

To evaluate the antipyretic activity, different doses (100, 200, and 300 mg/kg body wt. p.o.) of ethanolic leaf extracts showed significant dose-dependent reduction in normal body temperature and yeast-induced elevated temperature (pyrexia) in albino rats. The antipyretic effect of this extract was comparable to that of the standard antipyretic agent paracetamol at 150 mg/kg body wt., p.o. The effect extended up to 5 hours after drug administration compared to that of paracetamol (150 mg/kg.b.wt., p.o.) [2, 6].

3.12 Antituberculosis activity

3.12.1 Leaf extracts

Colorimetric microplate-based assay of methanolic (80%) leaf extract exhibited effect against *Mycobacterium tuberculosis* strain H37Rv with MIC value of 1600 μg/mL [2].

3.13 Anti-calpain activity

3.13.1 Fruit extracts

Calpains are calcium-dependent enzymes that determine the fate of proteins through regulated proteolytic activity. These enzymes have been linked to the modulation of memory and are keys to the pathogenesis of Alzheimer disease [37]. Calpain activity was examined after treatment of cells with dry extracts. Fig extracts decreased the fluorescence of the fluorogenic calpain substrate tert-butoxycarbonyl-Leu-Metchloromethylaminocoumarin (t-boc-LM-CMAC) and consequently inhibited the activity of calpain. Fig extracts showed the same capacity to inhibit calpain as carob and holm oak acorn extracts. The incubation time (2, 4, and 6 h) and the concentrations tested (25, 100, and 250 μg/ml) had no effect on the inhibitory activity of calpain in the presence of fig extracts. After 2 h of treatment, the extracts already inhibited more than 50% for all the concentrations tested. This inhibitory activity of the studied extracts could be attributed to its

chemical composition that contains several antioxidant groups, especially phenolic compounds such as flavonoids and flavonols [7].

3.14 Diuretic activity

3.14.1 Fruit extracts

Ethanolic fruit extracts were evaluated for the diuretic activity on individual rat through the control of the parameters, total urine volume, and urine concentration of Na^+, K^+, and Cl^-. Results showed a marked diuresis of ethanolic fruit extract treatment in rats based on the increase in urine volume and cation and anion excretions [6].

3.15 Immunity activity

3.15.1 Fruit extracts

The immunity activities of crude hot water-soluble polysaccharide (PS) were evaluated using the carbon clearance test and serum hemolysin analysis in mice. The PS (500 mg/kg) had a significant increase in the clearance rate of carbon particles and serum hemolysin level of normal mice [6].

3.16 Antispasmodic activity

3.16.1 Fruit extracts

Fig aqueous-ethanolic extract was investigated for antispasmodic effect (suppression of muscle spasms) on rabbit jejunum preparations. The extracts (0.1–3.0 mg/mL) produced relaxation of spontaneous and low K^+(25 mM)-induced contractions and with insignificant effect on high K^+ (80 mM). Similar results were observed with cromakalim, a potassium channel-opening vasodilator. This spasmolytic activity of *F. carica* fruits is probably due to the activation of K^+_{ATP} channels [2, 6].

3.17 Antiplatelet activity

3.17.1 Fruit extracts

Proteases derived from fig aqueous-ethanolic extract were investigated on human blood coagulation using *ex vivo* model of human platelets from volunteers free of medications for 1 week. Extracts at 0.6 and 1.2 mg/mL repressed the human platelet aggregation with the agonists adrenaline and adenosine 5′-diphosphate (ADP). Ficin, a mixture of proteases derived from figs, seems to be responsible for the activation of blood coagulation factor X (vitamin K-dependent plasma glycoprotein with pivotal role in hemostasis) [2, 6, 38].

4. Conclusions

Since ancient times, the fruits and leaves of *F. carica* have been used as food and for their different therapeutic effects. In recent years several scientific works have analyzed the chemical composition of both parts of the plant to know more in depth the phytochemical compounds responsible for the biological properties

demonstrated in several *in vitro* and *ex vivo* tests. In addition, the use of new environmentally friendly extraction processes, such as ionic liquids or deep eutectic solvents, and the use of fig phytochemicals as additives for new food applications (nutraceuticals and functional foods) are highly researched topics in recent times. However, research on different alcoholic beverages derived from both parts of the plant, such as wine, liqueur, and spirit, is still scarce. These beverages represent an important source of sustenance for the local economy of different countries from the Mediterranean basin, so that their study could provide an improvement in the quality of the products and publicize the chemical and biological properties derived from their consumption.

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Conflict of interest

The authors declare no conflicts of interest.

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