Chemical Composition and Biological Activities of *Fragaria* Genus

Subjects: Horticulture

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Fragaria genus *(Rosaceae),* commonly known as strawberry, represents one of the most important food plants all over the world, with a double global production compared with all other fruit berries combined. Usually appreciated because of their specific flavor, the strawberries also possess biological properties, including antioxidant, antimicrobial, or anti-inflammatory effects.

Fragaria genus chemical composition biological properties

1. Introduction

The production of different fruits all around the world exceeds millions of tons, depending on geographical zones, consumption, and growing traditions, inevitably leading to large amounts of by-products and wastes. *Fragaria* genus (*Rosaceae*), commonly known as strawberry, represents one of the most important food plants all over the world, with a double global production compared with all other fruit berries combined [1]. Their widespread use, primarily because of their flavor, can also lead to considerable benefits to human health. Among other characteristics, nonvisual properties like taste, nutritional values, or aroma make these fruits to be in the top of consumer preferences [2].

Among the 247 varieties known and listed, only few present commercial interest: *Fragaria x ananassa* Duchesne (octoploid hybrid-containing 56 chromosomes, known as garden strawberry, native to northern America, cultivated all over the world), and, to a lesser extent, *Fragaria vesca* L. (diploid species, known as wild strawberry, native to Northern hemisphere) and *Fragaria chiloensis* (L.) Mill. (octoploid species, known as Chilean strawberry, native to northern, pacific and southern America) [1].

2. Composition of *Fragaria* L. Genus

Giampieri et al. [3] reviewed the composition of the strawberry (*Fragaria x ananassa*), while Morales-Quintana and Ramos [4] reviewed the composition and potential applications of the Chilean strawberry (*Fragaria chiloensis* (L.) Mill.), while the functional properties of the berries, in general, and of the strawberries, in particular, were reviewed by Jimenez-Garcia et al. [5]. As resulting from various literature studies [3][4][5][6][7], the general composition of the strawberries (in terms of major components) can be summarized in **Table 1** (with a general image provided in **Figure 1**).

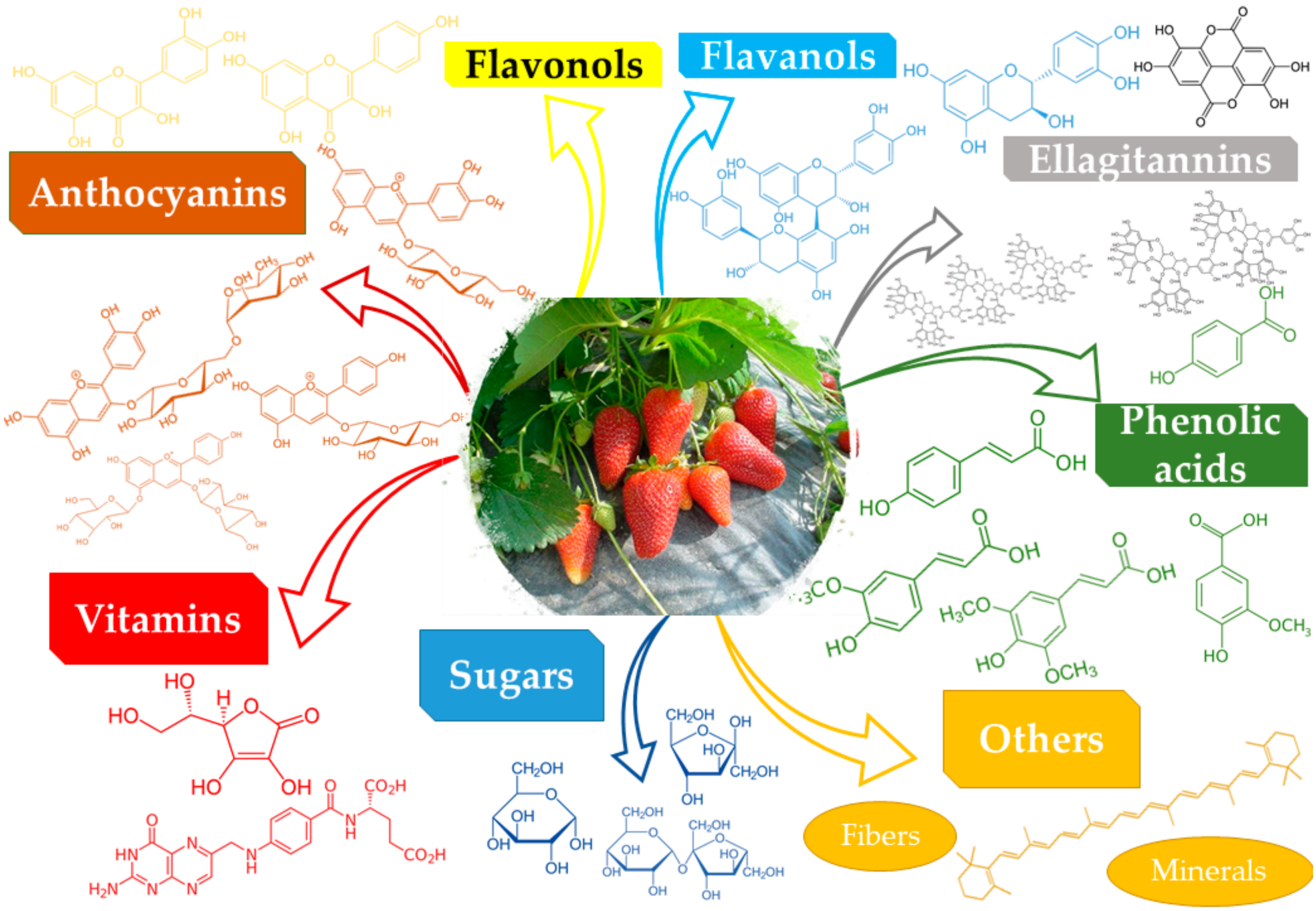

Figure 1. Main components *Fragaria* species identified according literature data.

Table 1. Major (common) components in *Fragaria* L. aggregate fruits (adapted from [3][4][5][6][7]).

Class	Compound	Ref.
Anthocyanins	Pelargonidin 3-glucoside, cyanidin 3-glucoside, cyanidin 3-rutinoside, pelargonidin 3-galactoside, pelargonidin 3-rutinoside, pelargonidin 3-arabinoside, pelargonidin 3-malylglucoside	[3][4][5]
Flavonols	Quercetin, kaempferol, fisetin, their glucuronides, and glycosides	[3][4][5][8]
Flavanols	Catechin, proanthocyanidin B1, proanthocyanidin trimer, proanthocyanidin B3	[3]
Ellagitannins	Sanguiin H-6, ellagitannin, ellagic acid, lambertianin C, galloylbis-hexahydroxydiphenoyl-glucose	[3]

Class	Compound	Ref.
Phenolic acids	4-coumaric acid, p-hydroxybenzoic acid, ferulic acid, vanillic acid, sinapic acid	[7]
Vitamins	Vitamin C, vitamin B9	[6]
Minerals	Mn, K, Mg, P, Ca	[3]
Others	Sugars (glucose, fructose, and sucrose), fibers	[3]

variation, and the degree of fruit ripeness. In the reviewed time period, several studies presented the evaluation of species belonging to *Fragaria* genus. Their main findings are presented in **Table 2**, while relevant studies are presented in the following paragraphs.

Table 2. Composition of *Fragaria* species (as presented by original works published in the reviewed period; references presented in chronological order).

Species	Plant Part, Other Variables	Identified Compounds and Main Findings	Identification Method	Ref.
F. chiloensis	Ripe fruits	Anthocyanins (cyanidin 3-*O*-glucoside, pelargonidin 3-*O*-glucoside cyanidin-malonyl-glucoside and pelargonidin-malonyl-glucoside); procyanidins, ellagitannins, ellagic acid and flavonol derivatives	HPLC-DAD, LC-ESI-MS	[9]
F. chiloensis	Leaves	Procyanidins, ellagitannins, ellagic acid and flavonol derivatives	HPLC-DAD, LC-ESI-MS	[9]
F. chiloensis	Rhizomes	Procyanidins, ellagitannins, ellagic acid and flavonol derivatives	HPLC-DAD, LC-ESI-MS	[9]
Fragaria × *ananassa*	Fruits	Anthocyanins (pelargonidin-3-glucoside, pelargonidin-3-rutinoside, cyanidin-3-rutinoside,	LC-MS/MS, HPLC-UV/Vis	[10]

Species	Plant Part, Other Variables	Identified Compounds and Main Findings	Identification Method	Ref.
		pelargonidin-3,5-diglucoside, pelargonidin-3-(6-acetyl)-glucoside, 5-carboxypyranopelargonidin-3-glucoside, delphinidin-3-glucoside, peonidin-3-glucoside, cyanidin-3-galactoside), *p*-hydroxybenzoic acid, (+)-catechin, ellagic acid, *p*-coumaric acid, quercetin glucoside		
Fragaria × *ananassa*	Fruits, cultivar and seasonal variations	Vitamin C, β-carotene, total phenolics, total anthocyanins; genotype influence is stronger than the environmental influence	Colorimetric	[11]
Fragaria × *ananassa*	Fruits, different cultivars on different ripeness stage	Total vitamin C, total phenolics, total anthocyanins, total ellagic acid/pelargonidin-3-glucoside and cyanidin-3-glucoside; higher amounts in pink fruits compared with fully ripped fruits	Colorimetric/HPLC-DAD	[12]
Fragaria × *ananassa*	Fruits, different farming methods	Total phenolics/pelargonidin-3-glucoside and cyanidin-3-glucoside, vitamin C, higher in organic farming fruits	Colorimetric/HPLC-DAD	[13]
Fragaria × *ananassa*	Fruits, different cultivars (27) and ripening stages	Phenolic compounds (multiple classes, including anthocyanins, flavanols and ellagitannins); composition dependent on cultivar, cinnamic acid conjugates and anthocyanins levels increased with the ripening stage	HPLC-DAD-MS	[14]
Fragaria × *ananassa*, *F. vesca*	Fruits	Quercetin and isorhamnetin glycosides (higher levels in wild strawberry)	HPLC-DAD, LC-ESI-MS	[15]

Species	Plant Part, Other Variables	Identified Compounds and Main Findings	Identification Method	Ref.
Fragaria × *ananassa*, *F. vesca*	Fruits, different cultivars	Volatile esters (including ethyl acetate, hexyl acetate, methyl butanoate, ethyl butanoate, hexyl butanoate, methyl hexanoate, ethyl hexanoate, hexyl hexanoate); higher levels in cultivated strawberries.	GC-MS	[16]
F. vesca	Fruits, two different cultivars	Anthocyanins (cyanidin 3-*O*-glucoside, pelargonidin 3-*O*-glucoside, peonidin 3-*O*-glucoside, cyanidin 3-*O*-malonylglucoside, pelargonidin 3-*O*-malonylglucoside, peonidin 3-*O*-malonylglucoside), dihydroflavonol and flavonols (taxifolin 3-*O*-arabinoside, kaempferol 3-*O*-glucoside, quercetin 3-*O*-glucoside, quercetin-acetylhexoside, kaempferol 3-*O*-acetylhexosides), flavan-3-ols and proanthocyanidins (catechin, B type proanthocyanidin dimers, trimers, and tetramers), ellagic acid and derivatives (glycosylated, methyl pentoside, methylellagic acid methyl pentoside, ellagitannins), other compounds (benzoic acid, ferulic acid hexose derivative, citric acid, furaneol glucoside)	HPLC-DAD	[17]
Fragaria × *ananassa*, *F. vesca*	Fruits	Anthocyanins (cyanidin, pelargonidin), cyanidin glycosides (cyanidin 3-glucoside, cyanidin 3-arabinoside, cyanidin 3-sambubioside, delphinidin 3-galactoside, delphinidin 3-glucoside, delphinidin 3-malonylglucoside); higher levels of cyanidin glycosides in wild species	HPLC-DAD	[18]
F. vesca	Leaves	Ellagitannins (sanguiin H-2 isomer, sanguiin H-10 isomer, sanguiin H-6/agrimoniin/lambertianin A isomer, castalagin/vescalagin isomer, sanguiin	LC-PDA-ESI-MS	[19]

Species	Plant Part, Other Variables	Identified Compounds and Main Findings	Identification Method	Ref.
		H-10 isomer, sanguiin H-2 isomer, casuarictin/potentillin isomer)		
Fragaria × *ananassa*	Fruits, different cultivars and production years	Vitamin C, anthocyanins (pelargonidin 3-glucoside, cyanidin 3-glucoside, pelargonidin 3-rutinoside), ellagic acid; strongly dependent on the cultivar and production year	HPLC-UV/Vis	[20]
Fragaria × *ananassa*	Fruits, at different ripening stage	Vitamin C, pelargonidin-3-rutinoside, ellagic acid, cyanidin-3-glucoside, quercetin (red fruits), neochlorogenic, pelargonidin-3-glucoside, pelargonidin-3-rutinoside, epicatechin, quercetin-3-β-d-glucoside, ellagic acid (green fruits)	LC-ESI-TOF	[21]
Fragaria × *ananassa*	Calyx (red and green)	Quercetin-3-β-d-glucoside, ellagic acid, kaempferol-3-*O*-glucoside, vitamin C (red), catechin, quercetin-3-β-d-glucoside, ellagic acid (green)	LC-ESI-TOF	[21]
Fragaria × *ananassa*	Flower	Catechin, quercetin-3-β-d-glucoside, ellagic acid, kaempferol-3-*O*-glucoside, vitamin C	LC-ESI-TOF	[21]
Fragaria × *ananassa*	Leaf	Procyanidin dimer and trimer, catechin, quercetin-3-β-d-glucoside, vitamin C, ellagic acid	LC-ESI-TOF	[21]
Fragaria × *ananassa*	Stolon	Neochlorogenic, procyanidin dimer, catechin, quercetin-3-β-d-glucoside, ellagic acid, vitamin C, kaempferol-3-*O*-glucoside	LC-ESI-TOF	[21]
Fragaria × *ananassa*	Stem	Procyanidin dimer, catechin, ferulic acid, quercetin-3-β-d-glucoside, ellagic acid	LC-ESI-TOF	[21]

Species	Plant Part, Other Variables	Identified Compounds and Main Findings	Identification Method	Ref.
Fragaria × *ananassa*	Crown	Procyanidin dimer and trimer, catechin, propelargonidin dimer, ellagic acid	LC-ESI-TOF	[21]
Fragaria × *ananassa*	Root	Procyanidin dimer and trimer, catechin, neochlorogenic, propelargonidin dimer	LC-ESI-TOF	[21]
Fragaria × *ananassa*	Fruits, different novel cultivars	Phenolic acids (p-coumaric acid, ellagic acid, ferulic acid derivative, *p*-coumaric acid derivatives), monomeric flavanols ((+)-catechin), flavonols (quercetin 3-*O*-glucoside, fisetin, quercetin 3-*O*-glucoside derivative), anthocyanins (cyanidin 3-glucoside, cyanidin 3-rutinoside, cyanidin pentoside, pelargonidin 3-galactoside, pelargonidin 3,5-diglucoside, pelargonidin 3-glucoside, pelargonidin 3-rutinoside, cyanidin 3-Oacetylglucoside, cyanidin hexoside, pelargonidin 3-*O*-monoglucuronide, pelargonidin derivatives)	HPLC-DAD, LC-ESI-QTOF	[22]
Fragaria × *ananassa*	Fruits, grown on different altitudes, on consecutive years	Hydroxybenzoic acid, *p*-coumaric acid, other hydroxycinnamic acids, (+)-catechin, (−)-epicatechin, procyanidins, flavonols, anthocyanins (cyanidin 3-glucoside, pelargonidin 3-glucoside, pelargonidin derivative); higher levels recorded at lower altitudes.	HPLC-DAD	[23]
Fragaria × *ananassa*	Fruits	Kaempferol 3-(6-methylglucuronide), quercetin 3-(6-methylglucuronide), isorhamnetin 3-(6-methylglucuronide), trichocarpin, 2-*p*-hydroxybenzoyl-2,4,6-tri hydroxyphenylacetate, 2-*p*-hydroxyphene thyl-6-caffeoylglucoside, zingerone 4-glucoside, b-hydroxypropiovanillone 3-glucoside, (+)-isolariciresinol 90-glucoside, (−)-	^{1}H NMR, ^{13}C NMR, HMBC, HPLC-UV/Vis, LC-MS/MS, HR-ESI-MS,	[24]

Species	Plant Part, Other Variables	Identified Compounds and Main Findings	Identification Method	Ref.
		isolariciresinol 90-glucoside, aviculin, (−)-secoisolariciresinol 4-glucoside, cupressoside A, cedrusin, icariside E4, dihydrodehydrodiconiferyl alcohol 90-glucoside, massonianoside A, urolignoside, (−)-pinoresinol 4-glucoside, 2,3”-epoxy-4-(butan-2-one-3-yl)-5,7,40-trihydroxy flavane 3-glucoside, kaempferol 3-(6-butylglucuronide), benzyl 2-glucosyl-6-rhamnosylbenzoate		
F. vesca	Fruits, wild and cultivated, from different geographical areas	39 phenolic compounds (including cyanidin 3-*O*-glucoside, delphinidin-3-*O*-glucoside, pelargonidin-3-*O*-glucoside, pelargonidin-3-*O*-rutinoside, (+) catechin, (−) epicatechin, procyanidin B1 and B2, isoquercetin, gallic acid, *p*-coumaric acid, phloridzin); composition dependent on the geographical area	LC-ESI-Orbitrap-MS, LC-ESI-QTrap-MS, LC-ESI-QTrap-MS/MS	[25]
Fragaria × *ananassa*	Fruits, different cultivars	Cyanidin 3-*O*-glucoside, pelargonidin-3-*O*-glucoside, pelargonidin-*O*-rutinoside, total anthocyanins content, dependent on the cultivar	UPLC-PDA-ESI-MS, HPLC-DAD	[26]
F. vesca	Fruits	Volatile composition—one hundred compounds (including esters, aldehydes, ketones, alcohols, terpenoids, furans and lactones).	GS-MS	[27]
F. vesca	Leaves	27 metabolites (organic acids, flavonoids, catechin and its oligomers, ellagitannins), including quinic acid, chelidonic acid, quercetin derivatives, catechin and procyanidins, phloridzin, pedunculagin, methyl ellagic acid glucuronide.	LC-ESI-Orbitrap-MS	[28]

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Species	Plant Part, Other Variables	Identified Compounds and Main Findings	Identification Method	Ref.
Fragaria × *ananassa*, *F. vesca*	White-fruited mutants, different genotypes	Anthocyanins, flavonols, flavan-3-ols, hydroxycinnamic acids, and ellagic acid—derived compounds, dependent on genotype	LC-ESI-MS/MS	[29]
F. chiloensis	Fruits	Anthocyanins (cyanidin-3-*O*-glucoside, pelargonidin hexoside, cyanidin manlonyl hexoside, pelargonidin-malonyl hexoside), ellagitannins (ellagic acid hexoside, pentoside, rhamnoside), proanthocyanidin dimers, epicatechin, flavonols (quercetin pentoside, glucuronide)	HPLC-DAD, LC-ESI-MS	[30]
Fragaria × *ananassa*	Fruits, different cultivars	Anthocyanins, flavonoids, cinnamic acid derivatives, tannins and related compounds, triterpenoids; concentration dependent on the cultivar	UPLC-ESI-QTOF-MS/MS, HPLC-DAD	[31]

where: ^{13}C NMR—Carbon-13 nuclear magnetic resonance; GC-MS—gas chromatography–mass spectrometry; ^{1}H NMR—proton nuclear magnetic resonance; HMBC—heteronuclear multiple bond correlation; HPLC-DAD—high-performance liquid chromatography with diode array detector; HPLC-UV/Vis—high-performance liquid chromatography equipped with UV/vis detector; HR-ESI-MS—high-resolution electrospray ionization mass spectrometry analysis; LC-ESI-MS(/MS)—liquid chromatography electrospray ionization (tandem) mass spectrometry analysis; LC-ESI-Orbitrap-MS—liquid chromatography electrospray ionization Orbitrap mass spectrometry; LC-ESI-QTrap-MS(/MS)—liquid chromatography electrospray ionization quadrupole ion trap mass spectrometry; LC–ESI–(Q)TOF—liquid chromatography electrospray ionization with (quadrupole) time-of-flight; LC-MS/MS—liquid chromatography–tandem mass spectrometry; LC-PDA-ESI-MS—liquid chromatography equipped with photodiode array detector coupled to mass spectrometry using the electrospray ionization interface; UPLC-ESI-QTOF-MS/MS—ultra-performance liquid chromatography equipped with quadrupole time-of-flight coupled to tandem mass spectrometry using the electrospray ionization interface; UPLC-PDA-ESI-MS—ultra-performance liquid chromatography equipped with photodiode array detector coupled to mass spectrometry using the electrospray ionization interface.

3. Biological Activities of *Fragaria* Genus

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3.1. Antioxidant Properties

Traditionally consumed in the form of fruits (as previously presented), *Fragaria* species have also found application in traditional medicine. For example, *Fragaria vesca* leaves and fruits were traditionally used for the treatment of external rashes, as well as internally, as blood purification and roborontarium, for the treatment of diarrhea [32], as maceration for renal stones, or as tea (together with other medicinal plants) for treating stomach inflammations, sedation or regulation of digestion [33]. The following paragraphs presents the main biological properties of different *Fragaria* species, as emerging from the literature data published in the past decade. Particularly, the anthocyanins family represent the subject of several review papers published in the last years, dealing with their bioavailability and potential health benefits [34][35][36]. The following chapters includes only the studies regarding the biological activity of compounds or extracts obtained from *Fragaria* species (not studies presenting the activity of compounds that are found in those plants). The antioxidant properties (**Table 3**) are among the most studied effects of *Fragaria* extracts.

Table 3. Antioxidant properties of different extracts obtained from *Fragaria* species (references presented in chronological order).

Species	Extraction Method	Antioxidant Assay	Antioxidant Potential	Responsible Compounds	Ref.
Fragaria × ananassa, *Camarosa* var. fruits	Anthocyanins isolated using CCC	ORAC, FRAP	ORAC: 2.7–24.46 mmol Trolox/g; FRAP: 2.75–12.5 mmol Fe^{2+}/g (depending on the fraction)	Anthocyanins	[10]
Fragaria chiloensis spp. *chiloensis* form *chiloensis* fruits	Methanol: formic acid (99:1 *v*/*v*) extraction	DPPH, SAS	DPPH assay: IC_{50} = 38.7 mg/L; SAS: 79.3%)	Aglycone and glycosylated ellagic acid and flavonoids	[9]
Fragaria chiloensis spp. *chiloensis* form	Methanol: formic acid (99:1 *v*/*v*) extraction	DPPH, SAS	DPPH assay: IC_{50} = 49.4 mg/L; SAS: 67.60%	Aglycone and glycosylated ellagic acid and flavonoids	[9]

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Species	Extraction Method	Antioxidant Assay	Antioxidant Potential	Responsible Compounds	Ref.
chiloensis leaves					
Fragaria chiloensis spp. *chiloensis* form *chiloensis* rhizomes	Methanol: formic acid (99:1 *v*/*v*) extraction	DPPH, SAS	DPPH assay: IC_{50} = 64.8 mg/L; SAS: 55%	Aglycone and glycosylated ellagic acid and flavonoids	[9]
Fragaria x ananassa Osogrande var. frozen fruits	Acetone (80%) extraction	DPPH, FRAP	DPPH: 11.91–12.83 µmol BHT eq./g FW; best results for ripe fruits FRAP: 27.37–36.75 µmol FS eq./g FW; best results for green fruits	Total phenolic content, vitamin C	[12]
Fragaria x ananassa Camino Real var. frozen fruits	Acetone (80%) extraction	DPPH, FRAP	DPPH: 9.75–12.01 µmol BHT eq./g FW, FRAP: 24.13–28.49 µmol FS eq./g FW (best results for pink fruits)	Total phenolic content, vitamin C	[12]
F. vesca leaves	Methanol, ultrasounds extraction	DPPH, FRAP	DPPH: IC_{50} = 13.46 mg/L; FRAP: 0.878 mmol Fe^{2+}/g DW	Total phenols, total tannins	[37]
F. vesca roots, wild-growing	Hydromethanolic extraction, infusion, decoction	DPPH, FRAP, β-Carotene bleaching	IC_{50}, mg/L: DPPH—50.03/50.56/50.62; FRAP—40.98/44.78/49.23; β-C bleaching—116.26/44.88/66.10; TBARS—35.76/4.76/6.14	Total phenolics, total flavan-3-ols, total dihydroflavonols,	[38]

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Species	Extraction Method	Antioxidant Assay	Antioxidant Potential	Responsible Compounds	Ref.
		inhibition, TBARS			
F. vesca roots, commercial	Hydromethanolic extraction, infusion, decoction	DPPH, FRAP, β-Carotene bleaching inhibition, TBARS	IC_{50}, mg/L: DPPH—68.89/255.81/51.32; FRAP—327.75/78.99/67.92; β-C bleaching—68.34/23.44/114.67; TBARS—6.69/24.25/10.62	Total phenolics, total flavan-3-ols, total dihydroflavonols,	[38]
Fragaria × *ananassa* var. *Amaou,* fruits, at different ripening stage	Ethanol or water room temperature extraction	Modified ABTS assay	Ethanol: 150.5/151.9; water: 227.2/189.4 (red/green fruits) μmol TE/100 g FW	Total phenolic content	[21]
Fragaria × *ananassa* var. *Amaou* calyx (red and green)	Ethanol or water room temperature extraction	Modified ABTS assay	Ethanol: 241.1/1239.9; water: 1716.6/577.7 μmol TE/100 g FW (red/green calyx)	Total phenolic content	[21]
Fragaria × *ananassa* var. *Amaou* flower	Ethanol or water room temperature extraction	Modified ABTS assay	4234.4/387.5 μmol TE/100 g FW (ethanol/water)	Total phenolic content	[21]
Fragaria × *ananassa*	Ethanol or water room temperature extraction	Modified ABTS assay	2401.7/241.1 μmol TE/100 g FW (ethanol/water)	Total phenolic content	[21]

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Species	Extraction Method	Antioxidant Assay	Antioxidant Potential	Responsible Compounds	Ref.
var. *Amaou* leaves					
Fragaria × *ananassa* var. *Amaou* stolon	Ethanol or water room temperature extraction	Modified ABTS assay	1089.4/1856.7 μmol TE/100 g FW (ethanol/water)	Total phenolic content	[21]
Fragaria × *ananassa* var. *Amaou* stem	Ethanol or water room temperature extraction	Modified ABTS assay	1338.6/1123.1 μmol TE/100 g FW (ethanol/water)	Total phenolic content	[21]
Fragaria × *ananassa* var. *Amaou* crown	Ethanol or water room temperature extraction	Modified ABTS assay	6213.3/128.7 μmol TE/100 g FW (ethanol/water)	Total phenolic content	[21]
Fragaria × *ananassa* var. *Amaou* root	Ethanol or water room temperature extraction	Modified ABTS assay	253.1/69.2 μmol TE/100 g FW (ethanol/water)	Total phenolic content	[21]
F. vesca vegetative parts (leaves and stems), wild-growing	Hydromethanolic and aqueous extracts; wild-growing infusion microencapsulated in alginate and incorporated in k-carrageenan gelatine	DPPH, FRAP, β-Carotene bleaching inhibition, TBARS	IC_{50}, mg/L: DPPH—123.67/86.17/109.10; FRAP—81.40/62.36/77.28; β-C bleaching—56.71/12.34/13.40; TBARS—12.63/3.12/5.03 (hydromethanolic/infusion/decoction); Final formulation (mg/mL)—DPPH—2.74; FRAP = 1.23	Total phenolics, total flavan-3-ols, total dihydroflavonols,	[39]

Species	Extraction Method	Antioxidant Assay	Antioxidant Potential	Responsible Compounds	Ref.
F. vesca vegetative parts (leaves and stems), commercial	Hydromethanolic and aqueous extracts	DPPH, FRAP, β-Carotene bleaching inhibition, TBARS	IC_{50}, mg/L: DPPH—139.33/121.94/118.89; FRAP—324.49/91.88/88.20; β-C bleaching—388.90/76.41/69.98; TBARS—24.36/23.07/17.52 (hydromethanolic/infusion/decoction).	Total phenolics, total flavan-3-ols, total dihydroflavonols,	[39]
Fragaria x ananassa cv. *Falandi* fruit	22 compounds isolated from ethanolic extracts	ABTS, DPPH, FRAP	Best results (IC_{50}): ABTS—4.42 μM kaempferol 3-(6-methylglucuronide); DPPH—32.12 μM quercetin 3-(6-methylglucuronide); FRAP—0.05 mmol/g—urolignoside.	Individual compounds	[24]
Fragaria x ananassa cv. *Albion, Aromas, Camarosa, Camino Real, Monte Rey, Portola*, and *San Andreas* fruits	Ultrasonic extraction with acidified methanol	DPPH	IC_{50} (mg/mL) ranging from 76.73 (*Camarosa*)—100 (*Camino Real*)	Total anthocyanin content	[26]
F. vesca leaves native to Italy	Ultrasonic extraction with ethanol: water solvent (70:30, *v*/*v*)	TEAC	0.34–0.35 mg/mL Trolox eq., compared with quercetin (0.40)	Condensed tannins and flavonoid derivatives	[28]

Species	Extraction Method	Antioxidant Assay	Antioxidant Potential	Responsible Compounds	Ref.
Fragaria x ananassa cv. *Tochiotome* leaves	Supercritical CO_2 extraction with different entrainers	DPPH	0.07 (simple supercritical extraction)—5.82 μmol BHT/g sample (with ethanol, dried at 40 °C)	Phenolic compounds	[40]
Fragaria × *ananassa* fruits (90 cultivars)	Ultrasonic aqueous methanol (70%) acidified with 1.5% formic acid, at room temperature	DPPH, ABTS	Average values (μmol Trolox/100 g):765.06 (DPPH), 1637.96 (ABTS)	Tannin-based compounds.	[31]

where: ABTS—2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) assay; BHT—butylated hydroxytoluene; DPPH—reduction of 2,2-diphenyl-1-picrylhydrazyl; DW—dry weight; eq.—equivalents; FRAP—ferric reducing ability of plasma; FS—ferrous sulphate; FW—fresh weight; IC_{50}—half maximal inhibitory concentration; ORAC—oxygen radical absorbance capacity; SAS—superoxide anion assay; TBARS—thiobarbituric acid reactive substances assay; TEAC—Trolox equivalent antioxidant capacity.

3.2. Anti-Inflammatory Properties

As previously stated, one of the traditional uses of *Fragaria* is as an *anti-inflammatory agent* [32][33]. Most of the authors assign the anti-inflammatory properties to the presence of anthocyanins (the most representative being pelargonidin and cyanidin derivates) [41], molecules with known anti-inflammatory potential [42][43], demonstrated both in vitro and in vivo [44][45]. Similar to the other biomedical potential, the anti-inflammatory action is also correlated with the composition of different *Fragaria* species. The traditional use of *F. vesca* as an anti-inflammatory agent was supported by the study of Liberal et al. [46]. The authors observed the decrease of a relevant mediator of the inflammatory response (nitric oxide) produced by macrophages, cultured in the presence of a NO-production inducing bacterial endotoxin (LPS). The ethanolic extract obtained from *Fragaria vesca* leaves, used at non-cytotoxic concentrations (80 and 160 mg/L), induced a 31%, and 40% inhibition, respectively. The authors assigned the NO decrease to a direct scavenging effect (as demonstrated by a 23% inhibition of the nitrite content in the culture media, correlated with the absence of a significant effect when quantifying the inducible nitric oxide synthase—iNOS and the pro-inflammatory cytokine IL-1β). The authors also observed a statistically insignificant increase in the phosphorylated IκBα (nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha) content, suggesting either an increase of its expression or a decrease in its degradation. More than that, the authors observed an increased conversion of the microtubule-associated protein light chain LC3-I to LC3-II (a marker of autophagy), suggesting further anti-cancer properties. Methanolic extracts of *Fragaria x ananassa,* var.

3.3. Other Potential Applications

The *anti-microbial properties* were evaluated within the reviewed time period, especially for *F. vesca.* Hydromethanolic extracts obtained from leaves and roots of *Fragaria vesca* L. were evaluated by Gomes et al. [47] as antimicrobial agents a series of *S. aureus* strains. The results suggested a weak antimicrobial potential of the extracts (5–9 mm inhibition halos in the qualitative assays), which did not qualify the extracts for quantitative determinations. Superior results in terms of antimicrobial properties were obtained by Cardoso et al. [48]. Using hydroalcoholic extracts, the authors observed good antimicrobial properties of the crude extract against a series of *Helicobacter pylori* isolates (inhibition zones ≥ 15 mm) at a 25 mg/mL concentration. The ellagitannin-enriched fraction was efficient against all isolates at lower concentrations (7.5 mg/mL), which led the authors to assume that the ellagitannins were the main class of compounds responsible for the anti-microbial properties. As the *H. pylori* represents a pathogen involved in several gastric pathologies (including gastritis, gastroduodenal ulcer disease, gastric adenocarcinoma and mucosa-associated lymphoid tissue lymphoma), the authors proposed the wild strawberry extract as a potential candidate for human health applications.

The *anti-allergenic* potential of several compounds (linocinnamarin, 1-*O*-trans-cinnamoyl-b-d-glucopyranose, *p*-coumaric acid, cinnamic acid, chrysin, kaempferol, catechin, and trans-tiliroside) isolated from *Fragaria x ananassa* var. *Minomusume* fruits were evaluated by Ninomiya et al. [49], through the determination of their inhibitory effects on antigen-stimulated degranulation in rat basophilic leukemia RBL-2H3 cells. Among the studied compounds, linocinnamarin (95% inhibition of control at 100 μM) and cinnamic acid (approx. 80% of control at 100 μM) were the most efficient in degranulation suppression (through direct inactivation of spleen tyrosine kinase), being proposed as promising tools for alleviating symptoms of type I allergy.

The commercially-available strawberry freeze-dried powder was demonstrated by Abdulazeez [50] to reverse alloxan-induced diabetes (results not presented in **Table 4** as authors used commercial powder product); in a similar study, Yang et al. [4] evaluated the potential *anti-diabetic application* of new and known compounds isolated from strawberry fruits (as presented in Section 2) by determining the α-glucosidase inhibitory activity. The best results were obtained for cupressoside A (IC_{50} = 25.39 μM), kaempferol 3-(6-methylglucuronide) (IC_{50} = 65.22 μM), and 2-*p*-hydroxybenzoyl-2,4,6-*tri* hydroxyphenylacetate (IC_{50} = 97.81 μM), with very good results obtained for a newly proposed structure (kaempferol 3-(6-butylglucuronide)-IC_{50} = 107.52 μM); results superior to the positive control (acarbose-IC_{50} = 619.94 μM) were also obtained for five other compounds.

Table 4. Main biological activities presented in the literature (references listed in chronological order).

Action	Plant	Extraction Method	Assay	Results	Responsible Compounds	Ref.
Anti-inflammatory on inflammatory bowel disease	*Fragaria vesca* leaves	Eth. extraction	MPO activity; GSH, SOD and CAT levels	Prevention of increase in colon weight and disease activity index, decrease in macroscopic and microscopic lesion score; significant improvement of MPO, CAT and SOD levels at 500 mg/kg 5 days oral treatment	Phenolic acids, flavonoids	[51]
Anti-inflammatory	*Fragaria vesca* leaves	Eth. extraction at room temperature, infusion	Nitric oxide production, western blot analysis (expression of pro-inflammatory proteins in lipopolysaccharide-triggered macrophages); nitric oxide scavenger activity	Inhibition of nitrite production on pre-treated cells (at 80 and 160 mg/L—31%/40%); 23% inhibition in culture media, at 160 mg/L	Phenolic content	[46]
Anti-inflammatory	*Fragaria x ananassa,* var. *Alba* fruits	Meth. extraction at room temperature, infusion	Determination of ROS intracellular levels, apoptosis detection, antioxidant enzyme activities,	Reduction of intracellular ROS levels (significant at 100 mg/L), decreased apoptotic rate	Vitamin C, anthocyanins, flavonoids	[52]

Action	Plant	Extraction Method	Assay	Results	Responsible Compounds	Ref.
			immunoblotting analysis, determination of mitochondrial respiration and extracellular acidification rate in cells	(significant at 50 and 100 mg/L); Increased ARE-antioxidant enzymes expression, reduced NO and inflammatory cytokines production (at 50 and 100 mg/L) to control levels		
Anti-inflammatory, hepatoprotective	*Fragaria chiloensis*ssp. *Chiloensis* fruits	Aq. extracts	Histological analyses, determination of transaminases, cytokines, F2-isoprostanes, and glutathione assays	maintained hepatocellular membrane, structural integrity, attenuated hepatic oxidative stress, and inhibited inflammatory response in LPS-induced liver injury; downregulation of cytokines (TNFa, IL-1β, and IL-6)	Phenolic content	[53]
Anti-inflammatory	*Fragaria x ananassa* var. *Camarosa* fruits	Ultrasonic-assisted, acidified meth.	*In vivo:* quantification of the leukocyte content, exudate	Inhibition of the carrageenan-induced leukocyte influx	Phenolic compounds, anthocyanins (particularly	[54]

Action	Plant	Extraction Method	Assay	Results	Responsible Compounds	Ref.
		extraction, separation	concentration, MPO and ADA activities, nitric oxide products, TNF-α and IL-6 levels; in vitro: MTT assay, measurement of nitric oxide products, TNF-α and IL-6 levels, western blot analysis	to the pleural cavity; reduction of myeloperoxidase activity, exudate concentration, NO levels.	pelargonidin-3-*O*-glucoside)	
Anti-inflammatory, wound healing	*Fragaria x ananassa* var. *San Andreas* fruits	Ultrasound-assisted extraction, acidified meth.: aq. (80:20); separation of different fractions	MTT assay, ROS, NO levels, effects on inflammatory markers and on skin fibroblast migration	ROS reduction, suppression of IL-1β, IL-6 and iNOS gene expressions; enhanced skin fibroblast migration	Polyphenolic compounds, especially anthocyanins	[55]
Anti-microbial	*Fragaria vesca* leaves and roots	Centrifugation extraction with meth.: aq. (80:20)	Disc diffusion assay	6–9 mm inhibition zones for leaves, 5–9 mm for roots (depending on *S. aureus* strain)	Phenolic compounds	[47]
Anti-microbial	*Fragaria vesca* leaves	Hydroalcoholic extraction, separation	Disc diffusion assay	Good inhibition potential at 25 mg/mL, better effect for the	Ellagitannins	[48]

Action	Plant	Extraction Method	Assay	Results	Responsible Compounds	Ref.
				ellagitannin-enriched fraction		
Anti-allergenic	*Fragaria x ananassa* var. *Minomusume* fruits	Methanol fraction of fruits juice (obtained by squeezing)	Antigen-stimulated degranulation in RBL-2H3 cells	degranulation suppression (95–60% inhibition for linocinnamarin, cinnamic acid, chrysin, kaempferol, trans-tiliroside)	Best results - phenylpropanoid glycoside	[49]
Anti-diabetic	*Fragaria x ananassa* var. *Falandi* fruits	Compounds isolated from eth. extracts	α-glucosidase inhibitory activity	IC_{50} values better than the positive control (acarbose) for nine compounds (537.43 to 25.39 μM)	Individual compounds	[24]
Anti-obesity, anti-allergy, skin-lightening	*Fragaria ×ananassa* var. *Amaou,* entire plant (red fruit, green fruit, red calyx, green calyx, flower, leaf, stolon, stolon leaf, stem,	Eth. or aq. room temperature extraction	Anti-lipase assay, adipocyte differentiation inhibition assay, melanogenesis inhibition assay, β-hexosaminidase inhibition assay, tyrosinase inhibition assay	Crown, stolon leaf and flowers extracts exhibited the highest effects	Total phenolic content	[21]

Action	Plant	Extraction Method	Assay	Results	Responsible Compounds	Ref.
	crown and root)					
Antihyperuricemic	*Fragaria x ananassa* cv. *Tochiotome* leaves	Supercritical CO_2 extraction with different entrainers	Uric acid production in AML12 hepatocytes	Reduction of uric acid at 100 mg/mL (96 mmol/2 h/mg protein), compared with the control (16,096 mmol/2 h/mg protein)	Kaempferol, quercetin	[40]
Cytotoxic, anti-proliferative	*Fragaria x ananassa* fruits	Meth. extraction	Ex vivo: cell viability assay; in vivo: developing tumor size determination	Cytotoxic on cancer cells, blocked the proliferation of tumor cells	Phenolic compounds	[56]
Antineoplastic	*Fragaria x ananassa* var. *Pajaro* fruits	Acidified hydro-eth. extraction	Transglutaminase assay and polyamine detection, immunoblot analysis	reduction of cell proliferation, lowering of the intracellular levels of polyamine, enhancement of tissue transglutaminase activity	Anthocyanins	[57]
Cytotoxic	*Fragaria vesca* L. leaves	Hydroalcoholic extract at room temperature,	Effects on HepG2 cells—cell viability assessment, cell proliferation, cell	Inhibition of HepG2 cell viability IC_{50} = 690 mg/L	Ellagitannins	[19]

Action	Plant	Extraction Method	Assay	Results	Responsible Compounds	Ref.
		ellagitannins-enriched fraction	cycle and cell death analysis, Western blot analysis, proteasome chymotrypsin-like activity	(extract)/113 mg/L (fraction); fraction induced necrosis and apoptosis, influenced the cellular proteolytic mechanisms		
Chemopreventive	Lyophilized *Fragaria x ananassa* fruits	Ultrasound-assisted extraction with acidified acetone	Histological studies, Western blot analysis, PGE_2 measurement, and nitrate/nitrite colorimetric assay	Decreased tumor incidence, decreased levels of TNF-α, IL-1β, IL-6, COX-2 and iNOS, inhibition of the phosphorylation of PI3K, Akt, ERK, and NFκB	anthocyanins, ellagitannin/ellagic acid/ellagic acid derivatives flavonols	[58]
Cytotoxic	*Fragaria x ananassa* leaves	Hydroalcoholic extracts (meth., eth., isopropanol) from in vitro cell suspension	Cell proliferation, cell viability	Under 50% viable cells for colorectal adenocarcinoma and colon adenocarcinoma upon treatment with extracts containing 0.29 mM ethoxy-dihydrofuro-furan	Polyphenols	[59]

where: ADA—adenosine-deaminase; Akt—Protein Kinase B; aq.—water (aqueous); CAT—catalase; COX-2—cyclooxygenase-2 enzyme; ERK—extracellular signal-regulated kinase; eth—ethanol; GSH—glutathione; HepG2—human liver cancer cell line; IC_{50}—half maximal inhibitory concentration; IL-1β—Interleukin 1 beta cytokine protein; IL-6—interleukin 6; iNOS—inducible nitric oxide synthase; meth.—methanol; MPO—myeloperoxidase; MTT—3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; NFκB—nuclear factor kappa-light-chain-enhancer of activated B cells; NO—nitric oxide; PGE_2—Prostaglandin E_2; PI3K—phosphatidylinositol 3-kinase; RBL—rat basophilic leukemia cells; ROS—reactive oxygen species; SOD—superoxide dismutase; TNF-α—tumor necrosis factor alpha;.