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REVIEW

FEIJOA SELLOWIANA FRUIT, AN AMAZING SOURCE OF ANTICANCER MOLECULES

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ABSTRACT

Feijoa sellowiana O. Berg is a tropical plant with edible fruits and characterised by a high content of flavonoids. Several studies have shown that *Feijoa* contains many bioactive components such as flavonoids, vitamin C, and essential minerals that contribute to multiple health benefits, such as antimicrobial, anti-inflammatory, antioxidant, and anticancer activities. Regarding anticancer activity, several authors have shown that the *Feijoa* fruit acetonic extract and the molecules isolated by it have a selective cytotoxic effect, induce apoptosis, modulate cell cycle against solid and hematologic tumours and are effective against sensitive and resistant cancer cells. This review summarizes *Feijoa* fruit biological activities that have so far been identified with a focus on anticancer activity.

KEY WORDS

Flavone; antitumoural; antioxidant; anti-inflammatory; MDR cells.

IMPACT STATEMENT

Feijoa sellowiana, due to its peculiar chemical characteristics, can give an important contribute in cancer prevention and therapy.

INTRODUCTION

Cancer is a pathological condition characterised by cells that resist apoptosis, respond abnormally to cell cycle regulation mechanisms, are self-sufficient about growth factors, can present impaired differentiation, and contact inhibition is suppressed (1). It is estimated that around three out of ten cancers are caused by poor eating habits (American Institute for Cancer Research) (2). Several epidemiological studies have highlighted that natural products such as fruits, vegetables, spices, and cereals are foods containing active ingredients capable of having beneficial effects on health, in particular having anti-tumour activity; in fact, the lack of consumption of these foods is linked to a series of neoplasms (3). In light of this, research is showing more and more interest in fruits rich in polyphenols, in particular the flavonoids that humans cannot synthesize, and must be taken with diet. Flavonoids are particularly known for their innumerable properties such as antioxidant, anti-inflammatory, as well as antiproliferative and pro-apoptotic for cancer cells, thanks to their ability to modulate different biological processes that characterize these cells (i.e. blocking apoptosis, migration, resistance to chemotherapeutic agents) (4, 5).

Feijoa sellowiana O. Berg, also known as *Acca sellowiana* or *Pineapple guava*, is a tropical evergreen shrub belonging to the *Myrtaceae* family, whose fruits are rich in interesting secondary metabolites such as flavonoids (**figure 1**). *F. sellowiana* is native to the area of South America between northern Argentina, southern Brazil, Uruguay, and Paraguay, where it grows spontaneously and luxuriantly, but it is cultivated in many other countries such as New Zealand, France, Israel, Italy, California, and Florida (6).

The *Feijoa* fruit is edible, oval and has a size of 4-8 cm, with a robust green exocarp, the pulp is white-yellowish translucent, gelatinous and very hard small seeds (**figure 1**). In Italy, the fruit harvest begins in October and ends in November. Its flavour is sweet-sour, a mixture of pineapple, strawberries, and guava and can be eaten fresh, in the form of yoghurt, juice, jam, *etc*. (7). The flower is white-pink and has numerous, very showy red-violet stamens. The petals are crunchy and sweet and can be used for salads. The leaves are 5 cm long; they are dark, thick, elliptical, and opposite. The dried leaves can be used to make infusions.

In traditional medicine, the infusion of *Feijoa* leaves was mainly given to children to treat bacterial and fungal diseases in general and in particular cholera (8). In vitro studies have shown that the acetonic extract of *Feijoa* leaves has antibacterial and antifungal activity; confirming these applications (9). The fruit is rich in pectin, vitamin C (28 mg 100 g^{-1} fresh weight), and essential minerals such as potassium, phosphorus, magnesium, calcium, and iodine (3 mg 100 g^{-1} of fresh fruit) (10,11). In addition, the fruit contains dietary fibre, quinones, terpenes, tannins, and steroid saponins; the aroma that characterizes *Feijoa* is largely due to the volatile esters of ethyl benzoate, ethyl butanoate, and the high amount of methyl benzoate (12). Furthermore, the *Feijoa* fruit contains bioactive phytochemicals, such as large amounts of polyphenols (flavones, catechins, procyanidins B1 and B2, quercetin-glycoside, flavonols, naphthoquinones, leucoanthocyanins, and proanthocyanidins) (13).

Different studies have reported potential therapeutic properties of Feijoa such as acetylcholine and butyrylcholine esterase inhibition (14), antifungal (15), and antibacterial (16-18).

Epidemiological data report that the populations of tropical and subtropical countries that habitually consume the fruits of *Feijoa* have a lower incidence of cancer in the gastrointestinal tract (19).

Numerous studies have been carried out on the anticancer properties and chemical characterisation of *F. sellowiana* (**table I**), as reported below:

- antibacterial activity on *Helicobacter pylori*, the presence of which is one of the causes of gastric cancer;
- immunomodulatory effect;
- antioxidant activity, in order to protect the populations who regularly consumed this fruit from

oxidative stress;
- anti-inflammatory activity;
- cytotoxic activity;
- anti-tumour action on different cell lines of solid and haematological tumours;
- chemical characterisation and activity-guided fractionation;
- selectivity of anti-tumour activity against tumour cells;
- antiproliferative and apoptotic effects on cancer gastric cells;
- anticancer activity against cancer cells that had developed multidrug resistance.

Figure 1. *Details of the Feijoa sellowiana fruits, flowers and leaves*

BIOACTIVITIES

Anti-Helicobacter pylori activity

Despite a sharp decline in incidence and mortality, stomach cancer is still the fourth most common cancer in the world. The best-known risk factor for stomach cancer is *H. pylori* infections (20) which are considered the leading cause of distal gastric adenocarcinoma, and gastric lymphoma (MALToma). Furthermore, *H. pylori* is associated with several diseases, including chronic gastritis and peptic ulcers (21, 22). The pathogenesis depends on the virulence of the strain, the genetic susceptibility of the host, and the environmental cofactors (23). Already in 1994, the International Agency for Research on Cancer classified *H. pylori* as a carcinogen, or cancer-causing agent, in humans (NIH, National centre institute). *H. pylori* is a spiral-shaped Gram-negative bacterium that grows in the mucus layer that coats the inside of the human stomach. Some studies on the inhibitory activity of the active components of plant extracts against *H. pylori* are reported (21, 22, 24-27).

Regarding *F. sellowiana*, Motohashi's group (28) subjected the fruit peel to extraction with hexane, acetone, MeOH and 70% MeOH at room temperature, obtaining 26 fractions (**table I**). All fractions were tested against Gram-positive and Gram-negative bacteria, and *Candida albicans*. The data obtained showed that the acetone extract and the MeOH extract have inhibitory activity against the microorganisms tested.

Basile *et al.* (9) and Vuotto *et al.* (29) also evaluated the antibacterial activity of *Feijoa* fruit extracts against Gram-positive and Gram-negative but using the various parts of the fruit (whole fruit, pulp, and peel). Subsequently, the *Feijoa* fruit was subjected to extraction with acetone, obtaining 11 fractions (A-M). All fractions were tested against *H. pylori*, and by activity-guided fractionation, it was possible to identify the compound responsible for anti-*H. pylori* activity. The substance most responsible for this activity is the Flavone (6). Therefore, these works confirm that flavonoids of natural origin, and in particular Flavone, could be considered a natural therapy in the treatment of infections, having an interesting therapeutic potential for the treatment of gastrointestinal diseases associated with *H. pylori* infection, as well as their generic antibacterial activity against various Gram-positive and Gram-negative bacterial strains (30).

Immunomodulant activity

Flavonoids are a heterogeneous group of plant phenolic compounds widely used in the medical field because they have numerous biological activities, including antioxidant and immunomodulating activity. Ielpo *et al.,* (31) tested natural catechin, and two of its derivatives (+)-3-O propionylcatechin and (-)-3-O-valerylcatechin, extracted from the *Feijoa* fruit on the oxidative metabolism of phagocytes through the luminol-dependent chemiluminescence emitted by resting human phagocytes and activated by PMA (phorbol myristate acetate) (**table I**). Chemiluminescence is a simple method to study the oxidative metabolism of phagocytes and indirectly phagocytosis; in fact, light is emitted following a chemical reaction of cells activated as granulocytes, when phagocytosis is activated as the first immune response to protect the body from invaders. The results demonstrated that the low concentrations of

BIOACTIVE COMPONENT	CELL LINES	EVALUATION METHOD/ TREATMENT	EFFECTS	REFERENCE
Natural catechin; (+)-3-*O*- propionylcatechin; (-)-3-*O*- valerylcatechin extracted from *Feijoa*	Human leukocytes induced by PMA	(50 µM) Luminol-dependent CL	Inhibition of ROS release	(25)
Aqueous extract of *Feijoa* fruit	Human whole blood phagocytes (1.0 microliters); PMN (1 × 10^5 cells ml^{-1})	(1 m/ mL–12 ng/ mL). Basal CL 0.5 mg OZ-stimulated. 150 nmol PMA-stimulated	Inhibition of emission of CL	(23)
Feijoa acetonic extract	J774 (macrophage cell line)	(50, 250, 750 µg/mL) LPS stimulation (10 µg/mL) for 24 h MTT assay Griess assay	Decrease of nitrite production in a concentration-dependent manner (attenuating the activation of NF-KB and/or MAPK)	(6)
[A3] fraction benzene-AcOEt (1:1) from *Feijoa* peel	HSC-2; HSG	MTT assay (IC50 > 100 µg/mL)	Cytotoxic activity	(22)
Feijoa acetonic extract	Caco-2	BrdU assay (50, 500 µg/mL for 24 h) MTT assay (5, 50, 500 µg/mL for 24 h) H2O2 1mM and 5, 50, 500 µg/mL for 24 h Dahlqvist test and glucose oxidase assay (5-500 µg/mL for 24 h)	Decrease in cell proliferation rate No significant cytotoxic effect Significant reduction of MDA Improved lactase and sucrase-isomaltase activity	(30)
Feijoa acetonic extract	HT-29	BrdU assay (50, 500 µg/mL for 24 h) MTT assay 5mg/mL (5, 50, 500 µg/mL for 24 h) H2O2 1mM and 5, 50, 500 µg/mL for 24 h Dahlqvist test and glucose oxidase assay (5-500 µg/mL for 24 h)	Decrease in cell proliferation rate No significant cytotoxic effect Significant reduction of MDA No improvement in lactase and sucrase-isomaltase activity	(30)
PAOF-1 derived from *Feijoa* fruits	OSCC cell lines: HSC2; HSC-3; HSC-4; CAS9-22 HGF; HPC; HPLF	MTT assay CC_{50} of PAOF-1 against OSCC cell lines:151 µM CC_{50} of PAOF-1 against HGF, HPC, HPLF: 477 µM	Selective cytotoxicity against OSCC cell lines	(12)
Feijoa acetonic extract	HeLa; MCF-7; SKBR3; MDA-MB231; NB4	Feijoa acetonic extract (5-3 mg/mL) Crystal violet assay Trypanblue assay	Anti-proliferative activity dose-dependent	(13)

Table I. *List of the bioactivities of F. sellowiana acetonic extracts, flavone and catechins.*

BIOACTIVE COMPONENT	CELL LINES	EVALUATION METHOD/ TREATMENT	EFFECTS	REFERENCE
Feijoa acetonic extract	HeLa; MCF7; U937; NB4 LnCap	(0,5-1-3-5 mg/mL) for 3 days Western blot FACS RT-PCR	Apoptosis in a dose dependent manner HeLa blocked in G1 phase MCF7, U937, NB4 blocked in S or G2/M phases Less sensitive to treatment.	(13)have been often claimed, although the corresponding molecular mechanism(s
Pure flavone (FP) *Feijoa* acetonic extract	NB4	Pure flavone (0,037 mg/mL 170M). Western blot. FACS RT-PCR	Apoptosis: NB4 blocked in G1 phase Induction of p16, p21, and TRAIL Inhibition of HDAC	(13)have been often claimed, although the corresponding molecular mechanism(s
Feijoa acetonic extract FS or FP	AML primary blasts; CD34+	Feijoa acetonic extract (1-3 mg/mL) FS, FP (0,37 mg/mL). FACS	Apoptosis in AML primary blasts increasing histone H3 acetylation levels	(13)have been often claimed, although the corresponding molecular mechanism(s
Feijoa acetonic extract	BALB/c 3T3 (nonmalignant murine cell line); SVT2 (malignant counterpart) HRCE (human primary renal cortical epithelial cells); HEK-293 (transformed human embryonic kidney)	MTT assays (0-5 mg/mL for 24, 48, 72 h)	Cytotoxic activity: IC_{50} 48h (2,5 mg/mL for SVT2; 1 mg/mL for HEK-293) Cytotoxic activity: IC_{50} 48h (4,5 mg/mL for BALB/c 3T3; 2,5 mg/mL for HRCE	(36)
Feijoa acetonic extract	hBMSC (human bone marrow mesenchymal stem cell)	5 ng/mL for 4 days MTT assay 5 ng/mL for 7 days MTT assay	Improved proliferation and reduction of PDT Reduction of proliferation	(11)
Feijoa acetonic extract Synthetic flavone (FS)	SNU-1	MTS and Annexin V FITC assays (5, 50, 500 µg/mL for 24/48 h) MTS and Annexin V FITC assays (5, 50, 100 µg/mL for 24/48 h)	Antiproliferative and apoptotic effect in a time- and dose-dependent manner	(31)
Feijoa acetonic extract Synthetic flavone (FS)	AGS; KATOIII	MTS and Annexin V FITC assays (5, 50, 500 µg/mL for 24/48 h) MTS and Annexin V FITC assays (5, 50, 100 µg/mL for 24/48 h)	No growth inhibitory effects Antiproliferative and apoptotic effect in a time and dose-dependent manner	(31)

BIOACTIVE COMPONENT	CELL LINES	EVALUATION METHOD/ TREATMENT	EFFECTS	REFERENCE
Feijoa acetonic extract Synthetic flavone (FS)	PMN (polymorphonuclear leukocytes)	Feijoa acetonic extract (567,7 µg/mL) Synthetic flavone (21,6 µg/mL) SOD (superoxide dismutase) CAT (catalase); GPx (glutathione peroxidase)	Improved antioxidant enzymes activity The activity of SOD, CAT GPx enzymes was greater in PMN cells treated with flavone	(31)
1) Whole flower ethanolic extract 2) Petals ethanolic extract 3) Petal juice	*In vitro* antioxidant activity	FRAP CUPRAC DPPH ABST Total polyphenols	Antioxidant activity: whole flower > petals > petals juice. Total polyphenols: whole flower > petals juice > petals. See reference for more details	(46)
Fruit ethanolic extract (80:20 v/v)	*In vitro* antioxidant activity	1) ORAC 2) ABST 3) Deoxyribose assay	1) 148.8-272.7 µM Trolox equivalent 2) IC_{50} = 10.8-52.5 µg/ml 3) IC_{50} = 67.5-174.5 µg/ml	(49)
Leaves methylene choloride: methanolic extract (80:20 v/v)	*In vitro* antioxidant activity	1) DPPH 2) ABTS 3) FRAP 4) CUPRAC	1) 90.58 ± 0.89 2) 113.80 ± 0.02 3) 102.58 ± 0.41 4) 180.23 ± 0.44 mg Trolox equivalent/g.	(14)

Table I. *List of the bioactivities of F. sellowiana acetonic extracts, flavone and catechins.*

the *Feijoa* acetonic extracts were able to inhibit the release of ROS in human leukocytes induced by PMA. The catechins [50 µM] inhibited the chemiluminescence emission of resting phagocytes in a dose-dependent manner. In particular, the inhibitory effect is more evident when valerylcatechin is used. The authors hypothesized that this effect might be due to myeloperoxidase, lipoxygenase, or inhibition of NADPH-oxidase. Flavonoids can inhibit the release of β-glycuronidase acting on A2 phospholipase, and they also inhibit the phosphorylation of proteins that mediate the activation of PMNs induced by PMA.

Antioxidant activity

Oxidative stress is the result of the imbalance between ROS production and levels of antioxidant systems. Normally, cells can maintain a balance between ROS production and removal. When the equilibrium shifts toward the production of ROS or the levels of antioxidant systems, a condition of oxidative stress is established (32), which damages crucial biomolecules such as nucleic acids, proteins, lipids, and carbohydrates (33).

Several studies have shown that oxidative stress can play a crucial role in human pathophysiological diseases (34) and, in particular, ROS influence cancer evolution by initiating tumorigenesis, causing cell death, or inducing cell proliferation (33). Plants are rich in antioxidants compound and, currently, an increasing focus is on flavonoids (35).

Schmidt *et al.* reported that the ethanolic fruit extracts (80:20 v/v) had antioxidant effects against

OH radical, ROO– radical and ABTS radicals. The authors tested the *in vitro* antioxidant properties of *Feijoa* hydroethanolic extracts from three different locations. All the measured antioxidant activities were correlated to the fruit phenolic contents (**table I**). Both the antioxidant activities and the total phenolic content varied among the three harvested *Feijoa* fruits, suggesting that edaphoclimatic conditions, cultivation techniques and plant management can affect the phenols contents and consequently the antioxidant activities of the extracts. Vuotto *et al.,* (29) tested the aqueous extract of *Feijoa* fruit at various concentrations (1 mg mL^{-1} –12 ng mL^{-1}) on the oxidative burst in human whole blood phagocytes (1.0 microliters) and on isolated polymorphonuclear leukocytes (PMN) (1 × 10^5 cells mL^{-1}) by measuring chemiluminescence without (basal CL) or with 0.5 mg of opsonised zymosan (OZ-stimulated) or 150 nmol of phorbol myristate acetate (PMA-stimulated), in 1.0 mL final volume (**table I**). In addition, to exclude the toxic activity of *Feijoa* in PMNs, the Trypan blue exclusion test was carried out before and after the chemiluminescence evaluation, which showed that leukocytes were viable at all concentrations of the extract. When OZ was used as the stimulant, CL activity was affected only by the highest concentrations of *F. sellowiana* extract. Whereas, when PMA was used, CL inhibition was still statistically significant at low *Feijoa* extract concentration (≈ 15 mg L^{-1}). It was hypothesized that the aqueous extract of *Feijoa* was able to inhibit the emission of CL of native and stimulated human leukocytes by OZ and PMA and that this action can be explained by the scavenger effect on free radicals. Subsequently, the acetonic extract of *Feijoa* was tested on human intestinal epithelial cells (Caco-2 and HT-29) to evaluate their viability, cell proliferation, sucrase-isomaltase activity and lactase, and the membrane lipid peroxidation induced by H_2O_2 (36). The *Feijoa* extract (5, 50 and 500 µg mL^{-1}) after 24 h improved the activity of lactase and sucrase-isomaltase, in Caco-2 cells, but not in HT -29. Furthermore, it was shown that *Feijoa* acetonic extract also exerts antioxidant activity when cells are treated with H_2O_2, used to mimic an oxidative environment. The results obtained highlighted that the *Feijoa* acetone extract did not cause oxidative damage, on the contrary, it was able to have a significant protective and curative effect against the damage induced by H_2O_2. When Caco-2 and HT-29 cells were treated with *Feijoa* extract (5, 50, and 500 µg mL^{-1}) 2 h before and 2 h after exposure to H_2O_2, a decrease in MDA (malondialdehyde, a marker of lipid peroxidation) was observed.

The antioxidant activity of *Feijoa* has also been demonstrated by Russi *et al.,* (37) by testing the enzymatic activity of SOD, CAT and GPx on PMN cells (polymorphonuclear leukocytes). In particular, this study highlighted that the activity of antioxidant enzymes in PMN increases when cells are treated with *Feijoa* extract, and the greatest effect occurs when the flavone is used.

Other studies have investigated the antioxidant activity of non-edible parts of *Feijoa* such as leaves. Saber *et al*., 2021 reported the *in vitro* antioxidant activity of methylene chloride: methanol extracts (80:20 v/v) of *Feijoa* leaves. The leaves extracts showed a good *in vitro* antioxidant activity, as shown in Table 1. Furthermore, the authors isolated several pure compounds from the extracts and tested them for *in vitro* antioxidant activity. The results showed that quercetin, avicularin, flavone, and α-tocopherol were the main contributors to the antioxidant activity of the extracts (for more details see supplemental materials in (14)).

Piscopo *et al.* (17) investigated the *in vitro* gastrointestinal digestion of *Feijoa* fruit proteins. Interestingly, the results showed that the antioxidant activity increases 19-fold after digestion (0.731 ± 0.056 mmol TE mg^{-1}) with respect to the non-digested protein sample (0.039 ± 0.005 mmol TE mg^{-1}), indicating the release of small peptides with strong antioxidant activities during the in vitro gastrointestinal digestion. The ability of Feijoa to protect reproductive tissues from oxidative stress has been studied by Horri *et al.* (38) in mice treated with cadmium. The researchers analysed the sperm parameters, testis morphology, testis histopathology, and serum hormone levels in mice after an intraperitoneal exposure to 0.1 mg kg^{-1} cadmium only, and after cadmium plus 400 mg kg^{-1} *Feijoa* fruit extract. Mice exposed to cadmium showed loss of testis volume, testis weight, sperm viability, sperm number, and histological alterations such as disruption of the epithelium of seminiferous tubules. The treatment with 400 mg kg^{-1} *Feijoa* fruit extracts had a significant effect on the above-mentioned parameters to a level closer to controls.

Anti-inflammatory activity

To explain the action mechanism of the anti-inflammatory activity of *Feijoa sellowiana*, Rossi *et al.* (7) used the cell line of murine macrophages J774 stimulated with an iNOS inducer, lipopolysaccharide (LPS), which determines the overproduction

of NO in inflammatory processes (**table I**). When macrophages were pretreated with 10 µg mL^{-1} LPS for 24h, a very significant increase in NO in the cell medium was observed (63.70 nmol/106 cells *vs*. 2.95 nmol/106 cells). Nitric oxide (NO) is known to play a key role in the physiological and pathological functions of many organs, such as vascular tone regulation, neurotransmission, microorganisms, tumour cell killing, and other homeostatic processes. Several pathophysiological processes such as inflammation and carcinogenesis are correlated with high levels of NO (39). Then the acetonic extracts of *Feijoa* fruit were tested for their anti-inflammatory properties since previous studies exhibited the highest antioxidant and antibacterial activities among different *Feijoa* extracts (9, 29). The addition of the acetonic extract of *Feijoa sellowiana* coincided with dose-dependent inhibition of NO production (35.6, 75.8, and 92.5% inhibition at 50, 250, and 750 µg mL^{-1}). To further investigate the NO modulation, western blot analysis of iNOS, IkBα, and pERK-1/2 was performed. The results showed that the *Feijoa* fruit acetonic extract was able to inhibit the expression of iNOS in a dose-dependent manner (50, 250 and 750 µg mL-1). Simultaneously, IkBα and pERK-1/2 decreased, indicating that the acetonic extract acted as a transcriptional control on the expression of iNOS by blocking the activation of NF-kB via IkBα degradation. In fact, in macrophages, LPS activates the transcription factor nuclear factor-κB (NF-κB), which controls the expression of many early immediate genes, including iNOS. The same experimental procedure was applied to determine which chromatographic fraction of the acetonic extract was the most active. Aliquots of the acetonic extract were dissolved in methanol and separated chromatographically with different proportions of n-hexane/EtOAc or EtOAc/MeOH. Only two of 11 fractions, B (eluted with n-hexane/EtOAc 60:40) and C (eluted with n-hexane/EtOAc 50:50) were the most active, showing modulation of iNOS (extract B from 0.30 µM to 4.5 µM and extract C from 1.30 µM to 3.9 µM. The molecules responsible for the fractions activity were identified as the flavone (B) and stearic acid (C), which were thus the most active compounds in the *Feijoa* fruit. Interestingly, the authors found that *Feijoa* acetonic fruit extract was not cytotoxic to murine macrophages J774 at the concentrations tested (50, 250 and 750 µg mL^{-1}), suggesting low toxicity to normal cells. In summary, the study showed that *Feijoa* acetonic extract, thanks to Flavone and stearic acid, was able to inhibit NO production in J774 cells by attenuating NF-KB and / or MAPK activation. In a study by Mahmoudi *et al.* (40), mice with carrageenan-induced edema were treated with *Feijoa* leaves and fruit extracts. Carrageenan-induced edemas were significantly inhibited by the extract at 50-400 mg kg^{-1}. The researchers tested the antinociceptive effects of both extracts. The leaves extracts showed an activity equivalent to diclofenac at 50 mg kg^{-1}. Fruit extracts showed higher activity than diclofenac at 400 mg kg^{-1} doses. In all tested doses, the extract significantly augmented the pain threshold in the hot plate thermal test. Furthermore, the extracts were demonstrated to be safe up to a dose of 1 g kg^{-1}.

Cytotoxic activity

Motohashi's group (28) subjected the *Feijoa* peel of the fruit to extraction with hexane, acetone, MeOH and 70% MeOH at room temperature (**table I**). All fractions were tested against two tumour cell lines, HSC-2 (human oral squamous carcinoma cells), HSG (human oral salivary gland tumour cells), and against the healthy cell line HGF (human oral gingival fibroblast). Most fractions showed low cytotoxicity against tested cells (IC50 > 100 µg mL^{-1}); only the A3 fraction (benzene-AcOEt 1:1) showed a relatively cytotoxic action for tumour cell lines and the healthy cell line.
By increasing the solubility in water, there was a decrease in cytotoxic activity against the healthy cell line (SI = HGF/HSG-2).
Turco *et al.* (36) evaluated the cytotoxic activity of the *Feijoa* acetonic extract of fruit on Caco-2 and HT-29 (**table I**). The MTT assay showed that with 5, 50 and 500 µg mL^{-1} of extract (for 24 h) no significant cytotoxic effects occurred. Aoyama *et al.* (13) identified and quantified different polyphenols in the various botanical parts of *Feijoa* (fruit, leaves, flowers, and branches) through High-Performance Liquid Chromatography coupled (HPLC-MS) and Nuclear Magnetic Resonance (NMR). They purified from leaves, fruits, and flowers of *Feijoa sellowiana*, in addition to other substances, proanthocyanidin oligomer PAOF-1. PAOF-1 derived from *Feijoa* fruits was tested on OSCC cell lines (HSC2, HSC-3, HSC-4, CAS9-22) and healthy oral cell lines (HGF, HPC, HPLF) and the data obtained showed selective cytotoxicity against OSCC cell lines.

Antiproliferative effects of *Feijoa* acetonic extracts on HeLa, MCF-7, SKBR-3, MDA-MB231, NB4 U937, LnCap

Bontempo *et al.* (19) tested the acetonic extract of *Feijoa sellowiana* fruit in solid and hematolog-

ic tumour cell lines (**table I**). The acetonic extract showed antiproliferative activity, measured with the Trypan blue viability test, on several tumour cell lines: HeLa, SKBR-3, MCF-7, MDA-MB231, while treatment of prostate cancer cell lines (LnCaP) registered the lowest decrease in viability. The highest antiproliferative activity was observed when using 5-3 mg mL^{-1} of raw *Feijoa* acetonic extract. As for the effect of the acetonic extract on the cell cycle and apoptosis of solid cancer cells and haematological cancer cells, HeLa, U937, MCF7 and NB4 cells responded to the extract with dose-dependent apoptotic action but with different sensitivity; while the prostate cells (LnCap) responded less sensitively, indicating that the action of the *Feijoa* acetonic extract has a certain specificity and confirming the results of the viability test. Furthermore, increasing amounts of *Feijoa* acetonic extract resulted in blockade of the cell cycle in the phases S or G2 / M in U937, MCF7, and NB4 cells, while in HeLa cells the blockage occurred in the phase G1. The difference in the blocking of these cells at various stages of the cell cycle may have to do with the cellular context. The activity test of caspases 8 and 3, 7 was also performed on NB4 cells, demonstrating that the cell block was followed by apoptosis. Furthermore, the measurement of CD11c and CD14 constituted a clear signal of the restoration of granulocytic differentiation activity in the NB4 line, indicating that treatment with *Feijoa* caused cell cycle block followed by differentiation and cell death.

The first activity-guided fractionation was performed by Bontempo *et al.* (19). Activity-guided fractionation was performed to understand which substance or group of substances was able to explain the anticancer action of acetonic *Feijoa* fruit extract. Eleven fractions (A, B, C-E, F-H, I-M) were produced and of these only the fraction B, consisting of pure flavone (0.75% by dry weight), was able to induce apoptosis in NB4 cells. Unlike, however, the complete extract of *Feijoa* which induced a cell cycle block in the S or G2 / M phases in NB4 cells, the pure flavone induced the cell cycle block in the G1 phase. This difference was probably due to the presence of other components in the acetonic extract of *Feijoa* that modulated the activity of the cell cycle. Subsequently, the action of the pure flavone (FP) was compared with the commercial flavone (FS) and both flavones had the same effect, that is, blocking the proliferation and inducing apoptosis of cancer cells. Their activity is maximised at concentrations of 100-200 μM. Hence, flavone was the most active compound against the treated cancer cell lines in the *Feijoa* extract. Then, to understand the molecular mechanisms underlying cell cycle block and apoptosis, *Feijoa* extract and FP or FS were tested on NB4 cells, focusing attention on key factors of cell cycle and apoptosis. Both the acetonic extract and flavone (FP-FS) caused overexpression of p21 and p16 (cell cycle inhibitors) and TRAIL (the TNF ligand that induces apoptosis) in NB4 cells, both at the RNA and protein levels; furthermore, they induced hyperacetylation of histone H3 and α-tubulin (which was used as an example of a non-histone target of acetylation) and finally the enzymatic assays showed that both *Feijoa* acetonic extracts and FP-FS were able to inhibit HDAC activity. Further investigations were carried out by Scafuri *et al*., 2020 (41), studying the in-silico docking of flavone and its derivatives apigenin and luteolin to HDAC1 and HDAC 2. The authors observed that flavone, apigenin and luteolin have binding energies similar to a known inhibitor of HDAC 1 and HDAC 2, suggesting that these molecules can target HDAC 1 and HDAC 2. These results indicated that the anti-tumour activities of the Flavone can act through epigenetic modulation (19).

Chemical characterization and activity-guided fractionation

Numerous chemical studies showed that *Fejioa* contains many bioactive components such as flavonoids, phenolic acids, vitamin C, dietary fibre, and potassium (16, 42-44), which contribute to several beneficial health effects such as antimicrobial, anti-inflammatory, antioxidant, and anticancer activities. Furthermore, different organs such as flowers, fruits and leaves have shown different phytochemical profiles. In particular, Monforte *et al.* (45) showed that *Feijoa* pulp is rich in ellagic acid, gallic acid, quercetin, pyrocatechol, rutin, syringic acid, catechin, eriodictyol and eriocitrin.

Aoyama *et al.* (13) identified and quantified different polyphenols in the various botanical parts of *Feijoa* (fruit, leaves, flowers, and branches) through -HPLC-MS and NMR. They purified gossypetin-3-O-α-L-arabinofuranoside, gossypetin-3-O-α-rhamnopyranoside, gossypetin-3-O-β-xylopyranoside, naringenin glycoside from leaves, fruits, and flowers of *Feijoa sellowiana*, aromadendrin glycoside, cyanidin glycoside, quercetin, kaempferol glycoside, ellagic acid and its derivatives, flavone, peduncolagin and proanthocyanidin oligomer PAOF-1 testing the latter compound on oral squamous cell carcinoma

cell lines (HSC-2, HSC-3, HSC-4, CAS9-22). Interestingly, flavone was the main constituent of the leaf extract.

Similar results were obtained by Saber *et al.* (14), where flavone was the most abundant compound in leaves followed by avicularin, and quercetin. Mosbah *et al.* (42) analyzed the phenolic fingerprint of the aqueous extract of *Feijoa* leaves through HPLC-DAD-MS. The results showed that *Feijoa* leaves extracts contained mainly flavan-3-ols, procyanidins and catechins; flavonols such as quercetin glycosides and ellagitannins.

Recently, Montoro *et al.* (46) investigated the phytochemical profile and antioxidant activity of *Feijoa* comparing the whole flower, petals only and petals juice. *Feijoa* is known for its massive flower production, which can be a valuable molecule source for the food, pharmaceutical and nutraceutical industries (46). The researchers found that *Feijoa* flowers showed a different phytochemical profile with respect to fruits and leaves. The whole flower ethanolic macerate and the two analysed fractions contained various amounts of ellagitannins, flavonoids and anthocyanidins. Ellagitannins were higher in the whole flower than the petal macerate (15 *vs*. 0.4 mg L^{-1}), while < LOQ in petal juice. Flavonols were found in comparable concentrations in whole flower and petals macerates (42.9 *vs*. 45.1 mg L^{-1}) and lower in petals juice (4.7 mg L^{-1}). The whole flower ethanolic macerate showed the highest polyphenolic content (395.14 mg GAE L^{-1} *vs*. 98.59 in petals and 114.53 mg GAE L^{-1} in petals juice), with a consequent higher antioxidant activity compared to petals macerate and petal juice, measured with various *in vitro* assays (FRAP, CUPRAC, DPPH, and $ABST^{+}$) (**table I**).

Smeriglio *et al.* (8) showed interest in the phytochemical profile and biological activity of essential oils (EO) extracted from the peel of the *Feijoa* fruit. Through GC-FID and GC-MS analyses, they identified and quantified 40 compounds belonging to sesquiterpenes (76.89%), monoterpene hydrocarbons (3.26%), and oxygenated monoterpenes (0.34%). The main compounds were γ-selinene (17.39%), α-caryophyllene (16.74%), β-caryophyllene (10.37%) and Germacene D (5.32%).

In a study carried out by Tuncel and Ylmaz (47), syringic and trans-cinnamic acids were identified in the pulp of the *Feijoa* fruit. Phan *et al*., 2019 (16) analysed whole fruit, peel and pulp methanolic extracts through UHPLC-PDA searching for phenolic compounds. The researchers found that *Feijoa* fruit peel contained the highest amounts of both free and bound phenolic compounds such as catechin, dihydroxyflavone, ellagic acid, p-coumaric acid, and ferulic acid.

However, it is important to note that the phytochemical profile of *Feijoa* can change according to the variety, depending on the portion of the fruit used, the ripeness, the climate, the origin of the plants, environmental conditions and the extraction method (8, 48). Schmidt *et al.* (49) found that *Feijoa* hydroethanolic extracts (80:20 v/v) of whole fruit collected in different sites showed a variable content in phenolic compounds. Furthermore, the authors reported for the first time the presence of castalagin, catechin and epicatechin.

Another research by Magri *et al.* (50) measured the phenolic content of *Feijoa* flowers at different flowering stages. The results indicated that *Feijoa* flowers in the early flowering stage (*i.e*., during petals opening) are characterized by the highest phenolic content.

Furthermore, the phenolic content can change between different Feijoa cultivars. In a study by Peng *et al.* (51), total phenolic contents of four Feijoa cultivars juice: Apollo, Wiki Tu, Unique, and Opal Star were investigated. The results showed that the Wiki Tu and Unique had the highest TPC (1.89 ± 0.01 mg GAE mL^{-1} juice) among the four cultivars, and the Opal Star cultivar had a significantly lower TPC (1.17 ± 0.01 mg GAE mL^{-1} juice).

Regarding environmental conditions, by comparing the composition of the essential oils of *Feijoa* fruits grown in polluted sites with those collected in nonpolluted sites, it was shown, by GC-MS, that the essential oils of *Feijoa* in polluted sites were characterised by a greater quantity of antioxidant compounds, in particular Flavone (the compound responsible for antitumoural and antioxidant activity), respect to the control site. Sixty compounds, representing 96.6% and 97.8% (unpolluted site and polluted site, respectively) of the oils were identified. The main constituents were β-caryophyllene (12.4% and 16.8%), ledene (9.6% and 11.1%), α-humulene (6.3% and 8.2%), β-elemene (4.9% and 5.3%) and δ-cadinene (4.7% and 5.2%) at the control site and the polluted site, respectively (48).

Selective cytotoxic activity of *Feijoa* extract

The activity of acetonic extract and flavone has been proven to be very specific as it does not manifest itself toward non-tumour cells.

In this regard, Dell'Olmo *et al.* (52) demonstrated

the selective cytotoxicity of *Feijoa* acetonic extract using healthy and cancerous eukaryotic cells, such as the nonmalignant murine cell line BALB/c 3T3 and its malignant counterpart, mouse fibroblasts SVT2, HRCE cells, and the malignant counterpart HEK-293 (Tab. 1).

In all cell lines, both time-dependent and dose-dependent inhibition of cell viability was shown. But the most surprising thing is that the extract was found to be more cytotoxic on cancer cells than on untransformed cells. Indeed, the 48-hour IC50 values were significantly lower for tumour cells (2.5 and 1 mg mL^{-1} for SVT2 and HEK-293 cells, respectively) than for untransformed cells (4.5 and 2.5 mg mL^{-1} for BALB / c 3T3 and HRCE cells, respectively). The goal of chemotherapy is to inhibit cell proliferation and tumour multiplication, thus avoiding invasion and metastasis. But, most conventional chemotherapy agents are toxic to both cancer cells and normal cells (53); in light of this, the selective, albeit partial, toxic action exerted by the *Feijoa* extract could represent an interesting feature for the future design of innovative chemotherapy strategies.

Bontempo *et al*. (19) studied, in addition to the selectivity of the acetonic also extract the activity of both Flavone and acetonic extract on AML primary blasts and CD34+ (**table I**).

The study showed that both *Feijoa* extract and FS or FP tested on AML samples induced apoptosis characterised by the overexpression of some molecular effectors (**table I**), namely p16, p21 and TRAIL; moreover, inhibition of deacetylases and, therefore, an increase in histone acetylation was found. The addition of FS or FP on the CD34+ did not result in significant biological effects, indicating that *Feijoa* and the flavones have a selective cytotoxic activity.

More recently, in a study by Rasekh *et al.* (12) the acetonic extract of *Feijoa sellowiana* was also tested in stem cells derived from human bone marrow (hBMSC) to assess their proliferative and apoptotic activity. The results obtained showed that with 5 ng mL^{-1} of *Feijoa* acetonic extract an increase in the proliferation of hBMSC was obtained up to day 4 thanks to the presence of bioactive components of the fruit (vitamins, polyphenols, essential minerals); after 7 days there was a decrease in proliferation due to the anticancer activity of *Feijoa*. Furthermore, overexpression of the Bax gene (pro-apoptotic protein) and a decrease of Bcl-2 (anti-apoptotic protein) were highlighted, confirming the role of *Feijoa* in the pro-apoptotic process.

Green synthesized silver nanoparticles (SNPs) prepared with *Feijoa* methanolic extract have shown selective antiproliferative activity against MCF-7 and AGS cells (18). The data indicated that the SNPs prepared with *Feijoa* methanolic extract at a concentration of 1.56 and 3.12 μg mL^{-1} were cytotoxic to MCF-7 and AGS cells, while no cytotoxicity was observed in human foreskin fibroblasts.

Antiproliferative and apoptotic effects on cancer gastric cells

Turco *et al.,* (36) measured the proliferation of intestinal epithelial cells by measuring the incorporation of the thymidine analogue 5-bromo-2-deoxyuridine (BrdU) into DNA (**table I**). The analysis showed that 50 and 500 μg mL^{-1} of *Feijoa* acetonic extract caused a decrease in the proliferation rate of Caco-2 cells, while a significant decrease in the proliferation rate of HT-29 cells was obtained using 500 μg mL^{-1}.

In another study, Russi *et al.,* (37) evaluate the proliferative and pro-apoptotic activity of *Feijoa* in gastric tumour cell lines (SNU-1, AGS, KATOIII). Cell lines were treated with *Feijoa* acetonic extract (5, 50, and 500 μg mL^{-1}) or flavone (5, 50, and 100 μg mL^{-1}) for 24 and 48 h. By MTS and Annexin V FITC assays, it was found that among the three cell lines tested, SNU-1 showed a significant decrease in cell proliferation and induction of apoptosis; in contrast, AGS and KATOIII were weakly influenced by treatment, confirming that gastrointestinal cancer is a disease characterised by cellular heterogeneity.

Effectiveness of *Feijoa* against multidrug-resistant cancer cells (MDR)

The phenotypic expression of MDR is the frustrating outcome of an initially successful chemotherapy treatment that affects and seriously compromises the effectiveness of conventional drugs, thus determining a consequent poor prognosis (54). Those responsible for drug resistance are the ATP-binding cassette transporters (ABCs), which pump a variety of drugs out of cells at the expense of ATP hydrolysis.

The P-glycoprotein (P-gp) is the most studied among ABC transporters and is responsible for transporting various xenobiotics out of cells by using ATP (55). It is now established that this protein is also expressed in many normal tissues at low levels (56), but the interest in this protein began when it was understood that its overexpression in cancer cells caused the MDR phenotype.

The analysis carried out in the study by Dell'Olmo *et al.* (52) highlighted that the *Feijoa sellowiana* extract can inhibit cell proliferation (measured by the MTT assay) of KB-3-1 (drug-sensitive cancer cell line) KB-C1, and KB - A1 (drug-resistant cells) in a dose-time dependent manner, thus indicating the ability of the *Feijoa* extract to also act on MDR tumour cells (**table I**).

This property of *Feijoa* leads us to consider the possible applicability of this natural extract to treat neoplasms characterised by multi-resistance.

However, specific studies on the modulation of MDR- related proteins (*e.g.,* P-glycoprotein) by *Feijoa* extracts would be advisable. Identification of compounds that are effective in MDR cancer cells could greatly contribute to the future design of alternative therapeutic approaches capable of overcoming this huge obstacle.

CONCLUSIONS

There is increasing evidence that polyphenols may protect cell constituents against oxidative damage and provide significant protection against the development of several chronic diseases (35).

Indeed, the *Feijoa* acetonic extract, (in particular the catechins), is able to inhibit the release of ROS in human PMNs induced by PMA, probably thanks to myeloperoxidase, lipoxygenase or inhibition of NADPH-oxidase. Furthermore, the aqueous extract of *Feijoa* was able to inhibit the emission of CL from native and stimulated human leukocytes by OZ and PMA. This action can be explained by the scavenger effect on free radicals (29). Since immune and inflammatory cells are also affected by diet, foods rich in flavonoids, such as vegetables, should promote good health (31).

Furthermore, it has been shown that the acetonic extract of the *F. sellowiana* fruit, in particular the flavone, exerts a powerful antifungal (*Candida albicans*), antibacterial activity against some Gram-positive and Gram-negative bacterial strains (28) and in particular, the action of the flavone was significantly effective against *H. pylori* (6). Therefore, these works confirm that flavonoids of natural origin can be considered a natural therapy in the treatment of infections.

In summary, *Feijoa* has been shown to have antioxidant activity when Caco-2 and HT-29 cells have been treated with H_2O_2 (36); anti-inflammatory activity, due to NO inhibition by attenuating the activation of NF-κB and/or MAPK in J774 cells (7); anti-tumour action blocking the cell cycle of cancer cells in S, G2/M or G1 phases and inducing apoptosis due to flavone, responsible for the overproduction of p16, p21 and TRAIL and inhibiting HDAC in cancer cells. Flavone has been demonstrated to act on epigenetic processes via HDAC. Currently, for many natural compounds, it is not completely clear whether for some observed beneficial effects, such as antineoplastic activity, a transcriptional action is necessary or whether they are mainly related to epigenetic action. For this reason, further studies should be carried out to evaluate whether some of these biological activities described could be attributable to a possible epigenetic action exerted by the second metabolites present in the bryophytes as demonstrated for other compounds of natural origin (57).

Russi *et al.,* (37) evaluated the antiproliferative and pro-apoptotic activity of *Feijoa* on gastric tumour cell lines. Dell'Olmo *et al.* (52) demonstrated the selective cytotoxic activity of the acetonic *Feijoa* extract using healthy and cancerous eukaryotic cells. Finally, the acetonic extract of *Feijoa sellowiana* is effective on sensitive and MDR tumour cells (**table I**) (52). The efficacy of *Feijoa* acetonic extract against cells with MDR phenotype is very interesting because although various anticancer drugs have been developed, the toxic effect even on healthy cells and the presence of the MDR phenotype are the main obstacles to the success of cancer chemotherapy treatment. Hence, the identification of compounds that are effective in MDR tumour cells could greatly contribute to the future design of combinatorial therapeutic approaches that are effective against disease states that now inevitably lead to death. Taken together, these data provide a new perspective for the use of plant products in alternative anticancer treatments, thanks to their ability to counteract the MDR phenotype and have a selective cytotoxic effect.

In conclusion, the ability of the *Feijoa sellowiana* fruit extract to induce selective proliferative arrest, cell differentiation, and apoptosis, together with the ability to counteract the MDR phenotype, opens interesting prospects for its future applicability in cancer therapy.

Furthermore, *Feijoa* can be considered a safe nutraceutical to improve pathologies characterised by reduced disaccharidase activity (lactose and sucrase-isomaltase) and having antioxidant properties that can have beneficial effects in diseases

caused by oxidative stress such as cancer (36, 37). All the evidence obtained here could contribute to the future identification of new compounds effective in pathologies that require innovative strategies.

ETHICS

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The data underlying this article are available in the article.

Authors' contribution

All authors contributed to write and revise the manuscript.

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