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Preventive effects of *Brassicaceae* family for colon cancer prevention: A focus on in vitro studies

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ABSTRACT

The emergence of adverse effects and resistance to colorectal cancer (CRC) current therapies calls for the development of new strategies aimed at both preventing and treating. In this context, functional extracts from *Brassicaceae* family contains abundant bioactive compounds directly related to a positive effect on human health including cancer. The main objective of this systematic review is to compile all recent studies that analyzed the in vitro antiproliferative activity of functional extracts or isolated molecules from the *Brassicaceae* family against CRC. A total of 711 articles published between January 2011 and May 2021 were identified. Of them, 68 met our inclusion criteria. Different standardized protocols using variable parts of plants of the *Brassicaceae* family resulted in diverse bioactive extracts and/or compounds. Most of them were related to isothiocyanates, which showed significant antitumor activity against CRC. These in vitro studies provide an excellent guide to direct research on the applications of plants of the *Brassicaceae* family to the prevention of this type of tumor. The extracts and molecules with demonstrated activity against CRC should be tested in vivo and in clinical trials to determine their usefulness in the prevention of this cancer to reduce its global incidence.

1. Introduction

According to data from 2020, colorectal cancer (CRC) represented the third most frequent tumor (10% of all neoplasms) and the second leading cause of cancer death (9.4%) worldwide [1]. Its increase in recent years has been related to the socioeconomic development of the country, which involves changes in lifestyle and dietary patterns associated with multiple risk factors such as sedentary habits, smoking, higher consumption of processed food or alcohol, and low intake of fruits, vegetables, and calcium [2]. In early stages, surgery is a curative treatment. However, patients with advanced disease need radiotherapy, chemotherapy (e.g., 5-Fluorouracil, Capecitabine, Irinotecan, Oxaliplatin, administered alone or in combination), targeted therapy or immunotherapy. In fact, approximately 20–25% of patients present with metastatic disease at disease onset and 50% of patients will eventually develop metastases [3,4]. In these cases, chemotherapy and targeted agents (e.g., EGFR antibody therapy) are indicated as first-line treatment. Despite therapeutic advances, the 5-year overall survival of patients with advanced disease is still less than 15% [5,6]. In addition, current chemotherapy drugs cause numerous adverse effects and drug resistance responsible for relapses and decrease patient's life expectancy and quality [7]. Therefore, it is necessary to develop new preventive and therapeutic strategies to improve the prognosis of patients with CRC.

In this context, functional extracts from different parts of plants represent a new way to enhance cancer therapy [8]. The *Brassicaceae* family, which includes up to 338–360 genus and 3709 species, contains abundant bioactive compounds such as antioxidants, vitamin C, E, flavonoids and glucosinolates [9], which have positive effects on human

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health [10]. The protective effect against several diseases has been directly linked to their phytochemical composition [10–12]. In fact, in response to stress, glucosinolates (more than 120 types) are hydrolyzed into bioactive molecules known as isothiocyanates (ITCs) [13], which exhibit antioxidant, anti-inflammatory and cardioprotective effects [10]. Interestingly, these compounds have been described as potent chemopreventive agents against breast, lung, prostate, and gastrointestinal cancers in both in vitro [14–17] and in vivo [18–21] assays. Finally, the bioavailability and safety of ITCs supplementation has been confirmed in clinical trials, but further studies are required to demonstrated antiproliferative effects [22,23].

The main objective of this systematic review is to collect all recently published studies that analyze the chemopreventive and/or antiproliferative activity of functional extracts or isolated molecules of the *Brassicaceae* family against CRC cell lines. This review summarizes the main active compounds and their utility in human colon cancer cells, supporting the need to develop new in vivo studies to understand their primary mechanism of action and the molecular targets that allow their application in patients with CRC.

2. Material and method

2.1. Research question

This systematic review focuses on analyzing the association between *Brassicaceae* plant extracts and their effects on in vitro models of CRC and follows Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [24]. First, the time period of the search was set to the last 10 years, assuming previous results to be obsolete. Hence, more than half of the current scientific texts published on this topic were included according to the Burton–Kebler index for obsolescence based on median age/median production [25].

2.2. Data sources

The bibliographic review was performed using different online databases, including PubMed, SCOPUS, Web of Science and Cochrane Library Plus (MedLars Online International Literature). For the search strategy, medical subject headings (MeSH) were set up as “Brassicaceae” and “Colorectal Neoplasms”. The search equation was ((((("Brassicaceae"[Mesh]) OR ("Brassicaceae"[Title/Abstract]) OR ("Cress*"[Title/Abstract]) OR ("Moricandia*"[Title/Abstract]) OR ("Brassic*"[Title/Abstract]) OR ("Crucifer*"[Title/Abstract])) AND (("Colorectal Neoplasms"[Mesh]) OR ("Colonic Neoplasms"[Mesh]) OR ("Rectal Neoplasms"[Mesh]) OR (("colon"[Title/Abstract]) OR ("colonic"[Title/Abstract]) OR ("colorectal"[Title/Abstract]) OR ("rectal"[Title/Abstract]) OR ("rectum"[Title/Abstract])) AND (("neoplasm*"[Title/Abstract]) OR ("cancer*"[Title/Abstract]) OR ("tumor*"[Title/Abstract]) OR ("carcinoma*"[Title/Abstract])))))). The search was limited by filters to journal articles published from 2011/01/01–2021/05/25, in English or Spanish. This strategy was used in all the databases mentioned above, in which syntax adaptations were made as appropriate.

2.3. Inclusion criteria

The selected articles were those studying in vitro antitumor effects against CRC cell lines of crude extract or isolated compounds from the Brassicaceae family. All articles chosen had full texts available, were published between January 2011 and May 2021, and were evaluated in peer-reviewed journals.

2.4. Exclusion criteria

Articles which did not analyze antiproliferative effects in colon cancer cell lines or did not detail extraction/isolation methods were excluded. Articles investigating anticancer effects of commercial or chemically synthesized compounds that had been previously described in the *Brassicaceae* family were also omitted. *In vivo* assays, clinical trials or observational studies and non-original articles such as reviews, systematic reviews, meta-analyses or books and documents were excluded.

2.5. Study selection

After identifying the preselected articles using the search strategy described above, two of the authors (Guzmán, A. and Peña, M.) performed an initial screening based on title and abstract reading. Duplicated records were eliminated at this point. Subsequently, full-text review of the selected studies was conducted to confirm whether they met the inclusion criteria. The selection of the studies was carried out by the two authors individually, comparing their results and making a joint decision at this stage. Fig. 1 shows the flow diagram of the selection process for this systematic review.

2.6. Data extraction

Once the articles were selected, data extraction was performed independtly by the same two authors. According to Cohen (1968), there was a good understanding among the two authors with a Cohen’s Kappa statistical test result of 0,8 [26]. If any disagreement was not resolved by consensus between A.G and M.P., two other authors reviewed the articles in question. To test the quality of the chosen studies, a detailed questionnaire was conducted for assays with in vitro models. The questionnaire consisted of two parts. The first one included questions to confirm their agreement with an in vitro model study (score > 6) and the second one included questions related to materials and methods, results, and conclusions to delimit the quality of the article (0–6 low; 7–14 good; 15–20 excellent). Low-quality articles (i.e., with a score equal or lower than six) were excluded from this systematic review. Tables 1 and 2 show different species of the *Brassica* genus and other genus of the *Brassicaceae* family, respectively, as well as the selected part of the plants and publication reference.

Tables 3 and 4 cover detailed information of the studies (plant material, processing methods, isolated compounds, cell line tested, administration routes, viability assay, cytotoxicity quantification and mechanisms of action) from species of the *Brassica* genus and other genus of the *Brassicaceae* family, respectively.

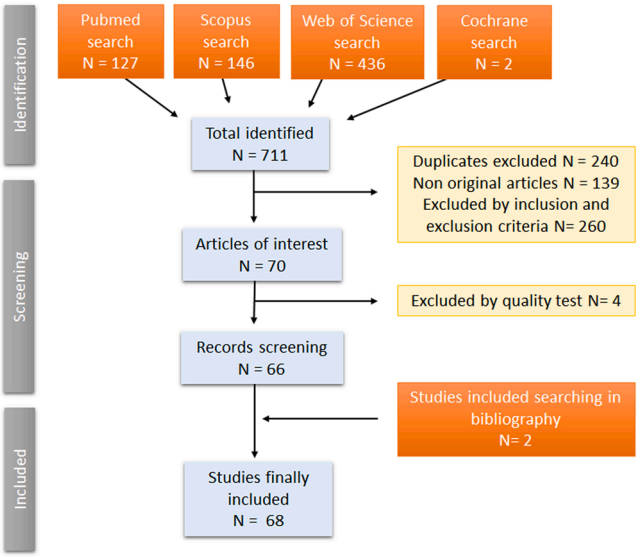

Fig. 1. Flow diagram of the eligible studies included in this systematic review.

Table 1
Summary of the species and varieties of the Brassica genus and plant parts used for the extraction.

Species	Variety	Nº articles	Parts of the plant
Brassica oleracea	var. *capitata*	3	Whole plant; Seeds; Leaves
	var. *sabauda*	2	Buds; Flowers
	var. *italica*	11	Seeds; Flowers; Leaves and stems; Microgreens; Sprouts
	L. cv Yanxiu	1	Flowers
	var. *italica x* var. *alboglabra*	2	Leaves
	var. *sabellica*	3	Leaves; seeds; microgreens
	var. *gongylodes*	1	Seeds
	var. *gemmifera*	1	Buds
	var. *botrytis*	2	Flowers
Brassica juncea	*Brassica juncea*	3	Leaves; Seeds
	var. *sareptana Sinskaja*	1	Leaves
	var. *gracilis*	1	Leaves
	L. Czern & Coss	1	Leaves
Brassica rapa	var. *pekinensis*	2	Leaves and flowers
	ssp. *rapa*	1	Roots
	ssp. *campestris*	1	Roots
Brassica chinensis	var. *parachinensis (Bailey) Tsen and Lee (bigger leaves)*	1	Leaves and flowers
	var. *parachinensis (Bailey) Tsen and Lee (smaller leaves)*	1	Leaves and flowers
Brassica tournefortii		1	Leaves, stems and roots
Brassica incana		1	Leaves and flowering top

Table 2
Summary of the species and varieties of other plants of the Brassicaceae genus and plant parts used for the extraction.

Species	Variety	Nº articles	Parts of the plant
Raphanus sativus	*Raphanus sativus*	6	Seeds; Microgreens
	var. *longipinnatus*	1	Roots
	var. *caudatus* Alef	3	Pods and flowers; Leaves, Roots; Stem and Seeds
	'Taebaek'	1	Seeds
Raphanus raphanistrum	ssp. landra (DC.) Bonnier &Layens.	1	Leaves
Moricandia arvensis	ssp. *eu-arvensis*	2	Leaves and Roots
Eruca sativa		3	Leaves and sprouts
Erucaria hispanica (L.) Druce		1	Aerilal parts
Sinapis alba Linn		3	Seeds; Microgreens; Leaves
Sinapis nigra		1	Seeds and Leaves
Iberis amara		1	Seeds
Diceratella elliptica		1	Aerilal parts
Diplotaxis harra (Forssk.) Boiss.		1	Flowers
Diplotaxis tenuifolia (L.) DC.		3	Leaves
Diplotaxis simplex		1	Flowers
Descurainia sophia		2	Seeds
Lepidium meyenii	Walpers	3	Whole plant; Rhizomes; Roots
Lepidium latifolium		1	Leaves
Lepidium sativum	ssp spinescens	1	Above-ground parts
Horwoodia dicksoniae		1	Aerilal parts
Orychophragmus violaceus		2	Seeds
Nasturtium officinale		2	Aerilal parts (leaves and stalks)
Mathiola incana		1	Leaves and flowers buds
Lobularia libyca		1	Seeds, leaves and roots
Armoracia rusticana		1	Whole plant
Wasabia japonica		1	Rizhomas
Zilla spinosa		1	Aerial plants

3. Results and discussion

A systematic review of the in vitro antitumoral activity in colon cancer cells of the *Brassica* (twenty-seven articles), *Raphanus* (eleven), *Diplotaxis* (five), *Lepidium* (five), *Sinapis* (three) and *Eruca* (three) genus was carried out. *Brassica oleaceae* was the most representative species (twenty articles) followed by *Raphanus sativus*, *Diplotaxis tenuifolia*, *Lepidium meyenii*, *Sinapis alba* and *Eruca sativa*. After a thorough analysis of the sixty-eight articles included in this systematic review, it can be concluded that ethanol was used as solvent in most of the plant extractions, HCT-116 was the most frequently colon cancer cell line, and the MTT assay was the preferred method of analysis. The antiproliferative capacity of most of these *Brassicaceae* extracts was related to the main mechanisms of action such as apoptosis (Fig. 2) and cell cycle modulation (Fig. 3).

3.1. *Brassica genus*

Twenty-seven of the sixty-eight articles analyzed were related to the *Brassica* genus, including *Brassica oleracea* (twenty articles), *Brassica rapa* (four), *Brassica juncea* (three), *Brassica tournefortii*, *Brassica incana* and *Brassica chinensis* (one).

3.1.1. *Broccoli (B. oleracea var. italica)*

Broccoli (var. *italica*) was the most studied *B. oleracea* variety (fourteen articles) and most analyses were carried out using the edible part (flowers or inflorescence). Fewer studies used seeds, sprouts or microgreens [27–30]. In fact, Hashem et al. [31] developed a flower ethanolic extract that showed a high antiproliferative effect on HCT-116 colon cancer cells (IC_{50} 3.88 μg/mL) while Paśko et al. [30] obtained a methanolic extract that effectively inhibited SW-480 cell proliferation. In addition, a flower extraction using supercritical CO_2 achieved a great antiproliferative effect in Caco-2 (IC_{50} of 35.7 μM of Sulforaphene-SFN) and in HT-29 (14.9 μM of SFN) cells [32]. In contrast, an extract of dichloromethane had less antiproliferative effect in HCT-116 cells showing an IC_{50} higher than 50 μg / mL [33]. Some authors showed that cooking methods can modify the effect of broccoli flowers in HT-29 cells, and that raw broccoli has the highest antiproliferative properties [34]. Moreover, biofortification of broccoli with selenium showed the ability to suppress HCT-116 viability [35]. Finally, broccoli has been mixed with other compounds to enhance its antiproliferative effect. In fact, its association with green tea using methanol extraction doubled the antiproliferative effect in the Caco-2 cell line (98%) compared to broccoli extract alone (55%) [36]. In addition, Su Yang Decoction (SYD), the association of broccoli to cabbage using ethanol extraction, was able to activate caspases and apoptosis in HT-29 (IC_{50} 94.23 μg / mL) and LS-174-T (IC_{50} 93.15 μg / mL) cells [37].

On the other hand, broccoli seed has also been analyzed. Paśko et al. [30] obtained a methanolic extract that demonstrated selective cytotoxicity against SW-480 cells. In addition, Kestwal et al. [28] used an ethanolic extract from sprouts which was supplemented with selenium. These authors found an increase in the proliferation inhibitory effect (from 56% to 22%) in CT26 cells. A similar ethanolic extract of sprouts showed an IC_{50} of 0.189 mg / mL in Caco-2 cells [29], which was directly related to an increase in cells in the $subG_1$ phase, loss of mitochondrial membrane potential, and apoptosis. Broccoli microgreens were analyzed by De la Fuente et al. [27], who found that their enzymatic digestion fractions induced apoptosis and a membrane potential reduction related to arrest in G_2 / M phase and variation of cellular redox state (increased ROS and reduced GSH). Broccoli sprout extract has been also administered in clinical trials against oral and prostate

Table 3
Antiproliferative activity of the functional extract or isolated compounds from Brassica genus of Brassicaceae family in colon cancer lines.

Material (Reference)	Processing Method	Isolated Compounds	Cell line/ Administration/ Cytotoxicity assay	Cytotoxicity quantification solution/compound	Mechanism of action
Sulphur supplemented and not supplemented sprouts of *B. oleracea* var. *italica* [28]	Ethanol 95%		CT26/ Serum-free DMEM/ MTT	*Cell Viability (%)* -Not supplemented: 56 -Supplemented (60 kg/ha): 22	
Inflorescences and leaves of *B. oleracea* var. *italica* [36]	Methanol (BC100); Infusioned with green tea (OGT50–BC50)		Caco-2 and CCD-18Co/ Methanol/ TP, MTT	*Inhibition of cell viability (%)* -BC100 (5%): 55 -OGT50–BC50 (5%): 98	
Oven steamed, basket steamed, microwaved, boiled and raw inflorescence of *B. oleracea* var. *italica* [34]	Water		HT-29/- /MTS	*LED* (g eq ww/mL) -Raw or microwaved: 0.25 -Bolied and steamed: 4.00	
Inflorescence of *B. oleracea* var. *italica* [31]	Ethanol 80%	Compound I, II, III, IV	HCT-116/ DMSO/ SRB	IC_{50} (μg/mL) *24 h:* -EtOH 80%: 3.88 -Myrosinase hydrolysate: 0.78 -Succesive extract: > 10	
Se-enriched inflorescence of *B. oleracea* var. *italica* [35]	Enzymatic digestion		HCT-116 and HCT-116 +Chr.3/- / MTT		
Flowers of *B. oleracea* var. *italica* [33]	Dichloromethane		HCT-116/ Acetonitrile/ MTT	IC_{50} (μg/mL) -Broccoli extract > 50	
Flowers of *B. oleracea* var. *italica* [32]	Supercritical CO_2		Caco-2 and HT-29/ Medium, ethanol/ CellTiter 96	EC_{50} 14.8 μM SFN = 51,5 μM in HT29 monolayer and 35.7 μM of ITC in Caco-2	G_2/M cell cycle arrest. Loss of cell-cell adhesion (E-cadherin downregulation).
Sprouts and flowers of *B. oleracea* var. *italica* [30]	Methanol		SW-480/ DMSO/ MTT		Flowers cytotoxicity mediated by necrosis. Sprouts exhibited selective cytotoxic and proapoptotic effect against CRC
Broccoli and green cabbage in a 1:1 mixture called Su Yang Decoction (SYD) [37]	Ethanol 70%		HT-29; LS-174-T and CRL-1790/ -/ MTS	IC_{50} (μg/mL) *48 h and 72 h:* -HT29: 103.89 and 94.23 -LS-174-T: 132.05 and 93.15 -CRL-1790 (no tumoral): No cytotoxic effect	Selective cytotoxicity against HT-29 and LS-174-T cells. ↑ apoptosis Modulates cell cycle regulators by the activation of caspases (CASP8 cleavage).
Sprouts of *B. oleracea* var. *italica* [29]	Ethanol 70%, Methanol 70% Hot water.		Caco-2/ -/MTT	IC_{50} (mg/mL) *24 and 48 h:* -Ethanol 70% extract: 0.338 and 0.189	↑ cell percentage in subG_1 phase and a loss of mitochondrial membrane potential, leading to apoptosis.
Bioaccessible fractions of *B. oleracea* var. *italica* microgreens [27]	Enzymatic digestion		Caco-2 and CCD18-Co/- / MTT		Selective cytotoxicity against Caco-2 cells. Redox cellular state alteration by ROS↑ and GSH↓. G_2/M cell cycle arrest and a ↓ G_0/G_1 phase. Mitochondrial membrane potential dissipation. Induction of programmed cell death via the mitochondrial pathway (absence of necrosis).
Flower balls of hybrid broccoli (*B. oleracea* L. cv Yanxiu) [41]	Methanol		SW-620/ PBS buffer/ MTT	IC_{50} (mg/mL) *16 h* 0.1	↑Expression of genes related to apoptosis (p-53 and caspase-3).
Dried leaves of Broccolini (*B. oleracea* var. *italica* x *B. oleracea* var. *alboglabra*) [39]	Ethanol 70%	Different fractions: BLF1: 85,4% quercitin BLF2: 78,5 kaempferol BLF3: kaempferol and apigenin (82,6%)	SW-480/ -/ MTT	IC_{50} (μg/mL) 24 h: -Ethanol extract (BL0): 88.14 -BLF1: 65.06 -BLF2: 72.62 -BLF3: 79.42	
Dried leaves of Broccolini (*B. oleracea* var. *italica* x *B. oleracea* var. *alboglabra*) [40]	Ethanol 70%		SW-480/ DMEM/ MTT	IC_{50} (μg/mL) *72 h* 88.14	Induction of apoptosis and necrotic death in a dose-dependent manner.
Sulphur supplemented and not supplemented sprouts	Ethanol 95%		CT26/ Serum-free DMEM/ MTT	*Viability percentage* -18% supplement sprouts -59% normal sprouts	

(*continued on next page*)

Table 3 (*continued*)

Material (Reference)	Processing Method	Isolated Compounds	Cell line/ Administration/ Cytotoxicity assay	Cytotoxicity quantification solution/compound	Mechanism of action
of *B. oleracea* var. *capitata* [28]					
B. oleracea var. *capitata* [42]	Ethanol 70%	Poliphenolic fraction (PBO)	HT-29/ DMSO/ MTT	IC_{50} (μg/mL) *24 h:* PBO: 50	
Leaves of *B. oleracea* var. *capitata* [33]	Dichloromethane		HCT-116/ Acetonitrile/ MTT	IC_{50} (μg/mL) *24 h:* 46.03	
B. oleracea var. *capitata* biostimulanted with different mixtures of sodium selenate (Na2O4Se) [47]	Acidified water	Sulforaphane (SFN) SAdenosyl- homocysteine (SAH)	Caco-2/- /MTT	IC_{50} (mg/mL) *72 h:* -Water-trated plants: 0.73 -Treated with betaine: 0.715 -Treated with Se;betaine: 0.63	Treated plant extracts induced a damaging effect on carcinoma cell morphology and ↓ their cell density
Edible parts of *B. oleracea* var. *sabauda* [44]	Etanol 50%		Caco-2/ PBS/ MTT	EC_{50} (μg GAE/ mL) -Extract stored in air X days after expiry date: 0 days: 11.27, 9 days: 11.80, 22 days: 11.09. -Extract stored under a modified atmosphere (MAP) X days after expiry date: 0 days: 11.27, 9 days: 11.86, 22 days: 12.37	
Oven steamed, basket steamed, microwaved, boiled and raw flowers of *B. oleracea* var. *gemmifera* and *B. oleracea* var. *botrytis* [34]	Water		HT-29/ -/ MTS	*LED* (g eq ww/mL) -var. *gemmifera:* Raw (0.50) and cooked (> 4). -var. *botrytis:* Raw (0.50), microwaved (1.00), boiled (2.00) and oven steamed (1.00)	
Biofortificated *Brassica oleracea* var. *botrytis* [43]	Acidified water	Sulforaphane (SFN) SAdenosyl-homocysteine (SAH)	Caco-2/ -/ MTT	*Cell viability (%) 72 h:* -76.91 for 1.5 mg/mL V3 treatment -62.78 for [2 mg/mL] -23.97 for [2.5 mg/mL]	
Selenium-fortified and unfortified sprouts of *B. oleracea* var. *gongylodes and B. oleracea* var. *sabellica* [45]	Methanol		SW-480; SW-620/ DMSO/ MTT		Induced significant ↓ in the viability differing in metastatic potential.
Bioaccessible fractions of *B. oleracea* var. *sabellica* microgreens [27]	Enzymatic digestion		Caco-2 and CCD18-Co/ -/ MTT		Selective cytotoxicity against Caco-2 cells. Redox cellular state alteration by ROS↑ and GSH↓. G_2/M cell cycle arrest and a ↓G_0/G_1 phase. Mitochondrial membrane potential dissipation. ↑ apoptosis via the mitochondrial pathway (absence of necrosis).
Fresh and thermal processed green and red cultivars of *B. oleracea* var. *sabellica* [46]	Methanol		Caco-2, HT-29 and HCT-116/ -/ MTT		↓growth and ↑apoptosis of different colon cancer cells.
Leaves of *B. Juncea* [51]	Ethanol 70%		HCT-116/ DMSO/ MTT	IC_{50} (μg/mL) *72 h and 96:* 253 and 153	↑ apoptosis. Suppress anchorage-independent colony formation. Pro-angiogenic factor secretion, invasion, and adhesion.
Leaves of *B. juncea*; *B. juncea* L. Czern & Coss; *B. juncea* var. *sareptana* Sin-skaja and var. *gracilis* [33]	Dichloromethane		HCT-116/ Acetonitrile/ MTT	IC_{50} (μg/mL) *24 h:* > 50	
Seeds of *B. juncea* var. *raya* [52]	Ethyl acetate (EA) Dichloromethane (DCM)		HCT-116/ -/ MTT	IC_{50} (μg/mL) *24 h:* -EA: 61.50 -DCM: 78.86	Mitochondria-dependent pathway possibly dependent on ROS generation
Dried leaves, stems, and roots of *B. tournefortii* [54]	Cyclohexane (CYHA) Dichloromethane (DCM) Methanol (MeOH)		HCT-116/ DMSO/ MTT	*Inhibition of cell viability* -Roots-CYHA and roots-DCM extracts: 30%	
Leaves and flowering top of *B. incana* [53]	Methanol 70%		Caco-2/ -/ MTT	IC_{50} (mg/mL) *48 h and 72 h:* -Flowering extract: 1.25 and 1.1	↓ on succinate dehydrogenase activity. ↑ of biochemical pathways related to necrotic
Leaves and flowers of *B. chinensis* (var.	Dichloromethane		HCT-116/ Acetonitrile/ MTT	IC_{50} (μg/mL) *24 h:* > 50	

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Table 3 (*continued*)

Material (Reference)	Processing Method	Isolated Compounds	Cell line/ Administration/ Cytotoxicity assay	Cytotoxicity quantification solution/compound	Mechanism of action
parachinensis-Bailey; var. Tsen and Lee) [33]					
Non-transgenic and transgenic hairy root of of *B. rapa* [48]	Ethanol 70%		HT-29/ DMSO/ MTT		
Roots of *B. rapa* [49]	Ethanol 95%	6-Paradol (1), Trans-6-Shogaol (2), Brassicaphenanthrene A (3)	HCT-116/ -/MTT	IC_{50} (μM) (1) No effect (2) 19.0 (3) 25.0	
Leaves of different *B. rapa:* commercial (SK), Amtak (AmK), and organically cultivated (OC) [50]	Methanol		HT-29/ -/ MTT	*Cell growth inhibition rate* (%) at 3 mg/mL -SK: 19.29 -AmK: 24.28 -AK: 33.05	AK induced apoptosis (↑expression of Bim, Bac, Bak, caspase-8, caspase-9, caspase-3 and p53; and ↓ expression of Bcl-2 and Bcl-xL) and p21 upregulation.

LED Lower Effective Dosis (LED), Half-maximal inhibitory concentration (IC50), Half maximal effective concentration (EC50), Cellular metabolic activity assay (MTT), Trypan blue (TP), Sulforhodamine B (SRB), MTS Assay Kit (MTS), CellTiter 96® AQueous One Solution Cell Proliferation Assay (CellTiter 96). ↓ Decrease ↑ Increase

cancer with good results in terms of bioavailability and pharmacodynamics. However, further studied are needed to confirm its chemopreventive activity [23,38].

Finally, Wang and Zhang [39,40] and more recently Wen et al. [41] analyzed the antitumor effect of a broccoli hybrid. The results of these authors showed that this effect is mediated by apoptosis. Specifically, Wen et al. [41] showed that the effect of a methanolic extract of *B. oleracea* L. cv Yanxiu flowers (IC_{50} of 0.1 mg / mL in SW-620) is mediated by overexpression of p53 and caspase-3 genes. In addition, ethanolic extracts of Brocollini leaves (*B. oleracea* var. *italica* x var. *alboglabra*) also showed antitumor activity with an IC_{50} of 88.14 μg / mL in SW-420 [39,40].

3.1.2. Cabbage (*B. oleracea var. capitata and var. sabauda)*

Five articles investigated the antiproliferative action of cabbage extracts, with the *capitata* variety being the most studied. Pocasap and Weerapreeyakul [33] tested cabbage leaf extracts using dichloromethane which showed a significant antiproliferative effect on HCT-116 cells (IC_{50} 46.03 μg / mL). Similar results were reported by Chandrasenan et al. [42] who exposed HT-29 cells to an ethanolic extract (IC_{50} 50 μg/mL). Moreover, cabbage stimulated by sodium selenite increased its antiproliferative effects against Caco-2 cells compared to normal cabbage (IC_{50} 0.630 and 0.730 mg/mL, respectively) [43]. Similar to Kestwal et al. [28] sulfur-supplemented shoots showed increased antitumor action compared to the non-supplemented sprouts (59% vs. 18%) in CT26 cells. Ge et al. [37] used an ethanolic extract of a mixture of cabbage and broccoli (1:1), testing selective cytotoxicity against HT-29 and LS-174-T cell lines (IC_{50} 94.23 and 93.15 μg / mL, respectively) through caspase-8 activation. Finally, Ombra et al. [44] used a leaf extract of *B. oleracea* var. *sabauda* to demonstrate that differences in storage time after expiration date, either in air or in modified atmosphere, do not affect the ability of this cabbage extract to inhibit Caco-2 cell proliferation.

3.1.3. Kale (*B. oleracea var. sabellica) and Cauliflower (B. oleracea var. botrytis)*

Different parts of the kale plant were used to determine its antiproliferative effects against colon cancer cells, including methanolic extracts of shoots or shoots treated with selenium (in SW-480 and SW-620 cells, respectively) [45], fresh or cooked leaves (in Caco-2 and HT-29 cells, respectively) [46], and bioaccessible fractions of enzymatically digested microgreens (in Caco-2) [27]. Overall, the highest antiproliferative action was detected in the methanolic extract of untreated shoots and in the extract of raw leaves. In the case of microgreens, the antiproliferative effect was related to an alteration of the redox state, G_2 / M phase arrest, mitochondrial membrane potential, and apoptosis induction [27].

On the other hand, Ferrarini et al. [34] and Oancea et al. [47], analyzed the antiproliferative activity of cauliflower (var. *botrytis*) in colon cancer. The former tested an aqueous extract of flowers under different cooking methods in HT-29 cells [34]. The latter tested a water extract of cauliflower flowers biofortificated with selenium in Caco-2 cells. They concluded that the highest antiproliferative effect was detected in uncooked plants, and those which were treated with sodium selenate (10 μM).

3.1.4. Brussels sprouts (*B. oleracea var. gemmifera) and Kohlrabi (B. oleracea var. gongylodes)*

Extracts from brussels sprouts subjected to different cooking methods showed a lower antiproliferative effect than the raw material extract in HT-29 cells [34]. In addition, Zagrodzki et al. [45] investigated the antiproliferative action of a kohlrabi methanolic extract with and without selenium biofortification in SW-480 and SW-620 cells. No significant differences were found between treatments, but kohlrabi sprouts had a greater inhibitory effect on SW-620 cells than on SW-420 cells [45].

3.1.5. Brassica rapa and Brassica juncea

Three articles studied the antitumor properties of *Brassica rapa*. Chung et al. [48] obtained ethanolic extracts from *B. rapa* ssp. *Rapa* and found a greater antiproliferative effect of transgenic hairy roots compared to normal roots in HT-29 cells. Wu et al. [49] isolated and tested three compounds from *B. rapa* ssp. *campestris*, two of which —trans-6-Shogaol (IC_{50} 19 μM) and Brassicaphenanthrene A (IC_{50} 25 μM)— showed strong antiproliferative effects against HCT-116 cells. The remaining biomolecule —6-Paradol— showed no antitumor activity. Finally, Yu et al. [50] studied the antiproliferative effects of a methanolic extract from *B. rapa* var. *pekinensis* against HT-29 cells. Their results showed different inhibition rates depending on the variety used: Baechu cabbage (19.29%), Amtak Baechu cabbage (24.28%) and Organically cultivated Baechu cabbage (33.05%).

On the other hand, three different extracts of *Brassica juncea* have been tested in the colon cancer cell line HCT-116. Kwak et al. [51] studied an ethanolic extract from *B. juncea* leaves that demonstrated an IC_{50} of 153 μg /mL at 96 h in this type of cells. In addition, Pocasap and Weerapreeyakul [33] used three other varieties (var. *sareptana*, var. *gracilis* and *B. juncea* L. Cxern & Cross) to obtain dichloromethane extracts, all of which showed an IC_{50} higher than 50 μg/mL at 24 h. Finally, two extracts using dichloromethane and ethyl acetate from *B. juncea* var. *raya* seeds showed an IC_{50} of 78.86 μg/mL and 61.50 μg/mL at 24 h, respectively [52].

Table 4
Antiproliferative activity of the functional extract or isolated compounds from other genus of Brassicaceae family in colon cancer lines.

Material (Reference)	Processing Method	Isolated Compounds/Fractions	Cell line/ Administration/ Cytotoxicity assay	Cytotoxicity quantification solution/compound	Mechanism of action
Bioaccessible fractions of radish microgreens [27]	Enzymatic digestion		Caco-2/ -/ MTT	*Cell viability (%) 24 h:* 87.8	Redox cellular state alteration by ROS↑ and GSH↓. G_2/M cell cycle arrest and ↓G_0/G_1 phase. Mitochondrial membrane potential dissipation. ↑of apoptosis via the mitochondrial pathway.
Seeds of 'Taebaek' radish (*Raphanus sativus* L. 'Taebaek') [67]	Dichloromethane	Sulforaphene (SFE)	HT-29/ DMSO/ MTT	*IC_{50} (μg/mL) 24 h:* SFE: 2.50	
Seed of *Raphanus sativus* [61]	Ethanol 70%	Sinigrin	HCT-15/ -/ MTT	*IC_{50} (μg/mL) 24 h:* Sinigrin-rich root extract: *21.42*	
Raphanus sativus defatted seeds [62]	Ethanol 70%	Glucoraphenin (GRE) GRE converted into Sulforaphene by addition of myrosinase enzime	HT-29/ Serum free medium/ MTT	*IC_{50}* (μM) SFN: 42.3	
Different plant parts of fresh *Raphanus sativus* L. var. *caudatus* Alef at different stages of growth [66]	Dichloromethane		HCT-116/ DMSO/ MTT	*IC_{50} (μg/mL) -Different ages:* 3 week (62.1); 4 week (33.9); 5 week (32.4); 6 week (19.2); 7 week (24.3). *-Different parts (at 7 week):* Leave and root (>250.0); Stem (168.6); Flower (17.4); Pod (42.7); Dry seed (78.7).	Apoptosis and necrosis
Pods and flowers of *Raphanus sativus* L. var. *caudatus* Alef; roots of *Raphanus sativus* var. *longipinnatus* [33]	Dichloromethane		HCT-116/ Acetonitrile/ MTT	*IC_{50} (μg/mL) 24 h:* -var. *caudatus* Alef: 9.42 -var. *longipinnatus:* No effect	
Leaves of *Raphanus raphanistrum L. subsp. landra (DC.)* Bonnier & Layens [58]	Ethanol 70%		LoVo/- /MTT	IC50 (μg/mL): -100 μg/mL: no effect	
Seeds of *Raphanus sativus* [59]	Methanol 80%	Raphasativuside A (1) and B (2); (3,4-O-disinapoyl)-β-D-fructofuranosyl-(2→1)-(6-O-sinapoyl)-α-D-glucopyranoside (3); (3-O-sinapoyl)-β-D-fructofuranosyl-(2→1)-(6-O-sinapoyl)-α-D-glucopyranoside (4); tenuifoliside C (5); (3-O-feruloyl)-β-D-fructofuranosyl-(2→1)-(6-O-feruloyl)-α-D-glucopyranoside (6), sibiricose A6 (7) and sucrose (8).	HCT-15/ -/ SRB	*IC_{50}* (μM) (1) 18.85 (2) 12.37 (3) 14.06 (4) 17.20 (5) 18.30 (6) 17.75 (7) 26.99 (8) > 30.0	
Seeds of *Raphanus sativus* [60]	Methanol 80%	Sinapoyl desulfoglucoraphenin (1); (E)− 5-(Methylsulfinyl)pent-4-enoxylimidic acid methyl ester(2); (S)− 5-((Methylsulfinyl)methyl)pyrrolidine-2-thione(3); 5-(Methylsulfinyl)− 4-pentenenitrile (4); 5-(Methylsulfinyl)-pentanenitrile (5); sulforaphene (6); sulforaphane (7)	HCT-15/ -/ SRB	*IC_{50}* (μM) (1) 14.08 (2) 14.06 (3) 13.53 (4) 14.00 (5) 18.06 (6) 23.97 (7) 8.49	
Edible parts (pod and flower) of Thai rat-tailed radish (Raphanus sativus L. var. caudatus Alef) [65]	Dichloromethane		HCT-166/ Acetonitrile/ MTT	*IC_{50}* (μg/mL) *24 h:* 9.42	Apoptosis
Sulphur supplemented and not supplemented sprouts of radish	Water, Ethanol 95%		CT26/ -/ MTT	*Cell viability (%)* Supplemented sprouts: 21 Normal radish sprouts: 80	

(*continued on next page*)

Table 4 (*continued*)

Material (Reference)	Processing Method	Isolated Compounds/Fractions	Cell line/ Administration/ Cytotoxicity assay	Cytotoxicity quantification solution/compound	Mechanism of action
(*Raphanus sativus*) [28]					
Leaves of Wild rocket (*Diplotaxis tenuifolia (L.)* DC.) [69]	Methanol		Caco-2/ -/ MTT	*IC_{50}* (mg/mL) *48 h:* 1.87	
Flowers of *Diplotaxis harra* (Forssk.) Boiss [70]	Methanol (ME)	Flower methanol extract (F6, L12): Isorhamnetin-3,7-di-O-glucoside (1); isorhamnetin-3-O-glucoside (2)	CaCo-2/ Ethanol 10% or DMSO 50%/ MTS	*Inhibition of cell viability (%)* -F6: 20 -L12: 30 -(1): 20	Flavonoid-enriched fraction was cytotoxic against Caco-2 cells through GSK3β modulation.
Flowers of *Diplotaxis simplex* [71]	Ethyl acetate and ethanol		CaCo-2/ Ethanol 70%/ MTT	*IC_{50}* (μg/mL) *48 h:* -Ethanol extract: 62.0 -Ethyl acetate extract: 63.25	Antioxidant potential associated with anti-inflammatory capacity.
Leaves of rocket or rucola (*Diplotaxis tenuifolia*) [68]	Ethanol 50% Chloroform-methanol (1:1, v/v)		HT-29/ -/ LDH and MTT	*IC_{50}* (μg/mL) Chloroform-methanol extract: 200 Ethanol-water extract: no effect	
Leaves of *Diplotaxis tenuifolia (L.)* DC. Bonnier &Layens [58]	Ethanol 70%		LoVo/ -/ MTT	*Inhibition of cell viability (%)* -100 μg/mL: 45%	
Bioaccessible fractions mustard [27]	Enzymatic digestion		Caco-2/ -/ MTT	*Cell viability* (%) (24 h) -1:10 dilution: 86.2%	Redox cellular state alteration by ROS↑ and GSH↓. G_2/M cell cycle arrest and ↓G_0/G_1 phase. Mitochondrial membrane potential dissipation. ↑apoptosis via mitochondrial pathway.
Leaves and seeds of *Sinapis nigra* L. and *Sinapis alba* L. [78]	Leaves: Ethanol 96% Seeds: Ethanol 80%, Water/ β-cyclodextrin 1.5% and Water (ppt Ethanol)		HCT-116 and HT-29/ -/ / ATP content and the CellTiter	*IC_{50}* (μg/mL) -Seeds of S. alba EtOH 80% extract HCT-116: 189.83 HT-29: 305.65 -S. nigra: > 500	Apoptosis and correlation to MAPK modulation.
Seeds of mustard *Sinapis alba Linn* [79]	Ether and ethanol		SW-480/ -/ CCK8	Extract inhibits cellular proliferation dose dependently	Apoptosis mediated by ↑ the caspase cascade and anti-oxidant activity that prevents AOM-induced colon carcinogenesis.
Maca, *Lepidium meyenii* [74]	Methanol	Total macamides fraction (TMM) Total macaenes fraction (TME)	SW-480/ DMSO/ MTS	*IC_{50}* (μg/mL) *48 h:* -TMM: 69.29	Antioxidant activity by scavenging DPPH free radical, ABTS free radical, and reducing power.
Leaves of *Lepidium latifolium* L. [77]	Ethanol, chloroform, supercritic fluids, water, protein, and glycerol	Epithionitrile 1–cyano-2,3–epithiopropane (CETP)	HT-29/ DMSO/ XTT	*Apoptosis (%) 72 h:* -Ethanol (20 mg/mL): 35.3 -Ethanol (2 mg/mL): 12.1 -Chloroform (1 mg/mL): 89.6 -Chloroform (0.1 mg/mL): 30.7 -Supercritic (250 mg/mL): 23.0 -Glycerol (20 mg/mL): 35.7 -Glycerol (2 mg/mL): 10.1	Caspase-dependent apoptosis.
Above-ground parts of dried *Lepidium sativum* Subsp *spinescens L.* [76]	Methanol 80%		DLD-1/ DMSO Neutral Red and MTT	*IC_{50}* (μg/mL) MTT assay: 110,42	Apoptosis
Fresh tubers (roots) of Maca, *Lepidium meyenii* Walpers [73]	Ethanol 95%	Macamides 3 (N-Benzyl-9-oxo-10E,12E-octadecadienamide) and 4 (N-Benzyl-9-oxo-10E,12Z-octadecadienamide)	HT-29/ DMSO / MTT	*IC_{50}* (μmol/L) *24 h:* -Macamide 3: 12.8 -Macamide 4: 5.7	
Roots of *Lepidium meyenii* (maca) [75]	Water and ethanol 95%	Tricin 4′-O-[threo-β-guaiacyl-(7″-O-methyl)-glyceryl] ether (1), tricin 4′-O-	Colo 205/ DMSO/ MTT		

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Table 4 (*continued*)

Material (Reference)	Processing Method	Isolated Compounds/Fractions	Cell line/ Administration/ Cytotoxicity assay	Cytotoxicity quantification solution/compound	Mechanism of action
		(erythro-β-guaiacyl-glyceryl) ether (2), tricin (3), pinoresinol (4), 4-hydroxycinnamic acid (5), guanosine (6), glucotropaeolin (7), desulfoglucotropaeolin (8), 3-hydroxybenzylisothiocyanate (9), malic acid benzoate (10), 5-(hydroxymethyl)− 2-furfural (11), D-phenylalanine (12), vanillic acid 4-O-β-D-glucoside(13), lepidiline B (14).		*IC_{50}* (μM) (1), (2), (3), (14)> 100	
Leaves and sprouts of Eruca sativa [17]	Maceration or ultrasonic extraction (Ethanol 70%)		HT-29/ -/ SRB	*IC_{50}* (μg/mL) Sprouts maceration extract and leaves ultrasonic (30 min) extract > 100	
Edible parts of Rocket (Eruca sativa) [44]	Ethanol 50%		Caco-2/ PBS/ MTT	*EC_{50}* (μg GAE/ mL) -Rocket salad extract stored in air X days after expiry date: 0 days: 31.04, 9 days: 33.21, 22 days: 35.5 -Rocket salad extract stored MAP X days after expiry date: 0 days: 31.04, 9 days: 32.1, 22 days: 33.78	
Fresh leaves of *Eruca sativa* [81]	Ethanol 70% (ES-EE)	Kaempferol 3-O-(2''-O-malonyl-β-D-glucopyranoside)− 4'-O-β-Dglucopyranoside (1); Rhamnocitrin 3-O-(2''-O-methylmalonyl-β-D-glucopyranoside)− 4'-O-β-D-glucopyranoside (3)	HCT-116/ -/ SRB	*IC_{50}* (μg/mL) -ES-EE: 10.3 -(1): 8.9 -(3): no effect	
Watercress (*Nasturtium officinale*) [32]	Supercritical CO_2		Caco-2 and HT-29/ Ethanol/ MTS reagent	*EC_{50}* 33.9 μM PEITC = 119,2 μM in HT-29 and 67.0 μM of ITC in Caco-2	G_2/M cell cycle arrest. ↓ cell self-renewal and in vitro colony formation by E-cadherin downregulation. ↓ the ALDH1-mediated chemoresistance by ↓ the expression of LGR5 and PROM1) and by impairing ALDH1 activity. Ability to target CRC progression by targeting the Wnt/β-catenin/ TCF7L2 signaling pathway
Aerial parts (leaves and stalks) of Watercress (*Nasturtium officinale*) [97]	Isothiocynates (ITCs) extraction methods: Supercritical CO_2 or fluid extraction (SFE); Conventional extract with hexane (ITC SE); CO_2-expandend ethanol extraction (CXE).		Caco-2; HT-29/ Ethanol/ MTS	*IC_{50}* (μM of PEITC) *24 h:* -SFE with 125% water in HT29 (A) 30 min, 35ºC, 25 MPa: 23.1 -SFE with 125% water in Caco-2 (B) 60 min, 35ºC, 25 MPa: 73.4 (E) 60 min, 25ºC, Patm: 97.8 (F) 120 min, 25ºC, Patm: 81.6 (G) 60 min, 35ºC, Patm: 67.0 -ITC SE in Caco-2: 57.7 -CXE in Caco-2 and HT29 (K)10% ethanol: 57.7 (L) 20% ethanol: 48.3 and 20.7 (M)40% ethanol: > 78 and 19.8	

(*continued on next page*)

Table 4 (*continued*)

Material (Reference)	Processing Method	Isolated Compounds/Fractions	Cell line/ Administration/ Cytotoxicity assay	Cytotoxicity quantification solution/compound	Mechanism of action
				(N) 50% ethanol: 34.6	
Roots of *Moricandia arvensis* subsp. *eu-arvensis* [100]	Macerated with methanol and extracted with petroleum ether and Chloroform (ChlR)		Caco-2; BE/ -/ MTT	IC_{50} (μg/mL) *48 h:* 230 in Caco-2 and 120 in BE cells	Apoptosis mediated by calpains in BE cells. Potent antioxidant effect against the ROS measured by lucigenin.
Leaves of *Moricandia arvensis* [99]	Methanol	MA51B: Para-Hydroxybenzoic Acid (p-HBA)	BE/ -/ MTT	*Inhibition of cell proliferation (48 h)* -Methanol extract: 56.84% (~200 μg/mL) and 89.23% (~800 μg/mL)	↑antioxidant effect against the ROS induced by lucigenin. Proapoptotic by ↑ of calpain Antimutagenic activity
Seeds of *Orychophragmus violaceus* [84]	Ethanol 70%	Orychophragines A−C (1–3)	HCT-116/ -/ MTT	IC_{50} (μM) *48 h:* (1): 9.83 (2): 22.47 (3): > 50	
Seeds of *Orychophragmus violaceus* [83]	Ethanol 70%	Orychophramarin A-D (1–4) and Orychovioside A (5)	HCT-116/ -/ MTT	IC_{50} (μM) *48 h:* -(1): 5.10 -(2): 28.30 -(3): 10.12 -(4): 44.71 -(5): > 50	Orychophramarin A: Apoptosis and cell cycle arrest in G_2 phase.
Above and underground parts of horseradish (*Armoracia rusticana*) [93]	Hydrolisis with diethyl ether	5-Phenylpentyl isothiocyanate (PhPeITC)	Caco-2/ DMSO and PBS/ MTT	EC_{50} (μg/mL) *72* h: Aboveground parts' autolysate: 3.0 Underground parts' autolysate:1.3	
Aerial parts (leaves and flower buds) of *Matthiola incana* (L.) R. [94]	Methanol 80%		Caco-2/ -/ MTT	Moderate to low cytotoxicity vs. CaCo-2 cells.	Necrotic effect related with ↑ in LDH release
Seeds, leaves and roots of *Lobularia libyca* [82]	Water Hydrolysis with Methylene cloride (seeds and roots) and petroleum ether (leaves)		HCT-116/ -/ MTT	IC_{50} (μg/mL) *72* h: -Seed hydrolysate: 0.31	
Rhizomes of *Wasabia japonica* [101]	Water		Colo 205/ Water or RAD001 in DMSO/ MTT	Dose- and time-dependent cytotoxicity in Colo 205 cells at dosages below 1 mg/mL.	Prevented formation of colonies by ↓ of anchorage-independent growth. ↑ apoptosis by mitochondrial death. Autophagy via ↓ of Akt, mTOR and ↑of LC3-II pathway.
Aerial parts of *Zilla spinosa* [89]	Deffated with petroleum ether, extracted firstly with ethanol 70% and then with chloroform	bergaptane, psoralene, umbleferone, ß-amyrin, friedelene and sterol-β-D-glucopyranoside, ß-Sitosterol and Stigmasterol	HCT-166/ -/ SRB	IC_{50} (μg/mL) Chloroform extract: 14,4	
Aerial parts of *Zilla Spinosa* [90]	Deffated with petroleum ether and extracted with Ethanol 70%	Quercetin 3-O-α-L-rhamnopyranosyl (166)-β-D-glucopyranoside (Rutin), Kaempferol 3-O-α-L-rhamnopyranosyl (166)-β-D-glucopyranoside, Quercetin-3-O-α-L-rhamnopyranoside, Quercetin-3-O-β-glucopyranoside, Kaempferol 3-O-β-Glucopyranoside, Quercetin, Kaempferol.	HCT-116/ -/ SRB	IC_{50} (μg/mL) Ethanolic extract: 16.1	
Aerilal parts of *Erucaria hispanica* (L.) Druce [87]	Methanol 70%	Kaempferol-3-O-b-sophoroside-7-O-b-glucopyranoside,Kaempferol-3-O-b-sophoroside-7-O-b-2'''feruloylglucopyranoside, Kaempferol-3,7-di-O-a-rhamnopyranoside, Luteolin 6,8-di-C-b-glucopyranoside [Lucenin 1], Kaempferol-3-O-b-glucopyranoside-7-O-a-rhamnopyr-anoside, Isorhamentin-3-O-b-glucopyranoside-7-O-a-rhamnopyr-anoside, Luteolin 8-C-b-glucoside [Orientin], Apigenin 8-C-b-glucopyra-noside [Vitexin], Quercetin 7-O-b-glu-copyranoside, Agathisflavone 7,7",4',4"'-tetra methyl ether, Isorhamnetin,	HCT-116/ -/ SRB	IC_{50} (μg/mL) *48* h: Methanol extract: 21.4	

(*continued on next page*)

Table 4 (*continued*)

Material (Reference)	Processing Method	Isolated Compounds/Fractions	Cell line/ Administration/ Cytotoxicity assay	Cytotoxicity quantification solution/compound	Mechanism of action
		3,7,4'-Trihydroxyflavone, Apigenin (5,7,4'-trihydroxy-flavone)			
Fresh seeds of *Iberis amara* [85]	Extraction of essential oil by steam distillation (SD), hydro-distillation (HD), ultrasound-assisted hydro-distillation (UAHD)		SW-480; HCT-116/ -/ MTT	*IC_{50} (μg/mL) 48 h* in SW480 and HCT116 -UAHD: 39.24 and 67.52 -HD: 35.02 and 63.13 -SD: 42.05 and 69.99	
Air-dried aerial parts of *Diceratella elliptica* [86]	Ethanol 70%	6-methoxy-5,7-dihydroxy-3,4-dihydrocoumarin-8-C-glucopyranoside (1), 5-vinyl-6,7-dimethoxy-3,4-dihydro-coumarin-8-C-glucopyranoside (2), kaempferol-3,7-di-O-α-Lrhamnopyranoside (3), kaempferol-3-O-β-D-glucopyranoside (4), kaempferol-7-O-β-D-glucopyranoside (5), kaempferol aglycone (6)	HCT-116/ -/ SRB	*IC_{50} (μg/mL) 48 h:* -(1): 21.1 -(2): 20.7	
Dried seeds of *Descurainia sophia* [91]	Ethanol 80% and ethanol 70%	BP10A (1:1 mixture of ethanolic extracts from D. sophia seeds and P. praeruptorum roots)	HCT-116; KM12SM/ DMSO alone and co-administrated with oxaliplatin (OXA) or CPT-11/ Ez-Cytox	*IC_{50} in* HCT116 and KM12SM -BP10A (μg/mL): 16.78 and 42.39 -BP10A + OXA (μM): 6.25 and 25 -BP10A + CPT (μM): 6.25 and 25	Degradation of PARP. ↑ caspase-3, − 8, and − 9 in HCT-116 cells. Induced the G_2/M arrest. ↓ cdc2/cdk1 and cyclin B1, and ↑ p21 protein. Acts synergistically with anticancer drugs.
Seeds of *Descurainia sophia* [92]	Ethanol 80%	1,3-di-O-sinapoyl-β-D-glucopyranose (sinapoyl glycoside) (1), 1,2-di-O-sinapoyl-β-D-glucopyranose (2), 1,2-dis-inapoylgentiobiose (3), helveticoside (4), drabanemoroside (5), quercetin 3-O-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranose (6), isorhamnetin (7), quercetin (8), isorhamnetin-3-O-β-D-glucopyranoside(9), isoquercitrin (10), syringaresinol (11), sinapic acid (12), 3,4,5-trimethoxy cinnamic acid (13), and daucosterol (14)	HCT-116/ DMSO/ EZ-Cytox cell viability assay kit	*IC_{50} (μM)* -(4): 0.052 -(8): 0.743	Inhibitied chronic inflammation that can lead to tumors
Aerial parts of *Horwoodia dicksoniae* [88]	Ethanol 80%	Luteolin 7-O-β-D-glucopyranoside (1), Luteolin 6-C-β-D-galactopyranoside (2), Apigenin 6-C-β-D-galactopyranoside (3), 5,7,3′,4′-Tetrahydroxyflavone (luteolin) (4)	HCT-116/- /SRB	*IC_{50} (μg/mL) 48 h:* -Ethanolic extract: 11.9 -(1): 9.3 -(2): 11.2 -(4): 9.5	

LED Lower Effective Dosis (LED), Half-maximal inhibitory concentration (IC_{50}), Half maximal effective concentration (EC_{50}), Cellular metabolic activity assay (MTT), Trypan blue (TP), Sulforhodamine B (SRB), MTS Assay Kit (MTS), CellTiter 96® AQueous One Solution Cell Proliferation Assay (CellTiter 96), Lactate dehydrogenase (LDH), Cell Counting Kit-8 assay (CCK8), XTT Cell Proliferation Assay Kit (XTT). Decrease (↓), increase (↑)

3.1.6. Other Brassica genus

Pocasap and Weerapreeyakul [33] investigated dichloromethane extracts from leaves and flowers of *Brassica chinensis* (var. *parachinensis* and var. Tsen and Lee) on HCT-116 cells. The extracts showed that a concentration higher than 50 μg/mL was necessary to achieve 50% inhibition rate. Recently, Miceli et al. [53] developed a similar extract from *Brassica incana* using methanol as solvent, showing high activity in Caco-2 cells (IC_{50} 1.1 mg / mL), while Rahmani et al. [54] obtained an extract from leaves, roots and stems of *Brassica tournefortii*, showing the highest antiproliferative effect in HCT-116 cells with the use of cyclohexane extracts of steam and leaves dissolved in DMSO.

Then, most studies analyzing the effects of the *Brassica* genus analyzed whole plant extracts rather than isolated compounds. Notably, *B. oleraceae* extracts always showed antiproliferative effect against the different CRC cell lines. HCT-116 was the most widely used cell line for cytotoxic assays. In these cells, the ethanolic extract of broccoli flowers (var. *italica*) showed the highest cell proliferation inhibition effect (IC_{50} = 3.88 μg / mL), followed by the extract of cabbage leaves (var. *capitata*) using the same solvent. In contrast, the dichloromethane extract needed more than 50 μg/mL to reach the IC_{50} in this cell line [31,33]. On the other hand, the mechanism of action of *Brassica* genus extracts against cancer cells has been related to apoptosis [29,40,46], expression of pro-apoptotic genes [37,41] (Fig. 2) and G_2/M cell cycle arrest [27,32] (Fig. 3). Although most of these studies do not focus on the role of isolated compounds, it has been amply described the involvement of organosulfur compounds such as sulforaphane in the induction of apoptosis and modulation of cell cycle, which may be associated with the antiproliferative effect of natural extracts [55].

The strongest effect was induced by extracts of uncooked [34,46,56] or selenium-biofortified [43,45] varieties. In fact, it has been demonstrated that biofortification with selenium or sulfur can enhance the antiproliferative effects of the *Brassicaceae* family [57].

3.2. Raphanus genus

The *Raphanus* genus is the second most studied genus from the *Brassicaceae* family in this systematic review. Eleven articles evaluated the cytotoxic activity of extracts from the *Raphanus* genus, ten of which related to *Raphanus sativus* (including four articles of Thai rat-tailed radish from var. *caudatus* Alef) and one to *Raphanus raphanistrum* [58]. Different parts of the plant, such as seeds, pods and flowers have been subjected to extraction with multiple solvents and most of them showed a potent cytotoxic activity against HCT-116, HCT-15 or HT-29.

Regarding *R. sativus*, Kestwal et al. [28] demonstrated that ethanolic

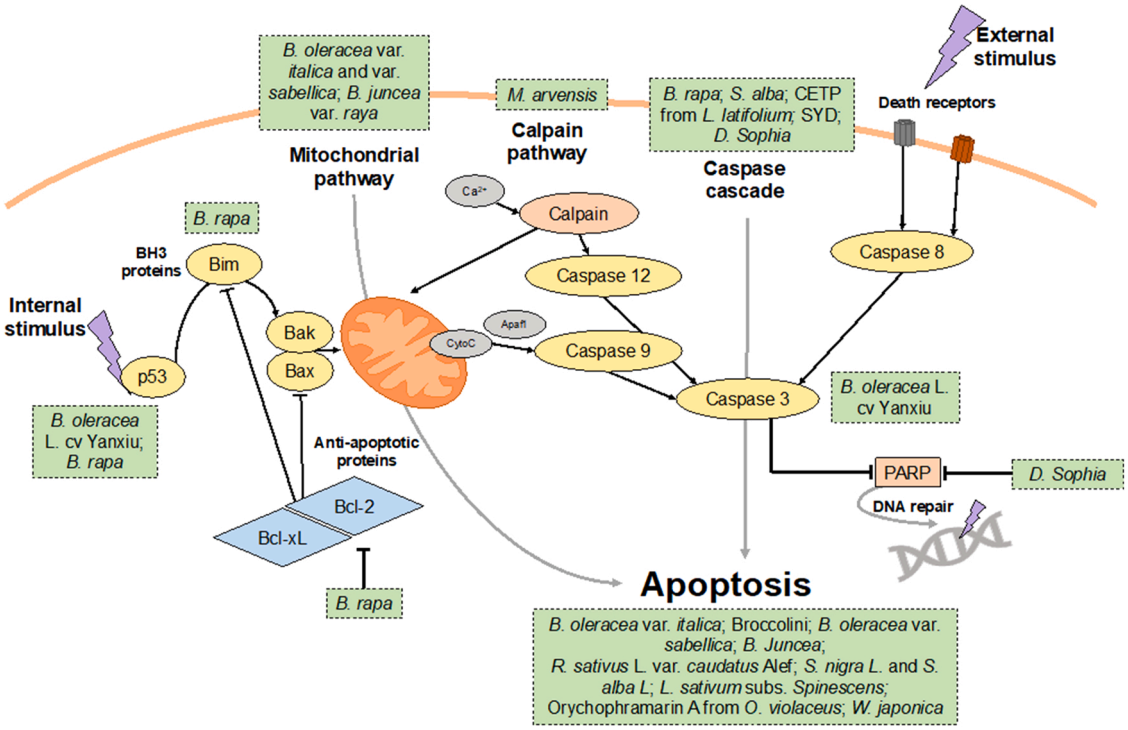

Fig. 2. *Brassicaceae* extracts induction of apoptosis in colon cancer cells by several pathways. (A) Mitochondrial pathway. Extracts from *B. oleraceae* var. *italica and* var. *savellica* and *B. juncea* var. *raya* were reported to induce apoptosis via mitochondrial pathway. In more detail, *B. oleraceae* L. cv Yanxiu and *B. rapa* extracts increased the expression of p53. Extracts of *B. rapa* also upregulated the expression of Bim, Bak and Bax and inhibited the expression of antiapoptotic proteins such as Bcl-2 and Bcl-xL. (B) (B) Calpain pathway. Apoptosis via calpains was induced by *M. arvensis* extracts. (C) Caspase cascade. Extracts from *B. rapa*, *S. alba*, SYD and *D. Sophia,* and CETP from *L. latifolium* modulated the expression of caspases to induce apoptosis via caspase cascade. *B. oleraceae* L. cv Yanxiu extract was also reported to increase the expression of caspase 3. (D) PARP cleavage. Extract of *D. Sophia* was involved in PARP degradation. The rest of *Brassicaceae* extracts in figure were associated with induction of apoptosis but the pathway was not specified. CETP: Epithionitrile 1–cyano-2,3–epithiopropane; SYD: Su Yang Decoction; PARP: Poly (ADP-ribose) polymerase.

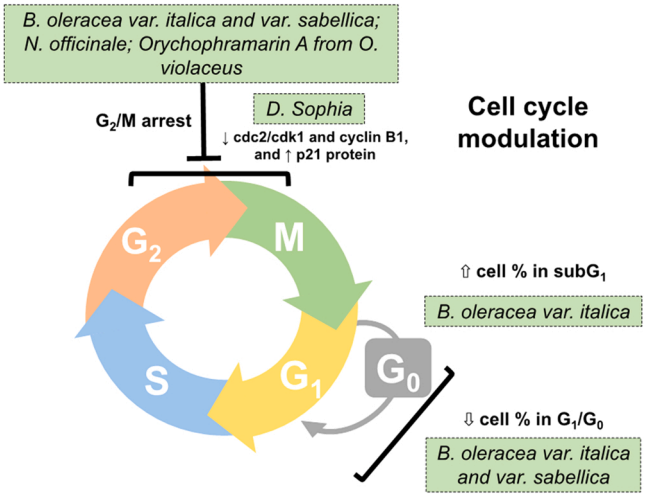

Fig. 3. Cell cycle modulation in colon cancer cells by natural extracts from *Brassicaceae* family. Extracts from *B. oleracea* var. *italica* and var. *sabellica*, *N. officinale* and *D. Sophia* and Orychophramarin A from *O. violaceus* has been reported to induce G_2/M cell cycle arrest. Specifically, *D. Sophia* decreased the expression of cdc2/cdk1 and cyclin B1 and increase p21 protein expression. G_2/M cell cycle arrest induced by *B. oleracea* var. *italica* and var. *sabellica* extracts was associated with a decrease in the percentage of cells in G_1/G_0 phase. An increment in cell percentage in sub G_1 has also been related with extracts from *B. oleracea* var. *italica*.

and aqueous extracts from sulfur-supplemented sprouts, decreased CT26 cell viability (up to 21%) compared to non-supplemented sprouts (80%). Different authors isolated active compounds from methanolic (sulforaphane, sinapoyl desulfoglucorafenin, raphasativuside AB, tenuifolyside C, sibiricose, sucrose and 5-(methylsulfinyl)-pentanenitrile) [59,60] and ethanolic seed extracts (sinigrin [61], and glucoraphenin converted into sulforaphene by addition of myrosinase [62]). These isolated compounds showed potent cytotoxicity against HCT-15 and HT-29 cell lines. Of note, sulforaphane and sulforaphene are of particular interest among these compounds because their involvement is key in the anticancer activity of *R. sativus* [63]. Several mechanisms of action have been associated with sulforaphane activity, such as apoptosis induction by different pathways or cell cycle arrest at G_1 and G_2/M phase [55].

Recently, De la Fuente et al. [27] subjected *R. sativus* to enzymatic digestion to obtain bioaccessible fractions, achieving positive results in Caco-2 cells. In addition, the intestinal anti-inflammatory activity of the aqueous extract of *R. sativus* seeds has also been tested in vivo, suggesting an important role in preventing the intestinal inflammation that may precede the development of CRC [64].

Four studies used dichloromethane-based methods for the extraction of *R. sativus* var. *caudatus* Alef, including acetonitrile or DMSO as solvents. The extracts demonstrated a potent cytotoxic effect on HCT-116 cells (IC_{50} 9.42 μg/mL) [33,65]. Moreover, the same authors [66] tested different parts of the plant, obtaining better results from extracts of flowers, followed by pods, dry seeds and stems. All extracts showed induction of apoptosis in HCT-116 cells. Only extracts from leaves and roots showed no cytotoxic effect at doses below 250 μg/mL.

On the other hand, extracts of seeds from *R. sativus* L. 'Taebaek' and roots from var. *longipinnatus* were obtained with dichloromethane. While the former was fractionated to isolate sulforaphane (SFE),

showing cytotoxicity in HT-29 cells (IC_{50} 2.50 μg/mL [67], the latter showed no cytotoxicity in HCT-116 (doses < 50 μg/mL) [33]. Finally, the ethanolic extract of *Raphanus raphanistrum* leaves showed no antiproliferative effects against LoVo cells [58].

Therefore, *R. sativus* demonstrated a clear cytotoxic effect against CRC cells and contains numerous bioactive compounds with promising effect against other conditions such as intestinal inflammation, liver damage and diabetes [62].

3.3. Diplotaxis and Lepidium genuses

The *Diplotaxis and Lepidium* genera (five articles each) have also been studied. Extracts from *D. tenuifolia* leaves —commonly known as 'rocket'— using different solvent (i.e., chloroform:methanol, methanol and ethanol) did not reach an IC_{50} value lower than 100 μg/mL in the CRC cell lines HT-29 (IC_{50} ~ 200 μg/mL), Caco-2 (IC_{50} 1.87 mg/mL) and LoVo cells (40% inhibition at 100 μg/mL) [58,68,69]. In a methanolic extract of *D. harra* flowers, the presence of isorhamnetin-3-O-glucoside and isoramnetin-3,7-di-O-glucoside was demonstrated, although only the first compound modified cancer cell viability [70]. Finally, ethyl acetate and ethanol extracts of *D. simplex* flowers were tested in Caco-2 cells, and both showed an antiproliferative effect (IC_{50} 62.0 and 63.25, respectively) on Caco-2 cells [71].

Regarding the genus *Lepidium*, antitumor properties for three species (*L. meyenii, L. latifolium* and *L. sativum* Subsp *spinescens* L.) were tested. Maca (*L. meyenii*) is one of the most widely studied. It has been traditionally used to treat health problems such as infertility, but its anticancer effects have also been assessed [72]. Some authors isolated macamides compounds from maca (methanolic and ethanolic extracts). Macamide 3 and 4 showed antitumor activity against SW-480 (IC_{50} 12.8 μmol/L and 5.7 μmol/L at 24 h, respectively) and total macamides fractions (TMM) were effective against HT-29 cells in culture (IC_{50} 69.29 μg/mL at 48 h) [73,74]. In contrast, none of the thirteen compounds isolated from the aqueous and ethanolic extracts of *L. meyenii* roots showed cytotoxicity against COLO 205 cells [75]. To continue with this genus, the ethanolic extract of above-ground parts of dried *L. sativum* Subsp *spinescens* L. demonstrated antitumor activity and apoptosis in the DLD-1 cell line (IC_{50} 110.42 μg/mL) [76]. In addition, Conde-Rioll et al. [77] demonstrated that the chloroform extract from *L. latifolium* leaves had the highest cytotoxic effect on HT-29 cells in relation to other extraction methods (ethanol, supercritical fluids, water, protein extract and glycerol). Furthermore, these authors identified epithionitrile 1–cyano-2,3–epithiopropane (CETP) as a potential anticancer agent in an in vivo model of CRC [77].

3.4. Sinapis and Eruca genera

Six articles analyzed the in vitro cytotoxicity of extracts obtained from plants of the genera *Sinapis* and *Eruca* against CRC cells. Extracts of seeds and leaves of *S. alba* L. (mustard) were obtained using different methods (ethanol, water/β-cyclodextrin, water) [27,78,79]. These authors demonstrated that the ethanolic extract of seeds induced high antiproliferative activity in HCT-116 and HT-29 cells (IC_{50} 189.83 and 305.65 μg/mL, respectively) mediated by increased ROS/decreased GSH, G_2/M arrest, and apoptosis through the mitochondrial pathway. In contrast, Boscaro et al. [78] reported that leaf and seed extracts of *S. nigra* (ethanol, water/β-cyclodextrin and water) showed no antiproliferative activity against the same colon cancer cells. Protective effects of mustard seeds against colonic tumors have also been studied in vivo, showing potent antioxidant and immunosupportive activity [80].

On the other hand, three articles focused on *E. sativa* as a source of functional extracts. Edible parts from rocket salad were subjected to ethanolic extraction (EE), isolating two compounds, namely Kaempferol 3-O-(2''-O-malonyl-β-D-glucopyranoside)− 4'-O-β-Dglucopyranoside and rhamnocitrin 3-O-(2''-O-methylmalonyl-β-D-glucopyranoside)− 4'-O-β-D-glucopyranoside. Potent antiproliferative effects in HCT-116 cells were demonstrated using EE (IC_{50} 10.3 μg/mL) and Kaempferol (IC_{50} 8.9 μg/mL [81]. In addition, Ombra et al. [44] observed similar effects in Caco-2 cells even 22 days after storage, concluding that the cytotoxic effect was not affected by the expiration date [44]. The most recent study related to *E. sativa* evaluated the antiproliferative effect of the extracts obtained from maceration of sprouts and ultrasonic processing of leaves, but no effect was observed against the HT-29 cell line [17].

3.5. Other genera

Multiple species belonging to other genera of *Brassicaceae* have been less studied. Despite the highly variable methodology described in this context, almost all studies demonstrated significant antiproliferative effects using both crude extracts and isolated compounds.

Aqueous extracts from seeds, leaves and roots of *Lobularia libyca* showed antiproliferative effects on HCT-116 cells (IC_{50} 0.31 μg/mL of the seed hydrolysate [82]. Some active compounds from the ethanolic extracts of *Orychophragmus violaceus* seeds (Orychophramarin (A-D), Orychovioside A and Orychophragines (A-C)) showed cytotoxicity against the same tumor cells, with Orychophramarin (A-D) being the most effective (IC_{50} between 5.10 and 44.71 μM) [83,84]. Other seeds such as *Iberis amara* seeds were subjected to different extractions (essential oil by steam distillation (SD), hydro-distillation (HD) and ultrasound-assisted hydro-distillation (UAHD)), showing notable antiproliferative activity against HCT-116 (IC_{50} 42.05, 63.13 and 67.52 μg/mL respectively), and SW-480 (IC_{50} 42.05, 35.02 and 39.24 μg/mL, respectively) cells [85].

Marzouk et al. [86] isolated six compounds from ethanolic extracts of *Diceratella elliptica* (aerial parts). Only compounds 6-methoxy-5, 7-dihydroxy-3,4-dihydrocoumarin-8-C-glucopyranoside and 5-vinyl-6, 7-dimethoxy-3,4-dihydrocoumarin-8-C-glucopyranoside showed antiproliferative activity in HCT-116 cells (IC_{50} 21.1 and 20.7 μg/mL, respectively). The same authors reported that methanol extracts from *Erucaria hispanica* (aerial parts) also had antitumor activity (IC_{50} 21.4 μg/mL) [87]. Using similar ethanolic extraction methods, Fawzy et al. [88] isolated three compounds from *Horwoodia dicksoniae* (luteolin 7-O-β-D-glucopyranoside, luteolin 6-C-β-D-galactopyranoside and luteolin) which showed an IC_{50} of 9.3 μg/mL, 11.2 and 9.5 μg/mL, respectively [88].

Extracts of *Zilla spinosa* (aerial part) using chloroform and ethanol showed potent cytotoxicity against HCT-116 cells (IC_{50} 14.4 μg/mL and 16.1 μg/mL, respectively) [89,90]. Recently, Kim et al. [91] mixed ethanolic extracts of *Descurainia sophia* seeds and *Peucedanum praeruptorum* roots (1:1) to prepare BP10A, which was used alone, or associated with oxaliplatin (BP10A + oxaliplatin) or CPT-11 (BP10A + CPT-11). These treatments showed a strong ability to damage HCT-116 (IC_{50} 16.78 μg/mL, 6.25 μM and 6.25 μM, respectively) and KM12SM cells (42.39 μg/mL, 25 μM and 25 μM, respectively) after 48 h. In addition, BP10A induced apoptosis in HCT-116 cells and G_2/M cell cycle arrest in both cell lines. The involvement of *D. sophia* in this cytotoxicity is supported by the results of Lee et al. [92], who described antiproliferative effects of two isolated compounds, helveticoside and quercetin (IC_{50} 0.052 and 0.743 μM, respectively), against the HCT-116 colon cancer cell line.

Dekić et al. [93] obtained extracts of above and underground parts of *Armoracia rusticana* by hydrolysis with diethyl ether, showing potent antiproliferative effect (EC_{50} 3.0 μg/mL and 1.3 μg/mL, respectively) in Caco-2 cells [93]. Recently, Taviano et al. [94] were only able to induce necrosis with high doses of methanolic extract *of Matthiola incana* (L.) R (aerial parts) in the same cell type.

Finally, ITCs extraction methods (supercritical CO_2 or fluid extraction (SFE), conventional solvent extract of ITCs with hexane (ITC SE) and CO_2-expanded ethanol extraction (CXE)) were applied to watercress (*Nasturtium officinale*). The antitumor effects of ITCs have been widely investigated. These molecules demonstrated antiproliferative effects in prostate cancer cells (PC-3 and DU 145) [16,95], breast cancer cells

[22], and myeloma cells [96]. In CRC, Pereira et al. [32] used ITCs-enriched watercress extract (by supercritical CO_2 extraction) and reported positive results in HT-29 (IC_{50} 33.9 ± 3.7 μM PEITC) and in Caco-2 (IC_{50} 67.0 ± 4.1 μM of ITC) cell cultures. These extracts also inhibited proliferation of HT-29 spheroids by cell cycle arrest in G_2/M, and specifically targeted CSCs subpopulation. On the other hand, Rodrigues et al. [97] obtained remarkable results in HT-29 and Caco-2 cells following the same methodology [97]. The antitumor mechanism of action of watercress included oxidative stress, apoptosis, cell cycle progression and MAPK signaling. Furthermore, antioxidant, anti-inflammatory, antipsoriatic, renoprotective, hepatoprotective, and antigenotoxic activities have also been studied [98]. In addition, Skandrani et al. [99] described the antiproliferative effect of the methanolic extract of leaves of *Moricandia arvensis* subsp. *eu-arvensis* in colon cancer BE cells (200–800 μg/mL). One year later, the same authors demonstrated a greater cytotoxic effect of the chloroform extract of the plant's roots (IC_{50} 230 μg/mL in Caco-2 and 120 μg/mL in BE cells) and described the proapoptotic and antioxidant activity of both extracts [100]. Finally, *Wasabi japonica* rhizomes were subjected to water extraction to evaluate their influence on Colo 205 cell viability. Its mechanism of action was thoroughly analyzed, and it was found to be related to inhibition of anchorage-independent growth, apoptosis induction and autophagy increase [101].

4. Conclusion

Despite the evidence that a vegetable-based diet helps prevent colon cancer, only a small part of the *Brassicaceae* family has been investigated. Most genera and species remain unexplored because they are wild species, with a low cultivation rate. Therefore, they may represent a novel source of bioactive compounds, many of them unknown, with potential biological activities. As shown in this systematic review, the *Brassica* genus is by far the most widely studied genus from the *Brassicaceae* family. Considering the articles that reported the use of these plants, flowers or inflorescences seem to be the preferred plant material. Further studies using different parts of the plants as extraction material or different solvents with standardized protocols would be desirable to obtain comparable results. Although the antitumor activity of functional extracts from multiple species of the *Brassicaceae* family has been explored in vitro, further research is still needed to gain a more comprehensive understanding of their potential role in cancer treatment. Finally, those extracts that have already been described in depth need to be tested in vivo, and then in clinical trials before they can be translated into clinical practice.

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CRediT authorship contribution statement

Mercedes Peña: Investigation, Resources, Formal analysis. **Guzman Ana Guzmán:** Investigation, Resources, Formal analysis. **Martinez Rosario Martínez:** Resources, Writing – original draft. **Cristina Mesas:** Investigation, Resources. **Jose Prados:** Conceptualization, Supervision, Writing – review & editing. **Jesús M. Porres:** Conceptualization, Supervision, Writing – review & editing. **Consolación Melguizo:** Conceptualization, Supervision, Writing – review & editing..

Conflicts of interest statement

The authors declare no conflict of interest.

Data Availability

No data was used for the research described in the article.

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