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Cancer and Traditional Plant Knowledge, an Interesting Field to Explore: Data from the Catalan Linguistic Area

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Abstract: Cancer is the second cause of death in the world and is foreseen to be responsible for about 16 million deaths in 2040. Approximately, 60% of the drugs used to treat cancer are of natural origin. Besides the extensive use of some of these drugs in therapies, such as those derived from the genus *Taxus*, a significant number of plants have revealed themselves as useful against cancer in recent years. The field of ethnobotany focuses on documenting traditional knowledge associated with plants, constituting a starting point to uncover the potential of new plant-based drugs to treat or prevent, in this case, tumour diseases and side effects of chemotherapy and radiotherapy. From a series of extensive ethnobotanical prospections across the Catalan linguistic area (CLA), we have recorded uses for 41 taxa with antitumour effects. The two most quoted botanical families are Asteraceae and Ranunculaceae, and the most frequently reported species is *Ranunculus parnassifolius*, a high-mountain species, which is widely collected for this purpose. The reported species have been used to treat an important number of cancer types, focusing on preventive, palliative, and curative uses, as well as to deal with the side effects of conventional treatments. Comparing our results in CLA with previous data available in the most comprehensive databases of pharmacology and a review of cytotoxicity assays revealed that for the several species reported here, there was no previous evidence of traditional uses against cancer. Despite the need for further analyses to experimentally validate the information presented here, combining traditional uses and phylogenetically-informed strategies to phytochemical and pharmacological research would represent new avenues to establish more integrative approaches, hence improving the ability to select new candidate taxa in cancer research.

Keywords: antitumor; cancer; cytotoxic activity; ethnobotany; medicinal plants; pharmacological activity; traditional plant knowledge

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1. Introduction

Cancer is one of the leading causes of death worldwide, accounting for nearly 10 million deaths in 2020 [1]. There is about a 20% risk of developing a cancer in a lifetime and a 10% risk of dying from the disease; this means that one in five persons will suffer from some type of cancer in their lifetime and one in ten will, unfortunately, die from the disease [2]. The International Agency for Research on Cancer estimates an incidence of 30 million people and more than 16 million deaths directly linked to this illness by 2040 [3]. Breast cancer was amongst the most diagnosed cancer types in 2020, followed by lung, colon and rectum, prostate, skin (non-melanoma) and stomach cancer. By far, lung cancer, followed by liver and stomach cancer, represent the most deadly types of cancer [2]. The World Health Organization [1] suggests that between 30% and 50% of cancers could be avoided

by reducing exposure to risk factors, especially those associated with sedentary lifestyles (e.g., elevated body mass index, low intake of fruits and vegetables and lack of physical activity), bad habits and addictions (including tobacco and recurrent alcohol consumption), or continued exposure to domestic mutagenic agents (e.g., ultraviolet or ionising radiation and air pollution exposure).

Approximately 60% of the drugs used in therapies against cancer are based on chemicals of natural origin [4]. Indeed, because of their recurrent use throughout history, some of them are already considered classical. These include vegetal alkaloids, such as paclitaxel, extracted from *Taxus brevifolia* Nutt. and related species, vinblastine and vincristine from *Catharanthus roseus* (L.) G.Don or cyclolignans, such as podophyllotoxin, extracted from *Podophyllum hexandrum* Royle and *P. peltatum* L. [5].

Among the c. 350,000 vascular plant species described, around 7% of them have documented traditional medicinal uses [6]. However, the search for new drugs is far from being over, and here, ethnobotany can play a very important role in uncovering both new species and uses, and thus contributing to finding new potential drugs for cancer research.

The field of ethnobotany focuses on documenting traditional knowledge and uses associated with plants, providing baseline information for plant screenings to be used during the treatment and/or prevention of certain diseases [7]. Among many other applications, access to such cultural data repositories constitutes a complementary, yet necessary step to further the field of medical research, especially for cancer treatment [8,9]. In fact, the value of ethnobotany in drug research is regulated and even recognised at the legal level. According to the European Medicines Agency (EMA), registration of traditional herbal medicines requires providing a bibliographic track record, or expert's evidence, regarding the use of a given product as medicinal for a minimum of 30 years prior to the registration process, of which at least 15 must be in the European Union [10]. The ethnopharmacological approach involves several methodologies from social and natural disciplines, and has been for long time the traditional way of selecting plant candidates for drug development [11,12]. However, in recent times, efforts are being made to move the field forward by combining sources of traditional knowledge with more modern "omic" approaches [13,14]. Certainly, the use of molecular phylogenetic frameworks provides unparalleled opportunities for tracing chemical activity and making predictions over evolutionary scales [15–17], thus making the identification of a candidate species with potential chemical activity more powerful than ever before (e.g., antineoplastic activity) [18].

Phytotherapy and pharmaceutical ethnobotany have been frequently used to address mild and chronic illnesses, but nonetheless, they have also proved to be useful against acute and more severe health issues, such as cancer [19,20]. Interest in medical plant research is not new, as back in 1994, The Lancet editorial [21] emphasised the need for investing more funds in the study of plants as the basis for new drug discovery, referring, among others, to cancer treatment. Nowadays, unlike in the past, natural medicinal product research considers the ecological consequences of overharvesting plants from the wild and the impact of exploiting biodiversity. Likewise, international agreements, legislations and conservation strategies have been developed to protect both the biodiversity as well as the ethical implications of traditional knowledge of indigenous communities [12,22].

Ethnobotanical studies focusing on plant applications for cancer research have been published worldwide [23–29], but never before has a study been published focusing on the Iberian Peninsula, nor the Catalan linguistic area (CLA). Based on this, and aiming at filling such caveat, the main objectives of this study were as follows: (i) to report the potential uses of plants in cancer treatment, including preventive and palliative applications, based on the information of traditional uses recorded in CLA; (ii) to carry out a literature review of pharmacological activity and uses of plants concerned; and (iii) to prove the importance of traditional knowledge as a starting point in the development of new plant-based drugs.

2. Results and Discussion

2.1. General Data

Over the last 30 years of ethnobotanical prospection across the Catalan linguistic area, we have gathered information on folk plant uses related to cancer for 41 plant species, including references to curative, palliative or preventative purposes (Table 1). It is however, worth mentioning that in some cases, the informants use local euphemisms to describe the origin of the illness, such as "mal dolent" or "mal lleig", which literally translate to bad or ugly illness [30]. One explanation for this is that still today, it is hard for many people to use the word cancer, being considered to some extent a taboo disease (or forbidden word). This is especially common among the elderly, and is clearly associated with traditional knowledge. Certainly, fears behind the use of the word cancer could be most likely associated with the high rates of deaths attributed to this illness, prior to the improvement of detection and subsequent therapies of treatment.

A systematic review of the traditional uses of medicinal plants to treat cancer was published in 2021 [31]. The review reported a total of 948 plants species used against cancer around the world. Surprisingly, despite the large number of species reported in this former global review, 21 (out of the 41) taxa reported in our study were not included before in any compilation of uses, and also, a total of 37 taxa are quoted for the first time for the Iberian Peninsula and the Balearic Islands following this review publication. Altogether, these findings contribute significantly to improve our understanding of traditional plant uses related to cancer management, but also emphasise the power of in-depth surveys at regional and local levels to uncover new potential candidate species, and thus complement global initiatives in cancer research.

Table 1. Plant taxa used against cancer in the Catalan linguistic area, grouped by curative, palliative, and preventive activities. Comparison of uses in the pharmacological comprehensive literature was extracted from: European Medicines Agency (EMA) monographs [32], Duke's CRC *Handbook of Medicinal Herbs* [33], and Fitoterapia.net webpage [34].

Taxon (Herbarium Voucher)	Family	Plant Part Used	Pharmaceutical Form	Pharmacological Literature
Curative				
Abies alba Mill. (BCN 24699)	Pinaceae	Resin	Without pharmaceutical form (internal use)	[33]
Agrimonia eupatoria L. (BCN 24704)	Rosaceae	Aerial part	Unknown	[33]
Allium cepa L. (BCN 27279)	Amaryllidaceae	Bulb	Tisane	[32–34]
Anemone hepatica L. (BCN 27247)	Ranunculaceae	Leaf	Tisane	
Angelica sylvestris L. (BCN 24712)	Apiaceae	Unknown	Unknown	
Brassica oleracea L. (BCN 24728)	Brassicaceae	Leaf	Tisane/Without pharmaceutical form (internal use)	[33,34]
Bryonia cretica L. (BCN 24730)	Cucurbitaceae	Root	Without pharmaceutical form (topical use)	[33]
Clematis flammula L. (BCN 29856)	Ranunculaceae	Aerial part	Poultice	
Crocus sativus L. (BCN 32170)	Iridaceae	Styles and stigmas	Poultice	[33,34]
Daucus carota L. subsp. *sativus* (Hoffm.) Arcang. (BCN 46847)	Apiaceae	Root	Tisane	[33,34]
Ecballium elaterium (L.) A.Rich (BCN 46846)	Cucurbitaceae	Aerial part	Unknown	
Geranium robertianum L. (BCN 24894)	Geraniaceae	Aerial part	Tisane	[33]
Helleborus foetidus L. (BCN 29705)	Ranunculaceae	Aerial part	Poultice	
Malva sylvestris L. (BCN 24924)	Malvaceae	Aerial part/Flower	Tisane	[33]
Plantago lanceolata L. (BCN 24949)	Plantaginaceae	Leaf	Without pharmaceutical form (topical use)	[33]
Plantago major L. (BCN 24950)	Plantaginaceae	Aerial part/Leaf	Without pharmaceutical form (internal and topical use)	[33]
Potentilla reptans L. (BCN 47660)	Rosaceae	Leaf	Tisane	[33]
Prunella vulgaris L. (BCN 29759)	Lamiaceae	Flower	Tisane	[33]
Prunus dulcis (Mill.) Weeb. (BCN 46833)	Rosaceae	Resin	Without pharmaceutical form (topical use)	[33]

Table 1. *Cont.*

Taxon (Herbarium Voucher)	Family	Plant Part Used	Pharmaceutical Form	Pharmacological Literature
Ranunculus bulbosus L. (BCN 24966)	Ranunculaceae	Root	Without pharmaceutical form (topical use)	[33]
Ranunculus parnassifolius L. (BCN 24967)	Ranunculaceae	Root/Whole plant	Tisane/Without pharmaceutical form (topical use)	
Rubus ulmifolius Schott (BCN 24978)	Rosaceae	Tender bud	Tisane	
Ruta chalepensis L. (BCN 24980)	Rutaceae	Aerial part	Unknown	[33]
Scrophularia alpestris J.Gay ex Benth. (BCN 29790)	Scrophulariaceae	Young leaf	Without pharmaceutical form (topical use)	
Thymus vulgaris L. (BCN 25023)	Lamiaceae	Flowering aerial part	Gargarism	[33]
Verbena officinalis L. (BCN 25036)	Verbenaceae	Aerial part	Poultice	[33]
Viola sylvestris Lam. (BCN 26791)	Violaceae	Leaf	Tisane	
Palliative				
Cannabis sativa L. (BCN 24735)	Cannabaceae	Leaf/Young aerial part	Tisane/Poultice	[33,34]
Papaver somniferum L. (BCN 24941)	Papaveraceae	Latex	Unknown	[33]
Plantago sempervirens Crantz (BCN 96761)	Plantaginaceae	Flowering aerial part	Mouthwash	
Santolina chamaecyparissus L. (BCN 24986)	Asteraceae	Flowering aerial part	Mouthwash	[33]
Preventive				
Achillea millefolium L. (BCN 24700)	Asteraceae	Inflorescence	Tisane	[33]
Angelica sylvestris L. (BCN 24712)	Apiaceae	Unknown	Unknown	
Apium graveolens L. (BCN 24714)	Apiaceae	Aerial part	Unknown	[33]
Beta vulgaris L. subsp. *vulgaris* var. *conditiva* Alef. (BCN 52089)	Amaranthaceae	Root	Tisane/Without pharmaceutical form (internal use)	[33]
Brassica oleracea L. (BCN 24728)	Brassicaceae	Leaf	Without pharmaceutical form (internal use)	[33,34]
Calendula arvensis L. (BCN 32863)	Asteraceae	Inflorescence	Liniment	
Helianthus tuberosus L.(BCN 24898)	Asteraceae	Tuber	Boiled	
Petroselinum crispum (Mill.) Hill (BCN 24943)	Apiaceae	Leaf	Poultice	[33]
Ranunculus parnassifolius L. (BCN 24967)	Ranunculaceae	Root/Whole plant	Tisane/Without pharmaceutical form (topical use)	
Sambucus nigra L. (BCN 24984)	Adoxaceae	Inflorescence	Fumigation	[33]
Urtica sp.	Urticaceae	Unknown	Tisane	[33]

2.2. Most Recurrent Taxa Used by Informants in Prospected Area

The most cited plant against cancer in our surveys across the area prospected was *Ranunculus parnassifolius* (Figure 1), a perennial herb belonging to the Ranunculaceae family, a botanical family widely studied over centuries in traditional ethnomedicine. In particular, this species grows in high-mountain screes in the Pyrenees and in other European mountain ranges. In the Catalan Pyrenees, this taxon is traditionally used for the treatment of "mal gra", a Catalan term that translates into "bad pimple", frequently used to designate some sort of skin cancer. It is usually prepared by combining it with chicken fat in the form of balm or unguent [35]. This plant is popularly very strongly associated with this specific use that it is, indeed, widely known by its local Catalan name "herba del mal gra" (i.e., "bad pimple herb") [30]. One of the negative consequences of this medicinal reputation is that, in recent years, this taxon has been intensively collected in the wild. Besides the impact of climate change in high mountain ecosystems, uncontrolled harvesting adds an extra level of threat to already damaged populations, many of which suffer the consequences of uncontrolled human activities, such as tourism and high-mountain sports, in these areas. Certainly, as already stated by Brower [36], unless action is taken, the rapid loss of biodiversity (to which we add the decline in traditional knowledge, particularly in heavily-industrialised societies) can adversely affect future cancer plant-based drug discovery.

Besides *R. parnassifolius*, another four species belonging to the buttercup family (Ranunculaceae) were also recorded in our study (see Table 1 for details). This result is not surprising, based on the previous investigation by Hao et al. [37], who already pointed out that several phylogenetically-related genera within the family from China contain a series of phytometabolites (e.g., alkaloids, terpenoids, saponins and polysaccharides) with

anti-cancer activity [38]. Altogether, this makes the species from the Ranunculaceae family reported here (and in particular *R. parnassifolius*) good potential candidates for future phytochemical and pharmacological investigation.

Figure 1. *Ranunculus parnassifolius* in its rocky high mountain habitat in the Catalan Pyrenees (image photo: Albert Mallol Camprubí).

Another family that was recurrently cited among the informants is the sunflower family (i.e., Asteraceae). According to our results, five species were claimed to be used against cancer by locals (Table 1). One of them is *Silybum marianum*, a very well-studied plant [39,40], which is indeed a great example to illustrate the importance of common plants for cancer research in particular, and for medicine in general. More specifically, *S. marianum* is known for its hepatoprotective properties, which has revealed promising results for cancer treatment in recent research [40]. In addition, other Asteraceae members were reported here with well-established traditional uses (Table 1). With such precedents, future analytical work should then focus on this group of candidate taxa for additional chemical exploration, and thus confirm whether any of these is of anticancer usefulness beyond the current knowledge. Among Rosaceae, four species in the family (Table 1) also play an important role in traditional medicine. Surprisingly, the utilised part of these species in the studied territories is not the fruit. In general, the presence of phytochemicals and antioxidants in Rosaceae fruits and their potential as cancer inhibitors are well known [41], but based on our results, investigating alternative tissues could indeed open new avenues in this field of research.

Beyond the above-mentioned botanical families, other plant species were reported to fight against the more frequent cancers associated with high mortality rates in rural areas. Among them, *Helleborus foetidus*, *Plantago lanceolata* and *Plantago major* have been reported by our informants to treat skin carcinogenic injuries, *Thymus vulgaris* for throat-related forms of cancer, *Crocus sativus* for breast tumors, *Anemone hepatica* for liver, and *Malva sylvestris* for colorectal cancers (Table 1).

2.3. Wild and Cultivated Vegetables and Their Role against Cancer

In the area of preventive strategies against cancer by WHO [1], specialists pointed out the low consumption of fruit and vegetables as an important cancer risk factor. Even if the relationship between food and vegetable intake and cancer does not seem to be clear in most cases, their consumption is encouraged in trouble-preventive healthy diets [42,43]. In this respect, we want to emphasise the idea around the role of folk functional foods or nutraceuticals [44] as preventative and curative. For example, the species *Brassica oleracea* (wild cabbage and its common infraspecific categories including broccoli, cauliflower, kale, etc.), was widely reported as an effective source against stomach cancer by our informants. In addition, epidemiological studies highlight the positive effects of the ingestion of plants belonging to the genus *Brassica* as a cancer preventive [45], providing support to our reports.

In addition, four frequently cultivated vegetables (*Allium cepa* and *Daucus carota* subsp. *sativus* were specifically cited for the treatment of stomach cancer; *Apium graveolens* and *Beta vulgaris*), a minor or neglected crop (*Helianthus tuberosus*), and a wild plant often consumed as a vegetable (*Urtica* sp.) complete the set of folk functional foods potentially useful as antitumour sources (representing 17.5% of the cited species; Table 1). Altogether, these results show the importance of plants (both cultivated and their wild crop relatives), whose regular intake in diets can be beneficial and cancer preventive.

2.4. Plants for Dealing with Side Effects of Cancer Treatments

As highlighted in previous sections, this study provides compelling evidence regarding the importance of assessing traditional knowledge linked to plants as a possible source of new drugs. Whilst efforts need to focus on the prevention and/or cure of cancer, another important issue to tackle is the side effects of standard medical treatments, and investigation into how plants can contribute to the alleviation of the effects of antitumour therapies. Reducing (or minimising) the negative effects—e.g., anaemia, appetite loss, nausea and vomiting, general pain and distress, mouth infections, among others—of chemotherapy and radiotherapy treatments is one of the goals that is being pursued in this field, and plants are also present in this line of research [46]. Based on our research, the most common species reported with analgesic activity (i.e., pain relief) are *Cannabis sativa* and *Papaver somniferum*, whilst *Plantago sempervirens* and *Santolina chamaecyparissus* were used for mouth infections derived from therapies against cancer.

2.5. Pharmacological Activity Review

The official monographs of the European Medicines Agency (EMA) [32] and European Scientific Cooperative on Phytotherapy (ESCOP) [47] include just one out of the forty-one species reported in our study. According to the EMA records, the monograph report for *Allium cepa* provides details regarding the anticarcinogenic and antimutagenic activities associated with this species [32]. Consulting other sources of literature on phytotherapy made it possible to validate a total of 68.29% of the species reported here. In fact, Duke's CRC *Handbook of Medicinal Herbs* [33] was by far the most inclusive, systematic and detailed work analysed of any of the sources consulted (Table 1).

In addition, we carried out a review of the cytotoxicity tests against cancer cell lines for the plants reported by informants in our field surveys. So far, a total of 26 species have been the focus of different studies to test inhibition of cell growth in cancer cell lines (see Table 2 for details). Some of the species currently lacking any information regarding the inhibitory activity, such as *Plantago major*, *Ranunculus bulbosus* or *Ranunculs parnassifolius,* have been otherwise well studied from a genus level perspective, and the results obtained in related species could be similar for these taxa, although this would require future confirmation. In fact, the lack of cytotoxicity assays does not necessarily mean that some of these species are not indeed active against cancer. Other pharmacological activities, such as antioxidant capacity by scavenging reactive oxygen, are important in preventing potential damage to cellular components such as DNA, proteins and lipids. The oxidative damage can cause major problems, such as carcinogenesis [48]. Some of the species reported here are not studied against cancer cell lines such as *Apium graveolens*, *Rubus ulmifolius* or *Sambucus nigra*, but are well known for their antioxidant activity [49–51], and could be, therefore, good candidates to test in future assays.

In summary, our study provides relevant information on the traditional uses of plants against cancer across the Catalan linguistic area, contributing to the global understanding of ethnomedicine to mitigate the impact of an illness that kills nearly 10 million people per year. We want to stress, however, that our efforts to collate and make such data available should be paralleled by an increase in pharmacological studies to experimentally validate the data reported here, and also by subsequent analyses regarding the impact of these chemicals on cancer cell lines.

Table 2. Review of the cytotoxic activity against cancer cell lines for plants quoted in the Catalan linguistic area to treat cancer.

Taxon	Plant Part Used	Extract	Chemical Compound	Cell Line	Cytotoxic Activity (Key Results)	Reference
Abies alba Mill.	Seed and cone	Aq	-	MCF7 and MDA-MBA-231	The influence of the essential oils on the cancer cells was weak. The IC_{50} values were similar to those found towards normal cells (100 μg/mL)	[52]
Achillea millefolium L.	-	EtOH	Phenolic acids (3,5-O-dicaffeoylquinic acid, 5-O-caffeoylquinic acid), flavonoids (luteolin-O-acetylhexoside, apigenin-O-acetylhexoside)	NCI-H460 and HCT-15	The extract showed an inhibitory effect on the growth of NCI-H460 and HCT-15 cell lines with IC_{50} values 187.3 μg/mL and 70.8 μg/mL, respectively	[53]
Agrimonia eupatoria L.	Aerial part	Aq and MeOH	-	RD and HeLa	The extracts showed anti-tumor properties in a concentration-dependent manner, and the MeOH extract recorded better values of percentage of growth inhibition than aqueous extract in HeLa and RD cell lines (IC_{50}: 96 μg/mL)	[54]
Allium cepa L.	Bulb	MeOH	-	HeLa, HCT 116 and U2OS	The IC_{50} values obtained were 24.79, 24.73 and 36.6 μg/mL for HeLa, HCT 116 and U2OS cell lines, respectively	[55]
	Bulb	MeOH	Quercetin and quercetin 4′-O-β-glucoside	B16	Quercetin and quercetin 4′-O-β-glucoside compounds showed inhibition in B16 cells with IC_{50} values of 26.5 and 131 μM, respectively	[56]
	Flower	MeOH	Polyphenols	K562, THP-1 and U937	The results revealed IC_{50} value less than 40 μg/mL for U937 cells and 60 μg/mL for THP-1 and K562	[57]
Beta vulgaris L. subsp. *vulgaris* var. *conditiva* Alef.	Root	EtOH	-	AGS	The highest concentration of extract (0.05%) induced significantly greater early apoptosis in relation to the other concentrations. At the same time, it activated the lowest level of late apoptosis and necrosis in AGS cells	[58]
Brassica oleracea L.	Sprout	Hx	Sulforaphane	AGS and MKN45	Significant dose-dependent and anti-proliferative effects were observed on AGS and MKN45 cells, with an IC_{50} value of about 112 and 125 μg/mL, respectively	[59]
	Leaf	HCl MeOH	-	HeLa and Hep G2	The IC_{50} values of the extract were 23.38 and 28.66 mg/mL for HeLa and Hep G2, respectively	[60]
	-	-	Sulforaphane, iberin and iberverin	A549	The IC_{50} values were 3.53, 4.93 and 7.07 μg/mL for sulforaphane, iberin and iberverin, respectively	[61]
Bryonia cretica L.	Root	EtOH	Cucurbitacin B and E	U937	The cucurbitacin B and E showed great effects with IC_{50} values of 9.2 and 16 nM	[62]
	Root	Aq	-	BL41	The IC_{50} of extract was estimated to be approximately 15.63 μg/mL	[63]
Calendula arvensis L.	Inflorescence	Aq and MeOH	-	AML	The extracts exhibited activity against AML (IC_{50}: 31 mg/mL)	[64]
Cannabis sativa L.	-	-	Cannabidiol (1), tetrahydrocannabinol (2) and cannabinol (3) para-quinones	Raji, Jurkat E6-1, SNB-19, MCF7, DU 145, NCI-H-226 and HT-29	The three compounds displayed antiproliferative activity in all cell lines	[65]
	Aerial part	Aq, Hx, DCM, DCM:MeOH and MeOH	-	Caco-2, HCT-15, HT-29, LS513	Aq and DCM:MeOH extracts moderately inhibited the growth in HCT-15 and LS513 cells (IC_{50}: 20–100 μg/mL). Aq and DCM extracts potently inhibited HT-29 cell growth (IC50: 7.52–10.06 μg/mL). Hx and DCM extracts slightly stimulated growth in Caco-2 cells (IC50: 100 μg/mL)	[66]
Clematis flammula L.	Aerial part	-	-	HCT 116	The extract showed apoptosis in HCT 116 cell lines	[67]
Crocus sativus L.	Leaf	PET	Crocetin (β-D-glucosyl) ester	MCF7	The antiproliferative activity of the compound against MCF7 cell line has showed inhibitory effect in a dose-dependent way with IC_{50} value of 628.36 μg/mL	[68]

Table 2. *Cont.*

Taxon	Plant Part Used	Extract	Chemical Compound	Cell Line	Cytotoxic Activity (Key Results)	Reference
	Stigma	-	-	HeLa, A-204 and Hep G2	All tested cell lines showed a good response to the effect of the saffron extract (50–400 µg/mL), but the A-204 cells showed a higher sensitivity to the inhibitory effect	[69]
	Stigma	MeOH	-	AGS, MDA-MB-468 and U-87	The IC_{50} are between 0.8 and 4.5 mg/mL	[70]
	Stigma	-	Crocetin	A549, B16-F10, MCF7 and SK-OV-3	The IC_{50} were 79.79, 55.39, 270.13 and 559.0 µg/mL for MCF7, A549, B16-F10 and SK-OV-3, respectively	[71]
	Stigma	-	Phenols	Caco-2	A significant 32% decrease in Caco-2 cell viability was observed, but only at a concentration of 50 µL/mL	[72]
	-	-	Crocin and safranal	K-562	Drug cytotoxicity experiments showed a dose-dependent cell growth inhibition after exposure of cells to crocin and safranal withIC_{50} values of 160.00 µM and 241.00 µM, respectively	[73]
Daucus carota L. subsp. *sativus* (Hoffm.) Arcang.	Root	MeOH	6-Methoxymellein	MCF7 and MDA-MB-231	The compound induced suppression of proliferation at >0.8 mM (MDA-MB-231) and >0.5 nM (MCF7)	[74]
Ecballium elaterium (L.) A.Rich	Fruit	MeOH	Cucurbitacin D, E and I	AGS	The cytotoxic effects on AGS gastric cancer cell line showed that cucurbitacin E has greater cytotoxicity in comparison with cucurbitacins D and I. The IC_{50} values were 0.3, 0.1, and 0.5 µg/mL for cucurbitacins D, E, and I, respectively.	[75]
	Seed	Hx	-	HT-29 and HT-1080	The extract showed a potent antiproliferative HT-29 AND HT-1080 cell lines and the IC_{50} values were 4.86 µg/mL and 4.16 µg/mL, respectively	[76]
	-	-	Cucurbitacin D	NSCLC-N6	The treatment with cucurbitacin D inhibited NSCLC-N6 proliferation (IC_{50}: 2.5 µg/mL)	[77]
Geranium robertianum L.	-	Aq and EtOH	-	Hep-2p	The extracts showed cytotoxic effect on Hep-2p cancer cells (6.1–25.39% in the EtOH extracts; 0.9–32.5% in the Aq extracts)	[78]
Helianthus tuberosus L.	Flower	Hx	-	HT-29 and HCT 116	Feradiol exhibited a significant growth inhibitory effect against HT-29 and HCT 116 cell lines (IC_{50} values of 3.93 and 6.02 µg/mL, respectively)	[79]
	Leaf	EtOAc	4,15-iso-Atripliciolide tiglate	A549, HeLa and MCF7	The compound exhibited significant activity against MCF7, A549 and HeLa (1.97, 7.79, 9.87 µg/mL, respectively)	[80]
Helleborus foetidus L.	Whole plant	MeOH	Bufadienolide glucosides	A549 and HL-60	The isolated compounds were cytotoxic to A549 and HL-60 cells, with the IC_{50} values ranging from 0.019 to 3.0 µM	[81]
Malva sylvestris L.	Leaf and flower	MeOH	Phenols	A-375 and B16	This extract showed a cytotoxic effect for B16 and A-375 cells, an antiproliferative activity of 97% and 85% with respect to the control	[82]
Petroselinum crispum (Mill.) Hill	Leaf and stem	Hx	Phenols	MCF7	The extract tested at 500 µg/mL showed a percentage inhibition of 48.4%, 25.5% and 49.9% on MCF7, MDA-MB-231 and HT-29 cells, respectively	[83]
Plantago lanceolata L.	Aerial part	MeOH	Phenols	HeLa, HT-29 and MCF7	The inhibition of cell growth exerted a stronger effect with IC_{50}: 172.3, 142.8, 405.5 and 551.7 µg/mL for HeLa, MCF7, HT-29 and MRC-5 cell lines, respectively	[84]
	Leaf	MeOH	Flavonoids	MCF7 and UACC-62	The extracts showed good values for IC_{50} (47.16 and 50.58 µg/mL for MCF7 and UACC-62, respectively)	[85]

Table 2. *Cont.*

Taxon	Plant Part Used	Extract	Chemical Compound	Cell Line	Cytotoxic Activity (Key Results)	Reference
Plantago major L.	Leaf	MeOH	Flavonoids	MCF7 and UACC-62	The extracts showed good values of IC_{50} (46.5 μg/mL for MCF7 and UACC-62)	[85]
	Seed	MeOH	Triterpene acids	SiHa and Hep G2	The extract exhibited cytotoxic activity for SiHa and Hep-G2 (IC_{50}: 174.42 and 246.38 μg/mL, respectively)	[86]
Potentilla reptans L.	Aerial part and rhizome	Aq	-	4T1	IC_{50} values were 280.51 μg/mL for rhizome extract and 310.79 μg/mL for aerial parts extract	[87]
	Aerial part	Aq	-	A549 and MCF7	Extract exhibited cytotoxic activity for A549 and MCF7 cells (IC_{50} < 130 μg/mL)	[88]
Prunella vulgaris L.	-	Aq	Polysaccharide–zinc complex	Hep G2	The polysaccharide–zinc complex inhibits the proliferation (98.4% inhibition rate at 500 μg/mL) of Hep G2 cells	[89]
Prunus dulcis (Mill.) Weeb.	Seed	Ace	Gallic acid and pyrogallol	MCF7 and MDA-MB-468	For MCF7, both compounds showed cytocidal effect at 10 μg/mL, whereas for MDA-MB-468, both compounds showed cytocidal effect at >20 μg/mL	[90]
Silybum marianum (L.) Gaertn.	-	-	Silymarin	HCT 116 and SW480	A HCT 116 cells treated with 50, 100, and 200 μM of silymarin reduced the cell growth by 11%, 22% and 48%, respectively. A SW480 cells treated with 50, 100, and 200 μM of silymarin reduced the cell growth by 13%, 28% and 47%	[91]
	-	-	Silybin	Jurkat E6-1	Silybin increased the reduction in Jurkat E6-1 cells in the concentration range of 50–200 μM	[92]
Thymus vulgaris L.	Aerial part	Hx	-	U2OS and PANC-1	The essential oil causes a very strong inhibition (60%) of cell viability in PANC-1 cells, compared to 40% of reduction observed in U2OS cells at 10 μg/mL	[93]
	Leaf	EtOH	-	T47D	The extract inhibited 75% of T47D cells at 200 μg/mL	[94]
	Leaf	$CHCl_3$	Polyphenol complex	SH-SY5Y and SK-N-BE(2)-C	The extract showed strong levels of cytotoxicity towards SH-SY5Y and SK-N-BE(2)-C cell lines at the highest tested dose level (125.0 μg/mL)	[95]
Verbena officinalis L.	Aerial part	Aq	Diacetyl-phenylethanoids	DHD/K12/PROb and HCT 116	Four diacetyl-phenylethanoid compounds exhibited extremely high antiproliferative activity against HCT 116 and DHD/K12/PROb. The IC_{50} values were similar to vinblastine sulfate (1.28 μg/mL)	[96]

Extract abbreviations: Ace (acetone); Aq (aqueous); $CHCl_3$ (chloroform); DCM (dichloromethane); EtOAc (ethyl acetate); EtOH (ethanol); HCl MeOH (HCl acidified methanol); MeOH (methanol); Hx (hexane); PET (petroleum ether). **Cell line abbreviations:** 4T1 (mouse breast cancer cells); A-204 (human rhabdomyosarcoma cells); A-375 (human melanoma cells); A549 (human lung cancer cells); AGS (human stomach cancer cells); AML (human acute myeloid leukemia cells); B16 (mouse melanoma cells); B16-F10 (mouse melanoma cells); BL41 (human Burkitt's lymphoma cells); Caco-2 (human colon cancer cells); DHD/K12/PROb (rat colon cancer cells); DU 145 (human prostate cancer cells); HCT 116 (human colon cancer cells); HCT-15 (human colon cancer cells); HeLa (human cervical cancer cells); Hep-2p (human epidermoid laryngeal cancer cells); Hep G2 (human hepatocellular cancer cells); HL-60 (human leukemia cell); HT-1080 (human fibrosarcoma cells); HT-29 (human colorectal cancer cells); Jurkat E6-1 (human lymphoblast cells); K562 (human leukemic cells); LS513 (human colon cancer cells); MCF7 (human breast cancer cells); MDA-MB-468 (human breast cancer cells); MDA-MBA-231 (human breast cancer cells); MKN45 (human gastric cancer cells); NCI-H-226 (human lung cancer cells); NCI-H460 (human non-small cell lung cancer cells); NSCLC-N6 (human non-small cell lung cancer cells); PANC-1 (human pancreatic cancer cells); Raji (human lymphoblast cells); RD (human rabdomyosarcoma cells); SH-SY5Y (human neuroblastoma cells); SiHa (human cervical cancer cells); SK-N-BE(2)-C (human bone marrow neuroblastoma cells); SK-OV-3 (human ovarian cancer cells); SNB-19 (human glioblastoma cells); SW480 (human colon cancer cells); T47D (human breast cancer cells); THP-1 (human leukemic cells); U2OS (human osteosarcoma cells); U-87 (human glioblastoma cells); U937 (human leukemia cells); UACC-62 (human melanoma cells).

3. Materials and Methods

3.1. Studied Area

The Catalan linguistic area constitutes a well-studied area from the following several perspectives: geographic [97], physiographic [98], floristic [99,100], vegetation [101], linguistic and cultural approach [102]. This territory, located in the eastern part of the Iberian Peninsula, also includes a northern Pyrenean portion, the Balearic Islands, and the city of L'Alguer on the island of Sardinia. Politically, this territory belongs to the following four states: Andorra (all the territory), France (Northern Catalonia or Eastern Pyrenees department), Italy (L'Alguer, Sardinia), and Spain (Balearic Islands, Carxe—a small area in Murcia, Catalonia, a portion of eastern Aragon, and Valencia) (Figure 2). It is home to around 14,000,000 people [103–107] and extends across 70,000 km^2 [100].

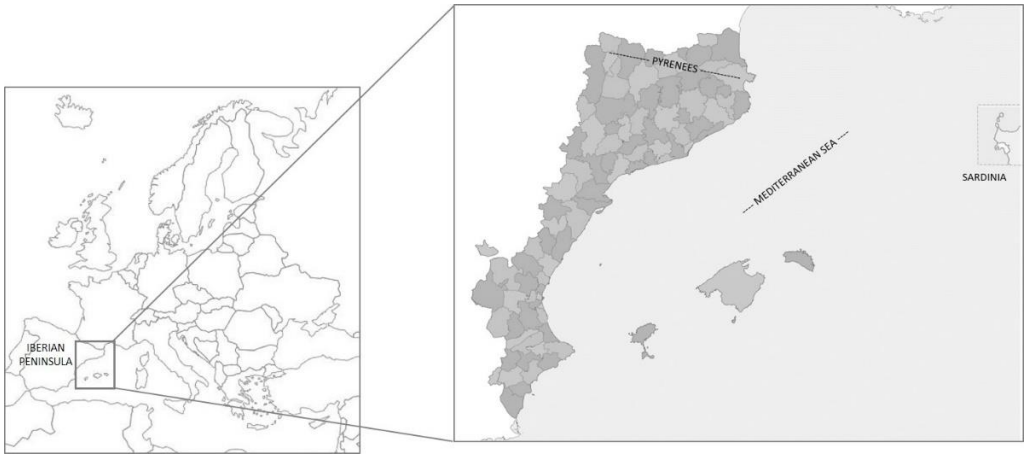

Figure 2. Map of Catalan linguistic area within Europe.

The orographic profile is quite diverse, from the Mediterranean Sea level to 3143 m a.s.l. at the summit of Pica d'Estats (Pyrenees). The landscape of the area of study is structured in several belts with distinct floristic and vegetation traits [99,100], harboring approximately 4300 autochthonous and 1200 allochthonous plant taxa, including species and subspecies [108].

3.2. Databasing and Data Selection

The information was collected through semi-structured ethnobotanical interviews [109], following the ethical principles of the International Society of Ethnobiology [110], and included in an open-access webpage (https://etnobotanica.iec.cat), which contains the ethnobotanical data for the Catalan linguistic area [111]. Herbarium vouchers were prepared for each species and are deposited in the herbarium BCN (Centre de Documentació de Biodiversitat Vegetal, Universitat de Barcelona). All the information available concerning plants used to treat, palliate or prevent cancer was retrieved from the open access webpage mentioned before. Data obtained from informants were compiled from interviews performed from 1990 to the present.

Bolòs et al.'s [100] was followed for taxonomic nomenclature, which is a specifically flora focused on the studied area. Plants of the World Online (https://powo.science.kew.org) was also consulted when exotic plants were involved. For family attribution, we followed the criteria stablished by the APG IV, the last Angiosperm Phylogeny Group's arrangement to date [112].

3.3. Pharmacological Activity Review

In order to confidently assess how many of the species cited in our surveys (i.e., the Catalan linguistic area) had been previously studied in depth, a review of pharmacological activities was carried out. Monographs of the official sources, such as the European

Medicines Agency (EMA) [32], the European Scientific Cooperative on Phytotherapy (ESCOP) [47], the encyclopedic bibliography on phytotherapy as Duke's CRC "*Handbook of Medicinal Herbs*" [33] and Fitoterapia.net webpage [34], were consulted.

In addition, an original publication search was carried out using four major online databases for scientific bibliographic resources, namely PubMed, ScienceDirect, Scopus and Web of Science, using the following set of keywords: "scientific name" AND "cancer" AND "chemical compounds". The aim of this search was mainly to review the existence of cytotoxic activity tests in cancer cell lines involving the plant species of interest.

4. Conclusions

Ethnobotanical research, when integrated into new fields of study, such as molecular phylogenetics, phytochemistry and other "omic" disciplines, can become a powerful tool to experimentally validate traditional plant knowledge, as well as to predict promising new sources of plant-based drugs. This study represents a step forward in our understanding of folk medicine as a resource to obtain relevant information to treat symptoms related to cancer. We are, nonetheless, aware that there is still a long way to go to before this information can be used in oncological procedures. Plants with an ethnobotanical tradition deserve to be studied more thoroughly, as they provide potential candidate scenarios to fight against cancer and its associated side effects. It is, of course, important to continue to stay in alliance with conventional medicine, which already includes plant-based products. Based on this, ethnobotanical research should become a standard tool in pharmacological and medicinal research, as it could help to guide pathways for drug discovery, and play a significant factor when applying new solutions to the many rising challenges when fighting against diseases such as cancer.

Author Contributions: A.G. and T.G. designed the research. A.G., M.P., J.V. and T.G. participated in ethnobotanical prospection and databasing. A.G., J.V. and T.G. carried out the botanical identification of the cited plants in the manuscript. A.G. wrote a first draft of the manuscript, which has been discussed, edited and corrected by the other authors. J.P. carried out a critical revision of the manuscript and an extensive English language revision. All the authors approved the final version. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: Not applicable.

Informed Consent Statement: The studies involving human participants (in the present case not as patients, but as informants) were reviewed and approved. The information has been collected through semi-structured ethnobotanical interviews following the ethical principles of the International Society of Ethnobiology. The participants provided their informed consent to participate in this study.

Data Availability Statement: The dataset analysed for this study are available in the manuscript, further inquiries can be directed to the corresponding authors.

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References

1. WHO (World Health Organization). Cancer. Available online: https://www.who.int/news-room/fact-sheets/detail/cancer (accessed on 22 March 2022).
2. Ferlay, J.; Colombet, M.; Soerjomataram, I.; Parkin, D.M.; Piñeros, M.; Znaor, A.; Bray, F. Cancer statistics for the year 2020: An overview. *Int. J. Cancer* **2021**, *149*, 778–789. [CrossRef] [PubMed]
3. The International Agency for Research on Cancer. Available online: https://www.iarc.fr/ (accessed on 22 March 2022).
4. Gordaliza, M. Natural products as leads to anticancer drugs. *Clin. Transl. Oncol.* **2007**, *9*, 767–776. [CrossRef] [PubMed]
5. Cragg, G.M.; Boyd, M.R.; Cardellina, J.H.; Grever, M.R.; Schepartz, S.A.; Snader, K.M.; Suffness, M. Role of plants in the National Cancer Institute drug discovery and development program. In *Human Medicinal Agents from Plants. ACS Symposium Series 534*; Kinghorn, D.A., Balandrin, M.F., Eds.; American Chemical Society: Washington, DC, USA, 1993; pp. 80–95.
6. MPNS Version 9. Medicinal Plant Names Services, the Royal Botanic Gardens, Kew. Available online: http://www.kew.org/mpns (accessed on 22 March 2022).
7. Park, E.J.; Pezzuto, J.M. Botanicals in cancer chemoprevention. *Cancer Metastasis Rev.* **2002**, *21*, 231–255. [CrossRef] [PubMed]
8. Gerson-Cwillich, R.; Serrano-Olvera, A.; Villalobos-Prieto, A. Complementary and alternative medicine (CAM) in Mexican patients with cancer. *Clin. Transl. Oncol.* **2006**, *8*, 200–207. [CrossRef]
9. Tascilar, M.; de Jong, F.A.; Verweij, J.; Mathijssen, R.H. Complementary and alternative medicine during cancer treatment: Beyond innocence. *Oncologist* **2006**, *11*, 732–741. [CrossRef]
10. European Parliament. Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use. *Off. J. Eur. Union* **2004**, *L136*, 85–90.
11. Heinrich, M.; Jäger, A.K. *Ethnopharmacology*; John Wiley & Sons: Chichester, UK, 2015.
12. Howes, M.J.R.; Quave, C.L.; Collemare, J.; Tatsis, E.C.; Twilley, D.; Lulekal, E.; Farlow, A.; Li, L.; Cazar, M.E.; Leaman, D.J.; et al. Molecules from nature: Reconciling biodiversity conservation and global healthcare imperatives for sustainable use of medicinal plants and fungi. *Plants People Planet* **2020**, *2*, 463–481. [CrossRef]
13. Garnatje, T.; Peñuelas, J.; Vallès, J. Ethnobotany, phylogeny, and 'omics' for human health and food security. *Trends Plant Sci.* **2017**, *22*, 187–191. [CrossRef]
14. Garnatje, T.; Peñuelas, J.; Vallès, J. Reaffirming 'Ethnobotanical Convergence'. *Trends Plant Sci.* **2017**, *22*, 640. [CrossRef]
15. Saslis-Lagoudakis, C.H.; Klitgaard, B.B.; Forest, F.; Francis, L.; Savolainen, V.; Williamson, E.M.; Hawkins, J.A. The use of phylogeny to interpret cross-cultural patterns in plant use and guide medicinal plant discovery: An example from *Pterocarpus* (Leguminosae). *PLoS ONE* **2011**, *6*, e22275. [CrossRef]
16. Saslis-Lagoudakis, C.H.; Savolainen, V.; Williamson, E.M.; Forest, F.; Wagstaff, S.J.; Baral, S.R.; Watson, M.F.; Pendry, C.A.; Hawkins, J.A. Phylogenies reveal predictive power of traditional medicine in bioprospecting. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 15835–15840. [CrossRef] [PubMed]
17. Pellicer, J.; Saslis-Lagoudakis, C.H.; Carrió, E.; Ernst, M.; Garnatje, T.; Grace, O.M.; Gras, A.; Mumbrú, M.; Vallès, J.; Vitales, D.; et al. A phylogenetic road map to antimalarial *Artemisia* species. *J. Ethnopharmacol.* **2018**, *225*, 1–9. [CrossRef]
18. Atanasov, A.G.; Waltenberger, B.; Pferschy-Wenzig, E.M.; Linder, T.; Wawrosch, C.; Uhrin, P.; Temml, V.; Wang, L.; Schwaiger, S.; Heiss, E.H.; et al. Discovery and resupply of pharmacologically active plant-derived natural products: A review. *Biotechnol. Adv.* **2015**, *33*, 1582–1614. [CrossRef] [PubMed]
19. Shoskes, D.A. Phytotherapy in chronic prostatitis. *Urology* **2002**, *60*, 35–37. [CrossRef]
20. Tag, H.; Kalita, P.; Dwivedi, P.; Das, A.K.; Namsa, N.D. Herbal medicines used in the treatment of diabetes mellitus in Arunachal Himalaya, Northeast, India. *J. Ethnopharmacol.* **2012**, *141*, 786–795. [CrossRef] [PubMed]
21. The Lancet. Pharmaceuticals from plants: Great potential, few funds. *Lancet* **1994**, *343*, 1513–1515. [CrossRef]
22. Fletcher, M.S.; Hamilton, R.; Dressler, W.; Palmer, L. Indigenous knowledge and the shackles of wilderness. *Proc. Natl. Acad. Sci. USA* **2021**, *118*, e2022218118. [CrossRef]
23. Abubakar, I.B.; Ukwuani-Kwaja, A.N.; Garba, A.D.; Singh, D.; Malami, I.; Salihu, T.S.; Muhammad, A.; Yahaya, Y.; Sule, S.M.; Ahmed, S.J. Ethnobotanical study of medicinal plants used for cancer treatment in Kebbi state, North-west Nigeria. *Acta Ecol. Sin.* **2020**, *40*, 306–314. [CrossRef]
24. Ahmad, R.; Ahmad, N.; Naqvi, A.A.; Shehzad, A.; Al-Ghamdi, M.S. Role of traditional Islamic and Arabic plants in cancer therapy. *J. Tradit. Complement. Med.* **2017**, *7*, 195–204. [CrossRef]
25. Alonso-Castro, A.J.; Villarreal, M.L.; Salazar-Olivo, L.A.; Gomez-Sanchez, M.; Dominguez, F.; Garcia-Carranca, A. Mexican medicinal plants used for cancer treatment: Pharmacological, phytochemical and ethnobotanical studies. *J. Ethnopharmacol.* **2011**, *133*, 945–972. [CrossRef]
26. Bhatia, A.; Arora, S.; Singh, B.; Kaur, G.; Nagpal, A. Anticancer potential of Himalayan plants. *Phytochem. Rev.* **2011**, *10*, 309–323. [CrossRef]
27. Jacobo-Herrera, N.J.; Jacobo-Herrera, F.E.; Zentella-Dehesa, A.; Andrade-Cetto, A.; Heinrich, M.; Pérez-Plasencia, C. Medicinal plants used in Mexican traditional medicine for the treatment of colorectal cancer. *J. Ethnopharmacol.* **2016**, *179*, 391–402. [CrossRef] [PubMed]
28. Koduru, S.; Grierson, D.S.; Afolayan, A.J. Ethnobotanical information of medicinal plants used for treatment of cancer in the Eastern Cape Province, South Africa. *Curr. Sci.* **2007**, 906–908.

29. Soladoye, M.O.; Amusa, N.A.; Raji-Esan, S.O.; Chukwuma, E.C.; Taiwo, A.A. Ethnobotanical survey of anti-cancer plants in Ogun State, Nigeria. *Ann. Biol. Res.* **2010**, *1*, 261–273.
30. Rigat, M.; Gras, A.; Vallès, J.; Garnatje, T. Estudis etnobotànics a la comarca del Ripollès (Pirineu, Catalunya, península Ibèrica). *Collect. Bot.* **2017**, *36*, e003. [CrossRef]
31. Aumeeruddy, M.Z.; Mahomoodally, M.F. Global documentation of traditionally used medicinal plants in cancer management: A systematic review. *S. Afr. J. Bot.* **2021**, *138*, 424–494. [CrossRef]
32. EMA (European Medicines Agency). Available online: https://www.ema.europa.eu/en (accessed on 18 March 2022).
33. Duke, J.A. *CRC Handbook of Medicinal Herbs*, 2nd ed.; American Botanical Council: Austin, TX, USA, 2003.
34. Fitoterapia.net. Available online: https://www.fitoterapia.net/index.html (accessed on 18 March 2022).
35. Vigo, J. *L'alta Muntanya Catalana, Flora i Vegetació*, 2nd ed.; Centre Excursionista de Catalunya/Institut d'Estudis Catalans: Barcelona, Spain, 2008.
36. Brower, V. Back to nature: Extinction of medicinal plants threatens drug discovery. *J. Natl. Cancer Inst.* **2008**, *100*, 838–839. [CrossRef]
37. Hao, D.C.; He, C.N.; Shen, J.; Xiao, P.G. Anticancer chemodiversity of Ranunculaceae medicinal plants: Molecular Mechanisms and Functions. *Curr. Genom.* **2017**, *18*, 39–59. [CrossRef]
38. Hao, D.C.; Xiao, P.G.; Liu, M.; Peng, Y.; He, C.N. Pharmaphylogeny vs. pharmacophylogenomics: Molecular phylogeny, evolution and drug discovery. *Acta Pharm. Sin.* **2014**, *49*, 1387–1394.
39. Sagar, S.M. Future directions for research on *Silybum marianum* for cancer patients. *Integr. Cancer Ther.* **2007**, *6*, 166–173. [CrossRef]
40. Bosch-Barrera, J.; Sais, E.; Cañete, M.; Marruecos, J.; Cuyàs, E.; Izquierdo, A.; Porta, R.; Haro, M.; Brunet, J.; Pedraza, S.; et al. Response of brain metastasis from lung cancer patients to an oral nutraceutical product containing silibinin. *Oncotarget* **2016**, *7*, 32006–32014. [CrossRef] [PubMed]
41. Soundararajan, P.; Won, S.Y.; Kim, J.S. Insight on Rosaceae family with genome sequencing and functional genomics perspective. *BioMed Res. Int.* **2019**, *2019*, 7519687. [CrossRef] [PubMed]
42. George, S.M.; Park, Y.; Leitzmann, M.F.; Freedman, N.D.; Dowling, E.C.; Reedy, J.; Schatzkin, A.; Hollenbeck, A.; Subar, A.F. Fruit and vegetable intake and risk of cancer: A prospective cohort study. *Am. J. Clin. Nutr.* **2008**, *89*, 347–353. [CrossRef] [PubMed]
43. Key, T.J. Fruit and vegetables and cancer risk. *Br. J. Cancer* **2011**, *104*, 6–11. [CrossRef]
44. Vallès, J.; D'Ambrosio, U.; Gras, A.; Parada, M.; Rigat, M.; Serrasolses, G.; Garnatje, T. Medicinal and food plants in ethnobotany and ethnopharmacology: Folk functional foods in Catalonia (Iberian Peninsula). In *Recent Advances in Pharmaceutical Sciences VII*; Muñoz-Torrero, D., Riu, M., Feliu, C., Eds.; Research Signpost: Trivandra, India, 2017; pp. 1–17.
45. Poppel, G.; Verhoeven, D.T.; Verhagen, H.; Goldbohm, R.A. *Brassica* vegetables and cancer prevention. *Adv. Exp. Med. Biol.* **1999**, *472*, 159–168. [CrossRef] [PubMed]
46. Nurgali, K.; Jagoe, R.T.; Abalo, R. Adverse effects of cancer chemotherapy: Anything new to improve tolerance and reduce sequelae? *Front. Pharmacol.* **2018**, *9*, 245. [CrossRef]
47. ESCOP (European Scientific Cooperative on Phytotherapy). Available online: https://escop.com/online-consultation (accessed on 18 March 2022).
48. Salganik, R.I. The benefits and hazards of antioxidants: Controlling apoptosis and other protective mechanisms in cancer patients and the human population. *J. Am. Coll. Nutr.* **2001**, *20* (Suppl. 5), 464S–472S. [CrossRef]
49. Kooti, W.; Daraei, N. A review of the antioxidant activity of celery (*Apium graveolens* L.). *Evid.-Based Complement. Altern. Med.* **2017**, *22*, 1029–1034. [CrossRef]
50. Dall'Acqua, S.; Cervellati, R.; Loi, M.C.; Innocenti, G. Evaluation of in vitro antioxidant properties of some traditional Sardinian medicinal plants: Investigation of the high antioxidant capacity of *Rubus ulmifolius*. *Food Chem.* **2008**, *106*, 745–749. [CrossRef]
51. Dawidowicz, A.L.; Wianowska, D.; Baraniak, B. The antioxidant properties of alcoholic extracts from *Sambucus nigra* L. (antioxidant properties of extracts). *LWT-Food Sci. Technol.* **2006**, *39*, 308–315. [CrossRef]
52. Wajs-Bonikowska, A.; Sienkiewicz, M.; Stobiecka, A.; Maciąg, A.; Szoka, Ł.; Karna, E. Chemical composition and biological activity of *Abies alba* and *A. koreana* seed and cone essential oils and characterization of their seed hydrolates. *Chem. Biodivers.* **2015**, *12*, 407–418. [CrossRef] [PubMed]
53. Pereira, J.M.; Peixoto, V.; Teixeira, A.; Sousa, D.; Barros, L.; Ferreira, I.C.; Vasconcelos, M.H. *Achillea millefolium* L. hydroethanolic extract inhibits growth of human tumor cell lines by interfering with cell cycle and inducing apoptosis. *Food Chem. Tox.* **2018**, *118*, 635–644. [CrossRef] [PubMed]
54. Ad'hiah, A.H.; Al-Bederi, O.N.; Al-Sammarrae, K.W. Cytotoxic effects of *Agrimonia eupatoria* L. against cancer cell lines in vitro. *J. Assoc. Arab Univ. Basic Appl. Sci.* **2013**, *14*, 87–92. [CrossRef]
55. Fredotović, Ž.; Soldo, B.; Šprung, M.; Marijanović, Z.; Jerković, I.; Puizina, J. Comparison of organosulfur and amino acid composition between triploid onion *Allium cornutum* Clementi ex Visiani, 1842, and common onion *Allium cepa* L., and evidences for antiproliferative activity of their extracts. *Plants* **2020**, *9*, 98. [CrossRef] [PubMed]
56. Arung, E.T.; Furuta, S.; Ishikawa, H.; Kusuma, I.W.; Shimizu, K.; Kondo, R. Anti-melanogenesis properties of quercetin-and its derivative-rich extract from *Allium cepa*. *Food Chem.* **2011**, *124*, 1024–1028. [CrossRef]
57. Han, M.H.; Lee, W.S.; Jung, J.H.; Jeong, J.H.; Park, C.; Kim, H.J.; Ryu, C.H.; Shin, S.C.; Hong, S.C.; Choi, Y.H. Polyphenols isolated from *Allium cepa* L. induces apoptosis by suppressing IAP-1 through inhibiting PI3K/Akt signaling pathways in human leukemic cells. *Food Chem. Toxicol.* **2013**, *62*, 382–389. [CrossRef]

58. Kazimierczak, R.; Hallmann, E.; Lipowski, J.; Drela, N.; Kowalik, A.; Püssa, T.; Matt, D.; Luik, A.; Gozdowski, D.; Rembiałkowska, E. Beetroot (*Beta vulgaris* L.) and naturally fermented beetroot juices from organic and conventional production: Metabolomics, antioxidant levels and anticancer activity. *J. Sci. Food Agric.* **2014**, *94*, 2618–2629. [CrossRef]
59. Kiani, S.; Akhavan-Niaki, H.; Fattahi, S.; Kavoosian, S.; Jelodar, N.B.; Bagheri, N.; Zarrini, H.N. Purified sulforaphane from broccoli (*Brassica oleracea* var. *italica*) leads to alterations of CDX1 and CDX2 expression and changes in miR-9 and miR-326 levels in human gastric cancer cells. *Gene* **2018**, *678*, 115–123. [CrossRef]
60. Hafidh, R.R.; Abdulamir, A.S.; Bakar, F.A.; Jalilian, F.A.; Jahanshiri, F.; Abas, F.; Sekawi, Z. Novel anticancer activity and anticancer mechanisms of *Brassica oleracea* L. var. capitata f. rubra. *Eur. J. Integr. Med.* **2013**, *5*, 450–464. [CrossRef]
61. Wang, N.; Wang, W.; Liu, C.; Jin, J.; Shao, B.; Shen, L. Inhibition of growth and induction of apoptosis in A549 cells by compounds from oxheart cabbage extract. *J. Sci. Food Agric.* **2016**, *96*, 3813–3820. [CrossRef]
62. Matsuda, H.; Nakashima, S.; Abdel-Halim, O.B.; Morikawa, T.; Yoshikawa, M. Cucurbitane-type triterpenes with anti-proliferative effects on U937 cells from an Egyptian natural medicine, *Bryonia cretica*: Structures of new triterpene glycosides, bryoniaosides A and B. *Chem. Pharm. Bull.* **2010**, *58*, 747–751. [CrossRef] [PubMed]
63. Benarba, B.; Meddah, B.; Aoues, A. *Bryonia dioica* aqueous extract induces apoptosis through mitochondrial intrinsic pathway in BL41 Burkitt's lymphoma cells. *J. Ethnopharmacol.* **2012**, *141*, 510–516. [CrossRef] [PubMed]
64. Abudunia, A.M.; Marmouzi, I.; Faouzi, M.E.A.; Ramli, Y.; Taoufik, J.; El Madani, N.; Essani, E.M.; Salama, A.; Khedid, K.; Ibrahimi, A. Anticandidal, antibacterial, cytotoxic and antioxidant activities of *Calendula arvensis* flowers. *J. Mycol. Med.* **2017**, *27*, 90–97. [CrossRef] [PubMed]
65. Kogan, N.M.; Rabinowitz, R.; Levi, P.; Gibson, D.; Sandor, P.; Schlesinger, M.; Mechoulam, R. Synthesis and antitumor activity of quinonoid derivatives of cannabinoids. *J. Med. Chem.* **2004**, *47*, 3800–3806. [CrossRef] [PubMed]
66. Mangoato, I.M.; Mahadevappa, C.P.; Matsabisa, M.G. *Cannabis sativa* L. Extracts can reverse drug resistance in colorectal carcinoma cells in vitro. *Synergy* **2019**, *9*, 100056. [CrossRef]
67. Guesmi, F.; Hmed, M.B.; Prasad, S.; Tyagi, A.K.; Landoulsi, A. In vivo pathogenesis of colon carcinoma and its suppression by hydrophilic fractions of *Clematis flammula* via activation of TRAIL death machinery (DRs) expression. *Biomed. Pharmacother.* **2019**, *109*, 2182–2191. [CrossRef]
68. Mir, M.A.; Ganai, S.A.; Mansoor, S.; Jan, S.; Mani, P.; Masoodi, K.Z.; Amin, H.; Rehman, M.U.; Ahmad, P. Isolation, purification and characterization of naturally derived Crocetin beta-d-glucosyl ester from *Crocus sativus* L. against breast cancer and its binding chemistry with ER-alpha/HDAC2. *Saudi J. Biol. Sci.* **2020**, *27*, 975–984. [CrossRef]
69. Abdullaev, F.I.; Riveron-Negrete, L.; Caballero-Ortega, H.; Hernández, J.M.; Perez-Lopez, I.; Pereda-Miranda, R.; Espinosa-Aguirre, J.J. Use of in vitro assays to assess the potential antigenotoxic and cytotoxic effects of saffron (*Crocus sativus* L.). *Toxicol. In Vitro* **2003**, *17*, 731–736. [CrossRef]
70. Behdani, M.A.; Hoshyar, R. Phytochemical properties of Iranian organic saffron stigma: Antioxidant, anticancer and apoptotic approaches. *Cell. Mol. Biol.* **2016**, *62*, 69–73. [CrossRef]
71. Chu, Y.; Gao, J.; Niu, J.; Huang, Y.F.; Chen, M.; Wang, M.Z.; Shang, Q.; Lu, W.Q.; Peng, L.H.; Jiang, Z.H. Synthesis, characterization and inhibitory effects of crocetin derivative compounds in cancer and inflammation. *Biomed. Pharmacother.* **2018**, *98*, 157–164. [CrossRef]
72. Tuberoso, C.I.; Rosa, A.; Montoro, P.; Fenu, M.A.; Pizza, C. Antioxidant activity, cytotoxic activity and metabolic profiling of juices obtained from saffron (*Crocus sativus* L.) floral by-products. *Food Chem.* **2016**, *199*, 18–27. [CrossRef]
73. Geromichalos, G.D.; Papadopoulos, T.; Sahpazidou, D.; Sinakos, Z. Safranal, a *Crocus sativus* L. constituent suppresses the growth of K-562 cells of chronic myelogenous leukemia. In silico and in vitro study. *Food Chem. Toxicol.* **2014**, *74*, 45–50. [CrossRef] [PubMed]
74. Liu, R.; Choi, H.S.; Kim, S.L.; Kim, J.H.; Yun, B.S.; Lee, D.S. 6-Methoxymellein isolated from carrot (*Daucus carota* L.) targets breast cancer stem cells by regulating NF-κB signaling. *Molecules* **2020**, *25*, 4374. [CrossRef] [PubMed]
75. Jafargholizadeh, N.; Zargar, S.J.; Yassa, N.; Tavakoli, S. Purification of cucurbitacins D, E, and I from *Ecballium elaterium* (L.) A. rich fruits and study of their cytotoxic effects on the AGS cell line. *Asian Pac. J. Cancer Prev.* **2016**, *17*, 4631. [CrossRef]
76. Touihri, I.; Kallech-Ziri, O.; Boulila, A.; Fatnassi, S.; Marrakchi, N.; Luis, J.; Hanchi, B. *Ecballium elaterium* (L.) A. Rich. seed oil: Chemical composition and antiproliferative effect on human colonic adenocarcinoma and fibrosarcoma cancer cell lines. *Arab. J. Chem.* **2019**, *12*, 2347–2355. [CrossRef]
77. Jacquot, C.; Rousseau, B.; Carbonnelle, D.; Chinou, I.; Malleter, M.; Tomasoni, C.; Roussakis, C. Cucurbitacin-D-induced CDK1 mRNA up-regulation causes proliferation arrest of a non-small cell lung carcinoma cell line (NSCLC-N6). *Anticancer Res.* **2014**, *34*, 4797–4806.
78. Paun, G.; Neagu, E.; Litescu, S.C.; Rotinberg, P.; Radu, G.L. Application ofmembrane processes for the concentration of *Symphytum officinale* and *Geranium robertianum* extracts to obtain compounds with high anti-oxidative activity. *J. Serb. Chem. Soc.* **2012**, *77*, 1191–1203. [CrossRef]
79. Jantaharn, P.; Mongkolthanaruk, W.; Senawong, T.; Jogloy, S.; McCloskey, S. Bioactive compounds from organic extracts of *Helianthus tuberosus* L. flowers. *Ind. Crops Prod.* **2018**, *119*, 57–63. [CrossRef]
80. Yuan, X.; Cheng, M.; Gao, M.; Zhuo, R.; Zhang, L.; Xiao, H. Cytotoxic constituents from the leaves of Jerusalem artichoke (*Helianthus tuberosus* L.) and their structure–activity relationships. *Phytochem. Lett.* **2013**, *6*, 21–25. [CrossRef]

81. Iguchi, T.; Yokosuka, A.; Kawahata, R.; Andou, M.; Mimaki, Y. Bufadienolides from the whole plants of *Helleborus foetidus* and their cytotoxicity. *Phytochemistry* **2020**, *172*, 112277. [CrossRef]
82. Alesiani, D.; Pichichero, E.; Canuti, L.; Cicconi, R.; Karou, D.; D'Arcangelo, G.; Canini, A. Identification of phenolic compounds from medicinal and melliferous plants and their cytotoxic activity in cancer cells. *Caryologia* **2007**, *60*, 90–95. [CrossRef]
83. Tang, E.L.H.; Rajarajeswaran, J.; Fung, S.; Kanthimathi, M.S. *Petroselinum crispum* has antioxidant properties, protects against DNA damage and inhibits proliferation and migration of cancer cells. *J. Sci. Food Agric.* **2015**, *95*, 2763–2771. [CrossRef] [PubMed]
84. Beara, I.N.; Lesjak, M.M.; Orčić, D.Z.; Simin, N.Đ.; Četojević-Simin, D.D.; Božin, B.N.; Mimica-Dukić, N.M. Comparative analysis of phenolic profile, antioxidant, anti-inflammatory and cytotoxic activity of two closely-related Plantain species: *Plantago altissima* L. and *Plantago lanceolata* L. *LWT-Food Sci. Technol.* **2012**, *47*, 64–70. [CrossRef]
85. Galvez, M.; Martın-Cordero, C.; Lopez-Lazaro, M.; Cortes, F.; Ayuso, M.J. Cytotoxic effect of *Plantago* spp. on cancer cell lines. *J. Ethnopharmacol.* **2003**, *88*, 125–130. [CrossRef]
86. Piyaviriyakul, S.; Siripong, P.; Vallisuta, O. HPTLC simultaneous quantification of triterpene acids for quality control of *Plantago major* L. and evaluation of their cytotoxic and antioxidant activities. *Ind. Crops Prod.* **2014**, *60*, 239–246. [CrossRef]
87. Radovanovic, A.M.; Cupara, S.M.; Popovic, S.L.; Tomovic, M.T.; Slavkovska, V.N.; Jankovic, S.M. Cytotoxic effect of *Potentilla reptans* L. rhizome and aerial part extracts. *Acta Pol. Pharm.* **2013**, *70*, 851–854.
88. Uysal, S.; Zengin, G.; Locatelli, M.; Bahadori, M.B.; Mocan, A.; Bellagamba, G.; De Luca, E.; Mollica, A.; Aktumsek, A. Cytotoxic and enzyme inhibitory potential of two *Potentilla* species (*P. speciosa* L. and *P. reptans* Willd.) and their chemical composition. *Front. Pharmacol.* **2017**, *8*, 290. [CrossRef]
89. Li, C.; Huang, Q.; Xiao, J.; Fu, X.; You, L.; Liu, R.H. Preparation of *Prunella vulgaris* polysaccharide-zinc complex and its antiproliferative activity in HepG2 cells. *Int. J. Biol. Macromol.* **2016**, *91*, 671–679. [CrossRef]
90. Dhingra, N.; Kar, A.; Sharma, R.; Bhasin, S. In-vitro antioxidative potential of different fractions from *Prunus dulcis* seeds: Vis a vis antiproliferative and antibacterial activities of active compounds. *S. Afr. J. Bot.* **2017**, *108*, 184–192. [CrossRef]
91. Eo, H.J.; Park, G.H.; Song, H.M.; Lee, J.W.; Kim, M.K.; Lee, M.H.; Koo, J.S.; Jeong, J.B. Silymarin induces cyclin D1 proteasomal degradation via its phosphorylation of threonine-286 in human colorectal cancer cells. *Int. Immunopharmacol.* **2015**, *24*, 1–6. [CrossRef]
92. Gharagozloo, M.; Khoshdel, Z.; Amirghofran, Z. The effect of an iron (III) chelator, silybin, on the proliferation and cell cycle of Jurkat cells: A comparison with desferrioxamine. *Eur. J. Pharmacol.* **2008**, *589*, 1–7. [CrossRef] [PubMed]
93. Catauro, M.; Bollino, F.; Tranquillo, E.; Sapio, L.; Illiano, M.; Caiafa, I.; Naviglio, S. Chemical analysis and anti-proliferative activity of Campania *Thymus vulgaris* essential oil. *J. Essent. Oil Res.* **2017**, *29*, 461–470. [CrossRef]
94. Heidari, Z.; Salehzadeh, A.; Sadat Shandiz, S.A.; Tajdoost, S. Anti-cancer and anti-oxidant properties of ethanolic leaf extract of *Thymus vulgaris* and its bio-functionalized silver nanoparticles. *3 Biotech* **2018**, *8*, 1–14. [CrossRef] [PubMed]
95. Pacifico, S.; Piccolella, S.; Papale, F.; Nocera, P.; Lettieri, A.; Catauro, M. A polyphenol complex from *Thymus vulgaris* L. plants cultivated in the Campania Region (Italy): New perspectives against neuroblastoma. *J. Funct. Foods* **2016**, *20*, 253–266. [CrossRef]
96. Encalada, M.A.; Rehecho, S.; Ansorena, D.; Astiasarán, I.; Cavero, R.Y.; Calvo, M.I. Antiproliferative effect of phenylethanoid glycosides from *Verbena officinalis* L. on colon cancer cell lines. *LWT-Food Sci. Technol.* **2015**, *63*, 1016–1022. [CrossRef]
97. Deffontaines, P. *Geografia dels Països Catalans*; Editorial Ariel: Barcelona, Spain, 1978.
98. Riba, O.; de Bolòs, O.; Panareda, J.M.; Nuet, J.; Gosàlbez, J. *Geografia física dels Països Catalans*; Ketres Editora: Barcelona, Spain, 1984.
99. De Bolòs, O.; Vigo, J. *Flora dels Països Catalans*; Editorial Barcino: Barcelona, Spain, 1984.
100. De Bolòs, O.; Vigo, J.; Masalles, R.M.; Ninot, J. *Flora Manual dels Països Catalans*, 3rd ed.; Editorial Pòrtic: Barcelona, Spain, 2005.
101. Folch, R. *La Vegetació dels Països Catalans*; Ketres Editora: Barcelona, Spain, 1984.
102. Badia, A.M. *Llengua i Cultura als Països Catalans*; Edicions 62: Barcelona, Spain, 1966.
103. Departament d'Estadística del Govern d'Andorra. Available online: https://www.estadistica.ad/ (accessed on 5 March 2022).
104. IBESTAT (Institut d'Estadística de les Illes Balears). Available online: https://ibestat.caib.es/ibestat/inici (accessed on 5 March 2022).
105. IDESCAT (Institut d'Estadística de Catalunya). Available online: https://www.idescat.cat/ (accessed on 5 March 2022).
106. ISTAT (Istituto Nazionale di Statistica). Available online: https://www.istat.it/ (accessed on 5 March 2022).
107. Portal Estadístic de la Generalitat Valenciana. Available online: https://pegv.gva.es/va/ (accessed on 5 March 2022).
108. Sáez, L.; (Universitat Autònoma de Barcelona, Bellaterra, Catalonia, Spain). Personal Communication, 2019.
109. Gras, A.; Serrasolses, G.; Vallès, J.; Garnatje, T. Traditional knowledge in semi-rural close to industrial areas: Ethnobotanical studies in western Gironès (Catalonia, Iberian Peninsula). *J. Ethnobiol. Ethnomed.* **2019**, *15*, 1–37. [CrossRef]
110. ISE (International Society of Ethnobiology). International Society of Ethnobiology Code of Ethics (with 2008 Additions). Available online: http://ethnobiology.net/code-of-ethics/ (accessed on 5 March 2022).
111. Garnatje, T.; Gras, A.; Parada, J.; Parada, M.; Vallès, J. La web 'Etnobotànica dels Països Catalans': Coneixement tradicional al servei de la societat. *Collect. Bot.* **2021**, *40*, e006. [CrossRef]
112. APG (Angiosperm Phylogeny Group). An update of the Angiosperm Phylogeny Group classification for the orders and families of flowering plants: APG IV. *Bot. J. Linn. Soc.* **2016**, *181*, 1–20. [CrossRef]