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Medicinal plants used in Mexican traditional medicine for the treatment of colorectal cancer

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ABSTRACT

Ethnopharmacological relevance: Cancer cases numbers are increasing worldwide positioning this disease as the second cause of mortality for both sexes. Medicinal plants have been used in the fight against cancer as the basis for drug discovery and nowadays more than 70% of anticancer drugs have a natural origin. Mexico is regarded for its cultural and biological diversity, which is reflected in the vast traditional knowledge of herbal remedies. In this review we examined herbal remedies employed in colorectal cancer treatment (CRC).

Aim of the study: The goal of this work was to gather scientific reports of plants used in Mexican traditional medicine for CRC treatment.

Materials and methods: We performed a search on scientific literature databases using as keywords: "colon cancer", "gastric cancer", "cytotoxicity", studies "*in vitro* and *in vivo*", in combination with "Mexican medicinal plants" or "Mexican herbal remedies". The selection criteria of cytotoxic activity for extracts or pure compounds was based on the National Cancer Institute of USA recommendations of effective dose 50 (ED_{50}) of ≤ 20 μg/mL and ≤ 4 μg/mL, respectively.

Results: In this review we report 25 botanic families and 39 species of plants used for the treatment of colon cancer in Mexico with evidence in studies *in vitro* and *in vivo*.

Conclusions: Medicinal plants are still a great source of novel chemical structures with antineoplastic potential as it is proven in this work. The selection criteria and activity was narrowed for methodological purposes, nevertheless, drug discovery of natural origin continues to be a highly attractive R&D strategy.

1. Introduction

1.1. Colorectal cancer

Cancer is a major public health problem around the world. The most common cancers are breast, prostate, lung, colorectal (CRC), cervix uteri and stomach (Ferlay et al., 2013). CRC is one of the highest incidence and mortality cancers worldwide. According to the last data published by Globocan in 2012, CRC and stomach cancers were placed the fourth and sixth, respectively for both sexes in Mexico (Ferlay et al., 2013); the standardized incidence rate by age in Mexico counts at 8651 cases per 100,000 inhabitants, and the mortality rate is of 4694. The CRC is a

Abbreviations: CAM, Complementary and Alternative Medicine; GI_{50}, growth inhibition 50%; ED_{50}, effective dose; IC_{50}, inhibitory concentration 50%; EtOH, ethanol extract; Hex, hexane extract; EtOAc, ethylacetate extract; MeOH, methanol extract; DCM, Dichloromethane; PE, petroleum ether; $CHCl_3$, chloroform extract; BuOH, buthanol extract; Aq, aquous extract; PTOX, podophyllotoxin; 6MPTOX, 6-methoxypodophyllotoxin; i.p., intra peritoneal

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heterogeneous disease, the majority of the cases are sporadic and there is a small percentage where hereditary factors are involved (Binefa et al., 2014; Brenner et al., 2014). Age is a primary risk factor, however lifestyle and a diet low in fibre and rich in carbohydrates and red meat, high consumption of alcohol and tobacco and obesity all together favours this type of cancer development (American Cancer Society, 2015; González and Riboli, 2010).

In early stages of CRC a local excision or resection and anastomosis for carcinomas in situ is required. When cancer is more advanced, the surgery procedure is followed by chemotherapy and in some cases radiotherapy (American Cancer Society, 2015). The standard chemotherapeutics currently employed in the clinic that have shown good results are: 5-Fluorouracil (5-FU) alone and in combination with the vitamin-like folinic acid (Leucovorin), capecitabine, which is the oral form of 5-FU, or 5-FU with oxaliplatin, (Binefa et al., 2014; American Cancer Society, 2015). However, recurrence and metastasis are very common in this type of cancer, highlighting the urge to search for more efficient and personalised therapies. The survival expectation after 5 years of CRC development is between 50% and 60%, decreasing in advanced stages (Verdecchia et al., 2007), thus treatment for CRC depends on the stage and age of the patient.

1.2. Natural products in cancer treatment

Studies from all over the world indicate that patients with cancer commonly resort to alternative therapies as a simultaneous resource to find a cure, particularly medicinal plants. In Alonso-Castro's review (2011), is mentioned that more than 3000 plants with anti-cancer properties are acknowledged around the world. As stated by this study and others done by Gerson-Cwilich et al. (2006) and Gómez-Martinez et al. (2007), in urban areas of Mexico, more than 30% of patients diagnosed with cancer use plant extracts as an alternative or complementary therapy. Therefore, we can infer the important role of Complementary and Alternative Medicine (CAM) in most societies and cultures of the Mexican population. Some possible explanations for this kind of behaviour are that social beliefs about causes and origins of the disease influence different responses and treatments. It is more likely that people find a cure among their social resources than in other methods (like biomedicine) unfamiliar to the population.

The use of medicinal plants and traditional treatments is related to a particular worldview. As Andrade-Cetto (2008) has pointed out, the presence of almost 10,000 indigenous groups with approximately 85 different languages shows the strength and recognition of a health conception that has been built for centuries. Nevertheless, it is not necessary to belong to any indigenous culture to have access to healing practices and beliefs influenced by ancestral knowledge (Taddei-Bringas et al., 1999). Even non-indigenous people turn to traditional medicinal plants to treat different diseases. In this article we consider traditional medicine as a concept that brings together indigenous and popular ancestral health awareness. The tendency to use CAM becomes clear with cancer. In a country such as Mexico, with strong economic inequalities, it can be difficult to get medical treatment. Such inequalities could be an explanation of why the population with limited resources use Alternative Medicine, which is less costly and more accessible than a biomedical treatment. Also, patients are exposed to standard treatments including chemotherapy and radiotherapy, which are not only expensive but also display several side effects that eventually discourage patients. Alternative therapies, on the contrary, are believed to have few consequences for the body and their proximity to people beliefs and perception of disease and well being make them popular.

Humanity has used plants to cure disease in all times and cultures, so it is not unexpected that 60% of the current drugs used in the treatment of cancer derive from sources found in nature (Gordaliza, 2007). Indeed, ethnopharmacological studies have helped in the construction of databases of medicinal plants that are used as a source of molecules with antineoplastic activity. For instance, the well-known alkaloids vinblastine and vincristine from *Catharanthus roseus* (L.) G. Don (Apocynaceae), the paclitaxel from *Taxus brevifolia* Nutt. (Taxaceae) (Srivastava et al., 2005), podophyllotoxin from *Podophyllum peltatum* L. (Berberidaceae) precursor of the drug etoposide, or the camptothecin from *Camptotheca acuminate* Decne. (Cornaceae) (Balunas and Kinghorn, 2005; Castro et al., 2010; Alonso-Castro et al., 2011; Safarzadeh et al., 2014). All of the above are remarkable examples of successful findings in natural sources for cancer treatment, thus justifying the search of new molecules in nature.

The rationale used in this review as a search criteria included cytotoxicity evaluation *in vitro* of plants against colorectal cancer cell lines, and/or *in vivo* models of colon/gastric cancers published in PubMed as the main searcher database, but also consulted ScienceDirect. Since the term “cancer” might be not clear in old Mexican medicine, for the inclusion of plants, we also considered their traditional use as a remedy for colon/stomach discomfort and related inflammation. As an exception, the plant *Galphia glauca* was also included, even when its traditional use is not directly related to colon cancer, but that showed significant cytotoxic activity against colon cancer cell lines. In this work, we found 25 botanic families and 39 species that accomplished our selection criteria.

2. Scientific evidence of plants used in the Mexican traditional medicine against colorectal cancer

For the review purposes we followed the parameters of the National Cancer Institute (NCI) to consider a plant extract or pure compound as active when the effective dose 50 (ED_{50}) was ≤ 20 μg/mL and ≤ 4 μg/mL, respectively. According to these parameters, we found 27 plant species with cytotoxic activity on human colon cancer cell lines. In Table 1, are listed the extracts or compounds with cytotoxic activity and in Table 2 the corresponding for animal models. In general, the activity of plants initially comprises a bioassay-guided fractionation of crude extracts until isolates. However, not always the bioactivity of the plant is determinate by a single compound, on the contrary, in many cases the therapeutic potential of a herb lies on the whole extract, with the complex interaction of the secondary metabolites of the plant.

The plants here are mainly distributed from Mexico down to Central America, an area that was known as Mesoamerica. Only the species *Viguiera decurrens* (A. Grey) A. Grey, *Bursera fagaroides* (Kunth) Engl., *Linum scabrellum* Planch., *Penstemon barbatus* (Cav.) Roth, and *Colubrina macrocarpa* (Cav.) G. Don, are endemic to Mexico. According to Table 1, the majority of the plants here included are used as a remedy for gastrointestinal disorders, where cancer and inflammation related to gastric problems are involved. Except for *Vitex trifolia* L. (fever with vomiting and thirst), *Persea americana* Mill. (mycotic and parasitic infections, anti-inflammatory), *Galphimia glauca* Cav. (sedative properties and treatment for nervous diarrhoea) and *Picramnia antidesma* Sw. (veneral diseases, fever), plants that had cytotoxic activity even tough their traditional use is not related to cancer. The *Zea mays* L., a representative plant of Prehispanic cultures and fundamental part of the Mexican diet, presented significant cytotoxic effect against cancer colon–gastric cell lines. In Fig. 1 are illustrated the most active compounds *in vitro*, the chemical structures were checked in the National Centre for Biotechnology Information (2015). PubChem Compound Datase; (http://pubchem.ncbi.nlm.nih.gov/).

Table 1

Cytotoxic activity of plants used in the Mexican traditional medicine against colorectal cancer.

Family	Species	Distribution	Traditional use	Extract/compound	Cytotoxic activity ED_{50} (μg/mL)*	Colon tumour cell line	Refs.
Annonaceae	*Rollinia mucosa* (Jacq.) Baill.	From Mexico to South America	Cancer treatment	Rollitacin (EtOH)	$4.6x10^{-3}$	HT29	Shi et al. (1997)
				Jimenezin	4.25	SW-480	Chávez et al. (1998)
				Membranacin	3.04		Chávez et al. (1999)
				Desacetyluvaricin	1.69		
				Laherradurin	IC_{50}=0.015		
	Annona diversifolia Saff.	Southern Mexico, Guatemala, Honduras, El Salvador	Gastrointestinal disorders and inflammatory diseases	Cherimolin-2	IC_{50}= 0.5	SW-480	Schlie-Guzmán et al. (2009)
	A. purpurea Moc. & Sessé ex Duna	Southeast Mexico, Guatemala, Honduras, Belize, El Salvador, Caribbean, Costa Rica, South America	Inflammatory diseases	$CHCl_3$–MeOH (1:1)	1.47	HT29	Chávez and Mata (1998)
				purpurediolin	$< 10^{-7}$		
				purpurenin	3.16×10^{-1}		
				annoglaucin	$< 10^{-7}$		
				annonacin A	1.18		
	A. muricata L.	From Mexico to Venezuela	Cancer	annopentocina A	1.63	HT29	Zeng et al. (1996)
				annopentocin B	1.64		Moghadamtousi et al. (2014)
				annopentocin C	1.24		
				cis- and *trans*-annomuricin-D-ones	$< 10^{-2}$		Moghadamtousi et al. (2015)
				EtOAc	IC_{50}=11.43	HT29	
					IC_{50}=8.98	HCT116	
				annomuricin E	IC_{50}=1.62	HT29	
Asteraceae	*Viguiera decurrens* (A. Grey) A. Grey	Mexico	Gastric ulcers	Hex; EtOAc; MeOH extract constituited by β-sitosteryl-3-O-β-D-glucopyranoside; β-D-glucopyranosyl-oleanolate; β-sitosteryl-3-*O*-β-D-glucopyranoside and oleanolic acidl-3-*O*-methy-β-D-glucuronopyranosiduronoate	3.6	Colon carcinoma	Marquina et al. (2001)
	Helianthella quinquenervis (Hook.) A. Grey	Western United States and Northern Mexico	Gastrointestinal diseases and ulcers	demethylencecalin	2	HT-29	Castañeda et al. (1996)
	Smallanthus maculatus (Cav.) H. Rob.	Mexico, Nicaragua, Guatemala, Honduras, Belize, El Salvador, Costa Rica	Gastrointestinal diseases	Acetone	17	HCT15	Ríos and León (2006)
				Fraction F-4	17.4		
				Fraction F-5	7.2		
				Ursolic acid	3.7		
Burseraceae	*Bursera fagaroides* (Kunth) Engl.[a]	Mexico	Antitumor	Hydroalcoholic extract	7.1×10^{-3}	HF6	Rojas-Sepúlveda et al. (2012)
				podophyllotoxin	1.8×10^{-4}		
				β-peltatin-A.methylether	3.8×10^{-2}		
				5'-desmethoxy-β-peltatin-A-methylether	0.40		
				desmethoxy-yatein	0.68		
				desoxypodophyllotoxin	1.23		
				burseranin	2.89		
				acetyl podophyllotoin	2.41		
Adoxaceae[b]	*Viburnum jucundum* C.V. Morton[b]	Mexico, El Salvador, Guatemala	Gastrointestinal diseases	Acetone	14.2	HCT15	Ríos et al. (2001)
				Ursolic acid	3.3		
Celastraceae[c]	*Hemiangium excelsum* (Kunth) A.C. Sm.[c]	From Mexico to Panama	Wounds, cancer	PE	7.6×10^{-1}	HCT-15	Popoca et al. (1998)
				EtOAc	2.5		
				MeOH	1.9		
Lamiaceae	*Hyptis pectinata* (L.) Poit.	From Mexico to Ecuador, Bolivia and Caribbean	Gastric disturbances	Pectinolide A	1	Col2	Pereda-Miranda et al. (1993)
				Pectinolide B	1.1		
				Pectinolide C	1.6		
				α-pyrone boronolide	4		
				deacetylepiol-guine	3		

Table 1 (*continued*)

Family	Species	Distribution	Traditional use	Extract/compound	Cytotoxic activity ED_{50} (μg/mL)[c]	Colon tumour cell line	Refs.
	H. verticillata Jacq.	From Mexico to Venezuela	Headache, stomach ache and gastrointestinal disorders	Dehydro-β-peltatin methyl ether Dibenzylbutyrolactone (−)-yatein 4'-demethyldeoxypodophyllotoxin deoxypicropodophyllin	3.2 0.08 0.03 0.3	Col-2	Novelo et al. (1993)
	H. suaveolens (L.) Poit.	From Mexico to Brazil	Gastrointestinal disorders	β-apopicropodophyllin	0.01	HF6 HT29	Lautié et al. (2008)
	Salvia leucantha Cav.	From Mexico to Venezuela	Gastrointestinal diseases	$CHCl_3$ (roots) $CHCl_3$ (stems) $CHCl_3$ (leaves)	12.7 9.9 14.9	HCT15	Aoyagi et al. (2008)
	Vitex trifolia L.[d]	Australia, Bolivia, Caribbean, China, Comoros, Costa Rica, El Salvador, Hawai, India, Indonesia, Madagascar, Mexico, Nicaragua, United States	Fever with vomiting and thirst	salvileucalin B Hex: leaf Hex: stem DCM: leaf DCM; stem	IC_{50}=1.88 3.6 2.8 < 1 1.9		Hernández et al. (1999)
Lauraceae	*Persea americana* Mill.	Mexico, Guatemala, Honduras, Belize, Bolivia, Argentina, Caribbean, Brazil, Costa Rica, Ecuador, El Salvador, China	Mycotic and parasitic infections, anti-inflammatory	1,2,4-trihydroxynonadecane 1,2,4-trihydroxyhep- tadec-16-ene 1,2,4-trihydroxyheptadec-16-yne	IC_{50}=3 IC_{50}=2.6 IC_{50}=8.9	HT-29	Oberlies et al. (1998)
Linaceae	*Linum scabrellum* Planch.	Mexico	Gastrointestinal disorders	$CHCl_3$ (roots) $CHCl_3$ (aerial parts) BuOH (roots) DCM:MeOH 6MPTOX PTOX	0.2 2.3 0.5 5.7×10^{-1} 7.9×10^{-2} 1.4×10^{-3}	HF6	Lautié, et al. (2008) Alejandre-García et al. (2015)
Santalaceae[e]	*Phoradendron reichenbachianum* (Seem.) Oliv.[e]	Mexico and Guatemala	Cancer	Moronic acid	3.6	HCT15	Ríos et al. (2001)
Lythraceae	*Cuphea aequipetala* Cav.	Mexico, Guatemala, Honduras	Antitumor	Acetone–water	18.70	HCT15	Vega-Ávila et al. (2004)
Malpighiaceae	*Galphimia glauca* Cav.	Mexico,Guatemala, Caribbean	Sedative properties and treatment of nervous diarrhoea	EtOH MeOH Aqueous	0.63 0.50 1.99	HCT-15	Aguilar-Santamaría et al. (2007)
Phrymaceae	*Mimulus* glabratus Kunth	Mexico and South America	Not known	MeOH	IC_{50}=12.64	HF6	Moreno-Escobar et al. (2011)
Picramniaceae	*Picramnia antidesma* Sw.	Mexico, Caribbean and Central America	Venereal diseases, fever	10-*epi*-uveoside uveoside picramnioside E picramnioside D	2.3 μM 4.7 μM 6.2 μM 6.3 μM	HCT15	Hernández-Medel and Pereda-Miranda (2002)
Plantaginaceae	*Penstemon barbatus* (Cav.) Roth	Mexico	Tumours	MeOH	IC_{50}=15.19	HF6	Moreno-Escobar et al. (2011)
	P. campanulatus (Cav.) Willd.	Mexico, Guatemala, Colombia		MeOH	IC_{50}=6.74		
	Veronica americana Schwein. Ex Benth.	North America	Wound healing	MeOH	IC_{50}=0.169		
Poaceae	*Zea mays* L.	America	Gastric cancer, gastrointestinal disorders	13-hydroxy-10-oxo–trans -11-octadecenoic acid	IC_{50}=1.6 IC_{50}=3.9 IC_{50}=4.0 IC_{50}=4.3 IC_{50}=3.9	HCT116 SW-480 SW-620 WiDr AGS stomach cancer	Kuga et al. (1993)

Rhamnaceae	*Colubrina macrocarpa* (Cav.) G. Don	Mexico	Gastric ulcers and cancer	PE	10	HCT-15	Popoca et al. (1998)
				EtOAc	2.1		
				MeOH	9.1		

All botanic names were validated and updated consulting www.theplantlist.org. The following families and species names were replaced from the original work publication:
GI_{50}: growth inhibition 50%; ED50=effective dose; IC50=inhibitory concentration 50%; EtOH: ethanol extract; Hex: hexane extract; EtOAc: ethylacetate extract; MeOH: methanol extract, DCM: Dichloromethane; PE: petroleum ether; CHCl3: chloroform extract: BuOH: buthanol extract; PTOX: podophyllotoxin; 6MPTOX: 6-methoxypodophyllotoxin
Worldwide distribution of plants was consulted on the webpage http://www.tropicos.org

[*] Cytotoxic activity is reported in ED_{50} values otherwise stated in the column.
[a] Bursera fagaroides var. fagaroides (Burseraceae).
[b] *Viburnum jucundum* (Caprifoliaceae).
[c] Hemiangium excelsum (Hippocrateaceae).
[d] Vitex trifolial (Verbenaceae).
[e] Phoradendron reichenbachianum (Loranthaceae).

2.1. Experimental evaluation of the cytotoxicity of medicinal plants in vitro.

2.1.1. Crude extracts cytotoxic activity

The organic extracts (hexane and dichloromethane) of the plant *Vitex trifolia* L. (Lamiaceae). Both extracts had cytotoxic effect especially on the HCT15 colon cancer cell line with ED_{50} values in a range of 3.5– < 1 μg/mL, however, the biological activity was not associated with any compound or family of secondary metabolites (Hernández et al., 1999). Subsequently, was found that its flavonoids induced apoptosis and cell cycle arrest at the G2/M phase in mammalian cancer cells (Li et al., 2005), and seven labdane-type diterpenoids were cytotoxic against HeLa cells with IC_{50} values in a range of 4–29 μM (Wu et al., 2009). A large study of Mexican medicinal plants used in cancer treatment, reported that only two species out of nine, *Colubrina macrocarpa* (Cav.) G. Don (Rhamnaceae) and Semialarium mexicanum (Miers) Mennega (Celastraceae) (synonym of *Hemiangium excelsum* (Kunth) A. C. Sm.), had cytotoxic activity against HCT-15 cell line with ED_{50} values lower than 10 μg/mL (Popoca et al., 1998). A similar investigation was performed on four families of the Lamiales order and tested as cytotoxic and antioxidant (Moreno-Escobar et al., 2011). The methanolic extract of the genus *Penstemon* inhibited cell growth in colon and cervix cancer cell lines, and the species *Mimulus glabratus* Kunth (Phrymaceae) in the colon and prostate cell lines. Importantly, the methanol extract of *Veronica americana* Schwein. Ex Benth. (Plantaginaceae) had a significant cytotoxic effect against colon and prostate cells (0.169 μg/mL and 1.46 μg/mL, respectively), with IC_{50} values lower than 4 μg/mL, a very remarkable achievement for an extract. Both mentioned works did not specify a single compound or group of compounds responsible for the biological activity.

The chloroform and butanol extracts of the herb *Linum scrabellum* Planch. (Linaceae) were tested against a panel of three different cancer cell lines (nasopharyngeal, colon and breast). Notably, both extracts exhibited values as lower as those for pure compounds (≤ 4 μg/mL) with no cell line preference (Lautié et al., 2008). Recently, following with the biological activity of *L. scrabellum*, Alejandre-Garcia et al. (2015) found the compounds podophyllotoxin and 6-methoxypodophyllotoxin in the dichloromethane/methanol root extract. The last one was responsible for the cytotoxic activity in a range of ED_{50} of 0.0632–2.7433 μg/mL in a panel of tumour cell lines. Moreover, they reported that the mechanism of action of 6-methoxypodophyllotoxin is related to the induction of cell cycle arrest in G2/M in PC3 at 0.0002 μM, and that also had proapoptotic effect in a range of 0.002–0.005 μM by inhibiting tubulin polymerisation. The acetone extracts of the plants *Viburnum jucundum* C. V. Morton (Adoxaceae) and *Smallanthus maculatus* (Cav.) H. Rob (Asteraceae) showed cytotoxic activity against HCT15, UISO-SQC-1, and OVCAR-5 cancer cell lines with ED_{50} values lower than 20 μg/mL (Rios et al., 2001; Rios and León, 2006). From both species was isolated the ursolic acid, detected as the active compound of the extract and fractions. In the two species, the cytotoxic activity was in a range of ED_{50}=3.2–3.7 μg/mL for the same panel of cells.

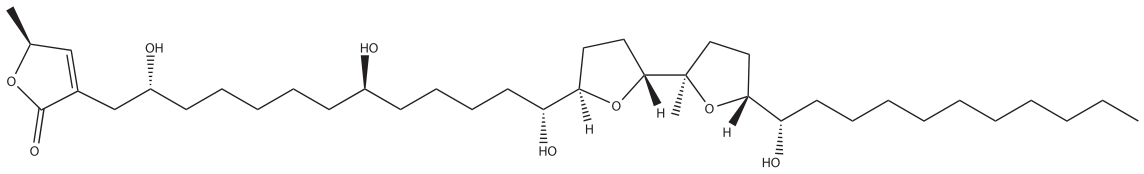
Aqueous and ethanol extracts are very common in ethnopharmacological evaluation since they are more close to traditional general practice. For instance, the aqueous and ethanol extracts obtained from *Ligusticum porteri* J. M. Coult. & Rose (Apiaceae) and *Anemopsis californica* (Nutt.) Hook. & Arn. (Saururaceae) were tested against breast and colon cancer cell lines (MCF-7/AZ and HCT8/E11, respectively) (Daniels et al., 2006). Both extracts of *A. californica* exhibited a concentration-dependent decrease in cell viability in the two cell lines. However, the used concentration was higher than 20 μg/mL. When cells were exposed to 50 μg/mL of *A. californica* decreased ERK protein

Table 2
Mexican plants tested against colon cancer in animal models.

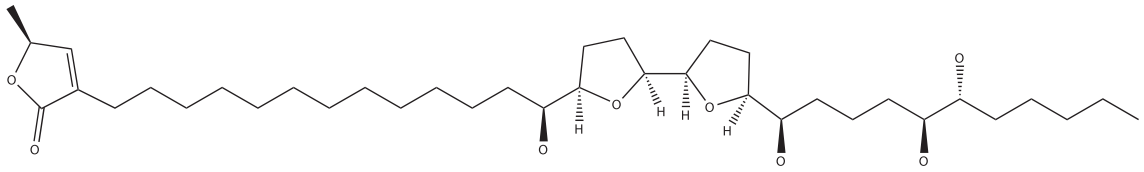
Family	Species	Traditional use	Extract/compound	Animal model	Administration/dose	Refs.
Anacardiaceae	*Rhus trilobata* Nutt.	Gastrointestinal diseases Stomach ache	Aq	Adenocardinoma of duodenum in hamster	Via i.p. 400 mg/Kg once a day	Abbott et al. (1966)
			$EtOH–CHCl_3$		Via i.p. 100 mg/Kg once a day	
Annonaceae	*Annona diversifolia* Saff.	Gastrointestinal disorders, inflammatory conditions	Laherradurin	Athymic mice SW-480 (colon)	1.5 mg/Kg/day and 7.5 mg/Kg/day 20 days treatment	Schlie-Guzmán et al. (2009)
	A. muricata L.	antitumoral	EtOAc	Azoxymethane-induced colonic aberrat crypt foci in rats	250/500 mg/Kg	Moghadamtousi et al. (2015)
Apocynaceae	*Plumeria acutifolia* Poir.	Inflammatory diseases	Aq	Adenocarcinoma of duodenum in hamster	Via i.p. 400 mg/Kg once a day	Abbot et al. (1966)
Asteraceae	*Lasianthaea podocephala* (A. Grey) K. M. Becker[a]	Diahrrea	Aq	Adenocarcinoma of duodenum in hamster	Via i.p. 200 mg/Kg once a day	Abbot et al. (1966)
		Gastrointestinal disorders	Aq		Via i.p. 350 mg/Kg once a day	
	Fluorensia cernua DC.					
	Ambrosia ambrosioides (Cav.) W. W. Payne[b]	Stomach ache	Aq		Via i.p. 400 mg/Kg once a day	
Betulaceae	*Alnus jorulenssis* Kunth[c]	Gastric cancer	Aq	Adenocarcinoma of duodenum in hamster	Via i.p. 175 mg/Kg once a day	Abbot et al. (1966)
Cruciferae	*Dimorphocarpa wislizeni* (Engelm.) Rollins[d]	Emetic, stomach ache	Aq	Adenocardinoma of duodenum in hamster	Via i.p. 100 mg/Kg once a day	Abbott et al. (1966)
Euphorbiaceae	*Euphorbia pulcherrima* Willd. Ex Klotzsch	Cancer (skin)	Aq	Adenocardinoma of duodenum in hamster	Via i.p. 200 mg/Kg once a day	Abbott et al. (1966)
	Acalypha monostachya Cav.[e]	Cancer	Aq		Via i.p. 400 mg/Kg once a day	
Fabaceae	*Crotalaria longirostrata* Hook. & Arn.	Purgative and emetic. Edible	$EtOH–CHCl_3$	Adenocardinoma of duodenum in hamster	Via i.p. 400 mg/Kg once a day Via i.p. 350 mg/Kg once a day	Abbott et al. (1966)
Lamiaceae	*Asterohyptis stellulata* (Benth.) Epling[f]	Vomiting	Aq	Adenocardinoma of duodenum in hamster	Via i.p. 50 mg/Kg once a day	Abbott et al. (1966)
Leguminosae	*Acacia constricta* A. Grey	Stomach ache and diarrhoea	Aq	Adenocardinoma of duodenum in hamster	Via i.p. 400 mg/Kg once a day	Abbott et al. (1966)
Rosaceae	*Holodiscus dumosus* (Nutt. Ex Torr. & A. Grey) A. Heller	Stomachache	Aq	Adenocardinoma of duodenum in hamster	Via i.p. 350 mg/Kg once a day	Abbott et al. (1966)

Aq: aquous extract; EtOH: ethanol extract; $CHCl_3$:chloroform extract; i.p.: intra peritoneal
All botanic names were validated and updated consulting www.theplantlist.org. The following families and species names were replaced from the original work publication:

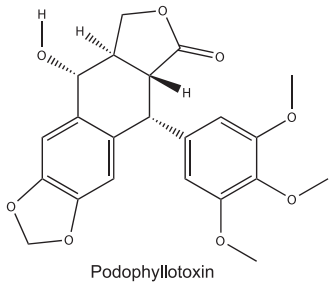
[a] Zexmenia podocephala (Asteraceae).
[b] Franseria ambrosioides.
[c] Alnus jorulenssis.
[d] Dithyrea wislizeni.
[e] Acalypha hederaceae.
[f] Hyptis stellulata.



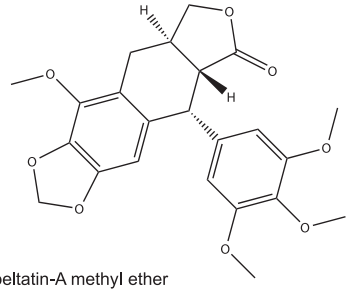
Annoglaucin



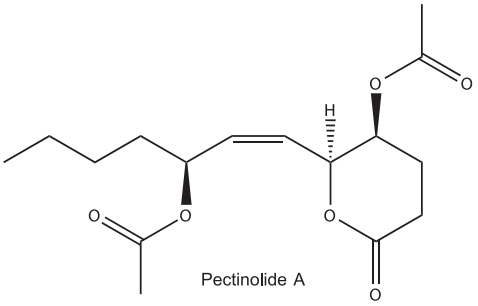
Purpurediolin



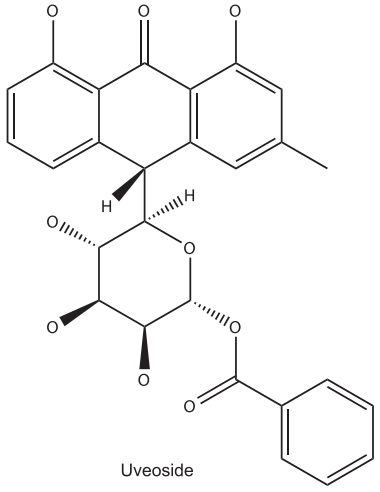
Podophyllotoxin



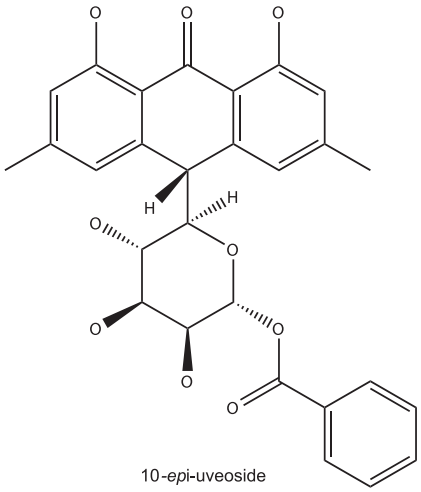
b-peltatin-A methyl ether



Pectinolide A



Uveoside



10-*epi*-uveoside

Fig. 1. Representative pure compounds with remarkable cytotoxic activity on human colon cancer cell lines.

expression, suggesting that the aqueous and ethanol extracts could act in an ERK-dependent way, a protein implicated in cell growth, differentiation and survival (Roskoski, 2012).

An example of a medicinal plant not used for colon or gastric problems, *Galphimia glauca* Cav. (Malpighiaceae), however, as sedative and tranquiliser was tested as cytotoxic on cancer cell lines including nasopharyngeal, ovary, uterus and colon (Aguilar-Santamaría et al., 2007). Unexpectedly, according to its traditional use, the ethanol, methanol, and aqueous extracts were active only on the colon cell lines, which suggest that the plant is selective to a certain cell type. However, such a result could justify the traditional use of the herb in the treatment as tranquiliser since it possible help for nervous diarrhoea (Tortoriello et al., 2011).

2.1.2. Pure compounds cytotoxic activity

In respect of pure compounds, an imperative chemical group with antitumor activity are the acetogenins (Fig. 1), derivatives of long-chain fatty acids and features of the Annonaceae family. From this particular secondary metabolites the rollitacin, laherradurin, cherimolin-2, jimenezin, membranacin and desacetyluvaricin obtained from *Rollinia mucosa* (Jacq.) Baill. and *Annona macroprophyllata* Donn. Sm. (synonym of A. *diversifolia* Saff.), presented cytotoxic activity against colon, cervix, kidney, prostate, pancreatic and breast cancer cell lines comparable to the effect of the drug doxorubicin, i.e. with ED_{50} values of $<10^{-3}$ (Shi et al., 1997; Chávez et al., 1998, 1999; Schlie-Guzmán et al., 2009). From *A. purpurea* Moc. & Sessé ex Dunal were isolated two novel compounds named purpurediolin and purpurenin, and the known annoglaucin and annonacin A, all of them highly cytotoxic exhibited ED_{50} values in a range of $<10^{-7}$–3 μg/mL (Chávez and Mata, 1998). From the species *A. muricata* L. the compounds annopentocins A, B and C and *cis*- and *trans*-annomuricin-D-ones displayed cytotoxic activity against pancreatic, lung and colon carcinoma cells (Zeng, et al., 1996). It has been documented that the acetogenins are the most potent compounds inhibitors of the mitochondrial complex I, related to their ability to inhibit ATP production and by inhibiting the NADH oxidase in cancer cells (Ahammadsahib et al., 1993). In addition, their activity is likely to be associated to the alkyl spacer that links the two toxophores, the hydroxylated tetrahydrofuran (THF) system and the g-lactone rings (Abe et al., 2005).

Other important chemical group are diterpenoids. A panel of eight abietane diterpenoids obtained from *Salvia pachyphylla* Epling ex Munz and *S. clevelandii* (A. Grey) Greene (Lamiaceae), were tested against five human cancer cell lines, including the colon. However, the compounds were no cytotoxic for colon (values over 26 μg/mL), whereas were selective against ovarian and breast cancer cell lines in a range of 3.6–5.4 μg/mL (Guerrero et al., 2006). Continuing with the same plant genus and diterpenoids, the isolate salvileucalin B (diterpene with a neoclerodane skeleton) from the Mexican plant *S. leucantha* Cav. exhibited significant cytotoxic activity against lung and colon cancers cell lines with IC_{50} values of 5.23 and 1.88 μg/mL, respectively (Aoyagi et al., 2008).

From the Lamiaceae family, nine lignans isolated from the species *Hyptis verticillata* Jacq. were tested on breast, colon, fibrosarcoma, lung, prostate and nasopharynx human cancer cell lines as cytotoxic agents (Novelo et al., 1993). In especial, the dibenzylbutyrolactone and the aryltetralin lignans presented nonspecific cytotoxic activity, similar to the effect of podophyllotoxin. The species *H. spicigera* Lam. commonly reported as insecticidal, seven labdane diterpenes were isolated and tested for their insecticidal and cytotoxic properties (Fragoso-Serrano et al., 1999). Only three compounds named 19-acetoxy-2R,7R,15-trihydroxylabda-8(17),(13Z)-diene, 19- acetoxy-2R,7R-dihydroxylabda-8 (17),(13Z)-dien-15-al and 19-acetoxy-7R,15-dihydroxylabda-8(17), (13Z)- dien-2-one presented moderate cytotoxic activity against HCT-15 and KB cell lines in a range of ED_{50}=8.7–19 μg/mL. Moreover, the chloroform and butanol extracts from *H. suaveolens* (L.) Poit. had cytotoxic activity against KB, HF6 and MCF-7 cell lines in a range of ED_{50} values of 12–2.8 μg/mL, and with high activity similar to that accepted for pure compounds in MCF7 (Lautié et al., 2008). From the species *H. pectinata* (L.) Poit. the pectinolides A, B and C (Fig. 1) had a similar cytotoxic activity (ED_{50}=0.7–3.8 μg/mL) in 12 cancer cell lines, showing nonspecific cytotoxicity (Pereda-Miranda et al., 1993). According to the authors, the biological activity of the pectinolides could be related to the a,b-unsaturated D-lactone nucleus, and that the presence of an acetyloxy group at carbon five favour the activity.

The Asteraceae is a big family of plants widely used in traditional medicine for the treatment of gastrointestinal diseases and ulcers. Therefore, several members of the family have been tested against a large number of cancer cell lines, but only a few pure compounds and extracts have shown significant cytotoxic activity against colon cancer *in vitro*. In this regard, the isolate demethylencecalin from *Helianthella quinquenervis* (Hook.) A. Grey, was very potent against MCF-7 (breast), HT-29 (colon) and A-549 (lung) in a range of ED_{50}=2–10 μg/mL (Castañeda et al., 1996). On the other hand, the hexane-ethyl acetate-methanol extract of *Viguiera decurrens* (A. Grey) A. Grey resulted with cytotoxic activity in the range of pure compounds values (ED_{50}=3.6 μg/mL), similar to the ursolic acid obtained from *Smallanthus maculatus* (Cav. H. Rob (ED_{50}=3.7 μg/mL) in colon cancer cell lines (Marquina, et al. 2001; Ríos and León, 2006).

Not always a botanic family has several bioactive members, otherwise is very common to find a single species with possible therapeutic activity. For instance, *Cuphea aequipetala* Cav. (Lythraceae) has a long history of use as a remedy to different tumours since Prehispanic times (Márquez et al., 1999), which the acetone–water extract resulted cytotoxic against colon and prostate tumour cells (ED_{50}=18.7 and 8.2 μg/mL, respectively). The extract, when fractioned, had even more notable results specifically against DU-145 (prostate cancer), with ED_{50} values of 0.418 and 2.40 μg/mL (Vega-Ávila et al., 2004). Those cytotoxic values are comparable to the pure compound moronic acid isolated from *Phoradendron reichenbachianum* (Seem.) Oliv. (Santalaceae) known as mistletoe, which presented activity against HCT15, UISO-SQC-1 and KB cell lines (ED_{50}=3.6, 3.9 and 4.3 μg/mL, respectively) (Ríos et al., 2001). The anthraquinone derivatives uveoside, the 10-epi-uveoside (Fig. 1), picramnioside and picramnioside E of the plant *Picramnia antidesma* Sw. (Picramniaceae) presented moderate cytotoxicity against KB, HCT15, OVCAR and SQC-1 cell lines. The compounds resulted more cytotoxic against KB, where ED_{50} values were in the range of 0.6–4.5 μM (Hernández-Medel and Pereda-Miranda, 2002).

Podophyllotoxin first isolated by Podwyssotzki in 1880 from *Podophyllum peltatum* L. and named after it, is an example of a chemical structure obtained from nature with important cytotoxic activity and precursor of semi-synthetic molecules used in anticancer treatment such as the etoposide, teniposide and epipodophyllotoxin (Srivastava et al., 2005). A study of the genus *Bursera* in Mexico found in the hydroalcoholic extract of the species *B. fagaroides* (Kunth) Engl. (synonym of *B. fagaroides* var. *fagaroides* (Kunth) Engl.) seven podophyllotoxin-type lignans with important cytotoxic activity against nasopharyngeal, colon, breast, and prostate cancer cell lines (Rojas-Sepúlveda et al., 2012). The extract and compounds were cytotoxic against the HF6 colon cancer cell line with ED_{50} values in a range of 1.8×10^{-4}–2.80 μg/mL, showing similar results to drugs such a camptothecin and etoposide. The biological activity of podophyllotoxin has been described as an inhibitor of microtubules and its ability to arrest cell cycle in the metaphase (Gordaliza et al., 2000).

The world famous avocado (*Persea americana* Mill, Lauraceae) has been also tested as antineoplastic. The fatty acids 1,2,4-trihydroxynonadecane, 1,2,4-trihydroxyhep- tadec-16-ene and 1,2,4-trihydroxyheptadec-16-yne obtained from the ethanol extract presented significant cytotoxic activity against different cancer cell lines including colon (Oberlies et al., 1998). The authors pointed out that the terminal alkyne groups were more potent than the terminal alkene, being especially selective to PC3 (prostate cancer) in a range of $IC_{50}=1.1 \times 10^{-1}$–$4.6 \times 10^{-1}$ μg/mL.

2.2. Experimental evidence of the antineoplastic activity of medicinal plants in animal models

Little has been done respecting antineoplastic activity of plants tested *in vivo* specifically for colon or gastric cancers. As it is shown in Table 2, few plants used in Mexican traditional medicine have been piloted in animal models. The list includes 15 species that belong to 11 botanic families.

In the 1960's a large study was performed where more than 1400 plants were evaluated in different animal models including adenocarcinoma of the duodenum, which is of interest for this review (Abbott et al., 1966). From the above mentioned work those species found in Mexico that are traditionally used for gastric disorders including Inflammatory conditions were selected and listed in Table 2. Most of the extracts were aqueous and administered via intra peritoneal once a day, in a range of 200–400 mg/Kg.

As it was mentioned before, acetogenins is a group of natural products that have shown important antitumor activity *in vitro*, driving to explore their potential *in vivo*. The pure compounds laherradurin and cherimolin-2 were administered daily for 20 days in athymic mice previously xenotransplanted with HeLa (cervix) and SW-480 (colon) cells (Schlie-Guzmán et al., 2009). Doses were calculated according to their IC_{50} values. In this study, laherradurin resulted more effective than cherimolin-2 reducing tumour size in both cancer cell lines. Its performance was comparable to the positive control drug doxorubicin, a conventional chemotherapeutic agent. The plant known as "cancer killer", *Annona muricata* L., was evaluated as antineoplastic in two colon cancer cell lines: the HC29 and HCT116. The ethyl acetate extract (EtOAc) exhibited cytotoxic effect on both cell lines with IC_{50} values of 11.43 ± 1.87 μg/mL and 8.98 ± 1.24 μg/mL, respectively (Moghadamtousi et al., 2014a) and the isolate annomuricin E was cytotoxic against HT29 ($IC_{50}=1.62 \pm 0.24$ μg/mL) (Moghadamtousi et al., 2015). Thereafter, the EtOAc extract was evaluated in rats on azoxymethane-induced colonic aberrant crypt foci (Moghadamtousi et al., 2015). The scholars found that the extract reduced the colonic formation at two different doses with no significant difference between them, 250 mg/Kg and 500 mg/Kg, very similar to the standard drug 5-FU used in patients with colorectal cancer. Moreover, the authors reported that the annomuricin E can arrest the cell cycle in the G1 phase and to induce apoptosis in early stages by activation of caspases 3/7 and 9, and also that annomuricin E and the EtOAc extract induced the up-regulation of Bax and down-regulation of Bcl-2 at RNA and protein levels in a time-dependent behaviour. The same research group (Moghadamtousi et al., 2014b) tested the EtOAc extract on lung cancer cells (A549), which resulted cytotoxic with an IC_{50} value of 5.09 ± 0.41 μg/mL after 72 h of treatment, leading as well to cell cycle arrest at G0/G1, to an up-regulation of Bax and down-regulation of Bcl-2, and interestingly that the plant extract induced the translocation of the nuclear factor kappa-B (NF-kB) from cytoplasm to nucleus.

One of the risk factors labelled for developing CRC is diet. Thus the chemo preventive effect is another approach for medicinal plants as food supplement. An example of this was the evaluation of seed oil and flaxseed meal performed on intestinal tumour development in APC^{Min} mice (Bommareddy et al., 2009). It was found in this work that animals fed with both food supplements decreased intestinal tumour multiplicity and the size of the tumour in the small intestine and colon. Such activity is related to ω-3 fatty acids, dietary oils also present in fish, mustard, among others, which have been demonstrated that reduce colon tumour development (Dwivedi et al., 2003, 2005). The regular use of dietary fibre is related to a healthy colon. In the searching of new antineoplastic compounds in edible plants, the popular corn (*Zea mays* L., Poaceae) was evaluated by a bioassay-based methodology (Kuga et al., 1993). It was found that the fatty acids 13-hydroxy-10-oxo-9-methoxy-trans-11-octadecenoic acid and the 13-hydroxy-10-oxo-trans-11-octadecenoic acid were cytotoxic against breast, colon and stomach cancer cell lines. The IC_{50} values were in the order of 1.6–5.0 μg/mL (Kuga et al., 1993). Another study analysed the effect of the anthocyanin purple corn colour, extracted from the seeds of corn and CRC risk *in vivo* (Hagiwara et al., 2001). In this research, rats were treated with AOM as a promoter of colon carcinogenesis and PhIP (2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine as an environmental carcinogen. Those animals fed with the purple corn colour exhibited non-colorectal lesion development, demonstrating that a diet supplemented with the anthocyanin could reduce the effect of a carcinogen such as the PhIP. Lately, the effect of high-amylose maize starch and butyrylated high-amylose maize starch was evaluated on an AOM-induced CRC in rats (Clarke et al., 2008), as a diet rich in fibre. The authors confirmed that a regular consumption of starch enriched with butyrate reduced tumour incidence in rats, and the number and size of them, supporting other investigations that confer a protective role of butyrate.

3. Discussion

There is a first question that appeared during the research over the use of medicinal plants and CAM in cancer: how is it defined cancer in Mexican traditional knowledge? The actors involved – patients, physicians, traditional and popular healers– build their definitions, and all the information together helps patients to understand the events happening in their body. In Biomedicine cancer is defined as the uncontrolled growth and spread of cells that can affect any part of the body (World Health Organisation, 2015). However, this concept of cancer interacts with other proposals including those made up by the patients who collect information from their social background, social structure and educative, economic and cultural levels. Such may explain why the approximation to find specific plants used as a remedy for cancer could be a hard task. The biodiversity of Mexico is one of the largest worldwide Mexican flora is calculated to be around 30,000 species (Villaseñor et al., 2005), a rich nest for novel chemical structures.

Cancer cases numbers are increasing worldwide, positioning it as the second cause of mortality for both sexes (World Health Organisation, 2015). The incidence, in general, is growing and, the death rate is distributed according to the countries' economy development. Thus, patient survival rates in countries with emergent economies are much lower than in countries with developed economies. Current therapeutic options include surgery, radiotherapy and chemotherapy; the application of one or the other depends on the tumour type, the stage of the disease, age, sex, and hereditable factors among others. Chemotherapy is highly toxic and its side effects are very costly to patients; prevention and early diagnosis are still the surest way to a cure. In Mexico, health care providers are aware and influenced by different kinds of alternative therapies, including herbal medicine. However, due to the asymmetrical relationship between physician and patient in a

biomedicine environment, the alternative therapies including herbal remedies are not widely accepted by medical doctors and thus making it difficult to be openly used by patients.

Anticancer therapies are mainly focused on targets such as telomerase or PARP inhibition, resistance cell death, sustenance of proliferative signalling, evasion of growth suppressors, or drugs that impede the hormone secretion (Hanahan and Weinberg, 2011), and less in the deregulation of cellular energetic, which is becoming a highlight in new therapeutic targets. Natural products have been a significant source for the discovery and development of antineoplastic drugs, remarkable is the fact that more than 100 compounds either directly isolated from natural sources or inspired by them, are undertaking clinical trials mainly for cancer and infectious diseases (Harvey, 2008). On the other hand, nutraceuticals and food supplements are gaining terrain in the general public consumption habits, due to their easy access and easy usage, opening an enormous field of work in the world of alternative medicine. Therefore, drug discovery of natural origin continues to be an extremely attractive R&D strategy.

In this scenario and considering the NCI of America criteria for active agents from plants (extracts ≤ 20 μg/ml and pure compounds ≤ 4 μg/ml), according to the data here show, we found *Annonaceous* acetogenins of particular relevance for further research, with high possibilities for the development of new pharmaceutical agents. The acetogenins are biologically potent compounds, it has been reported antimalarial, insecticidal and immunosuppressive activities, besides antitumor effect (Kojima and Tanaka, 2009), the formerly well illustrated in this work against different colon cancer cell lines. Their mechanism of action has been linked to the inhibition of NADH-ubiquitone oxidoreductase in mitochondria, which blocks ATP production and cell death by apoptosis of cells with high metabolic levels such as tumour cells (Morré et al., 1995; Kojima and Tanaka, 2009). Another promising chemical group are the pectinolides A, B and C from the genus *Hyptis*. Interestingly, these compounds also displayed antimicrobial properties against Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*) (Pereda-Miranda et al., 1993). Their biologic activity has been proposed to be related to the functional group of the α,β-unsaturated δ-lactone nucleus, being a potent base for the development of new agents.

However, as mentioned before medicinal plants in most of the cases their activity relays in the interaction of the different chemicals together, even losing effect when fractionating it. For instance, in this revision we found extracts with activity comparable to pure compounds (< 4 μg/ml), such is the case of the ethyl acetate extracts of *Colubrina macrocarpa*, *Hemiangium excelsum* (Kunth) A.C. Sm., the MeOH extract of *H. excelsum*, *Galphimia glauca*, and the Plantaginaceae family in special the species *Veronica americana* Schwein. Ex Benth., the $CHCl_3$–MEOH from *Annona purpurea* Moc. & Sessé ex Dunal, and the aquous extract of *G. glauca*. All of them worth to continue evaluating as antineoplastic agents.

Some of the major concerns on developing phytomedicines for the pharmaceutical industry are their bioavailability, time-consuming to obtain a new drug and high costs. Also, for their commercialisation is required high-quality control of the plant material, including a rational exploitation of the herbs, their propagation and culture and carefulness in intellectual rights. Secondary metabolites are very complex, usually orchestrated in a close network, making the identification of a single active compound a significant challenge. In this regard, the use of the metabolomic approach in herbs brings an opportunity for finding novel therapeutic alternatives in cancer. The metabolomic method gives an optimal overview of the chemical contents of the plants by detecting and identifying the principal secondary metabolites with spectroscopy tools such as nuclear magnetic resonance (NMR) and mass spectroscopy (MS), to generate the metabolomic fingerprint of the active medicinal herbs and eventually to accredit them (Michl et al., 2013). Experimentation *in vitro* is a priority in this research field, to determine toxicity, mechanism of action, therapeutic targets and signalling pathways, just to name a few possibilities. However, as observed in this review, *in vivo* studies so far are the less, most of the tests with medicinal plants stand on cell level. Animal models are complementary and determinant in the evaluation of natural products before going to clinical trials.

4. Conclusions

This review contributes to scientific evidence the traditional use of medicinal plants as antineoplastic agents. Such information should be taken carefully. Work has to be done to define safety, accumulation and biodistribution before their use in humans. However, we confirm once again the big role of nature, especially plants, as an excellent source of chemical structures able to give a fight to cancer.

Conflict of interests

The authors claim no conflict of interests.

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References

Abe, M., Murai, M., Ichimaru, N., Kenmochi, A., Yoshida, T., Kubo, A., Kimura, Y., Moroda, A., Makabe, H., Nishioka, T., Miyoshi, H., 2005. Dynamic function of the alkyl spacer of acetogenins in their inhibitory action with mitochondrial complex I (NADH-Ubiquinone Oxidoreductase). Biochemistry 44, 14898–14906. http://dx.doi.org/10.1021/bi051568t.

Abbott, B.J., Leiter, J., Hartwell, J.L., Caldwell, M.E., Beal, J.L., Perdue Jr., R.E., Schepartz, S.A., 1966. Screening data from the cancer chemotherapy national service center screenign laboratories. XXXIV. Plant extracts. Cancer Res. 26/7 (Pt 2), 761–935.

Aguilar-Santamaría, L., Ramírez, G., Herrera-Arellano, A., Zamilpa, A., Jiménez, J.E., Alonso-Cortés, D., Cortés-Gutiérrez, E.I., Ledesma, N., Tortoriello, J., 2007. Toxicological and cytotoxic evaluation of standardized extracts of *Galphimia glauca*. J. Ethnopharmacol. 109 (1), 35–40. http://dx.doi.org/10.1016/j.jep.2006.06.013.

Ahammadsahib, K.I., Hollingworth, R.M., McGovren, J.P., Hui, Y.H., McLaughlin, J.L., 1993. Mode of action of bullatacin: a potent antitumor and pesticidal *Annoneaceous acetogenin*. Life Sci. 53, 1113–1120. http://dx.doi.org/10.1016/0024-3205(93)90547-G.

Alejandre-Garcia, I., Alvarez, L., Cardoso-Taketa, A., Gonzalez-Maya, L., Antúnez, M., Salas-Vidal, E., Díaz, J.F., Marquina-Bahena, S., Villarreal, M.L., 2015. Cytotoxic activity and chemical composition of the root extract from the Mexican species *Linum scabrellum*: mechanism of action of the active compound 6-methoxypodophyllotoxin. Evid-Based Compl. Alt. 2015, 298463. http://dx.doi.org/10.1155/2015/298463.

Alonso-Castro, A.J., Villarreal, M.L., Salazar-Olivo, L.A., Gomez-Sanchez, M., Dominguez, F., Garcia-Carranca, A., 2011. Mexican medicinal plants used for cancer treatment: pharmacological, phytochemical and ethnobotanical studies. J. Ethnopharmacol. 133, 945–972. http://dx.doi.org/10.1016/j.jep.2010.11.055.

American Cancer Society. Available from: ⟨http://www.cancer.org/acs/groups/cid/documents/webcontent/003096-pdf.pdf⟩ (accessed 15.0915.).

Andrade-Cetto, A., 2008. Ethnobotanical study of the medicinal plants from Tlanchinol, Hidalgo, México. J. Ethnopharmacol. 122 (1), 163–171. http://dx.doi.org/10.1016/jep.2008.12.008.

Aoyagi, Y., Yamazaki, A., Nakatsugawa, C., Fukaya, H., Takeya, K., Kawauchi, S., Izumi, H., 2008. Salvileucalin B, a novel diterpenoid with an unprecedented rearranged neoclerodane skeleton from *Salvia leucantha*. Cav. Org. Lett. 10 (20), 4429–4432. http://dx.doi.org/10.1021/ol801620u.

Balunas, M., Kinghorn, A.D., 2005. Drug discovery from medicinal plants. Life. Sci.

78, 431–441. http://dx.doi.org/10.1016/j.lfs.2005.09.012.
Binefa, G., Rodríguez-Moranta, F., Teule, A., Medina-Hayas, M., 2014. Colorectal cancer: from prevention to personalized medicine. World J. Gastroenterol. 20 (22), 6786–6808. http://dx.doi.org/10.3748/wjg.v20.i22.6786.
Bommareddy, A., Zhang, X., Schrader, D., Kaushik, R.S., Zeman, D., Matthees, D.P., Dwivedi, C., 2009. Effects of dietary flaxseed on intestinal tumorigenesis in Apc (Min) mouse. Nutr. Cancer 61 (2), 276–283. http://dx.doi.org/10.1080/01633500802419764.
Brenner, H., Kloor, M., Pox, C.P., 2014. Colorectal cancer. Lancet 383 (9927), 1490–1502. http://dx.doi.org/10.1016/S0140-6736(13)61649-9.
Clarke, J.M., Topping, D.L., Bird, A.R., Young, G.P., Cobiac, L., 2008. Effects of high-amylose maize starch and butyrylated high-amylose maize starch on azoxymethane-induced intestinal cancer in rats. Carcinogenesis 29 (11), 2190–2194. http://dx.doi.org/10.1093/carcin/bgn192.
Castañeda, P., Gómez, L., Mara, R., Lotina-Hennsen, B., Anaya, A.L., Bye, R., 1996. Phytogrowth-inhibitory and antifungal constituents of *Helianthella quinquenervis*. J. Nat. Prod. 59 (3), 323–326. http://dx.doi.org/10.1021/np960199m.
Castro, M.A., Miguel del Corral, J.M., García, P.A., Rojo, M.V., de la Iglesia-Vicente, J., Mollinedo, F., Cuevas, C., San Feliciano, A., 2010. Synthesis and biological evaluation of new podophyllic aldehyde derivatives with cytotoxic and apoptosis-inducing activities. J. Med. Chem. 53, 983–993. http://dx.doi.org/10.1021/jm901373w.
Chávez, D., Acevedo, L.A., Mata, R., 1998. Jimenezin, a novel annonadeous acetogenin from the seeds of *Rollinia mucosa* containing adjacent tetrahydrofuran–tetrahydropyran ring systems. J. Nat. Prod. 61 (4), 419–421. http://dx.doi.org/10.1021/np990118x.
Chávez, D., Mata, R., 1998. Purpurediolin and purpurenin, two new cytotoxic adjacent bis-tetrahydrofuran annonaceous acetogenins from the seeds of *Annona purpurea*. J. Nat. Prod. 61, 580–584. http://dx.doi.org/10.1021/np970410.
Chávez, D., Acevedo, L., Mata, R., 1999. Tryptamine derived amides and acetogenins from the seeds of *Rollinia mucosa*. J. Nat. Prod. 62, 1119–1122. http://dx.doi.org/10.1021/np990118x.
Daniels, A.L., van Slambrouck, S., Lee, R.K., Arguello, T.S., Browing, J., Pullin, M.J., Kornienko, A., Steelant, W.F.A., 2006. Effects of extracts from two native American plants on proliferation of human breast and colon cancer cell lines *in vitro*. Oncol. Rep. 15, 1327–1331. http://dx.doi.org/10.3892/or.15.5.1327.
Dwivedi, C., Muller, L.A., Goetz-Parten, D.E., Kasperson, K., Mistry, V.V., 2003. Chemopreventive effects of dietary mustard oil on colon tumor development. Cancer Lett. 196 (1), 29–34.
Dwivedi, C., Natarajan, K., Matthees, D.P., 2005. Chemopreventive effects of dietary flaxseed oil on colon tumor development. Nutr. Cancer 51, 52–58. http://dx.doi.org/10.1207/s1532791nc5402_8.
Ferlay, J., Soerjomataram, I., Ervik, M., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., Parkin, D.M., Forman, D., Bray, F., 2013. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. International Agency for Research on Cancer, Lyon, France ⟨http://globocan.iarc.fr⟩ (accessed 15.09.15.)..
Fragoso-Serrano, M., Gonzalez-Chimeo, E., Pereda-Miranda, R., 1999. Novel labdane diterpenes from the insecticidal plant *Hyptis spicigera*. J. Nat. Prod. 62 (1), 45–50. http://dx.doi.org/10.1021/np980222z.
Gerson-Cwilich, R., Serrano-Olvera, A., Villalobos-Prieto, A., 2006. Complementary and alternative medicine (CAM) in Mexican patients with cancer. Clin. Trans. Oncol. 8 (3), 200–207.
Gómez-Martinez, R., Tlacuilo-Parra, A., Garibaldi-Covarrubias, R., 2007. Use of complementary and alternative medicine in children with cancer in Occidental Mexico. Pediatr. Blood Cancer 49, 820–823. http://dx.doi.org/10.1002/pbc.21101.
González, C.A., Riboli, E., 2010. Diet and cancer prevention: contributions from the European prospective investigation into cancer and nutrition (EPIC) study. Eur. J. Cancer 46, 2555–2562. http://dx.doi.org/10.1016/j.ejca.2010.07.025.
Gordaliza, M., Castro, M.A., del Corral, J.M., Feliciano, A.S., 2000. Antitumor properties of podophyllotoxin and related compounds. Curr. Pharm. Des. 6 (18), 1811–1839.
Gordaliza, M., 2007. Natural products as leads to anticancer drugs. Clin. Trans. Oncol. 9, 767–776. http://dx.doi.org/10.1007/s12094-007-0138-9.
Guerrero, I., Andrés, L., León, L., Machín, R., Padrón, J., Luis, J., Delgadillo, J., 2006. Abietane diterpenoids from *Salvia pachyphylla* and *S. clevelandii* with cytotoxic activity against human cancer cell lines. J. Nat. Prod. 68 (12), 1803–1805. http://dx.doi.org/10.1021/np060279i.
Hagiwara, A., Miyashita, K., Nakanishi, T., Sano, M., Tamano, S., Kadota, T., Koda, T., Nakamura, M., Imaida, K., Ito, N., Shirai, T., 2001. Pronounced inhibition by a natural anthocyanin, purple corn color, of 2-amino-1-methyl-6-phenylimidazo [4,5-b]pyridine (PhIP)- associated colorectal carcinogenesis in male F344 rats pretreated with 1,2-dimethylhydrazine. Cancer Lett. 171, 17–25. http://dx.doi.org/10.1016/S0304-3835(01)00510-9.
Hanahan, D., Weinberg, R.A., 2011. Hallmarks of cancer: the next generation. 2011. Cell 144 (5), 646–674. http://dx.doi.org/10.1016/j.cell.2011.02.013.
Harvey, A.L., 2008. Natural products in drug discovery. Drug. Discov. Today. 13 (19–20), 894–901. http://dx.doi.org/10.1016/j.drudis.2008.07.004.
Hernández, M.M., Heraso, C., Villarreal, M.L., Vargas-Arispuro, I., Aranda, E., 1999. Biological activities of crude plant extracts from *Vitex trifolia* L. (Verbenaceae). J. Ethnopharmacol. 67, 37–44. http://dx.doi.org/10.1016/S0378-8741(99)00041-0.
Hernández-Medel, M., Pereda-Miranda, R., 2002. Cytotoxic anthraquinone derivatives from *Picramnia antidesma*. Planta. Med. 68, 556–558. http://dx.doi.org/10.1055/S2002-32562.
Kojima, N., Tanaka, T., 2009. Medicinal chemistry of *Annonaceous* acetogenins: design, synthesis, and biological evaluation of novel analogues. Molecules 14, 3621–3661. http://dx.doi.org/10.3390/molecules14093621.
Kuga, H., Ejima, A., Mitui, I., Sato, K., Ishihara, N., Fukuda, K., Saito, F., Uenakai, K., 1993. Isolation and characterizacion of cytotoxic compounds from corn. Biosci. Biotechnol. Biochem. 57 (6), 1020–1021. http://dx.doi.org/10.1271/bbb.57.1020.
Lautié, E., Quintero, R., Fliniaux, M.A., Villarreal, M.L., 2008. Selection methodology with scoring system: application to Mexican plants producing podophyllotoxin related lignans. J. Ethnopharmacol. 120, 402–412. http://dx.doi.org/10.1016/jep.2008.09.014.
Li, W.X., Cui, C.B., Cai, B., Wang, H.Y., Yao, X.S., 2005. Flavonoids from *Vitex trifolia* L. inhibit cell cycle progression at G2/M phase and induce apoptosis in mammalian cancer cells. J. Asian. Nat. Prod. Res. 7 (4), 615–626. http://dx.doi.org/10.1080/10286020310001625085.
Márquez, A.C., Lara, F., Esquivel, B., Mata, R., 1999. Plantas medicinales de México II. Composición, usos y actividad biológica. Universidad Nacional Autónoma de México, México, D.F.
Marquina, S., Maldonado, N., Garduño-Ramírez, M.L., Aranda, E., Villarreal, M.L., Navarro, V., Bye, R., Delgado, G., Álvarez, L., 2001. Bioactive oleanolic acid saponins and other constituents from the roots of *Viguiera decurrens*. Phytochemistry 56, 93–97. http://dx.doi.org/10.1016/S0031-9422(00)00283-1.
Michl, J., Jennings, H.M., Kite, G.C., Ingrouille, M.J., Simmonds, M.S., Heinrich, M., 2013. Is aristolochic acid nephropathy a widespread problem in developing countries? A case study of *Aristolochia indica* L. in Bangladesh using an ethnobotanical–phytochemical approach. J. Ethnopharcacol. 149 (1). http://dx.doi.org/10.1016/jep.2013.06.028.
Moghadamtousi, S.Z., Rouhollahi, E., Karimian, H., Fadaeinasab, M., Mohammad, F., Ameen Abdulla, M., Abdul Kadir, H., 2015. The chemopotential effect of *Annona muricata* leaves against azoxymethane- induced colonic aberrant crypt foci in rats and the apoptotic effect of acetogenin annomuricin E in HT-29 cells: a bioassay- guided approach. PLoS. One. 10 (4), e0122288. http://dx.doi.org/10.1371/journal.pone.0122288.
Moghadamtousi, S.Z., Karimian, H., Rouhollahi, E., Paydar, M., Fadaeinasab, M., Abdul, Kadir, H., 2014. *Annona muricata* leaves induce G1 cell cycle arrest and apoptosis through mitochondria-mediated pathway in human HCT-116 and HT-29 colon cancer cells. J. Ethnopharmacol. 156, 277–289. http://dx.doi.org/10.1016/jep.2014.08.011.
Moghadamtousi, S.Z., Abdul Kadir, H., Paydar, M., Rouhollahi, E., Karimian, H., 2014b. *Annona muricata* leaves induced apoptosis in A549 cells through mitochondrial-mediated pathway and involvement of NF-κB. BMC. Complem. Altern. M. 14, 299. http://dx.doi.org/10.1186/1472-6882-14-299.
Moreno-Escobar, J.A., Bazald, S., Villarreal, M.L., Bonilla-Barbosa, J.R., Mendoza, S., Rodríguez-López, V., 2011. Cytotoxic and antioxidant activities of selected Lamiales species from Mexico. Pharm. Biol. 49 (12), 1243–1248. http://dx.doi.org/10.3109/13880209.2011.589454.
Morré, D.J., Cabo, R.D., Farley, C., Oberlies, N.H., McLaughlin, J.L., 1995. Mode of action of bullatacin, a potent antitumor acetogenin: Inhibiton of NADH oxidase activity of HELA and HL-60, but not liver, plasma membranes. Life Sci. 56, 343–348. http://dx.doi.org/10.1016/0024-3205(94)00957-0.
National Center for Biotechnology Information. PubChem Compound Database; CID=44575506, ⟨https://pubchem.ncbi.nlm.nih.gov/compound/44575506⟩ (accessed 11.12.15.).
Novelo, M., Cruz, J.G., Hernández, L., Pereda-Miranda, R., Chai, H., Mar, W., Pezzuto, J.M., 1993. Cytotoxic constituents from *Hyptis verticillata*. J. Nat. Prod. 56 (10), 1728–1736. http://dx.doi.org/10.1021/NP50100a011.
Oberlies, N.H., Rogers, L.L., Martin, J.M., McLaughlin, J.L., 1998. Cytotoxic and insecticidal constituents of the unripe fruit of *Persea americana*. J. Nat. Prod. 61, 781–785. http://dx.doi.org/10.1021/np9800304.
Pereda-Miranda, R., Hernández, L., Villavicencio, M.J., Novelo, M., Ibarra, P., Chai, H., Pezzuto, J.M., 1993. Structure and stereochemistry of pectinolides A-C, novel antimicrobial and cytotoxic 5,6-dihydro-alpha-pyrones from *Hyptis pectinata*. J. Nat. Prod. 56 (4), 583–593. http://dx.doi.org/10.1021/np50094a019.
Popoca, J., Aguilar, A., Alonso, D., Villarreal, M.L., 1998. Cytotoxic activity of selected plants used as antitumorals in Mexican traditional medicine. J. Ethnopharmacol. 59, 173–177. http://dx.doi.org/10.1016/S0378-8741(97)00110-4.
Ríos, M.Y., González-Morales, A., Villarreal, M.L., 2001. Sterols, triterpenes and biflavonoids of *Viburnum jucundum* and cytotoxic activity of ursolic acid. Planta Med. 67, 683–684. http://dx.doi.org/10.1055/s-2001-17357.
Rios, Y., León, I., 2006. Chemical constituents and cytotoxic activity of *Smallanthus maculatus*. Chem. Nat. Compd. 42 (4), 497–498. http://dx.doi.org/10.1007/s10600-006-0193-4.
Rios, M.Y., Salinas, D., Villarreal, M.L., 2001. Cytotoxic activity of moronic acid and identification of the new triterpene 3,4-seco-Olean-18-ene-3,28-dioic acid from *Phoradendron reichenbachianum*. Planta Med. 67 (5), 443–446. http://dx.doi.org/10.1055/s-2001-15823.
Rojas-Sepúlveda, A., Mendieta-Serrano, M., Antúnez Mojica, M., Salas-Vidal, E., Marquina, S., Villarreal, M.L., Puebla, A.M., Delgado, J., Alvarez, L., 2012. Cytotoxic podophyllotoxin type-lignans from the steam bark of *Bursera fagaroides* var. *fagaroides*. Molecules 17, 9506–9519. http://dx.doi.org/10.3390/molecules17089506.
Roskoski Jr., R., 2012. ERK1/2 MAP kinases: structure, function, and regulation. Pharmacol. Res. 66 (2), 105–143. http://dx.doi.org/10.1016/j.phrs.2012.04.005.
Safarzadeh, E., Sandoghchian, S.S., Baradaran, B., 2014. Herbal medicine as inducers of apoptosis in cancer treatment. Adv. Pharm. Bull. 4 (Suppl 1), 421–427. http://dx.doi.org/10.5681/apb.2014.062.
Shi, G., MacDougal, J.M., McLaughlin, J.L., 1997. Bioactive annonaceous acetogenins from *Rollinia mucosa*. Phytochemistry 45, 719–723. http://dx.doi.org/10.1016/

S0031-9422(97)00028-9.
Schlie-Guzmán, M.A., García-Carrancá, A., González- Esquinca, A.R., 2009. *In vitro* and *in vivo* antiproliferative activity of laherradurin and cherimolin-2 of *Annona diversifolia* Saff. Phytother. Res. 23, 1128–1133. http://dx.doi.org/10.1002/ptr.2760.
Srivastava, V., Negi, A.S., Kumar, J.K., Gupta, M.M., Khanuja, S.P.S., 2005. Plant-based anticancer molecules: a chemical and biological profile of some important leads. Bioorgan. Med. Chem. 13, 5892–5908. http://dx.doi.org/10.1016/j.bmc.2005.05.066.
Taddei-Bringas, G.A., Santillana-Macedo, M., Romero-Cancio, J.A., Romero-Téllez, B., 1999. Aceptación y uso de herbolaria en medicina familiar. Salud pública De. México 41 (3). http://dx.doi.org/10.1590/S0036-36419990003000009.
Tortoriello, J., Herrera-Arellano, A., Herrera-Ruiz, M.L., Zamilpa, A., González-Cortazar, M., Jiménez-Ferrer, J.E., 2011. New anxiolytic phytopharmaceutical elaborated with the standardized extract of *Galphimia glauca*. In: Kalinin, Vladimir (Ed.), Anxiety Disorders. InTechhttp://dx.doi.org/10.5772/24294, ISBN: 978-953-307-592-1 ⟨http://www.intechopen.com/books/anxiety-disorders/new-anxiolytic-phytopharmaceutical-elaborated-with-the-standardized-extract-of-galphimia-glauca1⟩.
Vega-Ávila, E., Tapia Aguilar, R., Jiménez Estrada, M., Villareal Ortega, M., Román-Ramos, R., 2004. Cytotoxic activity of *Cuphea aequipetala*. Proc. West Pharmacol. Soc. 47, 129–133. http://dx.doi.org/10.1016/j.jep.2010.11.055.
Verdecchia, A., Francisci, S., Brenner, H., Gatta, G., Micheli, A., Mangone, L., Kunkler, I., 2007. Recent cancer survival in Europe: a 2000-02 period analysis of EUROCARE-4 data. Lancet Oncol. 8, 784–796. http://dx.doi.org/10.1016/S1470-2045(14)70282-7.
Villaseñor, J., Ibarra-Manriquez, G., Meave, J., Ortiz, J.E., 2005. Higher taxa as surrogates of plant biodiversity in a mega-diverse country. Conserv. Biol. 19 (1), 232–238. http://dx.doi.org/10.1111/j.1523-1739.2005.00264.x.
World Health Organization, WHO. 2015. ⟨http://www.who.int/en/⟩ Consulted on the Internet September 15 2015.
Wu, J., Zhou, T., Zhang, S.W., Zhang, X.H., Xuan, L.J., 2009. Cytotoxic terpenoids from the fruits of *Vitex trifolia* L. Planta Med. 75 (4), 367–370. http://dx.doi.org/10.1055/s-0028-1112211.
Zeng, L., Wu, F.E., Oberlies, N.H., McLaughlin, J.L., Sastrodihajo, S., 1996. Five new monotetrahydrofuran ring acetogenins from the leaves of *Annona muricata*. J. Nat. Prod. 59 (11), 1035–1042. http://dx.doi.org/10.1021/np960447e.