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

Nadia J. Jacobo-Herrera a,*, Frida E. Jacobo-Herrera b, Alejandro Zentella-Dehesa a,c, Adolfo Andrade-Cetto d, Michael Heinrich e, Carlos Pérez-Plasencia f,g

a Unidad de Bioquímica, Instituto Nacional de Ciencias Médicas y Nutrición “Salvador Zubirán”, D.F. Mexico, Mexico
b Depto. Ciencias Sociales y Humanidades, Unidad Cuajimalpa Universidad Autónoma Metropolitana, D.F. Mexico, Mexico
c Medicina Genómica y Toxicología Ambiental, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, UNAM, D.F. Mexico, Mexico
d Laboratorio de Etnofarmacología, Facultad de Ciencias, Universidad Nacional Autónoma de México, UNAM, Tlalnepantla, Estado de México, Mexico
e Research Cluster Biodiversity and Medicines/Centre for Pharmacognosy and Phytotherapy, School of Pharmacy, UCL, London, UK
f UBIMED, FES-Iztacala, Universidad Nacional Autónoma de México, UNAM, Tlalnepantla, Estado de México, Mexico
g Laboratorio de Genomica, Instituto Nacional de Cancerología, D.F. Mexico, Mexico

A R T I C L E   I N F O
Article history:
Received 1 October 2015
Received in revised form 21 December 2015
Accepted 21 December 2015
Available online 22 December 2015

Keywords:
Mexican medicinal plants
Traditional Mexican medicine
Colon cancer
Cytotoxicity
In vivo models

A B S T R A C T

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 (ED50) 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.

© 2016 Published by Elsevier Ireland Ltd.

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
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), it 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-Cwilk et al. (2006) and Gómez-Martínez 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 (Cordaliza, 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 vinblunitzen 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 Deene. (Cornaceae) (Balunas and Kinghorn, 2005; Castro et al., 2010; Alonso-Castro et al., 2011; Sáfarzadeh 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 Galphita 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 (ED50) 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 decorrens (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 diarrhea) and Picramnia antidesma Sw. (veneral diseases, fever), plants that had cytotoxic activity even 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>
<thead>
<tr>
<th>Family</th>
<th>Species</th>
<th>Distribution</th>
<th>Traditional use</th>
<th>Extract/compound</th>
<th>Cytotoxic activity ED50 (µg/mL)</th>
<th>Colon tumour cell line</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annonaceae</td>
<td><em>Rollinia mucosa</em> (Jacq.) Baill.</td>
<td>From Mexico to South America</td>
<td>Cancer treatment</td>
<td>Rollitacin (EtOH)</td>
<td>4.6x10^{-3}</td>
<td>HT29</td>
<td>Shi et al. (1997)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Jimenezin</td>
<td>4.25</td>
<td>SW-480</td>
<td>Chávez et al. (1998)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Membranacin</td>
<td>3.04</td>
<td></td>
<td>Chávez et al. (1999)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Desacytethyluvacin</td>
<td>1.69</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Laherradurin</td>
<td>K_{IC_{50}}=0.015</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K_{IC_{50}}=0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Schlie-Guzmán et al. (2009)</td>
</tr>
<tr>
<td></td>
<td><em>Annona diversifolia</em> Saff.</td>
<td>Southern Mexico, Guatemala, Honduras, El Salvador</td>
<td>Gastrointestinal disorders and inflammatory diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>A. purpurea</em> Moc. &amp; Sessé ex Duna</td>
<td>Southeast Mexico, Guatemala, Honduras, Belize, El Salvador, Caribbean, Costa Rica</td>
<td>Inflammatory diseases</td>
<td>CHCl_{3}-MeOH (1:1)</td>
<td>1.47</td>
<td>HT29</td>
<td>Chávez and Mata (1998)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>purpurediolin</td>
<td>&lt;10^{-7}</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>purpurenin</td>
<td>3.16 × 10^{-1}</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>annonacin A</td>
<td>1.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>annonacin B</td>
<td>1.63</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>annonacin C</td>
<td>1.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>cis- and trans-annomuricin-D-ones</td>
<td>&lt;10^{-3}</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K_{IC_{50}}=11.43</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K_{IC_{50}}=8.98</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K_{IC_{50}}=1.62</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asteraceae</td>
<td><em>Viguiera decurrens</em> (A. Grey) A. Grey</td>
<td>Mexico</td>
<td>Gastric ulcers</td>
<td>_hex; EtOAc; MeOH extract constituted by β-sitosteryl-3-O-β-D-glucopyranoside; β-D-glucopyranosyl-oleanolate; β-sitosteryl-3-O-β-D-glucopyranoside and olea- nolic acid-3-O-methyl-β-D-glucuronomypyrano3ulronate demethylmecnealain</td>
<td>3.6</td>
<td>HT29</td>
<td>Marquina et al. (2001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burseraceae</td>
<td><em>Bursera fagaroides</em> (Kunth) Engl.</td>
<td>Mexico</td>
<td>Antitumor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adoxaceae</td>
<td><em>Viburnum jucundum</em> C.V. Morton</td>
<td>Mexico, El Salvador, Guatemala</td>
<td>Gastrointestinal diseases and ulcers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celastraceae</td>
<td><em>Hemiangium excelsum</em> (Kunth) A.C. Sm.</td>
<td>From Mexico to Panama</td>
<td>Wounds, cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamiaceae</td>
<td><em>Hyptis pectinata</em> (L.) Poit.</td>
<td>From Mexico to Ecuador, Bolivia and Caribbean</td>
<td>Gastric disturbances</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 1**

Cytotoxic activity of plants used in the Mexican traditional medicine against colorectal cancer.
<table>
<thead>
<tr>
<th>Family</th>
<th>Species</th>
<th>Distribution</th>
<th>Traditional use</th>
<th>Extract/compound</th>
<th>Cytotoxic activity ED&lt;sub&gt;50&lt;/sub&gt; (μg/mL)</th>
<th>Colon tumour cell line</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H. verticillata Jacq.</td>
<td>From Mexico to Venezuela</td>
<td>Headache, stomach ache and gastrointestinal disorders</td>
<td>Dehydro-β-peltatin methyl ether</td>
<td>3.2</td>
<td>Col-2</td>
<td>Novelo et al. (1993)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dibenzylbutyrolactone (−)-yatein 4'-demethoxydopophyllotoxin deoxypodophyllotoxin</td>
<td>0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Deoxypicropodophyllin</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>β-apopodophyllin</td>
<td>0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dehydro-β-peltatin methyl ether</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dibenzylbutyrolactone (−)-yatein</td>
<td>0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Deoxypicropodophyllin</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Deoxypicropodophyllin</td>
<td>0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>H. suaveolens (L.) Poit.</td>
<td>From Mexico to Brazil</td>
<td>Gastrointestinal disorders</td>
<td>CHCl&lt;sub&gt;3&lt;/sub&gt; (roots)</td>
<td>12.7</td>
<td>HT29</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CHCl&lt;sub&gt;3&lt;/sub&gt; (stems)</td>
<td>9.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CHCl&lt;sub&gt;3&lt;/sub&gt; (leaves)</td>
<td>14.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Salvia leucantha Cav.</td>
<td>From Mexico to Venezuela</td>
<td>Gastrointestinal disorders</td>
<td>salveleucalin B</td>
<td>3.6</td>
<td>HCT15</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hex: leaf</td>
<td>2.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hex: stem</td>
<td>&lt; 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DCM: leaf</td>
<td>1.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vitis trifolia L.&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Australia, Bolivia, Caribbean, China, Comoros, Costa Rica, El Salvador, Hawai, India, Indonesia, Madagascar, Mexico, Nicaragua, United States</td>
<td>Fever with vomiting and thirst</td>
<td>1,2,4-trihydroxynonadecane</td>
<td>1.9</td>
<td>HCT15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Persea americana Mill.</td>
<td>Mexico, Guatemala, Honduras, Belize, Bolivia, Argentina, Caribbean, Brazil, Costa Rica, Ecuador, El Salvador, China</td>
<td>Mycotic and parasitic infections, anti-inflammatory</td>
<td>1,2,4-trihydroxyheptadec-16-ene</td>
<td>1.9</td>
<td>HCT15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Linum scabrellum Planch.</td>
<td>Mexico</td>
<td>Gastrointestinal disorders</td>
<td>CHCl&lt;sub&gt;3&lt;/sub&gt; (aerial parts)</td>
<td>0.2</td>
<td>HT-29</td>
<td>Oberlies et al. (1998)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BuOH (roots)</td>
<td>2.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DCM:MeOH</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6MPTOX</td>
<td>5.7 × 10&lt;sup&gt;-1&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PTOX</td>
<td>7.9 × 10&lt;sup&gt;-2&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10-epi-uvosioide</td>
<td>1.4 × 10&lt;sup&gt;-3&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Santalaceae&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Mexico and Guatemala</td>
<td>Cancer</td>
<td>Moronic acid</td>
<td>3.6</td>
<td>HCT15</td>
<td>Ríos et al. (2001)</td>
</tr>
<tr>
<td></td>
<td>Malpighiaceae</td>
<td>Mexico, Guatemala, Honduras</td>
<td>Sedative properties and treatment of nervous diarrhoea</td>
<td>ETOH</td>
<td>0.63</td>
<td>HCT-15</td>
<td>Aguilar-Santamaría et al. (2007)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mexico, Guatemala, Caribbean</td>
<td></td>
<td>MeOH</td>
<td>0.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Aquous</td>
<td>1.99</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phrymaceae</td>
<td>Mimulus glabratris Kunth</td>
<td>Not known</td>
<td>1,2,4-trihydroxynonadecane</td>
<td>18.70</td>
<td>HCT15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Picramniaceae</td>
<td>Picramnia antidesma Sw. Kunth</td>
<td>Venereal diseases, fever</td>
<td>10-epi-uvosioide</td>
<td>6.3</td>
<td>HCT15</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mexico, Caribbean and Central America</td>
<td></td>
<td>10-epi-uvosioide</td>
<td>6.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>uvosioide</td>
<td>6.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plantaginaeae</td>
<td>Penstemon barbatus (Cav.) Roth P. campanulatus (Cav.) Wild.</td>
<td>Tumours</td>
<td>MeOH</td>
<td>1.6</td>
<td>HT116</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mexico</td>
<td></td>
<td>MeOH</td>
<td>3.9</td>
<td>SW-480</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MeOH</td>
<td>4.0</td>
<td>SW-620</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MeOH</td>
<td>4.3</td>
<td>WIDt</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poaceae</td>
<td>Zea mays L.</td>
<td>Gastric cancer, gastrointestinal disorders</td>
<td>13-hydroxy-10-oxo-trans -11-octadecenoic acid</td>
<td>1.6</td>
<td>AGS stomach cancer</td>
<td>Kuga et al. (1993)</td>
</tr>
</tbody>
</table>
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, it 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 *Vernonia 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 scabellum* 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. scabellum*, 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 0.0362–0.037 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>
<thead>
<tr>
<th>Family</th>
<th>Species</th>
<th>Traditional use</th>
<th>Extract/compound</th>
<th>Animal model</th>
<th>Administration/dose</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anacardiaceae</td>
<td><em>Rhus trilobata</em> Nutt.</td>
<td>Gastrointestinal diseases Stomach ache</td>
<td>Aq</td>
<td>Adenocarcinoma of duodenum in hamster</td>
<td>Via i.p. 400 mg/Kg once a day</td>
<td>Abbott et al. (1966)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EtOH–CHCl₃</td>
<td></td>
<td>Via i.p. 100 mg/Kg once a day</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.5 mg/Kg/day</td>
<td>Schlie-Guzmán et al. (2009)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.5 mg/Kg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20 days treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>250/500 mg/Kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>via i.p. 200 mg/Kg once a day</td>
<td>Abbott et al. (1966)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>via i.p. 350 mg/Kg once a day</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annonaceae</td>
<td><em>Annona diversifolia</em> Saff.</td>
<td>Gastrointestinal disorders, inflammatory conditions</td>
<td>Laherradurin</td>
<td>Athymic mice SW-480 (colon)</td>
<td>Via i.p. 400 mg/Kg once a day</td>
<td>Moghadamtousi et al. (2015)</td>
</tr>
<tr>
<td></td>
<td><em>A. muricata</em> L.</td>
<td>antitumoral</td>
<td>EtOAc</td>
<td>Azoxymethane-induced colonic aberrant crypt foci in rats</td>
<td>Via i.p. 250 mg/Kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20 days treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apocynaceae</td>
<td><em>Plumeria acutifolia</em> Poiret</td>
<td>Inflammatory diseases</td>
<td>Aq</td>
<td>Adenocarcinoma of duodenum in hamster</td>
<td>Via i.p. 200 mg/Kg once a day</td>
<td>Abbott et al. (1966)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>via i.p. 350 mg/Kg once a day</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asteraceae</td>
<td><em>Lasianthaea podocephala</em> (A. Grey) K. M. Becker*</td>
<td>Diarrhea</td>
<td>Aq</td>
<td>Adenocarcinoma of duodenum in hamster</td>
<td>Via i.p. 200 mg/Kg once a day</td>
<td>Abbott et al. (1966)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Via i.p. 400 mg/Kg once a day</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20 days treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betulaceae</td>
<td><em>Alnus jorulenssis</em> Kunth*</td>
<td>Gastric cancer</td>
<td>Aq</td>
<td>Adenocarcinoma of duodenum in hamster</td>
<td>Via i.p. 175 mg/Kg once a day</td>
<td>Abbott et al. (1966)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Via i.p. 100 mg/Kg once a day</td>
<td></td>
</tr>
<tr>
<td>Cruciferae</td>
<td><em>Dimorphocarpa wislizeni</em> (Engelm.) Rollins*</td>
<td>Emetic, stomach ache</td>
<td>Aq</td>
<td>Adenocarcinoma of duodenum in hamster</td>
<td>Via i.p. 100 mg/Kg once a day</td>
<td>Abbott et al. (1966)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Euphorbiaceae</td>
<td><em>Euphorbia pulcherrima</em> Wild. Ex Klotzsch</td>
<td>Cancer (skin)</td>
<td>Aq</td>
<td>Adenocarcinoma of duodenum in hamster</td>
<td>Via i.p. 200 mg/Kg once a day</td>
<td>Abbott et al. (1966)</td>
</tr>
<tr>
<td></td>
<td><em>Acalypha monostachya</em> Cav.°</td>
<td></td>
<td></td>
<td></td>
<td>Via i.p. 400 mg/Kg once a day</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20 days treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fabaceae</td>
<td><em>Crotalaria longirostrata</em> Hook. &amp; Arn.</td>
<td>Purgative and emetic. Edible</td>
<td>ETOH–CHCl₃</td>
<td>Adenocarcinoma of duodenum in hamster</td>
<td>Via i.p. 400 mg/Kg once a day</td>
<td>Abbott et al. (1966)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Via i.p. 350 mg/Kg once a day</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamiales</td>
<td><em>Asterohyptis stellulata</em> (Benth.) Epling°</td>
<td>Vomiting</td>
<td>Aq</td>
<td>Adenocarcinoma of duodenum in hamster</td>
<td>Via i.p. 50 mg/Kg once a day</td>
<td>Abbott et al. (1966)</td>
</tr>
<tr>
<td></td>
<td><em>Acacia constricta</em> A. Grey</td>
<td></td>
<td></td>
<td></td>
<td>Via i.p. 400 mg/Kg once a day</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosaceae</td>
<td><em>Holodiscus dumosus</em> (Nutt. Ex Torr. &amp; A. Grey) A. Heller</td>
<td>Stomachache</td>
<td>Aq</td>
<td>Adenocarcinoma of duodenum in hamster</td>
<td>Via i.p. 350 mg/Kg once a day</td>
<td>Abbott et al. (1966)</td>
</tr>
</tbody>
</table>

Aq: aqueous extract; ETOH: ethanol extract; CHCl₃: 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 publication:

a Zexmenia podocephala (Asteraceae).
b Franseria ambrosioides.
c *Alnus jorulenssis*.
d *Dithyrea wislizeni*.
e *Acalypha hederacea*.
f Hyptis stellulata.
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, *Calphinia glauca* Cav. (Malpighiaceae), however, as sedative and tranquilliser was tested as cytotoxic on cancer cell lines including nasopharyngeal, ovary, uterus and colon (Aguilar-Santamaria 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 tranquilliser 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 actogenins (Fig. 1), derivatives of long-chain fatty acids and features of the Annonaceae family. From this particular secondary metabolites the rollicitacin, laheradurin, cherimolín–2, jimenezin, membranacin and desacetylvarcinic obtained from *Rollinia mucosa* (Jacq.) Baill. and *Annona macrophyllata* 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 ED50 values of <10–4 (Shi et al., 1997; Chávez et al., 1998, 1999; Schie-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 ED50 values in a range of <10–2–3 μg/mL (Chávez and Mata, 1998). From the species *A. muricata* L. the compounds annpentocins A, B and C and cis- and trans-annomuricin-α-ones displayed cytotoxic activity against pancreatic, lung and colon carcinoma cells (Zeng, et al., 1996). It has been documented that the acetogens 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 (Ahammadshahi et al., 1993). In addition, their activity is likely to be associated to the alky spacer that links the two toxophores, the hydroxylated tetrahydrofuran (THF) system and the γ-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 IC50 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, liver, and prostate cancer cell lines comparable to the effect of the drug cytoxicity 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 ED50 = 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 (ED50 = 3.6 μg/mL), similar to the ursolic acid obtained from *Smallanthus maculatus* (Cav. H. Rob (ED50 = 3.7 μg/mL) in colon cancer cell lines (Marquina, et al., 2001; Rios 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 (ED50 = 18.7 and 8.2 μg/mL, respectively). The extract, when fractioned, had even more notable results specifically against DU-145 (prostate cancer), with ED50 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, USO-SQ1-1 and KB cell lines (ED50 = 3.6, 3.9 and 4.3 μg/mL, respectively) (Rios et al., 2001). The arthranquinone derivatives uvesoid, the 10-epi-uvesoid (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 ED50 values were in the range of 0.6–4.5 μM (Hernández-Medel and Pereda-Miranda, 2002).

Podophyllotoxin first isolated by Podwysotskii 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) Eng.) 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 H6F colon cancer cell line with ED50 values in a range of 1.8 × 10−4–2.80 μg/mL, showing similar results to drugs such as 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-trihydroxy-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 range of 1.6–5.0 μg/mL (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).

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). Days in athymic mice previously xenotransplanted with HeLa 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).

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 ± 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 APCMin 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 butyrate-lated 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
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 6-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, Hemianium 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 CHCl3–MeOH from Annona purpurea Moc. & Sessé ex Dunal, and the aqueous extract of G. glauca. All of them worth to continue evaluating as antineoplastic agents.

Some of the major concerns on developing phytochemicals 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.

Acknowledgements

F.J-H. is grateful for the postdoctoral fellowship given by Conacyt Project number: 43510446. We thank Beatriz Sánchez-Monroy and José Luis Ventura-Gallegos for the pictures and chemical structures drawings of the graph abstract.

References


