Chapter 11
Appraisal of Medicinal Plants with Anticancer Properties in South America

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11.1 Introduction

Cancer remains an important public health problem in both developed and developing countries, and the statistical numbers suggest that it is increasing steadily. It is well known that cancer is not a particular illness; it is considered more as a variety of diseases and many types of cancers can be manifested in various ways based on the organ or organs affected (Zaid et al. 2017). It is a leading cause of death worldwide, this explains the great amount of research in this area, making big efforts to identify compounds with anticancer activity that help to fight against this terrible disease. Historically, natural products have been used for treating various diseases, including tumor (Ekor 2013; Swamy and Sinniah 2015; Atanasov et al. 2015; Bailon-Moscoso et al. 2015). Plant- and marine-based natural products in the last few years have played a very crucial role as sources of anticancer compounds, and many of these drugs are in the clinical use at present. Thus nowadays, plant-based compounds remain as the principal source of drugs with anticancer potential. There are several approaches to drug discovery derived from plants. Some of them follow the strategy of ethnobotanical knowledge (Quiroga et al. 2012; Swamy and Sinniah 2016; Arumugam et al. 2016; Pinheiro-Ferreira et al. 2016; Mohanty et al. 2017). This approach is very common in South America and is based on the information derived from the medicinal use of plants by the population. This knowledge has been transmitted from generation to generation, from our ancestors, and it has been a guide to identify compounds derived from plants that may be of used in the cancer treatment.

South America is the fourth largest continent, which houses a huge biodiversity and contains a large fraction of the earth's forests. It is the region of the world's five most biodiverse countries: Brazil, Colombia, Ecuador, Peru, and Venezuela.

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Also, this region includes the Amazon rainforest, the Atlantic Forest, and the Andean region. On the other hand, there are vast zones of uncharted territory and some lesser known forests such as Guyana, French Guiana, and Suriname. The flora and fauna of this part of the world is unique, in addition to an immense cultural wealth with very old traditions in the knowledge of using plants to treat various illnesses (Jones 2003; Bailon-Moscoso et al. 2015; Pinheiro-Ferreira et al. 2016). It is coupled with the fact that many of the countries in this region are considered as developing countries with a very low income, meaning that the people do not have monetary resources to attend their health problems; thus they depend on the ancestral knowledge about medicinal plants that have allowed the survival of their ancestors. This is in agreement with the published by WHO, which estimates that 80% of the global population of developing nations mostly depend on the use of plant-based traditional medicines for their primary health-care requisites (Kumara et al. 2012; Swamy et al. 2016, 2017). Many of the modern medicines have been derived from plants, but only small ratio of them has been analyzed chemically. It is true that there is much more to discover, especially due to the rich flora of this continent. In this chapter, we present an appraisal of some studies that have been carried out with plants in different countries of South America emphasizing the ethnobotanical information reported for these plant species.

11.2 Medicinal Plants with Anticancer Potential from the South American Countries

11.2.1 Argentina

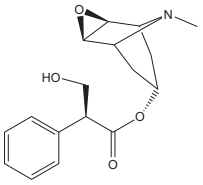
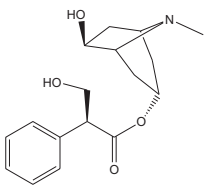
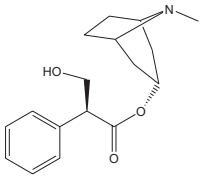
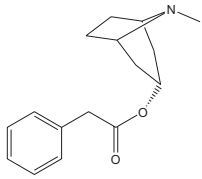
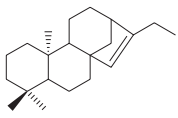
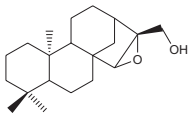
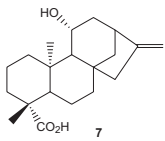
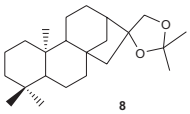
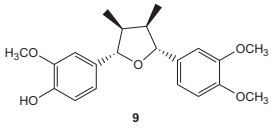
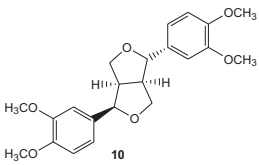
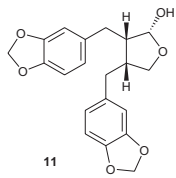
Argentina is a big country, which has an abundant and diverse flora ranging from subarctic to subtropical climates. The existing antecedents of ethnobotanical studies in the country indicate that many plant species are used by the inhabitants of this big country to help in the fight against ailments including cancer. Several studies related to the anticancer activity of medicinal plants used by Argentina inhabitants have been published, and some of them are mentioned here.

Medicinal plants of the central region of Argentina used in the domestic medicine were studied for their antiproliferative effect on breast cancer cells (MCF-7). The cell viability test using crystal violet staining allowed selecting plant extracts that inhibited tumor cell proliferation (Bongiovanni et al. 2006). A total of 17 indigenous species belonging to 9 different botanical families were evaluated: *Aspidosperma quebracho-blanco* Schlechtendahl, *Mandevilla pentladiana* (A. DC.) Woodson., and *Mandevilla laxa* (Ruiz and Pav.) Woodson. (Apocynaceae); *Aristolochia stuckertii* Speg. (Aristolochiaceae); *Eupatorium buniifolium* Hook. ex Hook. and Arn. (Compositae); *Baccharis* sp., *Gaillardia megapotamica* (Spreng.) Baker., *Thelesperma megapotamicum* (Spreng.) Kuntze, *Zexmenia bupthalmiflora*, and *Heterotheca latifolia* Buckley (Asteraceae); *Acalypha cordobensis* Müll. Arg.

and *Sebastiania commersoniana* (Baill.) L.B. Sm. and Downs (Euphorbiaceae); *Oxalis erythrorhiza* Gillies ex Hook. and Arn. (Oxalidaceae); *Lantana grisebachii* Stuckert ex Seckt. (Verbenaceae); *Larrea nitida* Cav. and *Larrea divaricata* Cav. (Zygophyllaceae); and *Monnina dictyocarpa* Griseb. (Polygalaceae). The authors have concluded that only eight species possess the antiproliferative activity. Among them, *T. megapotamicum*, *O. erythrorhiza*, and *L. divaricata* showed the higher values of inhibitory activity on MCF-7 cell line (Bongiovanni et al. 2006). In a similar work, 75 aqueous and methanol extracts of 45 Argentinean plants were evaluated on mammary adenocarcinoma cells (LM2), using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. From this wide screening, eight methanol extracts were considered for the second phase and evaluated against three more cancer cell lines, bladder (MB49), melanoma (B16), and lung (A549), and normal cell lines, keratinocytes (PAM212), mammary (Hb4a), and keratinocytes (HaCat). The results revealed that four plant species, namely, *Solanum chacoense* Bitter., *S. verbascifolium* L., *S. sisymbriifolium* Lam., and *S. amygdalifolium* Steud., showed higher values of cytotoxicity. These species belonging to the *Solanum* genera (Solanaceae) are a rich source of alkaloid metabolites, especially tropane alkaloids (Table 11.1-A). The other most promising species with anticancer potential included *Collaea argentina* Griseb (Fabaceae), *Iochroma australe* Griseb (Solanaceae), *Ipomoea bonariensis* Hook (Convolvulaceae), and *Jacaranda mimosifolia* D. Don. (Bignoniaceae). The phytochemical studies of some of these species indicated the presence of alkaloids; however some of these do not have phytochemical reports (Mamone et al. 2011). The species *Thelesperma megapotamicum* (Spreng.) Kuntze *(*Asteraceae), known by the population as Indian tea or Pampa tea, is generally used to treat various diseases in Argentina. The solvent fractions of this plant were found to be very active against MCF-7 cell lines, and the phytochemical studies revealed the presence of common flavonoids and phenylpropanoids reported from this species (Figueroa et al. 2012).

In a different research, eight species belonging to seven different families were investigated for their potential antiproliferative activity against the Hep G2 (human hepatocellular carcinoma) cell lines. The methanolic extracts obtained from these Argentinean medicinal plants such as *Schinus molle* L. commonly known as aguaribay, curanguay, and anacuita and *Lithraea molleoides* (Vell.) Engl. (Anacardiaceae) chichita and arbol malo; *Aristolochia macroura* B.A. Gomes (Aristolochiaceae) patito coludo and mil hombres; *Chenopodium ambrosioides* L. (Chenopodiaceae) paico and apazote; *Achyrocline satureioides* (Lam.) DC. (Compositae) marcela and marcela hembra; *Petiveria alliacea* L. (Phytolaccaceae) mapurite and ajillo; *Plantago major* L. (Plantaginaceae) llantén and torraja; and *Celtis spinosa* Spreng (Ulmaceae) tala and tala blanco were evaluated for cell proliferation using the non-radioactive 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2Htetrazolium (MTS) assay. The results showed the IC_{50} values between 50 and 237 μg/ml. The extracts of *S. molle* and *A. satureioides* were the most active. *S. molle* specially deserve considerations for further studies. Plants like *P. alliaceae* from other latitudes have been mentioned with potential anticancer activity; however the results obtained in this research are not conclusive for these

Table 11.1 Summary of chemical compounds extracted from the various plants

Plants	Extracted compounds
Solanum species	 Hyoscine (**1**)  Anisodamine (**2**)  Hyosciamine (3)  Liitorine (4) A
Aristolochia triangularis	 **5**  **6**  **7**  **8**  **9**  **10**  **11** B

(continued)

Table 11.1 (continued)

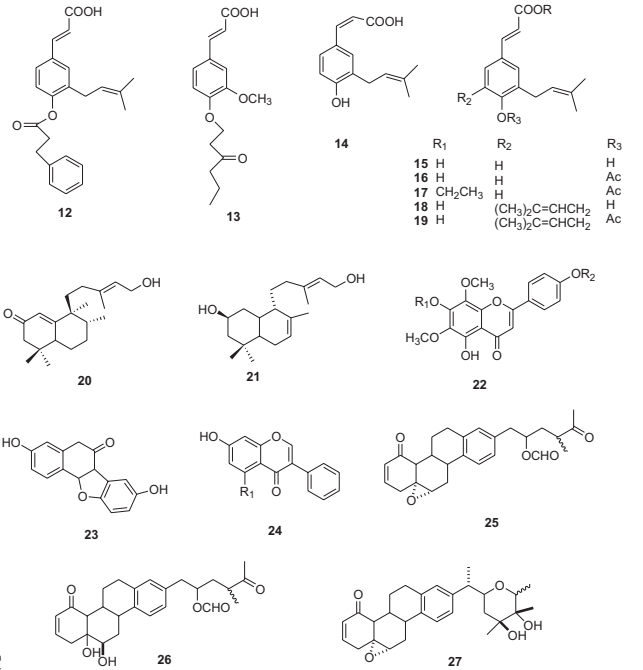
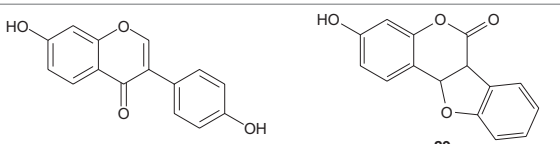
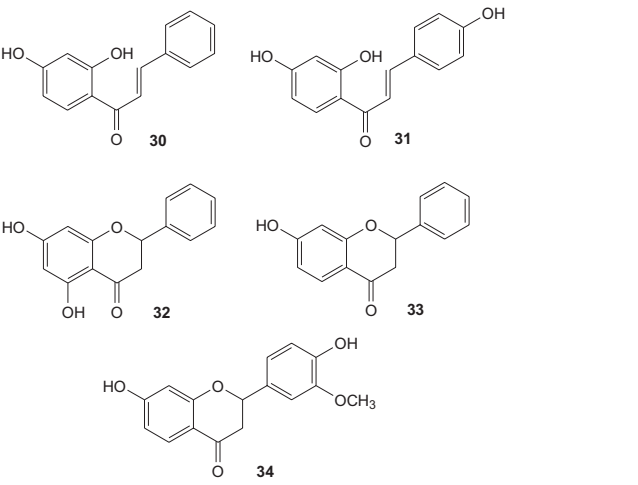
Plants	Extracted compounds
Argentinean plants	 C
Erythrina crista-galli	 D
Flourensia oolepis	 E

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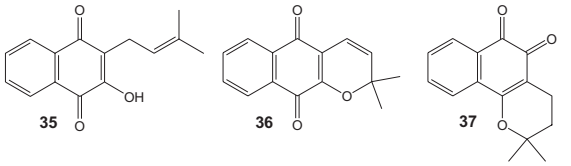
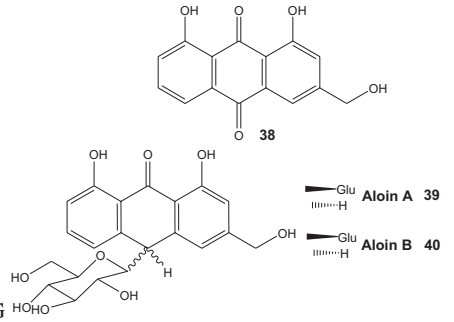
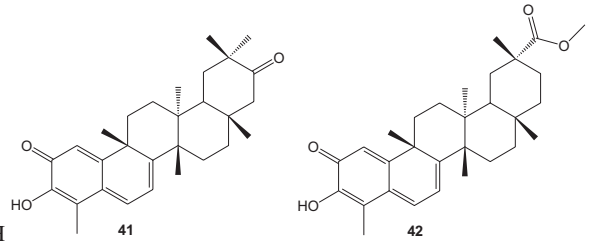
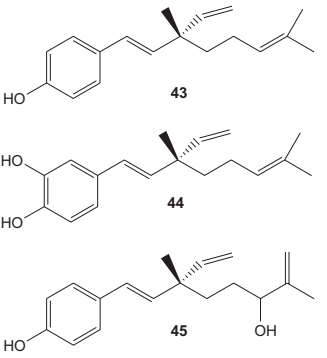
Table 11.1 (continued)

Plants	Extracted compounds
Tabebuia impetiginosa	 F
Aloe species	 G
Maytenus ilicifolia	 H
Psoralea glandulosa	 I

(continued)

Table 11.1 (continued)

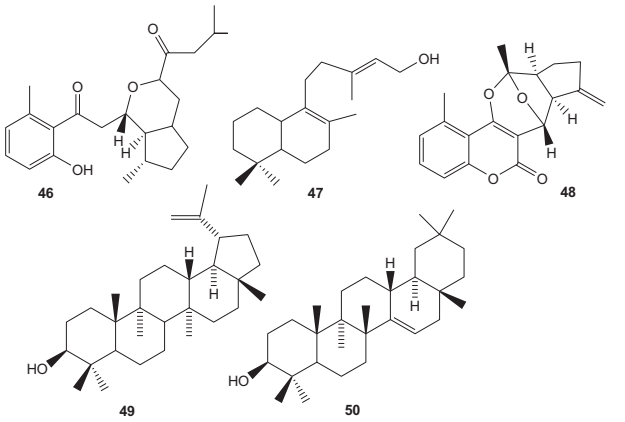
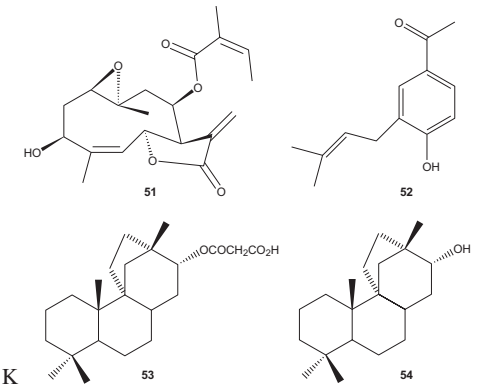
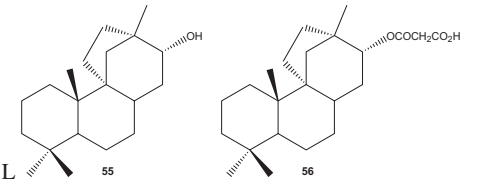
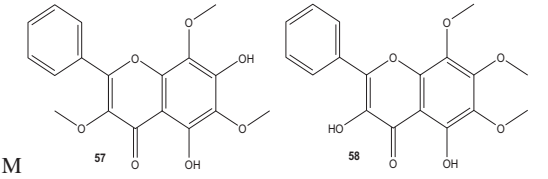
Plants	Extracted compounds
Gyphotamniun pinifolium	 J
Leptocarpha rivularis	 K
Calceolaria thyrsiflora	 L
G. elegans and *A. bogotensis*	 M

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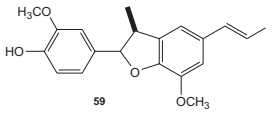
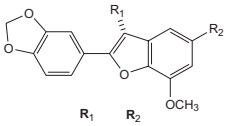
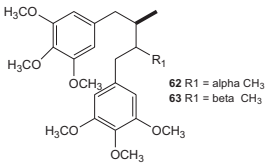
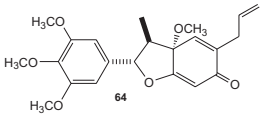
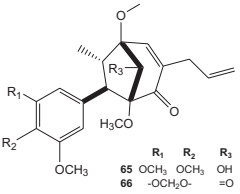
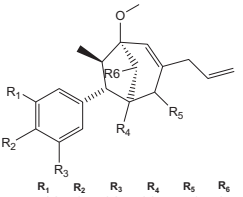
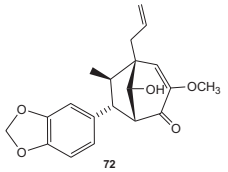
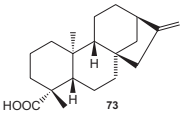
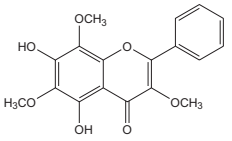
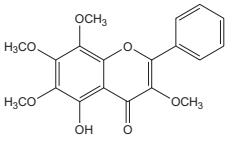
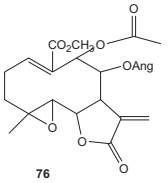
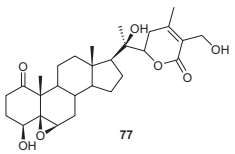
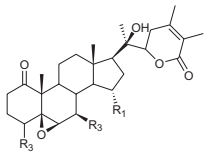
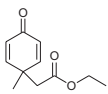
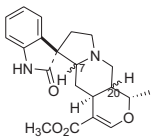
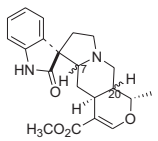
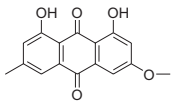
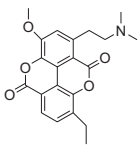
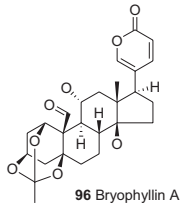
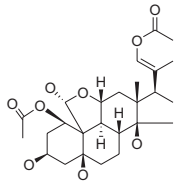
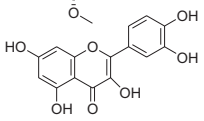
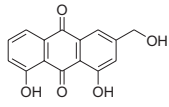
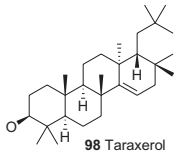
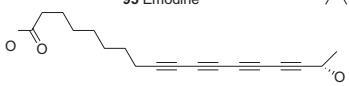
Table 11.1 (continued)

Plants	Extracted compounds
Colombian Lauraceae	 **59**  **60** H Allyl **61** CH_3 CHO  **62** R1 = alpha CH_3 **63** R1 = beta CH_3  **64**  **65** OCH_3 OCH_3 OH **66** $-OCH_2O-$ =O  **67** -OCH2O- OCH_3 OCH_3 =O OH **68** -OCH2O- OCH_3 OCH_3 b-OH =O **69** -OCH2O- OCH_3 OCH_3 =O =O **70** OCH_3 OCH_3 OCH_3 H =O OH **71** OCH_3 OCH_3 H H =O OH  **72**  **73**
Espeletia killipii	 **74**  **75**  **76**

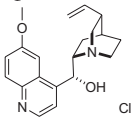
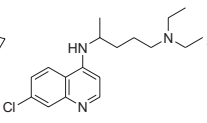
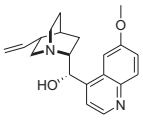
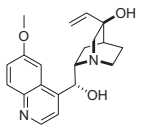
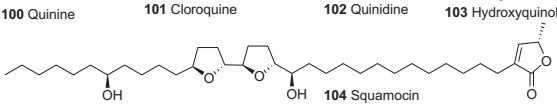
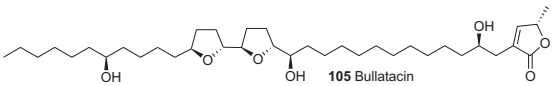
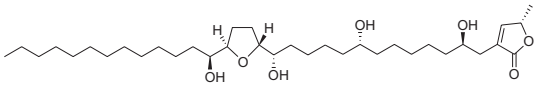
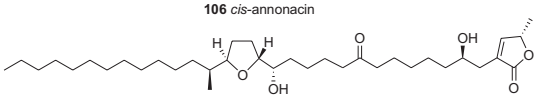
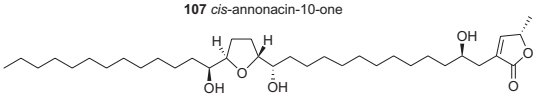
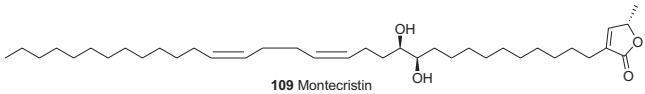
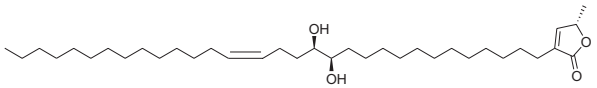
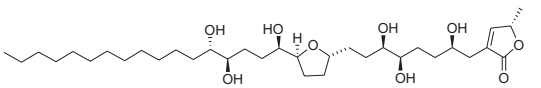
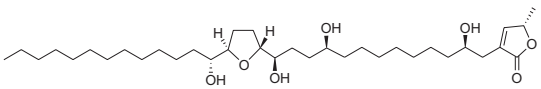
(continued)

Table 11.1 (continued)

Plants	Extracted compounds
Acnistus arborescens	 **77**  **78** -Δ^2, R_1 = H, R_2 = β-OH,α-H, R_3 = OAc **79** -Δ^2, R_1 = OAc, R_2 = β-OH,α-H, R_3 = OAc **80** -Δ^2, R_1 = OAc , R_2 = H2, R_3 = OAc **81** -Δ^2, R_1 = H, R_2 =β–OH, α-H, R_3 = H **82a** -Δ^2, R_1 = H, R_2 = β -OAc, α-H, R_3 = OAc **82b** -Δ^2, R_1 = H, R_2 = O, R_3= OAc **82c** -Δ^1, R_1 = H, R_2 = β-OH α-H, R_3 = OAc **83a** -Δ^2, R_1 = OAc, R_2 = OAc, R_3 = OAc **83b** -Δ^2, R_1 = OAc, R_2 = O, R_3 = OAc  **84**  **85** P
U. tomentosa, *C. lechleri*, *M. condurango*, *S. multiglandulosa*, and *M. guianensis*	Q  **86** Isopteropodine: H7, H20, Me-18 **87** Isomitraphylline: H7, H20, Me-18  **88** Pteropodine: H-7, H-20 **89** Uncarine F: H-7, H-20 **90** Mitraphylline: H-7, H-20  **91** Physcion  **92** Tapsine  **96** Bryophyllin A **93** Condurango glycoside A  **97** Bryophyllin B  **94**Quercetin  **95** Emodine  **98** Taraxerol  **99** Minquartynoic acid

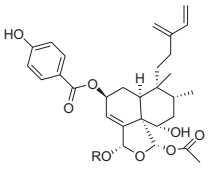
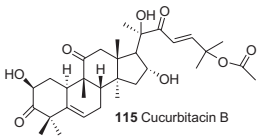
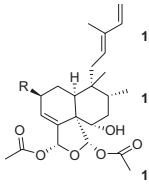
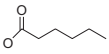
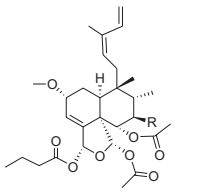
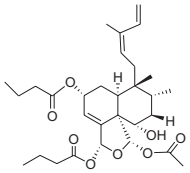
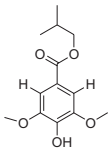
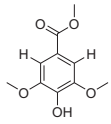
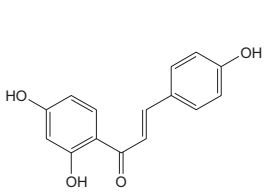
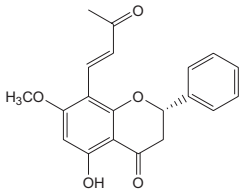
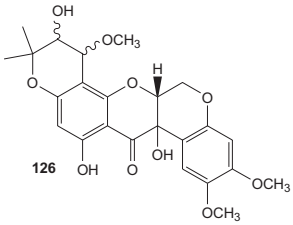
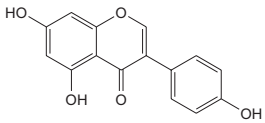
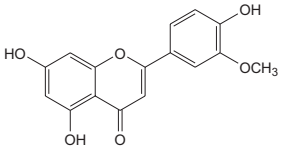
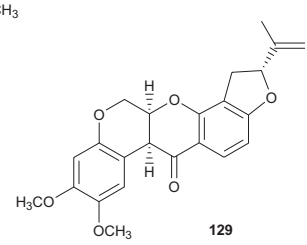
(continued)

Table 11.1 (continued)

Plants	Extracted compounds
C. officinalis and *A. squamosa*	Q  **100** Quinine  **101** Cloroquine  **102** Quinidine  **103** Hydroxyquinoline  **104** Squamocin  **105** Bullatacin  **106** *cis*-annonacin  **107** *cis*-annonacin-10-one  **108** Murisolin
A. muricata	R  **109** Montecristin  **110** Cohibin A  **111** Muriexocin  **112** Adrianacin

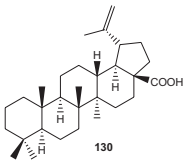
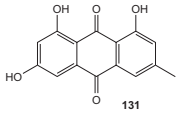
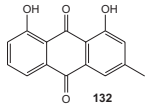
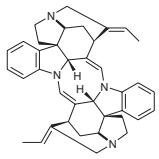
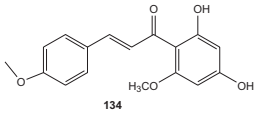
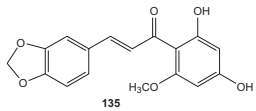
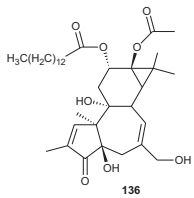
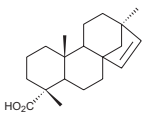
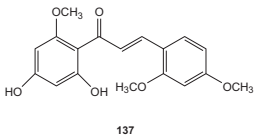
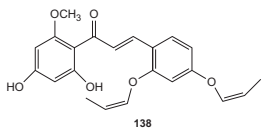
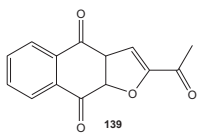
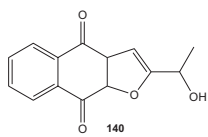
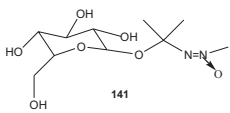
(continued)

Table 11.1 (continued)

Plants	Extracted compounds
L. intrapetiolaris and *C. sylvestris*	 **113** Intrapetacin A: R = Me **114** Intrapetacin B: R = Ac  **115** Cucurbitacin B  **116** Casearvestrin A: R =  **117** Casearvestrin B: R =  **118** Casearvestrin C: R =   **119** Casearin L: R = OH **120** Casearin O: R =   **121** Casearin X  **122** IGDE  **123** MGDE S
Tephrosia toxicaria and *Lonchocarpus* species	 **124**  **125**  **126**  **127**  **128**  **129** T

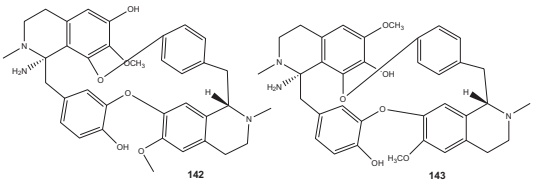
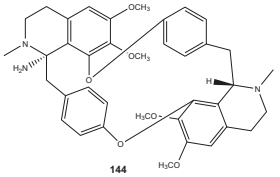
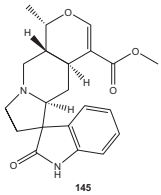
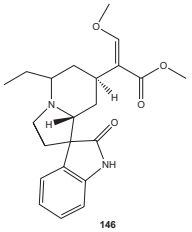
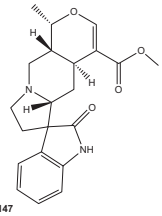
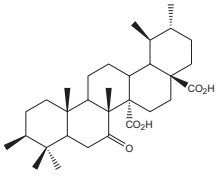
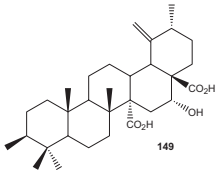
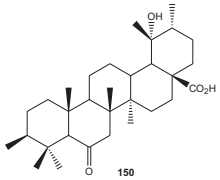
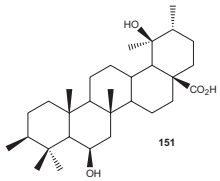
(continued)

Table 11.1 (continued)

Plants	Extracted compounds
D. dentatus, *P. sellowii*, *S. mitscherlichii*, *I. juruensis*, and *C. alnifolius*	 130  131  132  133  134  135  136  137 U
Peruvian plants	 137  138  139  140  141 V

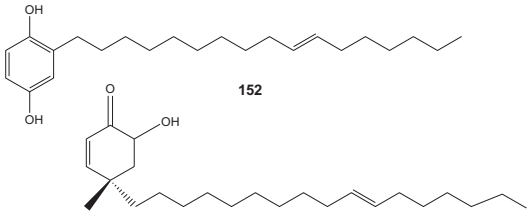
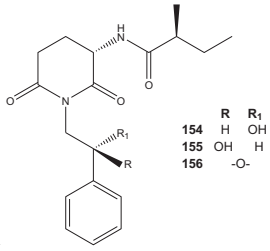
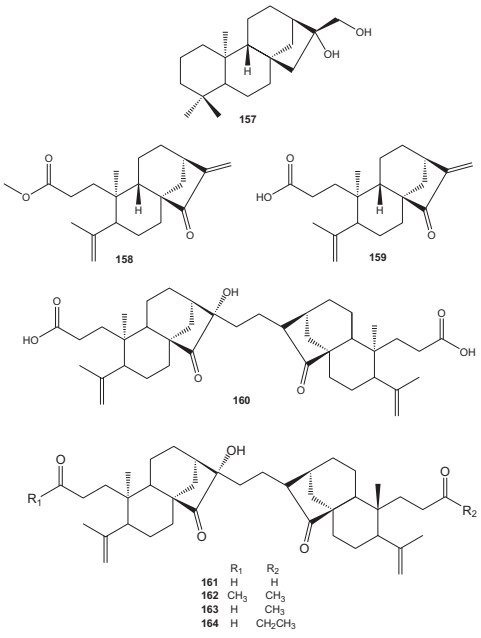
(continued)

Table 11.1 (continued)

Plants	Extracted compounds
Chondrodendron tomentosum	  W
Uncaria tomentosa	   X
Uncaria tomentosa	    Y

(continued)

Table 11.1 (continued)

Plants	Extracted compounds
Tapirira guianensis	 Z
Croton cuneatus	 AA
Croton species	 BB

(continued)

plants. Hence, they can be further considered for phytochemical analysis and also new assays in different cancer cell lines (Ruffa et al. 2002). Seven Argentine plants with cancer-related ethnobotanical uses were screened in a study to detect cytotoxic activity (Mongelli et al. 2006). The plants studied were *Aristolochia triangularis* (DC.) (Aristolochiaceae), *Baccharis grisebachii* Hieron (Asteraceae), *Bolax gum-*

mifera (Lam.) Spreng. (Apiaceae), *Eupatorium hecatanthum* (DC.) (Asteraceae), *Erythrina crista-galli* L. (Faboideae), *Pterocaulon polystachyum* (DC.) (Asteraceae), and *Salpichroa origanifolia* (Lam.) Baill (Solanaceae). DNA interaction, crown gall tumor inhibition, and the KB cell inhibition were evaluated by the use of the DNA-MG (DNA-methyl green), the potato disc, and the KB cell toxicity bioassays, respectively. The observations revealed that *A. triangularis*, *B. gummifera*, and *E. hecatanthum* could contain the KB cells inhibiting phytocompounds. Interestingly, all the evaluated plants exhibited the inhibition of the crown gall tumor growth. The results confirm the traditional use of these plants against tumors. In addition, the extracts of *E. hecatanthum* and *P. polystachyum* were reported to possess compounds which interact with the DNA (Mongelli et al. 2006). Nevertheless, other plants have been studied for their phytochemicals, for example, the phytochemical examination of *A. triangularis* led to the isolation of lignans and ent-kaurane-type diterpenes (Lopes et al. 1990) (Table 11.1-B). Likewise, *S. origanifolia* contains withanolides (Tettamanzi 1999), and *B. grisebachii* constitutes diterpenes, flavonoids, and coumaric acids (Feresin et al. 2003). Flavonoids from *E. hecatanthum* (Clavin et al. 2013), coumarins from *P. polystachyum* (Vera et al. 2001; Medeiros-Neves et al. 2015) (Table 11.1-C), and isoflavonoids and pterocarpanes from *E. crista-galli* (Redko et al. 2006; Tjahjandarie et al. 2015) have been reported (Table 11.1-D). *Flourensia oolepis* S.F. Blake (Asteraceae), commonly known as chilca, a species collected from the central region of Argentina, showed antibacterial activity. A group of investigators isolated five compounds present in an antibacterial extract that were evaluated against the CML (chronic myeloid leukemia) and ALL (acute lymphoblastic leukemia) cell lines including their multidrug-resistant (MDR) phenotypes. Among the isolated flavonoids (Table 11.1-E), the best cytotoxic activity was induced by the compound, 2,4-dihydroxychalcone. In addition, the compound showed a strong and selective cytotoxicity against CML and ALL cells and their MDR phenotypes (Joray et al. 2015).

11.2.2 Bolivia

Bolivia is located in the central zone of South America. With different climatic conditions and variations of soils, it has a wide range of environments and ecosystems. This country has a rich biodiversity, with a large number of plant species, being many of them used in folk medicines. Besides this, Bolivia has a great cultural diversity with a mainly indigenous population distributed in different ethnic groups. The indigenous communities have practiced herbal medicine therapy for hundreds of years, and these knowledge about medicinal plants have passed on through generations. Even today, Bolivians still prefer the use of folk medicines over modern medicine (Fernandez et al. 2003). In spite of this, there are only limited studies focused on ethnobotanical inventory of these plants used by Bolivians inhabitants to treat their health problems (Cussy-Poma et al. 2017). In these studies, we found that

the medicinal plants reported are used to treat pain, fever, inflammation, urological problems, diseases of the respiratory system, skin affections, and mainly gastrointestinal disorders. The species reported with use against cancer by Bolivians inhabitants are presented below.

Bourdy et al. (2000) reported a list of plant used as medicinal for the Tacana, an Amazonian Bolivian ethnic group. Among them, *Copaifera reticulata* Ducke (Fabaceae) and *Piper* sp. (Piperaceae) are used to treat uterine cancer. It is important to mention that the genus *Piper* contains various species that have been used in traditional medical practices in many countries for the treatment of cancer or cancer-related symptoms. Investigations have witnessed the occurrence of some cytotoxic compounds in the extracts of few *Piper* species. Among them are the amide alkaloids, the major active principles (Wang et al. 2014). In Bolivia, species of the genus *Piper* are widely distributed in the tropical regions, and the antecedents show their extensive use in the folk medicines for the treatment of parasitic diseases. Despite this, there are no phytochemical studies directed toward the search for bioactive compounds.

Uncaria guianensis (Aubl.) J.F. Gmel (Rubiaceae) and *Uncaria tomentosa* (Willd. ex Roem. and Schult.) DC., both known as "uña de gato," are distributed in different countries such as Bolivia, Brazil, Colombia, Peru, Guyana, Venezuela, and Surinam of South America. They are used in Bolivia to treat various health conditions. The stems and bark of *U. guianensis* are used to treat coughs, colds, rheumatism, arthritis, diabetes, cirrhosis, conjunctivitis, gastric ulcers, prostate cancer, as anti-inflammatory, anticonceptive, and antitumoral, while the roots of *U. tomentosa* are used as anti-inflammatory, anticonceptive, and anticancer. Other species reported with anticancer activity are *Baccharis trimera* (Less.) known in Bolivia as carqueja and *Curcuma longa* known as curcumina (Terceros et al. 2007). A study by Quiroga et al. (2012) reported the use of three plants, namely, *Acacia aroma* (Fabaceae), *Coronopus didymus* (L.) Sm. (Brassicaceae), and *Sambucus peruviana* Kunth (Caprifoliaceae), against cancer and tumors in the traditional medicine of Huacareta. On the other hand, some studies of the evaluation of diverse biological activities of Bolivian plants have also been performed, but to our knowledge, only one is related to the antiproliferative activity of extracts from plants frequently used in Bolivian folk medicine. Rodrigo et al. (2010) investigated the antiproliferative activity against Caco-2 cell lines (colon cancer) using the extracts of 26 plant species which are common in Bolivia. They found that the ethanolic extracts of *Schkuhria pinnata*, *Piper longestylosum*, *Parastrephia lepidophylla*, and *Erodium cicutarium* showed inhibitory activity against cell proliferation. The most potent of them was the ethanolic extract from *Schkuhria pinnata* showing 53% inhibition of growth, followed by *Piper longestylosum* with 43% inhibition, *Parastrephia lepidophylla* with 19% inhibition, and *Erodium cicutarium* with 10% inhibition. No significant effects could be observed for the rest of the ethanol extracts of the tested plant species.

11.2.3 Brazil

Brazil, the largest country of South America, has the highest plant diversity. Various medicinal plants are found in different ecosystems (Amazon forest, Atlantic forest, Caatinga, Cerrado, Pampas, and Pantanal). Many of these plants are used as natural medicines by the people living in these areas to treat diverse diseases, including cancer. The traditional therapists have more understanding on these herbs growing in their territory (Agra et al. 2007). Besides the great biological diversity, Brazil has a vast cultural diversity and, hence, influences in the diverse forms of plants being utilized in health-care needs. Many exotic species were introduced by both Europeans and Africans during the times of colonization, and the knowledge about their uses was mixed with those of the indigenous people. This has favored a large popular pharmacopeia based on medicinal plants (de Melo et al. 2011). Diverse ethnobotanical studies have been carried out in the different ecosystems in Brazil, and some plants or their metabolites have been studied for having activity against cancer. The results of some of these studies are presented below.

Various medicinal plants of Brazil with anticancer properties were reviewed by de Melo et al. (2011). Their analysis included research outcomes published between 1980 and 2008; however, the authors found that the highest numbers of ethnobotanical and ethnopharmacological studies citing plants with antitumor activity were published between 2000 and 2008. About 84 anticancer plant species distributed among 42 families were reported in their review. The plant families Euphorbiaceae (nine spp.), Fabaceae (seven spp.), Apocynaceae (six spp.), and Vitaceae and Asteraceae (four spp. each) had the largest number of species represented. On the other hand, *Aloe arborescens*, *Aloe vera*, *Tabebuia impetiginosa*, and *Euphorbia tirucalli* were the plants most frequently cited. However, *T. impetiginosa* (Mart. ex DC.) Standl. is the only native species of Brazil (Martins et al. 2011). It is a tree with rosy or purple flowers belonging to the family Bignoniaceae and native to the Amazon rainforest and few parts of Latin and South America including Bolivia, Brazil, Ecuador, Colombia, Argentina, French Guinea, Peru, Paraguay, Surinam, Tobago, Trinidad, and Venezuela (Castellanos et al. 2009; Ferreira et al. 2015). *T. impetiginosa* is commonly known as Ipê, Ipê cavatan, Ipê roxo, Ipê comum, Ipê de São Paulo, Aipê, Ipeuva, Lapacho, Guiraiba, Pau d'Arco, Pau d'Arco velmelho, Paud'Arco roxo, Peuva, Piuva, or Upeuva in Brazil; Lapacho Rosado in Argentina and Paraguay; Cortez negro and Ipé in Costa Rica; Lapacho negro in México; Tajibo morado in Bolivia; and Puy in Venezuela (Roman et al. 2012). Traditionally, the stem-bark and/or inner bark of this tree has been used to treat health problems such as arthritis, bacterial and fungal infections, eczemas, inflammation of the prostate, fever, pain, dysentery, ulcers, dermatitis, syphilis, malaria, trypanosomiasis, and cancer (Kim et al. 2006; Agra et al. 2008; de Melo et al. 2011; Castellanos et al. 2009). *T. impetiginosa* is one of the most common plants used in the traditional

medicines of Brazil to cure cancer (Castellucci et al. 2000; Gazzaneo et al. 2005; Botsaris 2007; de Albuquerque et al. 2007a; Negrelle and Fornazzari 2007; Agra et al. 2008). The bark of *T. impetiginosa* contains a large number of phytocompounds including anthraquinones and naphthoquinones (Manners and Jurd 1976), quinones (Sharma et al. 1988), benzoic acids and derivatives of benzaldehyde (Wagner et al. 1989), flavonoids (Blatt et al. 1996), cyclopentene dialdehydes (Koyama et al. 2000), and furanonaphthoquinones (Zani et al. 1991; de Oliveira et al. 1993; Diaz and Medina 1996). Among the quinones, lapachol (35), α-lapachone (36), and β-lapachone (37) (Table 11.1-F) have been extensively studied for their interesting activity against cancer cells (de Almeida 2009; Hussain and Green 2017). The investigations of the therapeutic effects of lapachol began in the 1960s (Hussain et al. 2007), but after some research on the antineoplastic activity of lapachol, studies were not continued because high doses were needed to achieve the anticancer effect, which produced many side effects. These results motivated the researchers to perform the synthesis of lapachol derivatives including the naturally occurring quinone β-lapachone (Hussain et al. 2007; de Almeida 2009). At the beginning of this year, Hussain and Green (2017) published a review that summarizes the large number of interesting patents published on the therapeutic potential of quinones lapachol, β-lapachone, and α-lapachone. In some publications, *T. impetiginosa* is considered a synonym species of *T. avellanedae* Lorentz ex Griseb, which is also popularly used against cancer in Brazil (Agra et al. 2007, 2008).

Aloe vera L. (synonym *Aloe barbadensis* Miller) is a tropical plant member of Liliaceae family and well adopted to dry and hot climatic conditions especially in the regions of Africa, Asia, and other tropical countries. In Brazil, a cultivated species locally known as "babosa" is widely used in customary medicines to treat pain in the bones, rheumatism, eczema, hair loss, gastritis, hemorrhoids, inflammation, wounds, cough, burns, and cancer (Soares et al. 2004; de Souza and Felfili 2006; Pilla et al. 2006; de Albuquerque et al. 2007a, b; Negrelle et al. 2007; Calábria et al. 2008; dos Santos et al. 2008). Many biological properties associated with *Aloe* species are contributed by inner gel of the leaves. In studies performed, the plant has exhibited many pharmacological activities such anti-inflammatory, antioxidant, antimicrobial, immune boosting, antitumor, hypoglycemic, hypolipidemic, antiulcer, wound healing, hepatoprotective, and antidiabetic (Radha and Laxmipriya 2014; Rahmani et al. 2015). This plant contains different biologically active substances, including vitamins, minerals, saccharides, amino acids, and anthraquinones, such as aloe-emodin (38), aloin A (barbaloin) (39), and aloin B (isobarbaloin) (40) (Table 11.1-G). *Aloe vera* and its anthraquinones have attracted much the attention as agents against cancer. In a study performed by Saini et al. (2010), the antitumor activity of *Aloe vera* against stage 2 skin tumorigenesis induced by *Croton tiglium* (croton) oil and 7,12-dimethylbenz[a]anthracene (DMBA) was investigated. They found that compared to 100% incidence of tumor development in group I (DMBA + croton oil only), the incidence of tumors decreased to 50% in group II (DMBA + croton oil + topical *Aloe vera* gel), to 60% in group III (DMBA + croton oil + oral *Aloe vera* extract), and to 40% in group IV (DMBA + croton oil + *topical*

Aloe vera gel + oral *Aloe vera* extract). Another study indicated that the ethanolic extract (50%) of *Aloe vera* exhibited antitumor effect against Ehrlich ascites tumor in mice (Naveena et al. 2011). Later, Chandu et al. (2012) evaluated the in vitro antitumor activity of *A. vera* extract against the B16F10 melanoma cell line. *A. vera* showed good cytotoxic activity, and it had less toxic effects to the normal blood lymphocytes, as compared to that of standard anticancer drug. Aloe-emodin is a subtype of anthraquinones isolated from *A. vera* leaves. This compound has been able to prevent the growth of several cancer cells including human lung carcinoma (CH27, H460) (Lee 2001; Lee et al. 2001; Yeh et al. 2003), hepatoma (Hep G2, Hep 3B) (Kuo et al. 2002, 2004), bladder (Lin et al. 2006), breast (Huang et al. 2013), human tongue squamous carcinoma (SCC-4) (Chiu et al. 2009), colon carcinoma (Pecere et al. 2003; Lin and Uen 2010; Suboj et al. 2012), and leukemia (HL-60, U937) (Chen et al. 2002, 2004; Tabolacci et al. 2011). Furthermore, aloe-emodin was found very effective against the neuroectodermal tumor cells (Pecere et al. 2000; Ahirwar and Jain 2011). In some of these studies, it has been determined that the mechanism of cytotoxic action of this compound is through the induction of apoptosis (Lin et al. 2011). Aloin (aloin A or barbaloin) is a natural anthraquinone glycoside derived from *A. vera* leaves that has the anticancer potential (Pan et al. 2013). Aloin has showed activity against various human cancer cells, including gastric (Guo et al. 2007), ovarian, breast (Esmat et al. 2005, 2006), uterine carcinoma (Niciforovic et al. 2007), human Jurkat T lymphocyte cells (Buenz 2008), and B16-F10 murine melanoma (Tabolacci et al. 2013), and moreover, some of these studies showed that this compound induced the arrest of cell cycle and apoptosis. Pan et al. (2013) found that aloin treatment inhibited VEGF-stimulated angiogenesis in human endothelial cells. VEGF is one cytokine that stimulates angiogenesis; thus, they suggest an antiangiogenic effect of aloin. In a recently study, aloin acted as a chemopreventive agent against preneoplastic lesions in the colon of Wistar rats induced by 1,2-dimethylhydrazine (Hamiza et al. 2014). They found that aloin might inhibit the cancer-stimulating effects of 1,2-dimethylhydrazine via activating anti-inflammatory and antioxidant responses.

Aloe arborescens Mill. is another species widely used in the traditional medicines of Brazil for the treatment of cancer (Dorigoni et al. 2001; Garlet and Irgang 2001; Soares et al. 2004; Vendruscolo et al. 2005; Vendruscolo and Mentz 2006; de Barros et al. 2007). *A. arborescens* is also commonly used to treat burns and other skin-related diseases (Di Luccia et al. 2013). In a recent study, Ceccarelli et al. (2012) evaluated the antiproliferative properties of the leaf extract of *A. arborescens* on murine myeloma cell lines using the MTT method, and they found the cell inhibition rate up to 80%. On the other hand, they carried out a bioassay-guided fractionation by thin-layer chromatography (TLC) that allowed the identification of a spot showing antiproliferative activity. Further exploration by high-performance liquid chromatography (HPLC) and nuclear magnetic resonance (NMR) spectra showed that the TLC spot consisting of aloenin A (41) and aloins A (39) and B (40) (Table 11.1-H). In a clinical study performed by Lissoni et al. (2009), a total of 240 patients with metastatic solid tumor were randomized to receive chemotherapy with

or without aloe (*A. arborescens*). The drugs etoposide, cisplatin, vinorelbine, oxaliplatin, gemcitabine, and 5-fluorouracil (5-FU) were used in the chemotherapy. Aloe was given orally at 10 ml thrice/daily. The patients treated with chemotherapy and aloe showed higher percentage of tumor regressions as well as higher disease control compared to the patients treated with chemotherapy alone. These results seem to suggest that aloe may be supplemented with chemotherapy to increase the efficacy of a cancer treatment. Likewise, Furukawa et al. (2002) evaluated the effect of freeze-dried aloe leaves powder in the course of *N*-nitrosobis (2-oxopropyl) amine (BOP)-induced tumorigenesis in hamsters was evaluated. The study showed that the rates of pancreatic cancer and hyperplasias were significantly reduced when treated with BOP and aloe (5%). In another study, aloenin was compared with its synthetic compound against Hep G2, HCT 116, and HCT 116/VCR 100-1-1 cells and found that aloenin isolated from *A. arborescens* had no distinct influence with IC_{50} values of more than 100 μM (Jin et al. 2005).

Ferreira et al. (2011) evaluated the antiproliferative prospects of the seed extracts of Brazilian plant species against HCT 8 (colon), HL-60 (leukemia), SF-295 (glioblastoma), and MDA/MB-435 (melanoma) cells. The results indicated that seed extract (ethanol) of only one plant (*Myracrodruon urundeuva*) showing potential anticancer activity and inhibited the cell proliferation up to 90%. This extract was more active against the HL-60 cells (IC_{50} = 12.5 μg/ml). Mans et al. (2000) have mentioned the importance of *Maytenus ilicifolia*, *A. vera*, or *A. arborescens* to evaluate their potential antineoplastic properties and represent a lead in finding novel anticancer compounds. Likewise, *Tabebuia* and *Hypericum* genera are also mentioned. *M. ilicifolia* belonging to the Celastraceae family is a native of south Brazil (especially of the forests of the Mato Grosso do Sul, São Paulo, and Rio Grande do Sul), Paraguay, Bolivia, Uruguay, and Northeastern of Argentina (Alonso and Desmarchelier 2007). In Brazil, it is popularly known as cancerosa, espinheira-santa, espinheira-divina, or maiteno (Cordeiro et al. 2006). It is used in folk medicine to alleviate nausea and stomach pain and mainly to treat ulcer and inflammation of the stomach lining (Camparoto et al. 2002), cancer, skin cancer, flu, rheumatism, pain, and inflammation (Soares et al. 2004; Tagliati et al. 2004; dos Santos et al. 2008; Santos et al. 2014). Espinheira-santa has pharmacological effects proven by the Ministry of Health of Brazil, approving its use as antiulcerogenic (de Moraes and da Cunha 2012). Furthermore, this plant presents activity against cancer, skin cancer, flu, rheumatism, pain, and inflammation (Tagliati et al. 2004; Santos et al. 2014). In Paraguay, this plant is used by the local people as an emmenagogue and a contraceptive, while in Argentina, it is used an emmenagogue, anti-abortive, and anticancer drug (Arenas and Moreno Azorero 1977). Many phytocompounds have been isolated from this plant including flavonoids (Leite et al. 2001; Cipriani et al. 2006; Baggio et al. 2007; Tiberti et al. 2007), tannins (de Souza et al. 2008; Pessuto et al. 2009), sesquiterpene pyridine alkaloids (Shirota et al. 1994a), triterpenes (Itokawa et al. 1991; Shirota et al. 1994b), and quinonemethide triterpenes (de Lima et al. 1971; Pereira and Borges 1960), of which maytenin (41) and pristimerin (42) have been reported with anticancer activity.

The antimutagenic activity of the infusion of *M. ilicifolia* against known mutagenic substances was determined by Horn and Vargas (2003). Of the doses of the infusion tested, 75% showed high and significant inhibition of the mutagenicity induced by aflatoxin B1, 2-aminofluorene, and 2-aminoanthracene. Araújo Junior et al. (2013) demonstrated that the leaf extract of *M. ilicifolia* induces apoptosis in Hep G2 (human hepatocellular cells) and HT-29 (colorectal carcinoma) cells by downregulating the expression of Bcl-2 and activating caspase-3-dependent signaling pathways. The compound pristimerin has shown antiproliferative activity against a series of cancer cells such as breast (MDA/MB-231, MCF-7, MDA/MB-435) (Chang et al. 2003; Wu et al. 2005; Costa et al. 2008), prostate cancer (PC-3) (Yang et al. 2008), leukemia (HL-60, K562), glioblastoma (SF-295), colon (HCT 8) (Costa et al. 2008), and glioma (Chang et al. 2003; Yan et al. 2013). Likewise, Wang et al. (2012) and Deeb et al. (2014) have demonstrated the antiproliferative activity of pristimerin against pancreatic cancer cells such as BxPC-3, AsPC-1, MiaPaCa-2, PANC-1, and PANC-1 by inducing apoptosis. Other species of the *Maytenus* genus reported for their use in Brazilian folk medicines are *Maytenus rigida* Mart. and *M. obtusifolia* Mart. A decoction of leaves from *M. obtusifolia* is used to treat common inflammations and tumor, while stem-bark powder is used for the treatment of skin ulcers. *M. rigida* is known as bom-nome, and the stem-bark of this plant is used against inflammations of ovaries, infections of kidneys, skin ulcers, and tumors (Agra et al. 2007, 2008).

Other species reported for their ethnobotanical use against cancer in Brazil are *C. multijuga* Hayne (Fabaceae), *Cissus decidua* J. A. Lombardi (Viscaceae), *Himatanthus articulatus* (Vahl) Woodson (Apocynaceae), *Marsdenia altissima* (Jacq.) Dugand (Apocynaceae), *Morinda citrifolia* L. (Rubiaceae), *Cnidoscolus urens* (L.) Arthur (Euphorbiaceae), *Crocus* sp. (Iridaceae), *Psychotria ipecacuanha* (Brot.) (Rubiaceae) (de Albuquerque et al. 2007b), *Bauhinia forficata* Link (Fabaceae), *Costus spicatus* (Jacq.) Sw. (Costaceae), *Hymenaea courbaril* L. (Fabaceae) (Santos et al. 2014), *C. decidua* Lombardi (Vitaceae) (de Melo et al. 2011), *Croton urucurana* (Euphorbiaceae) (de Souza and Felfili 2006), *C. spiralis* (Jacq.) Roscoe (Costaceae) (Pilla et al. 2006), *Symphytum officinale* (Boraginaceae) L., and *Stachytarpheta cayennensis* (Rich.) Vahl (Verbenaceae) (Merétika et al. 2010).

11.2.4 Chile

The Chile territory is a long and narrow strip land between the Pacific Ocean and the Andes mountains. All kinds of geographic conditions from deserts until rain forest extremes can be observed in this country. It is clear that this geographic diversity also offers floral diversity. The native inhabitants from Chile have a rich tradition of using plants to alleviate and fight diseases including cancer. This revision pretends to give information of some studies realized with native and endemic plants from Chile territory, against cancer.

One of the more recently published works on anticancer plants of Chile is *Psoralea glandulosa* L. (Papilionaceae) called as culen and hualhua. From the resinous exudate of this plant, the compounds such as bakuchiol (43), 2-hydroxy-bakuchiol (44), and 12-hydroxy-iso-bakuchiol (45) were isolated (Table 11.1-I). These metabolites and the resin showed a positive response against the A2058 (human melanoma) cells. However, the evaluated metabolites were not effective as that of the resin, which can indicate that synergistic effects gave the best results with the resin (Madrid et al. 2015). Various metabolites such as coumarins, labdane diterpenes, and sterols (Table 11.1-J) have been reported in *Gypothamnium pinifolium* Phil (Asteraceae), a native Chilean species (Zdero et al. 1988). In a study, a group of these isolated metabolites were evaluated against MCF-7 cells, and the observations showed that the compound 2-nor-1,2 secolylcoserone (46) (Table 11.1-J) had the highest cytotoxic effect and concluded it to be a good candidate for advanced anticancer research investigations (Simirgiotis et al. 2015).

Leptocarpha rivularis DC (Asteraceae), known as "palito negro" is traditionally used by the inhabitants of Chile. The plant has been demonstrated to decrease of cell viability in cancer cells (Martinez et al. 1995, 1998, 2006). A compound, named leptocarpin (51) (Table 11.1-K), the major metabolite, previously isolated from this plant was investigated for the cytotoxic mechanism on different cancer cell lines such as PC-3 (prostate cancer cell line), HT-29 (colon cancer cell line), MDA-MB-231 and MCF-7 (breast cancer cell lines), HDF (human dermal fibroblasts), and CCD 841 CON (human colon epithelial) cells. The outcomes revealed that leptocarpin treatment decreased the viability of cancer cells by inhibiting the NF-κB factor and inducing caspase-dependent apoptotic pathways (Bossio et al. 2015).

A different strategy in the way to find cytotoxic metabolites from plants is the use of synthetic methods to obtain better biologically active compounds from the natural one. This procedure is exemplified with the compound demalonyl thyrsiflorin A (55) which is a semisynthetic compound obtained for modification of natural one diterpene (56) isolated, together with other compounds from the Chilean species *Calceolaria thyrsiflora* Graham. (Scrophulariaceae) known with the common name capachito (Table 11.1-L). Traditionally, this plant is used as antidiuretic agent, for treating digestive problems, and is recognized with antibacterial properties (Betancur-Galvis et al. 2001). Further, the compound 55 was investigated for the cytotoxic effect on KB (oral squamous carcinoma) and Du-145 (androgen-insensitive prostate) cancer cells. Also, the study showed an apoptotic response and a necrosis effect at higher doses (Gabarino et al. 2007).

Senecio graveolens Wedd (Asteraceae) is a species belonging to one of the largest genera, *Senecio*, present in the mountains of the Andes, Chile. It is locally known as chachacoma and used for the ailments related to altitude. In a study, the antiproliferative effect of *S. graveolens* alcoholic extract and its most copious constituent, 4-hydroxy-3-(3-methyl-2-butenyl)acetophenone, were tested against MCF-7, ZR-75-1, MDA-MB-231 (breast cancer), and MCF-10F (non-tumorigenic) cells (Echiburú-Chau et al. 2014). The results of this study suggest a specific activity of the ethanolic extract on the breast cancer cells. However, the assayed phytocompound was not effective against the tested cancer cells. *Geum quellyon* Sweet

(Rosaceae), called by the Chilean inhabitants as hierba del clavo, is used for treatment of a series of health problems such as gastric inflammations and prostatitis as diuretic and also is endorsed with aphrodisiac activities (Muñoz et al. 2004). The anticancer potential of its methanolic extract was proved against Caco-2 (colon carcinoma), KB (oral squamous), and Du-145 (androgen-insensitive prostate) cancer cell lines. But, a necrosis effect was also observed on the Caco-2 and KB cells. Further studies are necessary to find the active metabolites from the extract to justify these results (Russo et al. 2007).

11.2.5 Colombia

Colombia owns a big territory under the South America and is one of the top 10 countries with the highest biodiversity worldwide. With a diverse climate and geography, this territory is the home of many unique flora and fauna. Under the Colombian population, the use of plants to treat diseases and ailments is common and practiced even now. Many plant species are used to fight against cancer; however the literature regarding the studies of anticancer plants is scarce, and some of the reported studies are considered in this review.

Plants belonging to Asteraceae family, such as *Gnaphalium elegans* H.B.K. and *Achyrocline bogotensis* (Kunt) DC., were isolated with two isoflavones, 57 and 58 (Table 11.1-M). These compounds were evaluated on colon (Caco-2, HCT 116), breast (MCF-7, SK-BR-3), prostate (PC-3, LNCaP), and pancreatic (MIA PaCa, Panc 28) cancer cells using the MTT assay. The results indicated the apoptotic effects of these two compounds as revealed from the terminal deoxynucleotidyl transferase (TdT) dUTP nick-end labeling (TUNEL) assays. Both compounds displayed a potent activity against the pancreas (Panc 28) and colon (Caco-2) carcinoma cells, whereas the cytotoxic activity of flavone 58 was observed in breast (SK-BR-3), colon (HCT 116), and pancreas (Mia PaCa) cancer cells (Thomas et al. 2012). Ten species of the *Euphorbia* genus (Euphorbiaceae) such as *E. heterophylla* L., *E. cyathophora* Murray, *E. graminea* Jacq., *E. tirucalli* L., *E. cotinifolia* L., *E. arenaria* Kunth, *E. pulcherrima* Willd. ex Klotzsch, *E. cotinifolia* L., and *Euphorbia* sp. are used by the Colombian traditional therapists to treat ailments such as cancer, ulcer, and warts. These plants were tested for their potential antitumor activity using the MTT colorimetric assay (Betancur-Galvis et al. 2002). About 47 different solvent extracts (petroleum ether, ethanol, dichloromethane, water, and water-methanol) from these 10 species were screened. Among them, the dichloromethane extracts of *Euphorbia* sp., *E. graminea*, and *E. cotinifolia* showed the highest activity. Later, these extracts showing positive response were further investigated for their antiproliferative effects against few cancer cells, and the results revealed the highest toxicity of the dichloromethane leaf extract of *E. cotinifolia* against Hep 2 and CHO cancer cells with an IC_{50} value of 35.1 and 18.1 μg/ml, respectively. Considering these results, *E. cotinifolia* deserves further studies to identify its antitumor compounds. In this chapter, the information about its phytochemical

composition is ignored. In a different study, where the inhibition of topoisomerase enzyme was the target to search for plants with anticancer activity, *Myriocarpa stipitata* Benth (Urticaceae) showed a good result, and the authors have suggested that this topoisomerase inhibitory activity is due to the presence of alkaloids in the dichloromethane extract of *M. stipitata*. The alkaloids are common metabolites in this genus, but there is no information regarding the alkaloid structures of this specific species (Niño et al. 2011). In another study, 14 phytocompounds isolated from 3 native Colombian plants, namely, *Pleurothyrium cinereum*, *Ocotea macrophylla*, and *Nectandra amazonum*, were tested against tumor cell lines A-549, HeLa, Hep 2, MCF-7, and PC-3 (Cuca et al. 2011). The results revealed that bicyclooctanoids and kaurenoic acid showed cytotoxicity against all tumorous cells, whereas benzofuranoids exhibited a selective action against the HeLa cells. In addition, (−)-cinerin A demonstrated a complete lethality against PC-3 and Hep 2 cells, while kaurenoic acid (73) completely inhibited A549 cell lines (Table 11.1-N). These plant species were reported to contain lignans, neolignans, diterpenes, and alkaloids (Coy and Cuca 2008, 2009a, b; Cuca et al. 2011). Likewise, the ethanolic extracts of leaves and fruits of *Cucumis dipsaceus* C.G. Ehrenb. ex Spach (Cucurbitaceae) from Colombia, called by the people as pepino diablito, were evaluated on the cancer cells (K562 and Hep 2). The phytochemical study of this plant only showed the presence of triterpenes and flavonoids and cucurbitacins, but their structures were not identified (Salama et al. 1999). The organic extracts of the species *Espeletia killipii* Cuatr. (Asteraceae) were investigated for cytotoxic activity, showing an interesting activity on few cancer cells (Jaimes et al. 2006). Further investigations showed that the cytotoxic principle of the *Espeletia killipii* (Asteraceae) was identified as the sesquiterpene lactone longipiline acetate (76) (Table 11.1-O). This compound was evaluated by the MTT method on Colombian cancer cell lines from thyroid gland, testicle, mouth, myeloid leukemia, Hodgkin's lymphoma, and K562 tumoral cell. The compound was active against the Hodgkin's lymphoma and the myeloid leukemia with IC_{50} value of 3.0 μg/ml. The results indicate that this molecule is an important target that deserves to be considered in further studies (Jaimes et al. 2006). The species *Acnistus arborescens* (L.) Schltdl. (Solanaceae), well known as guitite, is used in Colombia for inflammation, treatment of diseases of the liver and spleen, and treatment of cancerous growths. This plant was subjected to phytochemical and cytotoxic activity studies. Different organic fractions of butanol, methanol, and dichloromethane were screened against MCF-7, MKN-45, HT-29, SiHa, Hep 2, HeLa, and U937 cancer cell lines. The results indicated the highest activity of the dichloromethane extract with IC_{50} value of 50 μg/ml (Morantes et al. 2006). Later, withanolides (Table 11.1-P) with cytotoxic activity were isolated from the same plant (Minguzzi et al. 2011).

In an interesting work, the cytotoxic activity of extracts from six species including *Annona* sp. (Annonaceae), *Aristolochia cordifolia* Mutis ex Kunth. (Aristolochiaceae), *Crescentia cujete* L. (Bignoniaceae), *Callisia gracilis* (Kunth) D.R. Hunt (Commelinaceae), *Beta vulgaris* L., and *Chenopodium ambrosioides* L. (Chenopodiaceae) was evaluated against MDBK (bovine kidney) and Hep 2 (human larynx epidermoid) cancer cells. From the results, *Annona* sp. was shown to possess

a good cell toxicity and, thus, can serve as a good source for the identification and isolation of various active anticancer principles (Betancur-Galvis et al. 1999). Likewise, it has been reported that species from the *Annona* genus are rich in acetogenins, a kind of compounds with proven anticancer activity (Moghadamtousi et al. 2015; Gupta et al. 2011; Schlie-Guzman et al. 2009, Colman-Saizarbitoria et al. 1996, 1998).

The compounds extracted from three species (*Espeletia*, *Pentacalia*, and *Ageratina*) of the Asteraceae family, *Stemmadenia* from the Apocynaceae, and *Curatella* belonging to Dilleniaceae were evaluated against Hep 2, MCF-7, and four more breast cancer cell lines (CBC-1170, CSC-1595, CSC-3322, and CSC-3325) obtained and characterized at the National Cancer Institute in Colombia. The sesquiterpene lactone longipiline acetate (76) isolated from the species *E. killipii* and the quinol jacaranona (84) (Table 11.1-P) isolated from *P. corymbosa* exhibited very high cytotoxicity with IC_{50} values below 5 μg/ml. It is also important to indicate that these two compounds were very active against the Colombian tumoral breast cancer cell lines assayed (Téllez et al. 2004). Similarly, *P. abietina* containing two jacaranone compounds and a quercetin glycoside and kaurene diterpenes are considered as the metabolites with the cytotoxic activity (Santana and Varela 2013). Two very common flavonoids, quercitrin and quercetin isolated from *Brownea ariza* Benth. (Fabaceae), were effective against the VERO cells and Myeloma Murino SP2/0-Ag14 cells (Gil et al. 2008). The plant *Gnaphalium meridanum* Aristeg. (Compositae) is used in the folk medicines of Colombia to treat anti-inflammatory diseases and skin infections and also used as a hemostatic and anticancer agent. Interestingly, a scientific study has shown that flower and leaf extracts of this plant possess a potent anticancer activity against the cell line, J-774 (murine macrophages). Interestingly, the ethyl acetate extract from the flowers showed a strong activity against the cancer cell line and, thus, indicates a possible candidate for further exploration to isolate anticancer metabolites from this plant (Torrenegra et al. 2016).

11.2.6 Ecuador

Ecuador is one of the most biodiverse countries in the world and is well known for its old tradition of medicines. Importantly, indigenous communities of Ecuador present a good ethnomedical information about several medicinal plants (Bailon-Moscoso et al. 2015). In this chapter, we update the latest information on traditional plants of Ecuador which are proven scientifically as well as yet to be explored for their anticancer properties. *Uncaria tomentosa* (Will.) DC. is widely distributed in South America. It is traditionally used by Ecuadorian, Peruvian, Bolivian, and Asian population to treat ulcers, warts, intestinal problems, body pain, and microbial infections (Bourdy et al. 2000; Pohle and Reinhardt 2004; Heitzman et al. 2005; Tene et al. 2007). Plant extracts of *U. tomentosa* are reported to possess several biologically important phytocompounds including proanthocyanidins, alkaloids, terpenes, sterols, and flavonoids. The major alkaloids include isopteropodine (86),

isomitraphylline (87), pteropodine (88), and uncarine F (89) (Table 11.1-Q), which are known to exhibit antiproliferative activity against the acute lymphoblastic leukemia (CCRF-CEM-C7H2) cells. Moreover, uncarine F and pteropodine compounds also have the capability to induce apoptosis (Bacher et al. 2006). However, mitraphylline (90) (Table 11.1-P) failed to inhibit the CCRF-CEM-C7H2 cells but was found effective against neuroblastoma and glioma cells (IC_{50} of 12–40 μM) (Garcia Prado et al. 2007). Alkaloids such as pteropodine and isopteropodine inhibited the growth of medullary thyroid carcinoma cells by inducing caspase-associated cell death mechanisms (Rinner et al. 2009). Various organic extracts of *U. tomentosa* are capable of inducing apoptosis in the human promyelocytic leukemia (HL-60) cells (Sheng et al. 2000; De Martino et al. 2006; Cheng et al. 2007; Pilarski et al. 2010, 2013). In addition, the alkaloid-supplemented plant extracts are capable of inhibiting the growth of xenografts of HeLa (cervical cancer), HCT 116, and SW480 (colon cancer) cells by affecting the Wnt signaling pathways (Gurrola-Díaz et al. 2011). Likewise, the aqueous extract of this plant induced cytotoxicity mediated by apoptosis in both HL-60 and K562 leukemia cell lines (Sheng et al. 2000). Further, the quinovic acid glycosides were isolated from the ethanol/water bark extract. In another study, this plant was shown to inhibit the T24 growth of human bladder cancer cells with IC_{50} of 78.36 μg/ml. The cytotoxicity was mediated by activating the caspase-3-dependent apoptosis signaling pathways and through a mechanism that involves translocation of NF-κB to the nucleus (Dietrich et al. 2014). In addition, several studies have shown that the solvent extracts of this plant and its isolated pure compounds exhibit anti-inflammatory activity which might be involved in stimulating the immune system and prevent the proliferation of tumor cells (Heitzman et al. 2005; Allen-Hall et al. 2010).

A red sap, also identified as Dragon's blood, is produced from the bark of ≥3-year-old *Croton lechleri* Müll. Arg. (Euphorbiaceae) plants (Salatino et al. 2007). This sap has been used by the Amazon ethnic people to cure wounds and treat gastrointestinal illnesses and tumor (Cerón 2006; Gupta et al. 2008). Also, the sap has the capability to inhibit myeloid leukemia cells and K562 and SK23 melanoma cells at 1 mg/ml (Rossi et al. 2003). However, at higher concentrations (tenfold), both colon cancer cells HT-29 and LoVo were inhibited. Likewise, an alkaloid called tapsine (92) (Table 11.1-P) was shown to effectively inhibit both SK-23 and HT-29 cancer cells (Montopoli et al. 2012). The sap contains mainly flavonols and oligomeric proanthocyanidins. Interestingly, proanthocyanidin coded as SP-303 is reported to possess antiviral and antidiarrheal activity; however no cytotoxic activity is reported yet (Jones 2003). In contrast, catechin, epigallocatechin, epicatechin, and gallocatechin occurring in *C. lechleri* sap are shown to exhibit cytotoxicity against human cancer cells. They induce antiproliferative activity through various ways such as apoptosis, inhibiting protein kinases, activating caspases, and modulating cell cycle regulations (Fujiki et al. 2002; Forester and Lambert 2014). Previously, clerodane-type diterpenes were isolated from its sap (Cai et al. 1993). In another study, A431 epidermoid carcinoma cell line was inhibited by taspine (an alkaloid) by the induction of apoptosis by regulating the ratio of Bax/Bcl-2 and activating caspase-3 enzymes (Montopoli et al. 2012). Similarly, taspine has been reported to

prevent the proliferation of HUVEC (human umbilical vein endothelial) cells (Zhang et al. 2010). A derivative of taspine, HMQ1611, showed an antiproliferative effect in breast cancer (MCF-7, ZR-75-30, SK-BR-3) cells and xenografts in mice. Interestingly, HMQ1611 presented a cytotoxic effect against breast cancer cells, by activating the EGFR/MAPK, ERa, and EGFR/PI3K/AKT (vascular endothelial growth factors, EGFRs) pathways (Zhan et al. 2012).

Marsdenia condurango Rchb. f. (Apocynaceae), also well known as *Gonolobus condurango*, is used in the customary medications for treating syphilis, inflammatory diseases, and cancer (Tene et al. 2007). The bark of *M. condurango* is reported to contain few pregnane glycosides (Hayashi et al. 1980, 1981; Berger et al. 1988). A glycoside-rich extract of *M. condurango* was shown to inhibit NSCLC (non-small cell lung cancer) cells (IC_{50} = 0.22 μg/μl) through inducing apoptotic pathway. Further, DNA damage and the arrest of cell cycle at sub G0/G1 phase were confirmed (Sikdar et al. 2014). Similarly, condurango glycoside A (93) (Table 11.1-P), present as the major constituent of its bark extracts, was capable to inhibit HeLa cells via p53 activation and induction of reactive oxygen species, damaging DNA resulting in apoptosis-mediated cell death (Bishayee et al. 2013). The occurrence of coumarins and quercetin in the bark of *M. condurango* (94) (Table 11.1-P) has been reported to possess antitumor activity (D'Agostini et al. 2005; Gurib-Fakim 2006; Ji et al. 2009). The quercetin compound induces cytotoxicity in HeLa, HT-29, and A431 (human vulva carcinoma) cell lines through apoptosis by the modulation of tyrosine kinase EGFRs (Xavier et al. 2009). Further, it can be noted that quercetin has a higher affinity against wild-type EGFRs as well as two mutated EGFRs as evidenced by the molecular docking studies (Singh and Bast 2014). Likewise, many studies have reported their wide applications in various phytodrugs (Banerji and Campbell 2008).

Senna multiglandulosa (Jacq.) Irwin and Barneby (Fabaceae), a medicinal shrub native to Ecuador is spread alongside the Andean mountains. Emodin (95) (Table 11.1-P) and other bianthraquinones have been isolated from this species (Abegaz et al. 1994). Emodin, a natural anthraquinone, has been shown to effectively inhibit the growth of several cancer cells such as human proximal tubular epithelial (HK-2), prostate (LNCaP), and cervical cancer (Ca Ski, HeLa, Bu 25TK, and ME-180) cell lines (Zhang et al. 1998; Srinivas et al. 2003; Wang et al. 2007; Yu et al. 2008; Yaoxian et al. 2013) by inducing apoptosis. Emodin is a tyrosine kinase inhibitor and naturally induce ROS. Hence, it increases the anticancer activity when used together with along with other therapeutic agents (Ko et al. 2010; Dave and Ledwani 2012; Qu et al. 2013). Likewise, another cytotoxic molecule, physcion (91) (Table 11.1-P), an anthraquinone derivative has been reported to exert inhibitory property against HeLa cells by apoptosis mediated by the generation of ROS (Wijesekara et al. 2014). However, it failed to inhibit MCF-7 and SW620 (human colon adenocarcinoma) cell lines (Almeida et al. 2010).

Minquartia guianensis Aubl. (Olacaceae), a native tree of Ecuador, is used against lung cancer in ethnomedical preparations. Phytocompounds such as betulinic acid, erythrodiol, myristic acid, palmitic acid, and stearic acid have been isolated from the bark and roots of this plant. However, minquartynoic acid (99)

(Table 11.1-P) (El-Seedi et al. 1994) is the major compound with a proven anticancer ability. It was found effective against the colon (Col2), oral epidermoid (KB), and KB-V+ (multidrug-resistant KB) cancer cells when treated together with vinblastine (1 μg/ml). In contrast, it inhibited KB-V– cells even in the absence of vinblastine with an IC_{50} value ranging from 1.6 to 5.5 μg/ml (Ito et al. 2001). Further, few chemical derivatives are developed from minquartynoic acid against cancers, viruses, and parasites (Gung and Dickson 2002; Dembitsky 2006; Gachet et al. 2010). The anti-inflammatory compound taraxerol is also documented from this plant. Triterpenes, namely, taraxerol (98) (Table 11.1-P), lupin-3-one, squalene, and lupeol, occur in the leaves of *M. guianensis* (Cursino et al. 2009).

A native bush of Ecuador, *Monnina obtusifolia* H.B.K. (Polygalaceae), finds its application as antitumor agent. The metastatic spread of cancer involves the growth of new blood vessels, i.e., angiogenesis (Bailón-Moscoso et al. 2014). The butanol extract of *M. obtusifolia* leaves was shown to function as antiangiogenic agent by inhibiting vascular endothelial growth factors (VEGFs) and play a crucial role in regulating angiogenesis (Lepore et al. 2011). A recent study has shown that phytocompounds (Table 11.1-P; Q and 18) of Ecuadorian traditional plants are effective against various cancers. The bark of *Cinchona officinalis* L. (Rubiaceae) is known for antipyretic activity since ancient times, and it is an introduced plant to Europe (Ferreira Júnior et al. 2012). The bark was used mainly for treating malaria, and later, the antimalarial compound quinine (100) (Table 11.1-Q) was isolated. Quinine and its derivative, chloroquine (101) (Table 11.1-Q), were widely used to treat malaria. The bark mainly constitutes large number of alkaloids (5–14%) (Kacprzak 2013). Studies have witnessed the cytotoxic ability of many of these alkaloids against Hep G2 hepatoma, MCF-7 breast adenocarcinoma, HL-60 leukemia, and SH-SY5Y neuroblastoma cells with IC_{50} values ranging from 0.75 to 89 μM (Károlyi et al. 2012). In specific, chloroquine effectively inhibited many cancer cells by inducing autophagocytosis and apoptosis (Solomon and Lee 2009). Another major alkaloid is the quinidine (102) (Table 11.1-Q). It was shown to prevent the proliferation of MCF-7 cells by interrupting the cell cycle process (Solomon and Lee 2009). From phase I and II clinical trial studies, it has been proved that chloroquine and 3-hydroxyquinoline (103) (Table 11.1-Q) compounds when employed in the combinational treatments with other drugs showed synergistic and selective induction of apoptosis in the breast, lung, and glioblastoma cancer cells (Solomon and Lee 2009).

Traditionally, the tree species such as *Annona squamosa* L., *A. muricata* L., and *A. montana* Macfad. (Annonaceae) have been used for treating rheumatism. About 400 acetogenins (ACGs) have been isolated from these plant species (Liaw et al. 2010). ACGs possess a wide array of pharmacological properties including immunosuppressive, antimalarial, and anticancer activities (Rupprecht et al. 1990; Liaw et al. 2010). Interestingly, most of these ACGs inhibit various cancer cells with an IC_{50} value ranging between 10^{-6} and 10^{-14} M. The compounds squamocin (104) and bullatacin (105) (Table 11.1-Q) isolated from *A. squamosa* induce apoptosis in many cancer cells (Zhu et al. 2002; Chiu et al. 2003; Derbré et al. 2006; Yuan et al. 2006). Other ACGs such as montecristin (109), cohibin A (110), murihexocin (111),

and arianacin (112) (Table 11.1-R) isolated from *A. muricata* are demonstrated to possess antitumor properties (Rieser et al. 1996; Alali et al. 1999; Ragasa et al. 2012). In addition, the extracts of *A. muricata* induce necrosis, suspend the cell cycle, and reduce the viability of pancreas cancer cells (Torres et al. 2012). ACGs of *A. montana* seeds including annomonysvin, annonacinone, annomontacin, and annonacin were shown effective against L1210 (murine leukemia), MDA-MB231 (human breast adenocarcinoma), and MCF-7 cancer cells (Jossang et al. 1991). Likewise, ACGs such as *cis*-annoreticuin; montalicins A–E; montalicins G and H; montalicins F, I, and J; montalicins A and B; and monhexocin (+)-monhexocin isolated from *A. montana* seeds showed selective cytotoxic activity against 1A9 and Hep G2 cancer cells (Liaw et al. 2004a, b).

Licania intrapetiolaris Spruce ex Hook. f. (*Chrysobalanaceae*) is a tree from the Ecuadorian amazon rainforest. For the first time, intrapetacin A (113) and intrapetacin B (114), the clerodane-type diterpenoids were isolated from this plant. These two compounds showed cytotoxicity against KB cells (human oral epidermoid carcinoma) with IC_{50} of 2 and 0.8 μg/ml, respectively (Oberlies and Burgess 2002). Later, a very active triterpene, cucurbitacin B (115) (Table 11.1-S), was isolated (Mukherjee et al. 2013) and proved its cytotoxic ability against BEL-7402 (human hepatocellular carcinoma cells), osteosarcomas (MG-63 and SAOS-2), and Hep 2 laryngeal cells (Liu et al. 2010; Chan et al. 2010b; Lee et al. 2011). Also, cucurbitacin B inhibited several leukemia cells such as CCRF-CEM, MOLT-4, K562, SR, and RPMI-8226 with an IC_{50} between 15.6 and 35.3 nM. The cell toxicity was due to the cell cycle arrest (Chan et al. 2010b) and by mediating many signaling pathways (Chan et al. 2010a).

The plant, *Casearia sylvestris* Sw. (Flacourtiaceae), a native plant of Ecuador is traditionally used against tumors (Graham et al. 2000). The aqueous-ethanolic and chloroform extracts of *C. sylvestris* leaves were reported to inhibit the multiplication of MCF-7 cells with an IC_{50} value of 141 μg/ml for aqueous-ethanolic extract and 66 μg/ml for the chloroform extract. Moreover, *C. sylvestris* extract treated animals showed a reduced proliferation of tumor cells (Felipe et al. 2014). *C. sylvestris* containing casearvestrins A (116), B (117), and C (118) (Table 11.1-S) were shown to possess antitumor activity against LX-1 (lung cancer), HCT 116 (colon cancer), and A2780 (ovarian cancer) cell lines with IC_{50} values ranging between 0.12 and 0.89 μM (Oberlies and Burgess 2002). Likewise, casearins isolated form this plant have the antitumor activity (Gonzaga dos Santos et al. 2010; Felipe et al. 2014). Casearins L (119), O (120), and X (121) (Table 11.1-S) showed a strong anticancer activity against leukemia cells such as HL-60, CEM, and K562 (Ferreira et al. 2010). Another bioactive compound, casearin X, showed a greater inhibitory potential against HL-60 and CEM cell lines with an IC_{50} of 0.4 μM. This compound induced cell death through apoptotic pathways (Pinheiro-Ferreira et al. 2014, 2016). The leaves of *C. sylvestris* contain isobutyl gallate-3,5-dimethyl ether (IGDE) (122) and methyl gallate-3,5-dimethyl ether (MGDE) (123) (Table 11.1-S). Both these compounds were shown to exhibit antitumor activity in xenograft models of Lewis lung and Ehrlich tumor cell lines (Da Silva et al. 2009).

11.2.7 Guyana

Guyana has a rich flora biodiversity with 87% of its land area covered by forests (Tewari and Gomathinayagam 2014), but unlike many other tropical countries, most of these forests remain unexplored, and the ethnobotanical information is scarce, especially because in the few anthropological studies carried out, the scientific names of the species are not included. Austin and Bourne (1992) conducted a research on the uses of medicinal plants in the region of Guyana in order to improve ethnobotanical information. They found that the common names used on coastal Guyana are different from the neighboring English and non-English speaking areas, but the same plants are usually used for similar purposes in different countries.

Guyana's original inhabitants were the Amerindians (descendants of the indigenous people of Guyana), and they are often the only ones who know the properties of plants and how they should be used. Nevertheless, with the passage of time, the influences from the outside world, and the process of "civilization," indigenous language has been lost, and it implies the loss of ethnobotanical knowledge, because many of the species used in this region are known only by their indigenous names (van Andel 2000a). Amerindians have used the plants for the treatment of diseases and magic rituals and as a source of foods. In addition, many of these species are used as poisons for fish as a hunting practice to obtain food although this method is prohibited by law. For this reason local Amerindians have cultivated ichthyotoxic plants for a long time, and many of these plants are also used as medicine, such as the species of *Lonchocarpus* and *Tephrosia sinapou*, which have been attributed activity against cancer and acquired immune deficiency syndrome (van Andel 2000b).

Tephrosia sinapou (Buc'hoz) A. Chev. (Fabaceae) is a shrub known in Guyana as kunali, Surinam poison, yarro-cunali, aiari (Guyana Akawaio), yaurokonan (Guyana Arawak), and ai (Guyana Wapishana). The roots of this plant are used for treating cancer in the northwest Guyana, and a decoction of leafy branches is drunk to treat snakebite and as an antisyphilitic (DeFilipps et al. 2004). In South America, it is found in Bolivia, Brazil, Colombia, Ecuador, Guyana, Guyana Francesa, Peru, Surinam, and Venezuela. The main classes of compound isolated from this species include flavonoids and rotenoids (Jang et al. 2003; Vasconcelos et al. 2009). This species exhibits a cancer preventive potential (Jang et al. 2003), larvicidal activity (Ribeiro et al. 2006; Vasconcelos et al. 2012), antioxidant activity, anti-inflammatory and antinociceptive properties (Martinez et al. 2012, 2013, 2016; do Val et al. 2014). Jang et al. (2003) determined the potential cancer chemopreventive properties of the compounds isolated from the stems of *T. toxicaria* induced quinone reductase in cultured Hepa 1c1c7 (mouse hepatoma cells). The induction of quinine reductase reflects the inhibition of cancer initiation. They found that the chalcone, isoliquiritigenin (124), exhibited the most potent activity. Furthermore, the compounds (2*S*)-5-hydroxy-7-methoxy-8-[(E)-3-oxo-1-butenyl]flavanone (125), 4′,5′-dihydro-11,5′-dihydroxy-4′-methoxytephrosin (126), genistein (127), and chrysoeriol (128) (Table 11.1-T) significantly induced quinine reductase activity.

The genus *Lonchocarpus* (Fabaceae) is known as haiari. Various species of *Lonchocarpus* are used as fish poison in northwest Guyana, and of these, *L. chrysophyllus* Kleinh. (black haiari), *L. martynii* A.C. Smith, *Lonchocarpus* sp. (red haiari), and *L. martynii* A.C. Smith are associated with cancer treatment (DeFilipps et al. 2004; van Andel 2000b). The most known active ingredient of *Lonchocarpus* species is the rotenone (129) (Table 11.1-T), which has been shown to display anticancer activity through the induction of apoptosis in various cancer cells (Isenberg and Klaunig 2000; Armstrong et al. 2001; Deng et al. 2010; Siddiqui et al. 2013; Hu et al. 2016). However, studies have witnessed that rotenone induces many adverse side effects including neurodegeneration (Emmrich et al. 2013).

11.2.8 Paraguay

The Paraguay River running through Brazil, Bolivia, and Paraguay divides the country, Paraguay into the western region (Chaco) and the eastern region. Chaco is inhospitable, semiarid, and infertile with scrub forests. Only about 3% of the population live in the Chaco. However, the eastern Paraguay constitutes fertile soil with rolling hills, lavish semitropical forests, and grassy savannas. The consumption of medicinal and aromatic herbs in Paraguay is traditional and widespread; it is a custom that comes from the Guaraní Indians, who had extensive knowledge about the use of plants for medicinal purposes. Nowadays, the use of these plants by the Paraguayans is a mixture of the knowledge of the Guaraní Indians and the Spanish people, who introduced their own healing plants progressively. To treat the health problems, the Paraguayans use herbal remedies simultaneously with pharmaceuticals. Most people have knowledge about the medicinal uses of common plants and use them to treat many of their diseases, as for many, health services in clinics and hospitals are inaccessible, especially in rural areas. Many different species of medicinal plants are commercialized in Paraguayan markets but many of them with minimal studies that support their use in the population. In general, medicinal plants of Paraguay are basically unknown to the scientific community. In view of the great use of medicinal plants by the population of Paraguay, some ethnobotanical studies have been carried out, but species plants used for cancer have been mentioned sporadically in research works and compilations of the Paraguayan pharmacopeia (Schmeda-Hirschmann and Bordas 1990; Basualdo et al. 1991, 1995; Cáceres and Machain 2001; González et al. 2013; Basualdo and Soria 2014; Degen de Arrúa and González 2014; Soria and Ramos 2015).

In 1995, Basualdo et al. identified 17 species (12 families) that are being sold as medicinal plants in the market #4 of Asunción known as “Pettirossi” to treat ulcers, gastritis, cough, respiratory tract diseases, syphilis, amenorrhea, and rheumatism. They are also used as abortives, hemostatics, hypotensives, expectorants, diuretics, and refreshing beverages. In this work the only species used to treat cancer was *Maytenus ilicifolia* Reiss (Celastraceae), known as “kangorosa” in Guaraní for the

rhizome, and "Kangorosa rapo piré" in Guaraní for the bark of the rizhome. Suárez and Mereles (2006) collected verbal information about the uses of 35 species of medicinal trees, belonging to 18 families in Paso Jovái District of the Guairá Department, Paraguay. *Erythrina crista-galli* L. (Fabaceae) known as seibo was reported to treat uterus cancer and other types of cancer. In another ethnobotanical research, *Annona muricata* L. (Annonaceae), *Couepia grandiflora* (Mart. and Zucc.) Benth. (Chrysobalanaceae), and *Croton urucurana* Baill. (Euphorbiaceae) were reported used against cancer (Basualdo and Soria 2014). In a recent paper, Soria and Ramos (2015) identified 56 species used in the IV Health Region of Guairá, Paraguay, with diverse medicinal purposes, of which the most common were *Mentha x piperita* L. (Lamiaceae), *Eugenia uniflora* L. (Myrtaceae), *Lippia alba* (Mill.) N. E. Brown. (Verbenaceae), *Allophylus edulis* (St. Hil.) Radlk. (Sapindaceae), *Scoparia dulcis* L. (Plantaginaceae), and *Chenopodium ambrosioides* L. (Chenopodiaceae); nevertheless, the one species reported to prevent cancer was *Croton urucurana* Baill. (Euphorbiaceae), known in Paraguay as Sangreado.

11.2.9 Peru

Peru is a mega-diversity country, where the conventional medicine coexists with traditional, complementary, and alternative medicine. These kinds of medicines have been institutionally recognized by the Peruvian government, through the implementation of safety procedures and encouragement of research in this area. In a recent research, a multidisciplinary group from Peru, Czech Republic, and Belgium published an interesting work, where the phenolic composition and the antioxidant and antiproliferative activity of a group of edible and medicinal plants of Peruvian-Amazon were assayed (Tauchen et al. 2016). The selection of plants was done, considering the use for the treatment of ailments associated with oxidative stress. The extracts of different parts, fruits, leaves, and barks, of the group of plants were screened on the liver carcinoma cell line Hep G2, colon carcinoma cell line HT-29, and normal fetal lung cells MRC-5 by modified MTT method. The most active plants include *Annona montana* Macfad. (Annonaceae), Inga edulis Mart. (Fabaceae), *Myrciaria dubia* (Kunth) McVaugh (Myrtaceae), *Theobroma grandiflorum* (Willd. ex Spreng.) K. Schum. (Malvaceae), *Mauritia flexuosa* L. f. (Arecaceae), and *Oenocarpus bataua* Mart. (Arecaceae). Many known compounds have been characterized from these plants (Tauchen et al. 2016). In a similar work, an antiproliferative effect of bioassay-guided fractions of five Peruvian plants such as *Doliocarpus dentatus* (Dilleniaceae), *Picramnia sellowii* (Picramniaceae), *Strychnos mitscherlichii* (Loganiaceae), *Iryanthera juruensis* (Myristaceae), and *Croton alnifolius* (Euphorbiaceae) is reported. The study included few cancer cell lines such as A31 (embryonic mouse fibroblast), ME180 (human cervical), H460 (human large cell lung), DU145 (human prostate), M-14 (human melanoma), MCF-7 (human breast), HT-29 (human colon), PC-3 (human prostate) cancer cells,

Vero cells, and normal African green monkey kidney epithelial cells. Betulinic acid (130) (Table 11.1-U), a very well-known metabolite with many biological activities including cytotoxicity, was isolated from *D. dentatus*. The isolated compound, naftaloemodin (131), from *P. sellowii* was considered the cytotoxic principle of this plant. This compound and other metabolites such as chalcones isolated from this plant are shown in the Table 11.1-U.

In general, the *Strychnos* genus is rich in alkaloids. In a study, the bioassay-guided fractionation of *S. mitscherlichii* resulted in the isolation of a dimeric alkaloid 133 (Table 11.1-U) which showed good results against the HT-29 and K562 cell lines with a growth inhibition, GI_{50} <1.0 μg/ml.

Two chalcones, 134 and 135 (Table 11.1-U), isolated from *I. juruensis* were considered as the active principles in the cytotoxic evaluation on human cancer cell lines (Aponte et al. 2008a). Likewise, two different chalcones isolated from this plant also showed good cytotoxic activity (Table 11.1-U) (Aponte et al. 2008b). The *Croton* genus is well recognized with many species, which has been demonstrated with anticancer activity. A series of diverse structures, especially diterpenes, had been isolated from its species. The species *C. alnifolius* possess the phorbol ester 12-*O*-tetradecanoylphorbol-13-acetate (136) (Table 11.1-U), as the cytotoxic compound, especially active against the K562 cell line. In a similar study, 34 extracts from 8 ethnopharmacologically selected Peruvian plants were screened against leishmania, trypanosomiasis, and cell viability. The species included in the study were a representative of eight different families of the Peruvian Amazonia: *Aristolochia pilosa* L. (Aristolochiaceae), *Brunfelsia grandiflora* L. (Solanaceae), *Cedrela odorata* L. (Meliaceae), *Chondodendron tomentosum* Ruiz and Pavón (Menispermaceae), *Paullinia clavigera* Schltdl (Sapindaceae), Tabebuia serratifolia (Vahl) G. Nicholson (Bignoniaceae), *Tradescantia zebrina* (Rose) D.R. Hunt (Commelinaceae), and *Zamia ulei* Dammer (Zamiaceae). The cell viability was studied by using the modified MTT assay against the CHO (mammalian Chinese hamster ovary) cells (Gonzalez-Coloma et al. 2011). The results indicated that mostly all extracts showed at least some small activity against the cell viability, except few extracts from *C. odorata* bark, *C. tomentosum* bark, *P. clavigera* bark, and the hexane extract from leaves of *B. grandiflora*. Some known compounds including alkaloids and naphthoquinones were isolated and identified from these plants (Table 11.1-V) (Gonzalez-Coloma et al. 2011). In a study based on interviews of 88 patients and 117 noncancerous individuals who participated in the survey related to the use of herbal medicines to treat liver cancer in the Peruvian population, the plants *A. vera* and *M. citrifolia* were significantly associated with the treatment of liver cancer-related symptoms in the patient group (Rojas-Rojas et al. 2016).

Other big group of 341 Peruvian medicinal plants, from the northern part of the country, was screened using the brine shrimp lethality assay to determine the cytotoxicity of plant extracts (Meyer et al. 1982; Coe et al. 2010). The toxicity values obtained with this bioassay were later considered to obtain prospective candidates for further investigations. The authors mention in their conclusions that about 75%

of the evaluated species showed cytotoxic potential. However, the species showing higher levels of cytotoxic activity included *Bejaria aestuans* L. (Ericaceae), *Erodium cicutarium* (L.) L'Her (Geraniaceae), *Brachyotum naudine* Triana (Melastomataceae), *Miconia salicifolia* (Bonp. ex Naud.) (Melastomataceae), *Cuscuta foetida* Kunth (Convolvulaceae), *Caesalpinia spinosa* (Molina) Kuntze (Fabaceae), and *Phyllactis rigida* Humb. and Bonpl. (Valerianaceae) (Busmann and Glenn 2011).

The antitumor effect of aqueous extract of *Bomarea cornigera* Herb. (Alstroemeriaceae) from Peru was investigated in Swiss albino mice strain, inoculated with tumor cell line TG-180. The results demonstrated an inhibitory effect of the extract in the development of solid tumor in mice, where the TG-180 sarcoma was transplanted. The inhibition rates were 87.44% and 8.52% after 17 days of treatment. These results shows that this plant deserves further studies to identify the compounds responsible of this antitumor activity (Suárez et al. 2010). Likewise, *Uncaria tomentosa* (Willd. ex Schult.) DC. is another famous plant of Peru endorsed with anticancer activity. Several studies of anticancer assays had been reported on this species. The activity of *U. tomentosa* preparations on cancer cells was studied using in vitro and in vivo models; Lewis lung carcinoma (LL/2), cervical carcinoma (KB), colon adenocarcinoma (SW707), breast carcinoma (MCF-7), and lung carcinoma (A-549) cells were used in this study. Oxindole alkaloids, isolated from this plant, were screened to demonstrate the cytotoxic activity (Table 11.1-W) (Rojas-Duran et al. 2012; Pilarski et al. 2010). The antiproliferative and pro-apoptotic effect of fractions obtained from *U. tomentosa* was screened on medullary thyroid carcinoma (MTC) given interesting results (Rinner et al. 2009). Extracts of *U. tomentosa* bark were also investigated on B16/BL6 melanoma cells (Fazio et al. 2008). Today, it is a recognized species with good anti-inflammatory activity, but still the anticancer studies are not conclusive. Polyhydroxylated triterpenes and oxindole alkaloids are the most important metabolites reported from the phytochemical studies of *U. tomentosa*. Some examples of these triterpenes are shown in tabular form (Table 11.1-Y; Z) (Heitzman et al. 2005). Though many medicinal plants used in folk medicines are effective against several human ailments, however, therapeutical potential of these plants still requires the scientific validation. In a work of Bussmann and Glenn (2011), 47 plant species were documented and identified as anticancer and antidiabetic herbal remedies. From this study, 17 species were identified with anticancer remedies. In vitro studies of *Thevetia peruviana* (Pers.) K. Schum (Apocynaceae) (Haldar et al. 2015) and *Arctium lappa* L. (Asteraceae) (Ishihara et al. 2006) have shown good and interesting results against cancer cells.

11.2.10 Uruguay

Uruguay is the second-smallest country of the South America, after Suriname. It is a country sandwiched between Brazil, Argentina, and the Atlantic Ocean. In spite of this, it is a country with a distinct culture from its neighbors and has a population of

basically European origin; the original indigenous peoples have disappeared. The majority of the population are urban based and resides in the southern half of the country in or around the capital Montevideo. Most of the Uruguay is grassland, no forest. The largest natural area of Uruguay is tall-grass savanna, originally covered with many species of grasses (Burford 2014). During the colonization, native plants were merged with the European origin plants and formed the basis of Uruguay's popular medicine. Further, innate vegetation used in the neighboring countries was added over time to this basic pharmacopeia by adopting their use (González et al. 1993). Herbal/traditional products are a small category, with little use in the treatment of the health of Uruguayans since they still have certain distrust regarding the effectiveness of herbal/traditional products. For these reasons in Uruguay, a few published works on medicinal plants, their use and/or their chemical composition. The following are the results of two research studies carried out.

González et al. (1993) screened some selected medicinal plants traditionally used in Uruguay for their biological activities. They used two bioassays, namely, the *Artemia salina* toxicity test and the wheat rootlet growth inhibition (WRGI) assay. They found that seven plants (*Jaborosa runcinata*, *Dodonaea viscosa*, *Psidium incanum*, *Acanthospermum australe*, *Baccharis trimera*, *Anagallis arvensis*, and *Muehlenbeckia sagittifolia*) exhibited substantial dose-dependent growth inhibitions in the WRGI test. Among these, only three plants, namely, *D. viscosa*, *A. arvensis*, and *B. trimera*, inhibited up to 50% at 0.5% concentration. Three plants, namely, *Achyrocline satureioides*, *B. trimera*, and *Equisetum giganteum*, showed a strong concentration-related toxic activity on brine shrimps. *A. satureioides* showed toxicity even at the lowest concentrations tested. In other work, Barneche et al. (2010) reported a list of plants present in the gallery forest of the Uruguay River and its ethnobotanical information. Of these plants, the only species mentioned to treat cancer was *Maytenus ilicifolia*.

11.2.11 Venezuela

Venezuela is a tropical country located in the north of South America and is characterized by its great variety of ecosystems ranging from perpetual snow in the Andes to desert or semidesert areas in Falcón. Venezuela is a country that possesses an extraordinary biodiversity, being one of the ten countries with the highest biodiversity in the world. In general, it is usually divided into four major ecological regions, namely, the coastal zone, the Llanos (plains), the Andean mountain range, and the Guiana Highlands. Venezuela possesses an enormous wealth of useful and medicinal plants. In Guiana, where most natives live, there is a high percentage of the utilization of medicinal plants. Even in regions where there is a great rural population, people use medicinal plants in higher percentages. However, the urban people do not use many of these plants to treat their illnesses.

It is estimated that in Venezuela there are more than 20,000 plant species, of which over 1500 are being used by the native communities. Various ethnobotanical

studies on medicinal plants have been carried out; however, these have been concentrated mainly in indigenous communities of the Orinoco (Castillo 1998, 2001; Narváez et al. 2000). In the last years, several investigations have been carried out in other communities of the country (Játem-Lásser et al. 1998; Hidalgo-Báez et al. 1999; Bermúdez and Velásquez 2002; Cumana 2002; Gil et al. 2003, 2006; Aranguren 2005; Carrillo-Rosario and Moreno 2006; Lezama et al. 2007; Carmona et al. 2008; Jaramillo et al. 2014). In these studies, few species with anticancer activity used by the population are reported. Among the most mentioned are *Petiveria alliacea* (Phytolaccaceae) "mapuritico" (Gil et al. 2006; Jaramillo et al. 2014; Játem-Lásser et al. 1998), *Moringa oleifera* Ben. (Moringaceae) "ben," *Aloe vera* (L.) Burm.f. (Liliaceae) "zábila," *Roupala mollis* Pittier (Proteaceae) "mapurite" (Lezama et al. 2007), *Acanthospermum australe* (Loefl.) Kuntze (Asteraceae), *Porophyllum ruderale* (Jacq.) Cass. (Asteraceae) "mapurite," and *Argemone mexicana* L. (Papaveraceae) "Cardo Santo" (Játem-Lásser et al. 1998). On the other hand, some studies related to the anticancer activity of plant species collected in Venezuela have been published, and some of them we mention here.

Taylor et al. (2006) selected 17 species based on their ethnobotanical usage in Venezuela and other Neotropical countries to explore their potential anticancer activity. These plants were collected from the Yutaje area in the northern part of Amazon state, Venezuela, between 1999 and 2002. About 40 plant extracts were evaluated for their cytotoxicity at different concentrations (10, 100, and 1000 mg/ml) against lung (A549, CALU-6), colon (HT-29, Caco-2), pancreas (PANC-1), and breast (SKBR3, MCF7, MDA-MB231) carcinoma cells. Also, the extracts were tested on the proteases as they are known to be involved in the cancer induction. The results obtained indicated that 13 extracts from 10 species showed a cytotoxic effect at 100 mg/ml on more than one tumor cells. The species such as *Jacaranda copaia*, *Tapirira guianensis*, *Gnetum nodiflorum*, *Protium unifoliolatum*, *Protium heptaphyllum*, *Costus scaber*, and *Croton cuneatus* presented activity against some of the cancer cell lines tested. Among all extracts, *T. guianensis* bark and leaf extracts showed a higher cytotoxic activity at 100 mg/ml concentration against Caco-2, PANC-1, and CALU-6 cells. Besides, these extracts also exhibited protease inhibitory activity.

T. guianensis, a member of the Anacardiaceae family is known in Venezuela as jobillo and tapaculo. It is used in Venezuelan's folk medicine to treat measles and warts and as antidiarrheic agent (Taylor et al. 2006). This species has been previously studied to evaluate its anticancer activity. David et al. (1998) reported two compounds from the chloroform extract of their seeds with cytotoxic activity against BC1 (human breast cancer) with IC_{50} of 1.3–4.3 μg/ml and Col2 (human colon cancer) with IC_{50} of 0.8–1.8 μg/ml. These compounds correspond to 2-[10(*Z*)-heptadecenyl]-1,4-hydroquinone (152) and (4R,6R)-dihydroxy-4-[10(*Z*)-heptadecenyl]-2-cyclohexenone (153) (Table 11.1-Z). In a recent work, the effect of this species was tested on a panel of head and neck squamous cell carcinoma (HNSCC) cell lines. The extract showed a significant cytotoxicity effect, as well as an ability to inhibit tumor migration and invasion (Silva-Oliveira et al. 2016).

Villasmil et al. (2006) evaluated the antitumor activity of ethanolic extracts from 11 species collected in Amazon state, Venezuela. They screened the anticancer activity both in vitro and in vivo against (a) five tumor cell lines, (b) primary tumor growth and metastasis in the B16/BL6 melanoma/C57BL/6 mouse model, and (c) NF-κB inhibitory activity in HeLa cells transfected with an NF-κB/luciferase reporter gene plasmid. They found that *Byrsonima crassifolia* (Malpighiaceae), *T. guianensis* (Anacardiaceae), and *Vismia cayennensis* (Clusiaceae) were cytotoxic for more than two of the cell lines at lower concentrations. In in vivo assays, the treatment with the *Jacaranda copaia* (Bignoniaceae) extract delayed tumor growth by up to 40%, while *Piper marginatum* (Piperaceae) showed a pronounced inhibitory effect on tumor growth. *Xylopia aromatica* (Annonaceae) only inhibited tumor growth to a small degree, and the other plants were not inhibitory.

Continuing with this line of research, Taylor et al. (2012) evaluated the effect of 308 plant extracts from 102 different species (78 genera and 48 families) against 6 tumor cell lines. They found that extracts from *Annona squamosa*, *Heliotropium indicum*, *Hamelia patens*, *Jacaranda copaia*, *Clavija lancifolia*, *Physalis cordata*, and *Piper san-vicentense* were the most active with mean LC_{50} values of 750 mg/ml. Of these, the leaf and fruit *C. lancifolia* extracts exhibited the highest cytotoxicity against all cells except the Raw 264.7. In the literature, there are few reports on its use and phytochemistry. However, other plants such as *Calotropis gigantea*, *Chromolaena odorata*, *Hyptis dilatata*, *Jacaranda obtusifolia*, *Siparuna guianensis*, *Protium heptaphyllum*, *Piper arboretum*, *Tapirira guianensis*, and *Xylopia aromatica* extracts recorded a lower cytostatic activity.

Croton cuneatus Klotz. belonging to the Euphorbiaceae is widespread in tropical regions of the world. Several species of the genus *Croton* have a long role in the traditional use of medicinal plants in Africa, Asia, and South America. Generally it is used for the treatment of cancer, inflammation, hypertension, diabetes, hypercholesterolemia, malaria, constipation, indigestion, dysentery, pain, wounds, fever, intestinal worms, ulcers, and weight loss. Some species of this genus present in Venezuela have been studied, and their extracts or metabolites have presented cytotoxic activity. From the dichloromethane extract of the aerial parts of *C. cuneatus* were isolated three glutarimide alkaloids, julocrotol (154), isojulocrotol (155), and julocrotone (156) (Table 11.1-AA), along with other known compounds. The in vitro cytotoxic activity of these compounds was evaluated against five human tumor cell lines (MCF-7, X-17, Hep G2, Skhep-1, and LoVo) using the MTT bioassay. Compound 154 the most potent and selective on MCF-7 with an IC_{50} of 21.0 μg/ml (Suárez et al. 2004). Likewise, *C. malambo* H. Karst., a small tree that grows in the western region of Venezuela, was isolated with an *ent*-kaurane (157) (Table 11.1-BB) that showed activity against a human mammary carcinoma cell line (MCF-7), and it was determined that its anticancer effect is through the induction of apoptosis (Morales et al. 2005). From the flowers of *C. micans* Sw. (which was erroneously identified as *Croton caracasana* Pittier), two *ent*-3,4-*seco*-kauranes were isolated, caracasine (158) and caracasine acid (159) (Table 11.1-BB) (Suárez et al. 2008). Both compounds showed potent activity against a series of cancer cell lines (Suárez et al. 2009). In a later study, five new *ent*-3,4-*seco*-kaurane dimers, micansinoic acid

(160), isomicansinoic acid (161), and the dimethyl (162), monomethyl (163), and monoethyl ester (164) of micansinoic acid, were isolated from the stems of *C. micans* Sw. (Mateu et al. 2012). The compounds caracasine acid (monomer) and micansinoic acid (dimer) were evaluated against the prostate cancer cell line PC-3 and human dermis fibroblasts (control cells). In addition, the combination of the monomer and dimer was realized with the antitumoral drugs taxol and adriamycin. These two compounds exhibited practically the similar cytotoxic activity against human tumor cells but not to normal cells. Caracasine acid combined with adriamycin or taxol resulted in synergistically enhanced growth inhibitory activity to a 1:1 ratio in tumor cancer cell line PC-3. The synergistic effects on PC-3 were also demonstrated when micansinoic acid was combined with adriamycin or taxol. This result indicates that the sensitivity of tumor cells to drugs (adriamycin-taxol) was increased by natural products (Vivas et al. 2013). In a recent work, a series of *ent*-3,4-*seco*-kauranes derived from the natural diterpene caracasine acid (159) were prepared and evaluated for antibacterial, leishmanicidal, trypanocidal activities and against cancer cells. The synthesized derivatives exhibited moderate activities against PC-3 cancer cells, although less effective than caracasine acid. However, the breast cancer cells MCF-7 were less sensitive to all compounds evaluated (Chávez et al. 2015).

11.3 Conclusions and Future Prospects

Cancer is a terrible disease that greatly affects the world's population. At present, there is no effective treatment, since the drugs used produce numerous side effects and are toxic. Therefore, there is a need to seek new therapies to treat and prevent this disease, which is one of the leading causes of death worldwide. This need has led to an increase in research in the field of natural products and has increased the interest in the compounds of natural origin and/or their synthetic derivatives. In this sense, South America is a region that includes five of the countries with the greatest biodiversity in the world; in addition, many of the inhabitants in this region preserve the traditions of our ancestors in relation to the medicinal use of plants. This vast knowledge however has been losing over the years, due to several causes including urbanization, technology advancement, deforestation, population increase, etc. In this way, ethnobotanical knowledge is threatened, and many species of plants are at risk of disappearing if we do not do our best to conserve these resources. This chapter has provided the ethnomedicinal and scientific evidences on various South American medicinal plant species used against cancer. Also, some results of phytochemical and biological studies on plant species of this region are presented. In general, ethnobotanical knowledge of the inhabitants of these countries is broad, especially for the treatment of many diseases, such as those affecting the respiratory tract, skin, kidney, and digestive system; however knowledge of plants to treat cancer is smaller, which could be related to the absence of symptoms in the first stages of this disease. Even so, studies of many plants present in South America have contributed to the search for new treatments for cancer. There are many areas of virgin

forest and a large number of unknown species, which means a great opportunity to continue researching in this area without ignoring the traditional knowledge of the plants in these countries.

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