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REVIEW ARTICLE

Medicinal plants of Ecuador: a review of plants with anticancer potential and their chemical composition

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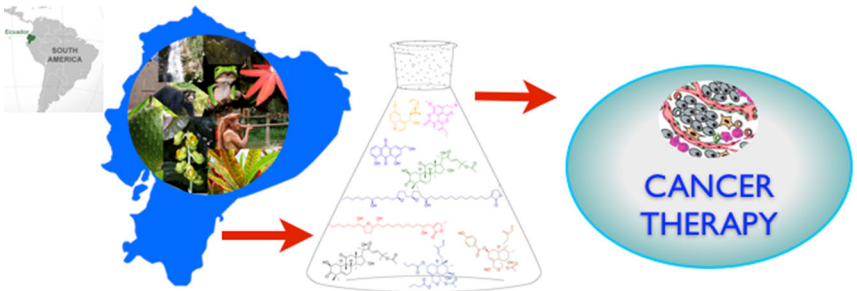
Abstract Ecuador is well known for its biodiversity and its ancient richness. This review provides an overview of Ecuadorian plant species in terms of the ethnobotany and chemistry of natural products in relation to anticancer activity. Plant species were classified into two groups: (a) Ethnomedical species with confirmed antitumor activity and (b) species indigenous to Ecuador with anticancer potential. This review shows that there is a great chemical diversity in Ecuadorian plants that can be used for potential antitumor therapeutics, and chemical and biological analysis confirms the biomedical use of the plant-derived compounds as cytotoxic agents for cancer cells.

Graphical Abstract



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Introduction

Currently, there are many curative and palliative treatments for cancer allowing to eradicate tumor cells; among them are chemotherapy, radiotherapy, immunotherapy, and even gene therapy (Weissleder and Pittet, 2008). During chemotherapy, the application of a series of chemical compounds, either natural or synthetic, lead to induction of cell death or cell cycle arrest in tumor cells. These anticancer chemical compounds can be used alone or more often in combination with other chemicals or non-chemical regimens. Secondary metabolites isolated

from microorganisms, plants, and marine species, among others, have been important sources of bioactive substances potentially with anticancer abilities (Cragg *et al.,* 2009). Approximately 66 % of the FDA-approved drugs for cancer treatment are secondary metabolites or are semi-synthetic or synthetic analogs based on pharmacophores obtained from secondary metabolites (Cragg and Newman, 2013).

The production of secondary metabolites is favored by a diverse microenvironment. There are approximately 20,000 various plant species, 20 % of which are endemic, were found in Ecuador (Gupta, 2001). Continental Ecuador is the region with the third highest density of endemic plant species worldwide (Joppa *et al.,* 2013). And this is a country in which the plant species with the highest cytotoxic activity against human cancer cells can be found, compared to other countries with similar biological diversity, such as Indonesia, Dominican Republic, Thailand, and Peru (Balunas *et al.,* 2006) Another important feature of Ecuador is the ethnomedical knowledge of many indigenous communities. In this article, we will review many plant species, their ethnomedical information, active molecules isolated from them, and research studies that validate their potential anticancer effectiveness. For this purpose, we have classified them into two large groups: Ethnomedical species with informed antitumor activity and species indigenous to Ecuador with anticancer potential.

Ethnomedical species with informed antitumor activity

Many studies have reported the use of existing plant species against cancer by ethnic groups in Ecuador, many of which are shown in Table 1. Some of these species are endemic to Ecuador; however, regional and worldwide species are also included. The compositions of the chemicals derived from these plant species are described in Table 2. Antitumor activity has been studied either with extracts or with isolated metabolites and is shown in Fig. 1.

Uncaria tomentosa (Will.) DC

This plant is a native liana from Ecuador, distributed along the coast and in the Amazon rainforest. Its populations have been found in the Napo, Orellana, Sucumbíos, and Zamora Chinchipe provinces at altitudes from 0 to 900 meters above sea level (m.a.s.l.) (de la Torre *et al.,* 2008). This plant is also known as a "cat's claw", with distribution in South America and Asia. It used as a traditional medicine by Ecuadorian (Tene *et al.,* 2007) (Pohle and Reinhardt, 2004) Peruvian, and Bolivian indigenous people (Bourdy *et al.,* 2000), as well as by the Asian population to treat warts, ulcers, headaches, intestinal problems, fungal and bacterial infections (Heitzman *et al.,* 2005). The *U. tomentosa* organic extracts contain active secondary metabolites such as oxindole alkaloids, proanthocyanidins, triterpenes, sterols, and flavonoids. The oxindole alkaloids include isopteropodine (**1**), isomitraphylline (**2**), pteropodine (**3**), and uncarine F (**4**), all of which exhibit cytotoxic activity against the acute lymphoblastic leukemia cells (CCRF-CEM-C7H2 T-ALL cell line) (Bacher *et al.,* 2006). In addition, pteropodine and uncarine F are capable of inducing apoptosis (Bacher *et al.,* 2006). Although mitraphylline (**5**) failed to exhibit cytotoxicity against the CCRF-CEM-C7H2 T-ALL cells (Bacher *et al.,* 2006), it displayed a cytotoxic activity in human glioma and neuroblastoma cell lines with an IC_{50} between 12 and 40 μM (García Prado *et al.*, 2007). However, isopteropodine and pteropodine alkaloids inhibit the growth of medullary thyroid carcinoma (MTC-SK) cells and induce caspase-mediated apoptosis (Rinner *et al.,* 2009). In in vivo mouse models, various organic extracts and *U. tomentosa* alkaloid-enriched extracts induce apoptosis in human promyelocytic leukemia cells (HL-60 cell line) (Sheng *et al.,* 2000) (Cheng *et al.,* 2007) (Pilarski *et al.,* 2013) (De Martino *et al.,* 2006) (Pilarski *et al.,* 2010). Additionally, the alkaloid-enriched extracts inhibit the growth of xenografts of cervical cancer (HeLa cell line) and colon cancer (HCT116 and SW480 cell lines) by affecting the WNT signaling pathway (Gurrola-Díaz *et al.,* 2011). Sheng et al. reported that the aqueous extracts of this plant induce cytotoxicity via apoptosis in the human leukemia cell lines HL-60 and K-562 (Sheng *et al.,* 2000). Another example is quinovic acid glycosides, which were isolated using the ethanol:water extraction and shown to inhibit the growth of human T24 bladder cancer cells (at the IC_{50} of 78,36 μg/mL) by activating the caspase-3-dependent apoptotic pathway and translocation of NF-κB to the nucleus (Dietrich *et al.,* 2014). Moreover, many studies show the anti-inflammatory activity presented in extracts of this species as well as by its components, which could assist in preventing and potentiating the effect against tumor cells by stimulating the immune system (Allen-Hall *et al.,* 2010) (Heitzman *et al.,* 2005).

Croton lechleri Mull. Arg

Belonging to the Euphorbiaceae family, in Ecuador, this plant is widely distributed in the Andes and the Amazon rainforest, especially in Carchi, Esmeraldas, Loja, Morona-Santiago, Napo, Orellana, Pastaza, Sucumbios, Tungurahua, and Zamora Chinchipe provinces at altitudes from 0 to 2,000 m.a.s.l. (de la Torre *et al.,* 2008). *Croton* is a traditional medicinal plant that produces a red sap known as "Dragon's blood", obtained by carving the bark of two- and three-year-old plants or older (Salatino *et al.,* 2007). The

Table 1 Ethnomedical species with confirmed antitumor activity

Family	Scientific name	Common name	Part used	Reference
Apiaceae	*Foeniculum vulgare* Mill	Hinojo, anís, eneldo, hinojo común	Leaf, flower	Tene *et al.* (2007)
Apocynaceae	*Prestonia mollis* Kunth	Bejuco del Cáncer; Arachillas, betilla, falso condurango, sánalo todo, malacapa	Root, stem, leaf	Tene *et al.* (2007)
Apocynaceae	*Marsdenia condurango* Rchb. f.	Condurango	bark, leaf	Tene *et al.* (2007)
Asteraceae	*Aristeguietia glutinosa* (Lam.) R.M. King & H. Rob	Matico; *Chusa lunku, Hierba del soldado, Matico silvestre, Melga, Migla*	leaf	Cerón (2006)
Crassulaceae	*Bryophyllum pinnatum* (Lam.) Oken	Monte del aire; Chukri yuyu, paki panka, pichi panka, raku panka (kichwa) llaga panka, sebachuccaque (áingae), jëye, soma ëco (pai coca), koyobimo (Wao tededo), espíritu santo, hojas del aire, chigriyuyo, tomalillo	Stem, leaf	Tene *et al.* (2007)
Crassulaceae	*Echeveria quitensis* (Kunth.) Lindl.	Condorcol; siempre viva; cundur cul	Leaf	Tene *et al.* (2007)
Equisetacee	*Equisetum giganteum* L.	Caballo chupa; Sukillu, cola de caballo, hierba platero, tubakavache	Stem	Cerón (2006)
Euphorbiaceae	*Croton lechleri* Mull. Arg	Sangre de drago, Tulan wiki, tulan yura, yawar kaspi, yawar wiki, yawar wiki panka (Kichwa), sacha tucufais; masujin (áingae), ao yëhui (pai coca), koñiwe, koyibe (wao tededo), urúchmas (shuar chicham), uruch numi (achuar chicham), hoja de sangre, resina de sangre, sulsul, tupic.	Latex	Graham *et al.* (2000)
Fabaceae	*Crotalaria sp.* L.	Fenogreco	leaf	Tene *et al.* (2007)
Fabaceae	*Myroxylon balsamum* (L.) Harms	Chaquino; bálsamo kara, sesepëquësoquë (pai coca), yemenga tanoe (Wao tededo), chikawinia (shuar chicham), chikiáiniua, kaip (achuar chicham), bálsamo del Perú, corteza de bálsamo, isturaki	Bark	Tene *et al.* (2007)
Fabaceae	*Senna multiglandulosa* (Jacq.) H.S. Irwin & Barneby	Chinchín		Cerón (2006)
Malvaceae	*Lavatera arborea* L	Malva; Puka malva, malva blanca	Stem, bark	Cerón (2006)
Olacaceae	*Minquartia guianensis* Aubl.	Wayakan chi, yatyutya, chi jaki (chafiki), wanpula, yura wanpula (kichwa), señámba quini´cco,tsindócho (áingae), yaji siu (pai coca), kayeyakawe, kobakadetapo, kobakadewe (wao tededo), paini (shuar chicham), cuayacán, palo de barbasco	bark	El-Seedi *et al.* (2008)
Polygalaceae	*Monnina obtusifolia* H.B.K.	Iwilan (kichwa), reloj de campo, sagitaria	Aerial parts	Cerón (2006)
Rosaceae	*Eriobotrya japonica* (Thunb.) Lindl.	Níspero; *Níspero del Japón, Míspero*	Leaf	Cerón (2006)
Rubiaceae	*Uncaria tomentosa* (Will.) DC	Uña de gato; eygawe (wao tededo), kenkuk (shuar chicham)	Bark	Tene *et al.* (2007)

Amazon indigenous people use this sap for wound healing and to treat gastro-intestinal diseases and cancer (Cerón, 2006; Gupta *et al.,* 2008). The sap (at 1 mg/ml) has been able to inhibit the proliferation of K562 myeloid leukemia cells (Rossi *et al.,* 2003) and SK23 melanoma cells (Rossi *et al.,* 2003). At concentrations 10-fold higher, it inhibits the growth of HT-29 colon cancer cells and the LoVo colon cancer cells (Montopoli *et al.,* 2012). Using confocal microscopy, it was observed that *Croton lechleri* sap at 1 mg/mL causes a loss of the microtubular structure in SK23 melanoma cells (Montopoli *et al.,* 2012). The phytochemical characterization of the sap has led to the conclusion that the oligomeric proanthocyanidins and flavonols constitute almost 90 % of the dry weight. However, one of flavonoids most studied in this species is the SP-303. This flavonoid is known for its antiviral and antidiarrheal activity but has no cytotoxic activity in tumor cells (Jones, 2003). Unlike the SP-303, other catechins present in the sap of *C. lechleri*

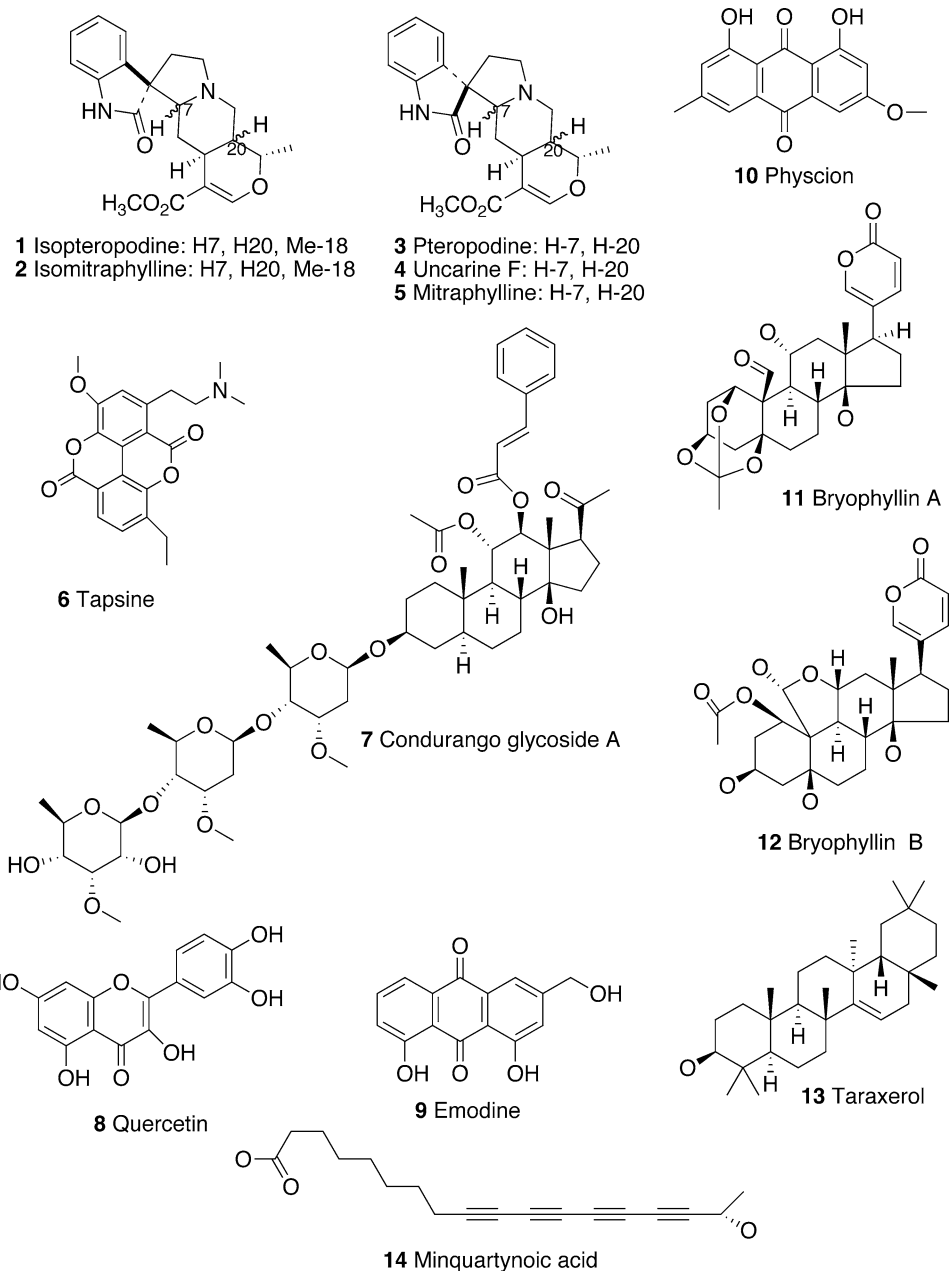


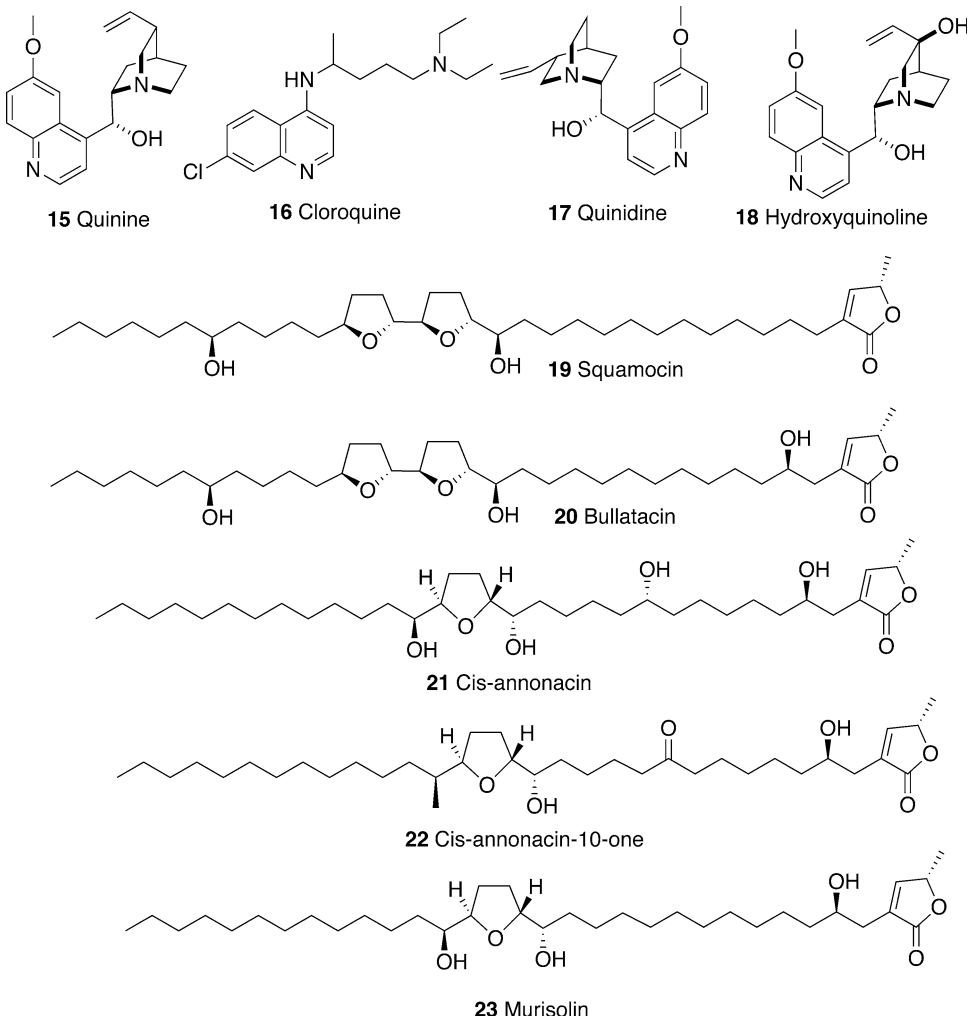
Fig. 1 Structures 1 to 14

(catechin, gallaocatechin, epicatechin, epigallocatechin) have been extensively studied with human cancer cells. They were shown to display in vitro cytotoxicity, as well as inhibited cell proliferation, induced of apoptosis, activated caspases, inhibited protein kinases and modulated cell cycle regulation (Fujiki *et al.,* 2002; Forester and Lambert, 2014). Clerodane-type diterpenes such as korberin A and korberin B have been also isolated (Cai *et al.,* 1993). An alkaloid called taspine (**6**) has been found in small amounts and also present in other plants such as *Radix and Rhizoma leonticis*. It has been shown that taspine inhibits the proliferation of SK-23 melanoma cells and HT29 colon carcinoma cells (Montopoli *et al.,* 2012). Taspine can also inhibit the proliferation of A431 epidermoid carcinoma cells and induce caspase-3 activation and regulation of the Bax/Bcl-2 ratio leading to cell death through apoptosis (Montopoli *et al.,* 2012). Taspine and its certain derivatives can significantly inhibit the cell proliferation of human umbilical vein endothelial cells induced by the vascular endothelial growth factor, which is crucial for angiogenesis (Zhang *et al.,* 2010). Additionally, its derivative HMQ1611 has a cytotoxic effect on ZR-75-30, MCF-7, SK-BR-3, and MDA-MB-231 breast cancer cells and in xenografts in mice. HMQ1611 shows a marked inhibiting effect on breast cancer cells, apparently through the

Table 2 Composition chemical of species indigenous to Ecuador with anticancer potential

Scientific name Parte used	Metabolites secondary isolated	Reference
Croton lechleri Mull. Arg Sap Bark Leaves	Taspine; 3′, 4-O-dimethylcedrusin; procyanidin B-1 and B-4; catechin; epigallocatechin; epicatechin; gallocatechin; (4-α-8)-gallocatechin; (4-α-6) gallocatechin; (4-α-6)-epigallocatechin; (4-α-8)-epicatechin; (4-α-8)-epi-gallocatechin; bincatriol; crolechinol; crolechinic acid; hardwickiic acid; koberins A and B; korberin B; 4-O-methylcedrusin; SP-303; blumenol B and C; 4,5-dihydroblumenol A	Cai *et al.* (1993), Gupta *et al.* (2008), Jones (2003), De Marino *et al.* (2008), Salatino *et al.* (2007)
	Bincatriol; crolechinol; crolechinic acid; hardwickiic acid; and koberins A and B	
	β-sitosterol-β-D-glucopyranoside; β-sitosterol	
	Sinoacutine; glaucine; isoboldine; and thaliporphine	
Marsdenia condurango Rchb. f. Bark	4-hydroxy-3-methoxybenzaldehyde; vanillin; vanillaldehyde; 4-hydroxy-3-methoxybenzaldehyde; 4-coumarate; p-coumaric acid; trans-4-hydroxycinnamate; trans-p-hydroxycinnamate; 4-hydroxycinnamic; chlorogenate; chlorogenic acid; caffeoylquinic acid; trans-5-O-caffeoyl-D-quinate; caffeate; caffeic acid; 3,4-dihydroxycinnamic acid; quercitrin; quercetin 3-L-rhamnoside; quercetin 3-O-α-L-rhamnopyranoside; rutin; 3-[[6-O-(6-Deoxy-α-L-mannopyranosyl)-β-D-glucopyranosyl]oxy]-2-(3,4-dihydroxyphenyl)-5 coumarin; coumarine; cumarin; 2H-1-benzopyran-2-one; 1,2-benzopyrone; 2-propenoic acid; 3-(2-hydroxy) saponarin; isovitexin-7-O-beta-D-glucopyranoside; cichoriin; esculetin; aesculetin; umbelliferone; 7-hydroxycoumarin; hyperin; quercetin 3-galactoside; kaempferol-3-O-galactoside; kaempferol 3-O-beta-D-galactoside; trifolin; neochlorogenic acid; trans-neochlorogenic acid; neochlorogenate; condurango glycoside A and C; condurangogenin C; condurangogenin A; condurango glycoside A0; condurango glycoside C; condurangin	Kanehisa Labs (2015)
Minquartia guianensis Aubl. Leaves Bark	Squalene; lupen-3-one; taraxerol; lupeol; taraxer-3-one; oleanolic acid; 3β-methoxy-lup-20(29)-ene	Cursino *et al.* (2009), Cursino *et al.* (2012), Dembitsky (2006), El-Seedi *et al.* (1994)
	Lichexanthone; 17-hydroxy-9,11,13,15-octadecatetraenoic acid; 7-deoxyloganic acid; betulin 20-(29)-lupen-3,28-diol; 13,28-epoxy-3-acetoxy-ll-oleanane; minquartynoic acid; erythrodiol, betulinic acid, palmitic acid, myristic acid	
Monnina obtusifolia H.B.K. Aerial parts	1-O-(4-hydroxy-2-methylene-butanoic acid)-6-O- β-D-(4-hydroxy-2-methylene-butanoyl)-glucopyranose; 1-O-(isopentenyl)-6-O-β-D-(4-hydroxy-2-methylene-butanoyl)-glucopyranose; 1-O-(4-hydroxy-2-methylene-butanoic acid)-6-O-β-D-(isovaleroyl)-glucopyranose; 1-O-(3-methylbut-3-enyl)-6-O-β-D-(isovaleroyl)- glucopyranose; sucrose esters: 3,4-O-β-D-di-feruloyl-fructofuranosyl-6-O-α-D- (p-coumaroyl)-glucopyranoside; 3,4-O-β-D-di-feruloyl-fructofuranosyl-6-O-α-D-(caffeoyl)-glucopyranoside; 1,3,5-trihydroxy-2-methoxyxanthone; 1,3,6-trihydroxy-2,5-dimethoxyxanthone; 1,5-dihydroxy-3-methoxyxanthone; 1,3,6-trihydroxy 2, S dimethoxyxanthone	Lepore *et al.* (2011), Pinto *et al.* (1994)
Senna multiglandulosa (Jacq.) H.S. Irwin & Barneby Leaves Seeds	Emodin; floribundone-1; torosanin-9′, 10′-quinone; anhydrophlegmacin; 1,4 quinone moiety, 9-(physcion-7′-yl)-5,10-dihydroxy-2-methoxy-7-methyl-1,4- anthraquinone; anhydrophlegmacin-9, 10-quinone B_2; quercetin 7, 3′ -dimethyl ether-3-O-galactoside; kaempferol -3-O-galactorhamnoside; α-amyrin, β-sitosterol	Abegaz *et al.* (1994), Alemayehu and Abegaz (1996), Dave and Ledwani (2012), Ganapaty *et al.* (2002)
	Torosachrysone; physcion; floribundone-1; anhydrophlegmacin; isosengulone; physcio-9-antrone. phlegmacin A_2 and B_2	
Uncaria tomentosa (Will.) DC. Bark Leaves	Mitraphylline; isomitraphylline; pteropodine (uncarine C); speciophylline (uncarine D); isopteropodine (uncarine E); uncarine F; speciophyllin; isomitraphylline; isopteropodin; 7-deoxyloganic acid; quinovic acid glycosides	Bacher *et al.* (2006), Dietrich *et al.* (2014), Muhammad *et al.* (2001), Oktayoglou and Mericli (2003), Sheng *et al.* (2000)
	Rhynchophylline; isorhynchophylline; mitraphylline; isomitraphylline; dihydrocornynyntheune; hirsutine; hirsuteine	

Fig. 2 Structures 15 to 23

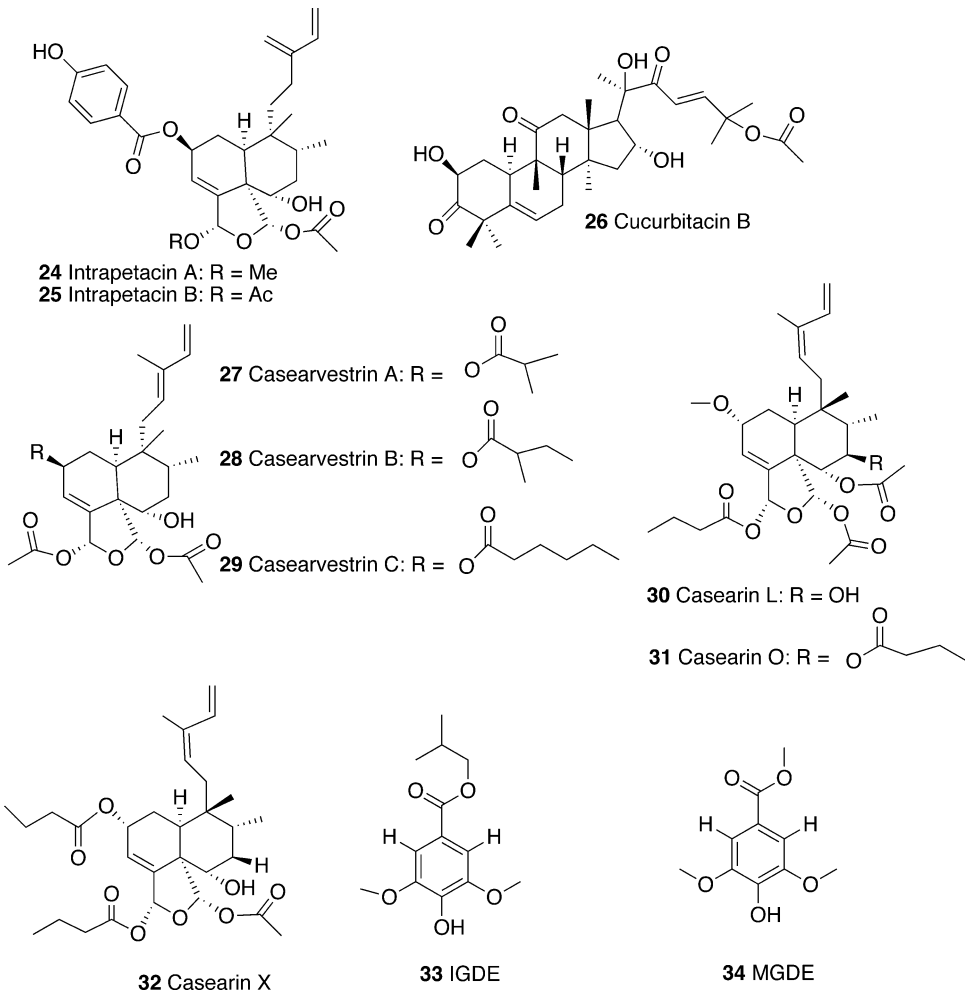


ERa, EGFR/MAPK, and EGFR/PI3 K/AKT pathways (Zhan *et al.,* 2012).

Marsdenia condurango Rchb. f

Also known as *Gonolobus condurango*, this plant belongs to the Apocynaceae family. It is a native liana from Ecuador and is distributed along the Andes and the Amazon rainforest, in particular in Azuay, El Oro, Guayas, Loja, and Zamora-Chinchipe provinces at altitudes from 1,000 to 2,000 m.a.s.l. (de la Torre *et al.,* 2008). It is used in traditional medicine to treat cancer, syphilis and other inflammatory processes (Tene *et al.,* 2007). Some pregnane glycosides have been isolated from the condurango's bark (Berger *et al.,* 1988; Hayashi *et al.,* 1980, 1981). Chemotherapeutic potential of condurango glycoside-rich extract (condurangoglycoside A, A0 E2) was evaluated in non small cell lung cancer, NSCLC cells, with a IC_{50} of 0.22 µg/µL. Condurango glycoside-rich extract-induced apoptosis via DNA damage was evidenced, cell cycle arrest at subG0/G1(Sikdar *et al.,* 2014). The major component described in the bark's extracts is the condurango glycoside A (**7**), which is capable of inducing DNA damage resulting in reduction of the cell viability of HeLa cervical cancer cells, reactive oxygen species (ROS) induction and subsequent p53 activation, and induction of cell death through apoptosis (Bishayee *et al.,* 2013). A large amount of coumarins and flavonoids have been isolated from the bark of M. condurango (Table 2), many possesses antitumor activity (Gurib-Fakim, 2006; Agostini *et al.,* 2005), as the case of quercetin un flavonol (Ji *et al.,* 2009). Quercetin (**8**) is an efficient anticancer agent that induces apoptosis in HeLa cervical cancer cells, HT29 colon carcinoma (Xavier *et al.,* 2009) and A431 epidermal carcinoma cells with the modulation of tyrosine kinase epidermal growth factor receptor (EGFR). Using the in silico molecular docking analysis with Maestro 9.3 molecular docking software indicated that quercetin possesses affinity against wild-type EGFR, as well as two mutated EGFR (Singh and Bast, 2014). Although there are several isolated secondary metabolites that present antitumor activity individually,

Fig. 3 Structures 24 to 34



there are many reports of their effectiveness in tinctures and other phyto-derived drugs (Banerji *et al.,* 2008).

Senna multiglandulosa (Jacq.) H.S. Irwin and Barneby

This plant is a native shrub form Ecuador, distributed along the Andes, and can be found in Azuay, Carchi, Chimborazo, Imbabura, Napo, Pichincha, and Tungurahua provinces at altitudes from 2,000 to 3,500 m.a.s.l (de la Torre *et al.,* 2008). Emodin (**9**) and other bianthraquinones (Table 2) (Abegaz *et al.,* 1994) have been isolated from this species. Emodin is a well-known cytotoxic molecule, capable of inducing apoptosis and halting growth in many human cell lines, including human proximal tubular epithelial cells (HK-2 (Wang *et al.,* 2007)), cervical cancer cells (HeLa, Ca Ski, ME-180 and Bu 25TK)(Yaoxian *et al.,* 2013; Srinivas *et al.,* 2003), prostate (LNCaP) cancer cells (Yu *et al.,* 2008), and breast cancer cells overexpressing HER-2/neu (MDA-MB453) (Zhang *et al.,* 1998) (Ko *et al.,* 2010). The use of this molecule to increase the susceptibility of tumor cells to cytotoxic therapeutic agents has also been suggested as an innovative strategy, as emodin is an ROS generator (Dave and Ledwani, 2012; Qu *et al.,* 2013). Another molecule with cytotoxic activity isolated from this species is physcion (**10**), an anthraquinone derivative, which is widely distributed in nature. While physcion has been shown no cytotoxicity against human breast cancer (MCF-7) and human colon adenocarcinoma (SW620) cells (Almeida *et al.,* 2010), it exerted an inhibitory activity against HeLa cell proliferation by causing apoptosis (IC_{50} ~ 100) with formation of intracellular ROS. Furthermore, physcion induced the apoptotic cell death in HeLa cells by activating the expression of caspase family enzymes and p53 followed by Bax and Bcl-2 deregulation (Wijesekara *et al.,* 2014).

Bryophyllum pinnatum (Lam.) Oken

This plant is an herb or subshrub introduced and grown in Ecuador and has been found in Azuay, Cotopaxi, Galápagos, Guayas, Imbabura, Loja, Los Ríos, Manabí, Napo, and Pichincha provinces at altitudes from 2,000 to 3,000 m.a.s.l.

Table 3 Composition chemical of species indigenous to Ecuador with anticancer potential

Scientific name Parte used	Metabolites secondary isolated	Reference
Annona squamosal L. Bark Twigs Seeds	Squamone; bullatacin	Rupprecht *et al.* (1990), Kumar and Kumar (2013), Zafra-Polo *et al.* (1996) Chen *et al.* (2012), Rupprecht *et al.* (1990)
	5-((6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline-1-yl)methyl)-2-methoxybenzene-1,3-diol; (1*R*,3*S*)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline-1,3-diol; 6,7-dimethoxy-2-methylisoquinolinium; rutin	
	Annonacin A; squamosten A; neoannonin; squamocin: B, D, E, F, I, K, and N, annonin-III (or motrilin), squamostatin: A, D, and E; annosquacins: A, B, C, and D; annosquatin: A and B; squamocin	
Annona montana Macfad Bark Leaves Seeds	Phenanthrene-l,4,quinone; annoquinone A; physcion; β-sitostenone	Wang et al. (1999), Liaw *et al.* (2004, 2005), Alvares *et al.* (2009)
	Montanacins: B and E	
	Montacin; cis-montacin; annonacin; cis-annonacin; annomontacin, cis annomontacin; montalicins: G and H; monlicins: A and B; (+)-monhexocin and (−)- monhexocin; murisolin; 4-deoxyannomontacin; muricatacin.; aromin; cis-annonacin-10-one; gigantetronenin; tucupentol	
Annona muricata L Roots Bark Leaves Fruit Seeds	Montecristin; cohibin: A, and B; cis-solamin; cis-panatellin; cis-uvarimicin IV; cis-reticulatacin-10-one; cis-reticulatacin	Alali *et al.* (1999) Ragasa *et al.* (2012), Sun *et al.* (2014), Zafra-Polo *et al.* (1996)
	Epoxymurin A (or epomuricenin A); epoxymurin B; muricatin: A, B and C	
	Annoreticuin-9-one; cis-annoreticuin; sabadelin; annopentocin: A, B, and C; (2,4-trans)-annomuricin-D-one; muricoreacin; murihexocin; muricapentocin; annomuricin E	
	Muricins J, K, and L	
	Epomuricenin A (or epoxymurin A); epomuricenin B; diepomuricanin A; corepoxylone; solamin; murisolin; corossolin; corossolone; gigantetrocin B; muricatetrocin: A and B	
Casearia sylvestris Sw. Leaves	Casearins: A – T; (2β-methoxy-cleroda-3, 13-dien-18-carboxy-15, 16-olide, 15E-methoxy-cleroda-3, 12-dien-18-carboxy-15, 16-olide; 15-hydroxy- 3-cleroden-2-one; (+)-hardwickiic acid; 15-oxo-echinophyllin A; casearvestrins: A - C; echinophyllin A, (−)-patagonic acid; tyrosol; oplopanone; 4-hydroxy-4-methyl-2-[(1R)-1-(1 methylethyl)-4-oxopentyl]-2-cyclohexen-1-one; 1β,6α-dihydroxy- eudesman-4(15)-ene	Oberlies and Burgess (2002), Gonzaga dos Santos *et al.* (2010), Wang *et al.* (2009)
Cinchona officinalis L Bark	Quinine; quinidine; cinchonine; cinchonidine; tannin; quinate; quinic; cinchotannic	Kacprzak (2013)
Licania intrapetiolares Spruce ex Hook f Roots	Intrapetacin: A and B; cucurbitacin B	Oberlies *et al.* (2001)

(de la Torre *et al.,* 2008). It is used in the traditional medicine of many countries, including India, Mexico, and Nicaragua (Afzal *et al.,* 2012). In addition to being a commonly grown plant, it is also of great importance in the everyday life of the Kichwa people (Innerhofer and Bernhardt, 2011). *B. pinnatum* is used to cure many infections, intestinal diseases, wounds, and other ailments. Bufadienolides such as bryophyllin A (**11**) and bryophyllin B (**12**) have been isolated from this plant, in addition to bersaldegenin-3-acetate. Bryophyllin A and B show cytotoxic activity in many tumor cell lines. It is important to highlight that bryophyllin B has shown potent in vitro cytotoxicity in KB cervical cancer cells with an IC_{50} of 80 ng/mL (Yamagishi *et al.,* 1989; Supratman *et al.,* 2001). Additionally, the chloroform extract of the leaves inhibits the growth of HeLa cells, in addition to anti-HPV activity (Mahata *et al.,* 2012).

Minquartia guianensis Aubl

This plant is a native tree of Ecuador. It is distributed along the coast, in the Andes Mountains, and in the Amazon rainforest. Its populations can be found in Esmeraldas, Morona-Santiago, Napo, Pastaza, Sucumbíos, and Tungurahua provinces at altitudes from 0 to 2,000 m.a.s.l. (de la

Torre *et al.*, 2008). According to ethnomedical information, it is used to treat lung cancer. From the bark of the root of this plant, erythrodiol, betulinic acid, palmitic acid, myristic acid, and stearic acid have been isolated, but the major component is minquartynoic acid (**13**) (El-Seedi *et al.,* 1994), which has proven to have cytotoxic activity in the following: Col2, human colon cancer; KB, human oral epidermoid carcinoma; KB-V+, multidrug-resistant KB assessed in the presence of vinblastine (1 μg/mL); KB-V−, multidrug-resistant KB assessed in the absence of vinblastine; LNCaP, hormone-dependent human prostate cancer; and SW626, human ovarian cancer; SKNSH, human neuroblastoma cancer, with an IC_{50} of between 1.6 and 5.5 μg/ml (Ito *et al.,* 2001). Certain derivatives have been developed from this acid to increase not only its activity as an antitumor agent but also its antiviral and antiparasitic properties (Dembitsky, 2006; Gung and Dickson, 2002; Gachet *et al.,* 2010).

From the leaves of this plant, triterpenes such as taraxerol (**14**), lupeol, lupin-3-one, and squalene have been isolated (Cursino *et al.,* 2009). Taraxerol is known for its anti-inflammatory properties, which could contribute to the reported ethnobotanical effect.

Monnina obtusifolia H.B.K

A native bush of Ecuador, this plant is distributed in the Andes Mountains. Its populations can be found in Bolívar, Carchi, Chimborazo, Cotopaxi, Imbabura, Napo, Pastaza, Pichincha, and Tungurahua provinces at altitudes from 1,500 to 4,000 m.a.s.l. (de la Torre *et al.*, 2008). Since angiogenesis, the growth of new blood vessels, is important in the metastasis and growth of tumors (Bailón-Moscoso *et al.,* 2014), the n-BuOH extract obtained from the leaves of *Monnina obtusifolia* was shown to inhibit VEGF-A or the interaction of placental growth factor with Flt-1 (VEGF receptor 1) (Lepore *et al.,* 2011).

Species indigenous to Ecuador with anticancer potential

This group of plants encompasses those plants that have initially been reported for various uses according to Ecuadorian traditional medicine. In addition, recent studies show that their components (Figs. 2, 3) are effective in treating certain types of cancer and the composition chemical of species are described in Table 3

Cinchona officinalis L

A bush or tree belonging to the Rubiaceae family, this plant is native to Ecuador and distributed in the Andes Mountains. Its populations can be found in Azuay, Bolívar, Cañar, Chimborazo, El Oro, Loja, Morona-Santiago, and Zamora-Chinchipe provinces at altitudes from 1,000 to 3,500 m.a.s.l. (de la Torre *et al.,* 2008). The bark of the *Cinchona spp.* was used in ancient times by the Paltas in Ecuador as an antipyretic agent; it was introduced to Europe in the year 1,640 (Ferreira Júnior *et al.,* 2012). This bark was the main therapy against malaria in Europe until 1,820, when pure quinine (**15**) was isolated. Alongside its derivative chloroquine (**16**), it has been widely used against paludism; Bark of *C. officinalis* may contain 5–14 % of alkaloids(Kacprzak, 2013). Many alkaloids isolated from *C. officinalis* and analogs have been effective cytotoxic agents in HL-60 leukemia, HepG2 hepatoma, MCF-7 breast adenocarcinoma and SH-SY5Y neuroblastoma cells with IC_{50} of between 0,75 and 89 μM (Károlyi *et al.,* 2012). Chloroquine has proven to be effective against many cell lines, especially in low-pH cancer types, in addition to inducing apoptosis and autophagocytosis (Solomon and Lee, 2009). Quinidine (**17**), another major alkaloid presents in *C. officinalis*, promotes the interruption of the cell cycle in G1/G0, causing the accumulation of lipid droplets in the membrane and the expansion of the cytoplasm, allowing cellular differentiation in MCF7 human breast cancer cells (Solomon and Lee, 2009). In addition, the alkaloid synthesis of *Cinchona* conjugates with fluorophores with cytotoxic properties in the KB cell line has been reported; these conjugates can also be used as markers (Baraniak *et al.,* 2011). In the early 1990s, it was demonstrated that quinine alkaloids were capable of reverting the effects of cellular resistance to anthracyclines and doxorubicin (Solary *et al.,* 1991; Genne *et al.,* 1992), and thus, they are currently used as ATP shuttle inhibitors (Gottesman *et al.,* 2002). Chloroquine and 3-hydroxyquinoline (**18**) are both being tested in the clinical trials (Phase I and II) for use in combination treatments with various drugs, as there is a synergy and some selectivity of the induction of apoptosis in cancer cells of the lung, breast, and glioblastoma (Solomon and Lee, 2009).

Annona squamosa L., *A. montana* Macfad y *A. muricata* L

These three species have been used in traditional medicine for rheumatism. They belong to the Annonaceae family, which is widely distributed in the tropical and subtropical regions. A. *squamosa* is a tree cultivated in Ecuador and is distributed along the coast. Its populations can be found in the Guayas province at altitudes from 0 to 500 m.a.s.l. A. *muricata* is a native small tree or tree grown in Ecuador; it is also distributed along the coast, on the Galapagos Islands, and in the Amazon rainforest (de la Torre *et al.,* 2008). Collections can be found in Esmeraldas, Galápagos, Guayas, Imbabura, Los Ríos, Manabí, Morona-Santiago,

and Napo provinces at altitudes from 0 to 500 m.a.s.l. (de la Torre *et al.,* 2008). *A. montana* is a native tree of Ecuador that is distributed along the coast and in the Amazon rainforest. Its populations can be found in Esmeraldas, Guayas, and Napo provinces at altitudes from 0 to 500 m.a.s.l. The most representative secondary metabolites of this family species are the acetogenins (ACGs) (Liaw *et al.,* 2010). The ACGs are characterized by a wide range of biological activities, such as immunosuppressive, pesticide, antisedative, antimalarial, and antitumor cytotoxicity (Liaw *et al.,* 2010; Rupprecht *et al.,* 1990). The action mechanism by which ACGs are cytotoxic is related to the inhibition of complex I in the electron transport system in the mitochondrion (Zafra-Polo *et al.,* 1996). ACGs also inhibit NADH oxidase, which is found in the plasma membrane of the tumor cells. The immediate effect is a decrease in ATP levels (Alali *et al.,* 1999; Fantin and Leder, 2006). The high demand for ATP by tumor cells could explain the sensitivity of carcinoma cells to complex I inhibitors (Glover *et al.,* 2007), suggesting that the ACGs could be excellent candidates for the development of new antitumor agents, even more effective against multiple drug-resistant (MDRs) tumors due to the flux of the ATP pump (Alali *et al.,* 1999). Most studies of the antitumor activity of ACGs are performed in tumor cell; the impressive characteristic about these compounds is that their IC_{50} is between 10^{-6} and 10^{-14} M. Squamocin (**19**) was also found to inhibit the proliferation of K562 cells via G2/M arrest in association with the induction of p21 and p27, and the reduction of Cdk1 and Cdc25C kinase activities (Liaw *et al.,* 2010). Bullatacin (**20**) has been demonstrated to induce apoptosis in various types of cell lines (HL-60, Hep G2, KB and CCM2) (Chang et al. 1993; Chiu *et al.,* 2003; Zhu *et al.,* 2002; Yuan *et al.,* 2006; Derbré *et al.,* 2006). Bullatacin was found to be effectively cytotoxic to the human mammary adenocarcinoma (MCF-7/Adr) cells, while it was more cytostatic to the parental non-resistant wild-type (MCF-7/wt) cells (Oberlies *et al.,* 1997). Cis-annonacin (**21**) was selectively cytotoxic to colon adenocarcinoma cells, with a potency 10,000 times that of Adriamycin (Lim, 2012), while cis-annonacin-10 (**22**)-one was powerful inhibitor of NADH oxidase mitochondrial complex I (IC_{50}:0.8nM). Murisolin (**23**) was reported to show cytotoxic activity against human tumor cell lines with potency from 105 to 106 times that of adriamycin (Lim, 2012).

Licania intrapetiolaris Spruce ex Hook. f

A tree from the Ecuadorian amazon rainforest, this plant belongs to the Chrysobalanaceae family. Its populations can be found in Sucumbíos province. The clerodane-type diterpenoids intrapetacin A (**24**) and intrapetacin B (**25**) were isolated for the first time from this species and were found to be cytotoxic in KB cells (human oral epidermoid carcinoma), with IC_{50} of 2 and 0.8 μg/mL, respectively (Oberlies and Burgess, 2002). In addition, a highly potent triterpene, cucurbitacin B (**26**) was found (Oberlies and Burgess, 2002; Mukherjee *et al.,* 2013), with proven cytotoxic activity in human hepatocellular carcinoma cells (BEL-7402)(Chan *et al.,* 2010b), osteosarcomas (MG-63 and SAOS-2), (Lee *et al.,* 2011), and Hep-2 laryngeal cells (Liu *et al.,* 2010). Cucurbitacin B is capable of inhibiting various leukemia cell lines (CCRF-CEM, K562, MOLT-4, RPMI-8226, and SR). The growth of leukemia cells was inhibited by cucurbitacin B with IC_{50} ranged from 15.6 nM to 35.3 nM and arrest of cell cycle (Chan *et al.,* 2010b) and plays a role of an inhibitor of many signaling pathways in cancer cells (Chan *et al.,* 2010a).

Casearia sylvestris Sw

This plant is a shrub or tree belonging to the Flacourtiaceae family, which is native to Ecuador. It is distributed along the coast, in the Andes Mountains and in the Amazon rainforest. Collections can be found in Carchi, El Oro, Esmeraldas, Los Ríos, Manabí, Morona-Santiago, Napo, Pastaza, Pichincha, and Zamora-Chinchipe provinces at altitudes from sea level to 2,000 m.a.s.l. (de la Torre *et al.,* 2008). It is used in traditional medicine in Colombia to treat tumors (Graham *et al.,* 2000). Aqueous-ethanolic and chloroform extracts of the leaves of *C. sylvestris* Sw exhibit activity cytotoxic in MCF-7 cells, the IC_{50} value was determined at 141 μg/mL for aqueous-ethanolic and 66 μg/mL for chloroform. Also in vivo, reduced proliferation was observed in tumor cells from animals treated with the extract from Casearia sylvestris (Felipe *et al.,* 2014). From samples collected in Ecuador, casearvestrins A (**27**), B (**28**), and C (**29**) were isolated for the first time, with antitumor activity observed in the following cell lines: lung cancer (LX-1), colon cancer (HCT116), and ovarian cancer (A2780), with IC_{50} doses between 0.12 and 0.89 μM. (Oberlies and Burgess, 2002). Casearins with antitumor activity have also been isolated from this species (Gonzaga dos Santos *et al.,* 2010; Felipe *et al.,* 2014). Casearins L (**30**), O (**31**), and X (**32**) have a strong cytotoxic effect on leukemia cell lines (CEM, HL-60 and K-562) (Ferreira *et al.,* 2010). Casearin X was the most active compound studied, showing the dramatic cytotoxic effects on CEM and HL-60 cell lines (IC_{50} of 0.4 μM) and causing cell death via apoptotic pathways (Pinheiro *et al.,* 2014). Two compounds derived from gallic acid have been isolated from *C. sylvestris* leaves, isobutyl gallate-3, 5-dimethyl ether (IGDE) (**33**) and methyl gallate-3, 5-dimethyl ether (MGDE) (**34**) and have shown the antitumor activity in xenograft models of Ehrlich tumor cells and Lewis lung cancer cells (Da *et al.,* 2009).

Conclusion

It is clear that Ecuador holds a wide variety of plant species, resulting in a wide chemical diversity. Similarly, the few studies so far have shown the great potential of using these plant species against cancer, many of which traditionally used by various ethnic groups, not only from Ecuador. However, most studies have been conducted in vitro and a few in vivo; therefore, the need to increase research on extracts and secondary metabolites in preclinical studies and to look for the understanding of the mechanisms involved.

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