Research, Society and Development, v. 9, n. 10, e9149109241, 2020
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v9i10.9241

Antitumor activity of Apocynaceae species used in Amazon traditional medicine

Atividade antitumoral de espécies de Apocynaceae utilizadas na medicina tradicional amazônica

Actividad antitumoral de especies de Apocynaceae utilizadas en la medicina tradicional amazónica

Received: 10/12/2020 | Reviewed: 10/21/2020 | Accept: 10/25/2020 | Published: 10/25/2020

Mirian Letícia Carmo Bastos
ORCID: https://orcid.org/0000-0002-5205-1198
Universidade Federal do Pará, Brasil
Universidade do Estado do Pará, Brasil
E-mail: mirian.c.bastos@hotmail.com
Rosana Moura Sarmento
ORCID: https://orcid.org/0000-0002-9471-0593
Universidade Federal do Pará, Brasil
E-mail: rosana.sarmento@hotmail.com
Marcelo de Oliveira Bahia
ORCID: https://orcid.org/0000-0001-6820-6521
Universidade Federal do Pará, Brasil
E-mail: mobahia1970@yahoo.com.br
Jaqueline da Silva Rodrigues
ORCID: https://orcid.org/0000-0002-6017-7057
Universidade de Brasília, Brasil
E-mail: sol.jaque@gmail.com
Valdicley Vieira Vale
ORCID: https://orcid.org/0000-0001-6570-4875
Universidade Federal do Pará, Brasil
E-mail: valdicleyvale@gmail.com
Sandro Percário
ORCID: https://orcid.org/0000-0002-9528-0361
Universidade Federal do Pará, Brasil
E-mail: rosana.sarmento@hotmail.com
Maria Fâni Dolabela
ORCID: https://orcid.org/0000-0003-0804-5804

Universidade Federal do Pará, Brasil
E-mail: fanidolabela20@gmail.com

Abstract

This study reviews the use of Apocynaceae species for cancer and tumor treatment in the Amazon. Databases and books were searched for ethnobotanical and phytochemical evaluations of the cytotoxic and anticancer activities of Apocynaceae species. The literature reports the use of several Amazonian species, such as *Asclepias curassavica*, *Himatanthus articulates,* and *Macoubea sprucei*, in treating tumors and cancers. Phytochemical studies on *A. curassavica* and *H. articulatus* have shown their chemical compositions to be variable, possessing cardenolides, iridoids, flavonoids, steroids, and terpenes. Most of the species have not been subjected to *in vitro* experiments for anticancer activity, and the evaluated species showed moderate-to-weak responses or were inactive. Other studies have shown that iridoids, flavonoids, and steroids are promising as antitumor treatments. The following action mechanisms have been attributed to iridoids: topoisomerase I-DNA complex stabilization, cellular cytoskeleton alteration, and induction of apoptosis. The activities of flavonoids have been reported to include apoptosis induction in liver tumor cells. Some authors suggest that flavonoids reduce oxidative stress cellular response which reduces mitochondrial dysfunction and cell death. In summary, Apocynaceae species appear to be promising as a source for antitumor agents; however, further studies are required to confirm their antitumor activities and to better elucidate the underlying mechanisms involved.

Keywords: Apocynaceae Cancer; Phytochemistry; Cytotoxicity.

Resumo

Este estudo revisa o uso de espécies de Apocynaceae para o tratamento de câncer e tumores na Amazônia. Bancos de dados e livros foram pesquisados para avaliações etnobotânicas e fitoquímicas das atividades citotóxicas e anticâncer de espécies de Apocynaceae. A literatura relata o uso de várias espécies amazônicas, como *Asclepias curassavica*, *Himatanthus articulatus* e *Macoubea sprucei*, no tratamento de tumores e cânceres. Estudos fitoquímicos em *A. curassavica* e *H. articulatus* mostraram que suas composições químicas são variáveis, possuindo cardenolideos, iridoides, flavonoides, esteroides e terpenos. A maioria das espécies não foi submetida a experimentos *in vitro* para atividade anticâncer, e as espécies avaliadas apresentaram respostas moderadas a fracas ou eram inativas. Outros estudos mostraram que iridoides, flavonoides e esteroides são promissores nos tratamentos antitumorais. Os seguintes

mecanismos de ação foram atribuídos aos iridóides: estabilização do complexo topoisomerase I-DNA, alteração do citoesqueleto celular e indução de apoptose. Foi relatado que as atividades dos flavonoides incluem a indução de apoptose em células tumorais do fígado. Alguns autores sugerem que os flavonoides reduzem a resposta celular ao estresse oxidativo, o que reduz a disfunção mitocondrial e a morte celular. Em resumo, as espécies Apocynaceae parecem ser promissoras como fonte de agentes antitumorais; no entanto, mais estudos são necessários para confirmar suas atividades antitumorais e para melhor elucidar os mecanismos subjacentes envolvidos.

Palavras-chave: Apocynaceae; Câncer; Fiquímica; Citotoxicidade.

Resumen

Este estudio revisa el uso de especies de Apocynaceae para el tratamiento del cáncer y tumores en la Amazonía. Se buscaron bases de datos y libros para realizar evaluaciones etnobotánicas y fitoquímicas de las actividades citotóxicas y anticancerígenas de las especies de Apocynaceae. La literatura reporta el uso de varias especies amazónicas, como Asclepias curassavica, Himatanthus articulate y Macoubea sprucei, en el tratamiento de tumores y cánceres. Los estudios fitoquímicos sobre A. curassavica y H. articulatus han demostrado que sus composiciones químicas son variables y poseen cardenólidos, iridoides, flavonoides, esteroides y terpenos. La mayoría de las especies no se han sometido a experimentos in vitro para determinar la actividad anticancerosa, y las especies evaluadas mostraron respuestas de moderadas a débiles o estuvieron inactivas. Otros estudios han demostrado que los iridoides, flavonoides y esteroides son prometedores como tratamientos antitumorales. Se han atribuido a los iridoides los siguientes mecanismos de acción: estabilización del complejo topoisomerasa I-ADN, alteración del citoesqueleto celular e inducción de apoptosis. Se ha informado que las actividades de los flavonoides incluyen la inducción de apoptosis en células tumorales hepáticas. Algunos autores sugieren que los flavonoides reducen la respuesta celular al estrés oxidativo, lo que reduce la disfunción mitocondrial y la muerte celular. En resumen, las especies de Apocynaceae parecen prometedoras como fuente de agentes antitumorales; sin embargo, se requieren más estudios para confirmar sus actividades antitumorales y para dilucidar mejor los mecanismos subyacentes involucrados.

Palabras clave: Apocynaceae; Cancer; Fitoquímica; Citotoxicidad.

1. Introduction

Tumors are tissues of very complex molecular characteristics. They have several cell types in their composition that participate in heterotypic interactions with one another enabling varied biological capabilities. Disordered cell proliferation is only one of these distinct abilities and enables tumor growth and metastatic spread (Hanahan & Weinberg, 2000). Study review demonstrate on the cancer characteristics understand a sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis. In addition, there is the instability of the genome instability, which generates the genetic diversity that expedites their acquisition, and inflammation, which fosters multiple hallmark functions. Another important fact added to characteristics related to the evolution of tumor cells was the reprogramming of energy metabolism and evading immune destruction (Hanahan & Weinbert).

Plants have a long history of use in cancer treatment (Hartwell, 1982; Cragg & Newman, 2005). In ancient times, many people could not diagnose "cancer;" however, they used different plant species to treat symptoms such as "hard lumps," abscesses, corns, warts, polyps, or tumors [4]. Therefore, plants play an important role as a source of drugs against cancer. Approximately 60% of the drugs used for cancer treatment nowadays are derived from natural sources, including plants, marine organisms, and microorganisms (Cragg & Newman, 2005; Newman, et a., 200).

Research on anticancer agents from plants began in the 1950s with the discovery of the vinca alkaloids — vinblastine and vincristine (Cragg & Newman, 2005). These alkaloids were isolated from *Catharanthus roseus* (L) G. Don. (Apocynaceae) (Moreno, et al., 1995; Brandão, et a., 2010; Kumar, et a., 2013) and with this discovery triggered a great interest in the isolation of natural compounds with anticancer activities (El-Sayed, et al., 2011; Suffredini, et al., 2006)..

The Apocynaceae family comprises essentially tropical plants, with some subtropical species, and includes more than 5,100 species and 366 genera (Nazar, et al., 2013; Endress, et al., 2014; Pereira, et al., 2016). Approximately 95 genera and 850 species are found in Brazil (Lorenzi & Souza, 2008; Santos, et al., 2013), occurring in several biomes, such as the Amazonian Rainforest, Atlantic and *Tabuleiro* forests, Dry Forest, *Cerrado*, and *Caatinga* (Santos, et al., 2013; Quinet & Andreata, 2005).

The present study reviewed the *Apocynaceae* species used in Amazonian traditional

medicine for tumor and cancer treatment, and the phytochemical studies of their cytotoxic and anticancer activities.

2. Metodology

This study used qualitative research methodology and bibliographic review (Pereira, et al., 2018). Data collection for this review was conducted using combinations of the following keywords: medicinal plants, Amazon, cytotoxicity, cell lines, phytochemical compounds, anticancer, and Apocynaceae. The search for articles was carried out on the databases Periódicos Capes, Pubmed, Web of Science, and Scopus. Articles in English and Portuguese published between 1975 to 2016 were included.

For the selection of ethnobotanical and ethnopharmacological studies, the following criteria were used: the study was conducted in the Brazilian Amazonian region or American countries in the Amazon region. After the selection of species, a broad review about their chemical properties and their cytotoxic and anticancer activities was conducted.

3. Results and Discussion

People native to the Amazon region use 3 species of Apocynaceae for cancer treatment (Table 1), with *Himatanthus* being the most often quoted genus. Of the species commonly used as anticancer in folk medicine, phytochemical studies with isolation of components have been reported only on two of them (Table 2). The Apocynaceae family, in general, contains alkaloid constituents, and the antitumor drugs obtained from the species of this family are usually alkaloids. However, the species listed as having antitumor properties in the Amazon do not possess these compounds, they are composed of iridoids, flavonoids, steroids, terpenes, and glycosylated cardenolides, instead.

Table 1. Medicinal use of Apocynaceae species by natives to the Amazon region.

No.	Species	Popular use	Form of use	Reference
1	*Asclepias curassavica*	Tumor and Cancer	Poison	Santos, et al., 2013; Neto, et a., 2002
2	*Himatanthus articulatus*	Tumor and Cancer	Latex dripped in water	Santos, et al., 2013; Neto, et a., 2002; Agra, et a., 2007
3	*Macoubea sprucei*	Cancer	Macerated stem	Suffredini, et al., 2006; Barreto ,et a., 1998

Source: Authors.

The antitumor activity of alkaloids is widely studied, but there have been few studies on other compounds isolated from Apocynaceae species, and consequently the mechanisms involved in their anticancer effects remain unclear. Only few studies have evaluated the antitumor activity of the extracts, fractions, and isolated compounds on certain tumor cell lines.

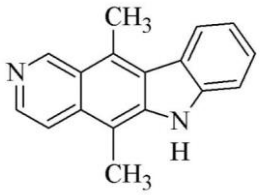
3.1. Apocynaceae and its Reported Use in Treating Cancer and Tumors

In the Amazon, several species of Apocynaceae are used in traditional medicine, particularly species belonging to the genera *Aspidosperma* and *Geissospermum*. The main reported uses of these species are the treatment of febrile diseases and malaria (Chierrito, et al., 2014). *Tabebuia impetiginosa* (Mart. Ex. DC) Standl (Ipê-roxo) is considered by the shamans of the Amazon forest, one of the rare master plants, to be used in the treatment of the most varied diseases. The most common use is in the form of tea, made by infusion of dry and powdered tissues; it is also used in the form of liquid extract, dry extract, and tincture (Lübeck, 2001). For example, latex of the *amapudo* (*Parahancornia fasciculata*) is one of the most important products for the market of Belém, but the official use of latex for the disease is an important word for the airways and tonic (Serra, et al., 2010; Silva, et al., 2011).

Different types of monoterpenoid indole alkaloids (Aimi, et al., 1991; Pereira, et al., 2007) and indole beta carbonyl alkaloids (Allen & Holmstedt, 1980) have already been isolated from *Aspidosperma*. The indole alkaloids ellipticine (Figure 1) and olivacine (Figure 2) showed anticancer activity and have been used in clinical trials (Shi, et al., 1998; Henrique,

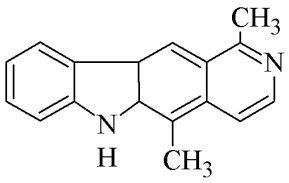
et al., 2010).

Figure 1. Chemical structure of ellipticine.



Source: Authors.

Figure 2. Chemical structure of olivacine



Source: Authors.

The main species used in Brazilian traditional medicine as a treatment for tumors or cancer, especially in the Amazon region, are from the *Himatanthus* genus. Species belonging to this genus contain latex, which is widely used for tumor treatment (Amaro, et al., 2006; Mousinho, et al., 2011; Table 1). A *Himatanthus* species is described in the Brazilian Pharmacopoeia First Edition (Silva, 1929) originally under the name *Plumeria lancifolia* Mull. Arg. (Brandão, et al., 2006).

The *Himatanthus* genus is common in the Amazon region. Species of this genus are widely spread from Panama to the southeast of Brazil, within the Tropic of Capricorn (Spina, 2004). Several chemical constituents and some substances of medicinal interest were isolated from *Himatanthus* species; however, little is known about the pharmacological effects of these substances (Sousa & Grangeiro, 2010).

Ethnobotanical studies on the anticancer and antitumor activities of Amazonian species of *Himatanthus* involved *H. articulatus* and *H. sucuuba*. Botanically, these two plants were classified as different species; however, in revising the genera, they were considered synonymous. Nowadays, the accepted name is *H. articulatus* (Vahl) Woodson, synonymous with *H. sucuuba* (Spruce) Woodson (Tokarnia, et al., 2000). This plant is known in the northern region of Brazil as sucuuba, janaguba, or sucuba (Perdue & Blomster, 1978; Endo, et al., 1994).

In general, the popular use of *H. articulatus* is related to its latex and decoctions of its bark. People in the Peruvian and Brazilian Amazon use these for the treatment of malaria (Milliken, 1997). However, this plant is also widely used in traditional medicine as an antitumor, antifungal, anthelmintic, and antianemia agent (Perdue & Blomster, 1978; Endo, et al., 1994).

This species has already been subjected to phytochemical studies (Table 2). Steroids from *H. articulatus* were identified, and triterpenic esters such as plumieride, isoplumieride, and plumierin were isolated (Silva, et al., 1998; Rebouças, et al., 2011; Vale, et al., 2015). The hexanic extract of *H. articulatus* had mixed triterpenic esters from the lupane and ursane series as a major proportion of the constituents in the mixture. They were identified, using gas chromatography and mass spectrometry, by the presence of cinnamates (lupeol cinnamate, α-amyrin and β-amyrin) and of the iridoids plumericin and isoplumericin (Silva, et al., 1998). Another study also showed plumieride to be the major iridoid of *H. articulatus* (Vale, et al., 2015). The presence of depsides and terpenes has also been reported in this species (Perdue & Blomster, 1978).

The aqueous extract of the bark of *H. articulatus* was evaluated for anticancer activity in different cell lines and showed activity against the lung epithelial cancer cells (NCI-H460; Table 3; Rebouças, et al., 2011). An ethanolic extract from the bark of *H. articulatus* was subjected to acute and subchronical toxicity evaluation and did not show significant clinical changes. In addition, no changes were observed in weight or anatomical histology (Vale, et al., 2015)

Another Apocynaceae species used in traditional medicine against cancer is *Asclepias curassavica* L. (Neto, et al., 2002; Li, et al., 2008). It is a toxic herbaceous plant, known since ancient times in Latin America and that grows throughout Brazil (Tokarnia, et al., 2000). According to the electronic databases “Tropicos” and “Flora of Brazil,” this species also belongs to the Apocynaceae family; however, some authors report it as belonging to the Asclepdaceae family (Li, et a., 2008; Tokarnia, et al., 2000; Trópicos, 2017; Flora do Brasil, 2017; Mena-Rejon, et al., 2009).

This species has already been subjected to phytochemical studies, and several constituents have been isolated (Table 2), including flavonols, flavonol glycosides, triterpenes, and cardenolides. The isolated cardenolides from this plant include calactin, asclepain CI, asclepain CII, asclepine (asclepiadin), uzarin, uzarigenin, corotoxigenin, asclepogenin, curassavogenin, calotroposide, clepogenin, desglucouzarin, and kidjolanin. The isolated polyphenols include quercetin, kaempferol, rutin, and isorhamnetin (Al-Snafi, 2015).

The leaf and stem of *A. curassavica* showed the presence of fixed oils, flavonoids, phenols, tannins, terpenoids, saponin, and steroids. The leaf and root contain carboxylic acids, fixed oils, flavonoids, phenols, quinine, resins, steroids, glycosides, and coumarins (Al-Snafi, 2015).

From an ethanolic extract of the aerial parts of *A. curassavica*, a new cardenolide, 12β,14β-dihydroxy-β3,19-epoxy-3α-methoxy-α5-card-20(22)-enolide, a new cardenolide glycoside, 12β-hydroxycalotropin, and the following eleven compounds, coroglaucigenin, 12 β-hydroxycoroglaucigenin, calotropagenin, desglucouzarin, 6′-O-feruloyl-desglucouzarin, calotropin, uscharidin, asclepin, 16α-hydroxyasclepin, 16α-acetoxycalotropin, and 16α-acetoxyasclepin, were isolated; their antitumor activity against the HepG2 cell line and lymphocytic leukemia (Raji) cell line were evaluated. Among them, asclepin exhibited the most potent activity against the HepG2 and Raji cell lines. The new compound showed significant cytotoxicity in both cell lines, and the new cardenolide displayed weak inhibitory activity against them (Li, et al., 2009).

Another study, also using an ethanolic extract from the aerial parts of *A. curassavica*, isolated six new steroidal glycosides denominated as curassavosides (curassavoside A-F) and two oxypregnanes (12-O-benzoyldeacylmetaplexigenin and 12-O-benzoylsarcostin; Table 2). In this study, only the compound curassavoside A showed weak inhibitory activity against Raji cell lines and AGZY83-a lung adenocarcinoma in the MTT assay (Li, et a., 2008).

Other studies with *A. curassavica* extracts evaluated the anticancer activities of this species. However, the activity of isolated compounds was not evaluated. A methanolic extract from the leaves of *A. curassavica* was evaluated for antitumor activity against various cell lines, and showed the highest activity against the human cervix carcinoma cell line Hep-2[1](established via HeLa cell contamination), with an IC_{50} of 19 µg/mL (Table 3; Mena-Rejon, et al., 2009). An *A. curassavica* ethanolic extract also showed anticancer activity against nasopharyngeal carcinomas (KB). In this study, the cardiac glycoside calotropin was isolated. Its cytotoxic activity was not evaluated, but the author suggested this metabolite as responsible for the cytotoxic activity detected (Kupchan, et al., 1964). A feature of this species is its high toxicity. Since the cardenolides have positive inotropic effects (Patnaik &

[1] Cells of this line contain HeLa marker chromosomes and were derived via HeLa contamination. This line was originally thought to be derived from an epidermoid carcinoma of the larynx, but was subsequently found, based on isoenzyme analysis, HeLa marker chromosomes, and DNA fingerprinting, suggesting HeLa cell contamination.

Köhler, 1978), it is believed that the toxic effects are related to these constituents (Al-Snafi, 2015).

Another Apocynaceae species also used in folk medicine for cancer treatment is *Macoubea sprucei (Müll. Arg.)*, a species native to the Amazon and Atlantic rainforests (Suffredini, et al., 2006; Myers, et al., 2000). We did not find any phytochemical studies isolating the constituents of this plant; however, there were studies on its cytotoxic effects against tumor cells, performed with aqueous extracts from the stem.

Moreover, the aqueous extract of *M. sprucei* stem was evaluated for antitumor activity against the prostate carcinoma cell line PC-3, and an inhibitory effect was observed at concentrations of 100 µg/mL, 20% [10]. Similarly, the antitumor activity of the aqueous extract was evaluated in another study using a carcinoma cell line of large human lung cells (NCI-H460). A similar inhibitory effect was observed (100 µg/mL = 31.98%; Suffredini, et al., 2007).

Table 2: Phytochemical studies and validation of the medical use of Apocynaceae species

No.	Species	Phytochemistry	Anticancer activity	Toxicity	References
1	*Asclepias curassavica*	Steroidal glycosides: 12-O-benzoyldeacylmetaplexigenin, 12-O-benzoylsarcostin, curassavoside A, curassavoside B, curassavoside C, curassavoside D, curassavoside E, and curassavoside F Cardenolides: calactin, calotropin, calotropagenin, coroglaucigenin, asclepin, asclepain CI, asclepain CII, asclepine (asclepiadin), uscharidin, uzarin, uzarigenin, corotoxigenin, asclepogenin, curassavogenin, calotroposide, clepogenin, desglucouzarin, kidjolanin, and uscharidin Flavonoids: quercetin, kaempferol, rutin, and isorhametin.	Moderate to Inactive	Toxic	Li, et al., 2008; Mena-Rejon, et al., 2009; Al-Snafi, 2015; Li, et al., 2009; Kupchan, et al., 1964
2	*Himatanhtus articulatus*	steroids and triterpenic steroids: stigmasterol, sitosterol, cycloartenol, α-amyrin-3β-O-cinnamoyl, βamyrin-3β-O-cinnamoyl, α-amirin-3β-O-acetyl, β-amirin-3β-O-acetyl, lupeol-3β-O-cinnamoyl, lupeol-3β-O-acetyl, ursolic acid, methylmyoinositol, Iridoide: 1β-O-β-D-glucopyranosylplumeric acid, plumeride-1β-O-β-D-glucopyranosyl, plumericin, isoplumericin e plumerideo	Weak to Inactive	Non-toxic	Rebouças, et al., 2011; Vale, et al., 2015; Suffredini, et al., 2007
3	*Macoubea sprucei*	There are no studies on the isolation of constituents	Inactive*	Non-toxic	Suffredini, et al., 2006; Neto, et al., 2002

IC_{50}- activity: strong <5 μg/mL; moderate = 5–20 μg/mL; weak = 20–50 μg/mL; inactive >50 μg/mL [121]. Source: Authors.

* Aqueous extracts were tested at a dose of 100 μg/ml, and a percentage of cell lethality < 15 was considered selective in the assays, when compared to untreated cells

Table 3. Antitumor activity of Apocynaceae species used in folk medicine.

Species	Cell lines CC_{50} ± SD (µg/mL)											
	NHI-3T3	**Raji/ AGZY**	**HT-29**	**Hep-2**	**KB**	**SiHa**	**HeLa**	**NCI-H460**	**MCF-7**	**OVCAR-3**	**RXF-393**	**MDCK**	**Ref**
A. curassavica (ME; L*)*				19±1.1	71±0.9	65±0.6	56±0.7					40±1.2	Mena-Rejon, et al., 2009
A. curassavica (ME; ST)				25±2.1	41±1.1	-	-					50±2.1	Mena-Rejon, et al., 2009
A. curassavica (ME; RB)			-	26±0.6	98±1.2	53±1.1	41±1.5	-	-		-	60±1.0	Mena-Rejon, et al., 2009
A. curassavica (Curassavoside A; AP)		15.47/ 26.83*	-	-	-	-	-	-	-		-	-	Li, et al., 2008
H. articulates (AE; ST)	-	-	42.3±6.3	-	-	-	-	27.3±2.0	82.0±1.6	86.3±9.1	40.5±5.4	-	Rebouças, et al., 2011
H. articulates (CF; ST)	3.7±2.3	-	2.0±0.4	-	-	-	-	3.7±0.7	4.1±0.1	3.6±0.7	4.2±0.5	-	Rebouças, et al.,

													2011
H. articulates (EAF; ST)	41.6±2.3	-	54.4±3.4	-	-	-	-	62.2±2.7	52.4±6.6	39.9±0.6	29.4±4.2	-	Rebouças, et al., 2011
H. articulates (BF; ST)	-	-	14.4±1.7	-	-	-	-	63.2±4.0	26.0±3.9	19.7±5.0	12.8±4.1	-	Rebouças, et al., 2011

CC_{50}: cytotoxic concentration 50; activity: <5 µg/mL strong, 5–20 µg/mL moderate, 20–50 µg/mL weak, >50 µg/mL inactive;
NIH-3T 3: mouse embryo fibroblast, Raji: lymphocytic leukemia, AGZY: lung adenocarcinoma, HT-29 human colon adenocarcinoma, Hep-2: human cervix carcinoma (established via HeLa cell contamination), KB: nasopharynx carcinoma, SiHa: cervix squamous carcinoma, HeLa: cervix adenocarcinoma, NCI-H460: human non-small cell lung carcinoma, MCF-7 human breast cancer, OVCAR-3: human ovarian adenocarcinoma, RXF-393 human renal cell carcinoma, MDCK: normal cell Madin-Darby canine kidney;
ST: Stem bark, L: leaves, RT: Root bark, AP: arterial parts, ME: Methanolic extracts, AE: Aqueous extracts, CF: Chloroform fraction, EAF: Ethyl acetate fraction, BF: Butanolic fraction; Ref: references; * Standard deviation not shown
Source: Authors.

In summary, there are no reports on the alkaloids present in the plants of the Apocynaceae family that are reported to treat cancer or tumors in folk medicine. These Apocynaceae species contain latex, which is mainly used topically. It is therefore also important to assess its biological activity and chemical composition.

Sometimes, the fractionation of the crude extract enhances the biological activity. In order to verify whether this in the case in these species, the anticancer activities of iridoids, flavonoids, steroids, terpenes, and glycosylated cardenolides were investigated.

3.2. Antiproliferative and Antitumor Activity of Isolated Iridoids and Flavonoids and the Mechanisms Involved

Several studies have shown the antitumor activity of different iridoids, and their mechanisms of action may include the following: DNA polymerase inhibition (Pungitore, et al., 2004), activation of the apoptotic cascade PKCd/JNK/Fas/caspase-8 and caspase-3 (Chang, et al., 2004; Peng, et al., 2005), topoisomerase I-DNA complex stabilization (Galvéz, et al., 2005), interruption of microtubule formation preventing cellular replication, motility, and invasiveness (Hamdi & Castellon, 2005).

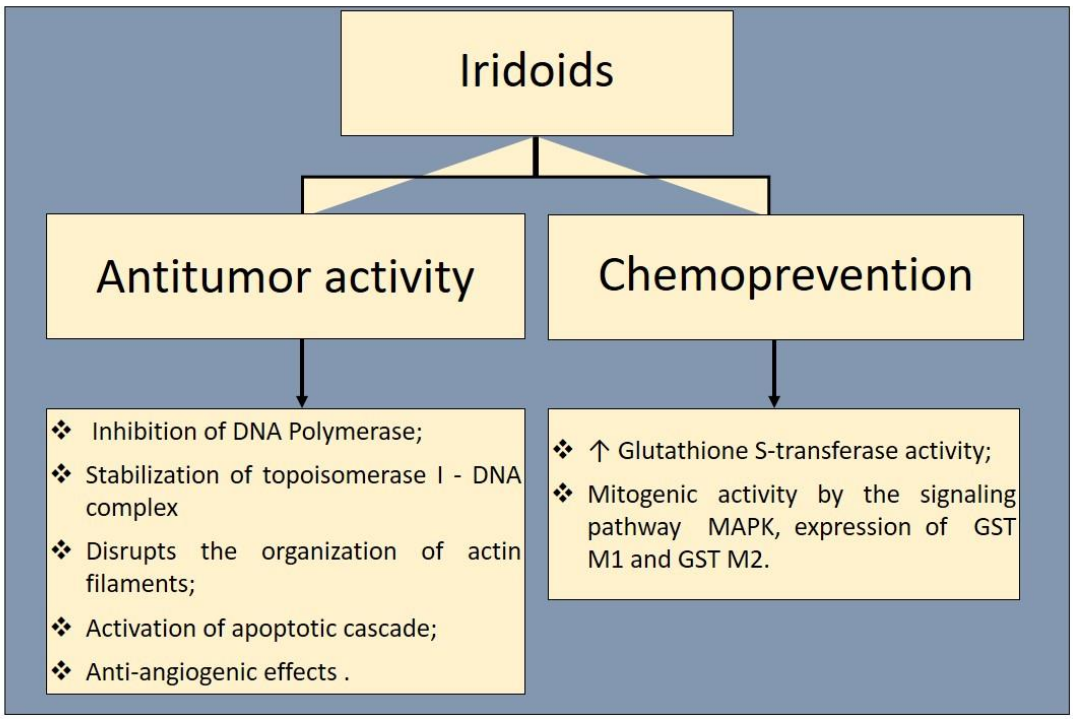
The iridoids fulvoplumierin, isoplumericin, and plumericin have already been assigned anticancer action (Silva, et al., 2007; Abdel-karder, et al., 1997). The following compounds were isolated from extracts obtained from the barks of *Plumeria rubra L.*(Apocynaceae): iridoids (plumericin, fulvoplumierin, allamandin, 15-alamin, desmethyl plumieride, plumieride, α-allamcidin, β-allamcidin, and 13-O-p-coumaroyl plumieride), 2,5-dimethoxy-p-benzoquinone, and the lignan liriodendrin. All these compounds were evaluated *in vitro* using a cell line panel composed of lymphocytic leukemia murine cells (P-388) and several types of human cancer cells (breast, colon, lung, melanoma, fibroblastic sarcoma, and KB). The iridoids 15-desmethyl plumieride, plumieride, α-allamcidin, β-allamcidin, and 13-O-p-coumaroyl plumieride were considered inactive because they did not significantly inhibit cell growth. However, fulvoplumierin, allamcin, and allamandin, as well as 2,5-dimethoxy-p-benzoquinone, were found to be active (Kardono, et al., 1991).

Iridoids such as aucubin and geniposide were found to stabilize the topoisomerase I-DNA complex but had no effect on topoisomerase II (Galvés, et al., 2005). The activity of geniposide can be related to the absence of a hydroxyl group at C6 and the presence of a methyl ester group at C4, which is responsible for binding to free amino groups (Tundis, et al., 2008).

Geniposide application for the chemoprevention of cancer has been investigated. This metabolite increased the activity of glutathione S-transferase (GST) by inducing expression of the subunits GST M1 and GST M2 (Tundis, et al., 2008). Mitogenic activity was also evaluated through the activated protein kinase (MAPK) signaling pathway, and the expression of GST M1 and GST M2. The geniposide-induced increase in GST M1 and M2 levels was blocked by pretreatment with an extracellular MAPK inhibitor and mitogen-activated protein kinase (MEK), but not by pretreatment with other MAPK inhibitors. This result suggests that the effects induced by geniposide on the transcription of GST M1 and GST M2 are mediated by MEK-1, extracellular MAP, and the regulation of the pathway MEK-1. In summary, the effect of geniposide on the MEK-1 pathway seems to be caused by increased activity of Erk1/2 (a downstream effector of MEK-1), which immediately responds to increases in phosphorylated forms of MEK-1 and induces the long-term expression of Ras, Raf, MEK-1, and Erk1/2 (Tundis, et al., 2008; Kuo, et al., 2005).

In short, iridoids are very promising as antitumor agents, therefore, it is worth investigating their anticancer activities (Figure 3).

Figure 3. Mechanisms involved in the antitumor and chemoprevention activities of iridoids.



MAPK, mitogen-activated protein kinase; GST M1, subunit M1of the glutathione S-transferase; GST M2, subunit M2 of the glutathione S-transferase. Source: Authors.

Many studies have suggested that flavonoids are effective antioxidants, as well as displaying strong inhibitory effects on the proliferation of several human cancer strains (Nguyen, et al., 2003; Luo, et al., 2009; Luo, et al., 2011; Li, et al., 2014), and interfering with apoptosis and cell death [61]. In the present review, we reported the possible mechanisms involved in the antitumor activity of two flavonoids present in *A. Curassavica*—kaempferol and quercetin—two of the most abundant flavonoids in the plants used for food in the Amazon region (Luo, et al., 2009; Behlin, et al., 2004).

Kaempferol presents antioxidant, anti-inflammatory, and antitumor effects. The antitumor activity seems to involve regulation of the cell cycle, inhibition of metastasis, inhibition of angiogenesis, and induction of apoptosis (Kim & Choi, 2013).

The antiangiogenesis potential of kaempferol and its underlying mechanisms were investigated against two ovarian cancer cell lines, OVCAR-3 and A2780/CP70. This study demonstrated that kaempferol inhibits angiogenesis and vascular endothelial growth factor (VEGF) expression in these cells, through both hypoxia-inducible factor (HIF)-dependent (Akt/HIF) and HIF-independent pathways. Both cell lines were treated with kaempferol for 24 h. OVCAR-3 cell viability was inhibited (20 μM=91%); however, in A2780/CP70 cells, the viability was slightly promoted to 102% at low concentrations, and then inhibited to 94% and 79% by 40-μM and 80-μM treatments, respectively. Kaempferol treatment for 8 h at 40 μM did not influence VEGF mRNA expression; however, by increasing the exposure time of the cells to kaempferol treatment, the levels of VEGF mRNA were decreased (24 h, 20-μM OVCAR-3= 73% and A2780/CP70= 81%; Luo, et al., 2011).

OVCAR-3 cells were implanted in chicken embryos to evaluate kaempferol's effects on *in vivo* angiogenesis and it was found that the growth and angiogenesis of implanted tumors were inhibited by kaempferol (20 μM). When compared with the negative control (the implanted cancer cells grew into a 70-mg tumor, with 26 blood vessels), the tumor reduced growth down to 38 mg and inhibited blood vessel development to 16, demonstrating that further study on the possible applications of this flavonoid for angiogenesis prevention and the treatment of ovarian cancers is warranted (Luo, et al., 2009).

VEGF gene expression is regulated by oxygen tension, growth factors, hormones, and oncogenes (Thorburn, 2004). Hypoxia induces VEGF expression through HIF-1, which is composed of HIF-1α and HIF-1β subunits (Kim, et al., 2007). Kaempferol treatment led to the inhibition of the HIF-1α protein to 75% in OVCAR-3 cells (5 μM) and 70% in A2780/CP70 (10 μM). Increased kaempferol concentration resulted in increased inhibitory effects.

Notwhitstanding, HIF-1β proteins were not affected by kaempferol treatment (Luo, et al., 2009).

Another study also evaluated the possible mechanisms involved in the activity of kaempferol in 3 cell lines of ovarian cancer. The metabolite inhibited cell proliferation by inducing apoptosis in A2780/wt cells, on a concentration-dependent manner. The induction of caspase 3/7 and a decrease of Bcl-xL protein levels occurred the in ovarian cancer cells, whereas p53, Bad, and Bax proteins were regulated by the kaempferol treatment. In summary, this flavonoid induces apoptosis through the regulation of the expression of pro-apoptotic and anti-apoptotic proteins in the intrinsic pathways of apoptosis. This substance may be a candidate for the chemoprevention of ovarian cancer in humans (Luo, et al., 2011).

In the extrinsic pathway of apoptosis, there are death receptors on the cell surface, which include tumor necrosis factor (TNF), first apoptosis signal (FAS), and TNF-related apoptosis-inducing ligand (TRAIL; Thorburn, 2004). Kaempferol reduced TNF-α production in rat gingival tissues through the inhibition of the nuclear transcription factor kappa B (NF-kB; Kim, et al., 2007). In osteoblasts and osteoclasts, this flavonoid acts by antagonizing TNF-α and inhibiting the receptor activator of the NF-kB ligand [69]. Kaempferol also sensitizes U251 and U87 human glioma cells for TRAIL-mediated apoptosis (Siegelin, et al., 2008).

The effects of kaempferol were evaluated on the growth of human lung cancer cells (A549) and on signal transduction pathways. Treatment of these cells with kaempferol resulted in a reduction in cell viability and a reduction in DNA synthesis in a dose- and time-dependent manner. There was an increase in Bax and Bad proteins, and the expression of Bcl-2 and Bcl-x was inhibited. Upon kaempferol treatment, MAPK was activated, whereas Akt-1 and phosphorylated Akt-1 were inhibited and MEK 1/2 was activated. In that study, kaempferol induced apoptosis was associated with the cleavage of caspase-7 and poly ADP-ribose polymerase (PARP). According to the authors, the inactivation of Akt-1 and alteration of the Bcl-2 family of proteins were not sufficient for kaempferol to induce apoptosis, and the activation of MEK-MAPK is a requirement for kaempferol-induced cell death in A549 cells (Nguyen, et al., 2003).

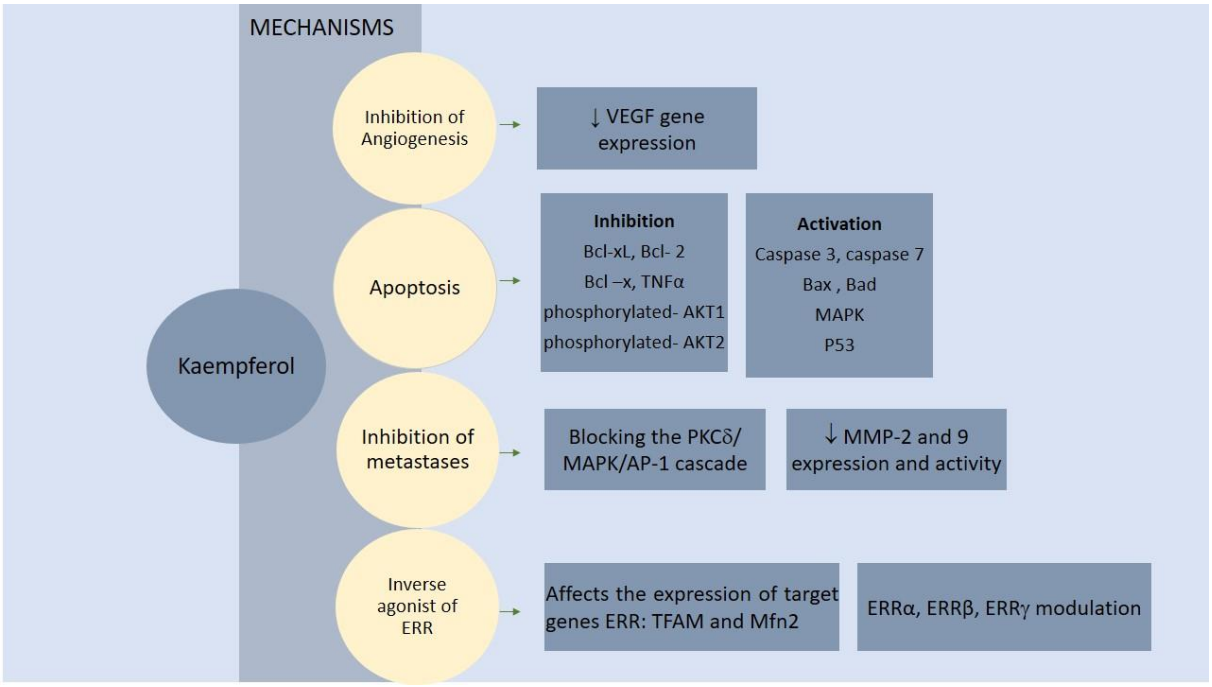
The kaempferol-induced apoptosis in MDA-MB-453 cells (human breast carcinoma cells) was associated with the upregulation of p53. Exposure to kaempferol also resulted in cell cycle arrest at the G2/M phase. In addition, small DNA fragments at the sub-G0 phase increased after 24 and 48 hours of treatment with 10 and 50 μM of kaempferol (Choi & Ahn, 2008).

Another important mechanism involved in the antitumor effects of kaempferol in breast cancer is the inhibition of metastases. Kaempferol could inhibit the adhesion, migration, and invasion of MDA-MB-231 human breast carcinoma cells. Kaempferol treatment led to reduced activity and expression of the matrix metalloproteinases (MMP) MMP-2 and MMP-9, which assist tumor cells during metastasis as accessory components in extracellular matrix degradation, and cancer cell invasion. Kaempferol inhibited the activation of transcription factor activator protein-1 (AP-1) and the MAPK signaling pathway, as well as repressed phorbol-12-myristate-13-acetate (PMA)-induced MMP-9 expression and activity, via suppression of the translocation of protein kinase C (PKC). Therefore, these results showed that kaempferol could inhibit cancer cell invasion by blocking the PKC/MAPK/AP-1 cascade, subsequently inhibiting MMP-9 expression and activity. Thus, kaempferol may be a potential therapeutic candidate for the treatment of cancer metastasis (Li, et al., 2014).

In addition, the activity of kaempferol in breast cancer has been attributed to the modulation of estrogen receptors (ERRα, ERRβ e ERRγ). ERRα has an important role in energy metabolism, and its overexpression can be a poor prognostic marker for breast, ovarian, colon, and prostate cancers (Ariazi, et al., 2002; Suzuki, et al., 2004; Cavallini, et al., 2005; Cheung, et al., 2005; Sun, et al., 2005). When kaempferol binds directly to ERRα and ERRγ and suppresses their activities (Wang, et al., 2009), it also affects the expression of the target-ERRs genes, which, together with their PGC-1 interacting cofactors, regulate mitochondrial biogenesis and oxidative phosphorylation (Huss, et al., 2002; Kamei, et al., 2003). Kaempferol affects the expression of the transcription target genes of mitochondrial transcription factor A (TFAM) and Mitofusin-2 (Mfn2; Wang, et al., 2013).

Figure 5 summarizes the main mechanisms involved in the antitumor activity of kaempferol, as well as its effects over cell signaling pathways. It is noted that the antitumor activity of kaempferol may be the result of its actions over various cell signaling pathways.

Figure 4. Some mechanisms and signaling pathways involved in the antitumor activity of kaempferol.



ERR, estrogen receptors; VEGF, vascular endothelial growth factor; Bcl-xL, Bcl-2, Bcl-x, proapoptotic proteins belonging to the BCL-2 protein family; TNF-α, tumor necrosis factor; AKT1, AKT 2, protein kinase B, Bax, Bad, antiapoptotic proteins belonging to the BCL-2 protein family; MAPK, mitogen-activated protein kinase; p53, tumor protein; PKC, protein kinase C; MMP, matrix metalloproteinases; TFAM, gene that encodes the mitochondrial transcription factor A protein; Mfn2, gene that encodes the mitofusin-2 protein. Source: Authors.

Another very important flavonoid, quercetin, presents cancer preventive and antitumor properties. The preventive effects have been attributed to several mechanisms, including antioxidative activity, the inhibition of carcinogen-activating enzymes, modifications of signal transduction pathways, and interactions with receptors and other proteins (Murakami, et al., 2008).

Quercetin is shown to act both as an antioxidant and as a pro-oxidant. Due to the high number of the hydroxyl groups and conjugated π orbitals this flavonoid is a potent antioxidant, reacting with H_2O_2 to form semiquinone radicals. These radicals are unstable and undergo oxidation reactions, producing quinone (QQ; Wang, et al., 2013; Murakami, et al., 2008) which is highly reactive to thiols and reacts preferentially with reduced glutathione (GSH) to form oxidized GSH–quercetin (GSQ; 6- GSQ and 8- GSQ; Metodiewa, et al., 1999; Gibellini, et al., 2011; Boots, et al., 2003).

In the presence of high GSH concentrations, quercetin is reoxidized with GSH to form GSQ again and the reversibility of the reaction ensures protection against the toxicity of the

QQ. However, at low concentrations of GSH, oxidized quercetin reacts with proteins, exerting a toxic effect on the cells (Gibellini, et al., 2011; Boots, et al., 2007; Boots, et al., 2007).

Similarly, prolonged exposure to quercetin together with high concentrations, causes a reduction in the content of the GSH, and the pro-oxidant effect of quercetin may prevail over the antioxidant effect, resulting in cell death or damage to cellular compartments (Gibellini et al., 2011; Ferraresi, et al., 2007; Kim & Jang, 2009). The antioxidant capacity of quercetin strongly depends on the intracellular availability of GSH, since, in cells treated with quercetin, typical changes in apoptosis appear when intracellular GSH is completely depleted (Gibellini, et al., 2011)..

Aryl hydrocarbon receptors (AhRs) are targets that are probably involved in the chemopreventive effects of flavonols and flavones such as quercetin and Kaempferol, which bind antagonistically to naturally occurring AhR receptors, interfering with the naturally occurring interactions between AhRs and polycyclic aromatic hydrocarbons (PAHs), which may be associated with the development of lung cancer. In summary, flavonoids exert preventive effects on the carcinogenicity of AhRs evoked by exposure to PAHs (Marakami, et al., 2008).

Quercetin has been shown to inhibit the production of heat shock proteins in several malignant cell lines (Koishi et al., 1992; Elia, et al., 1996; Hansen, et al., 1997). Heat shock proteins form a complex with mutant p53. This allows tumor cells to ignore the stop mechanisms in cell division present in normal cells. Heat shock proteins also allow increased survival of cancer cells under different body stresses (low circulation, fever) and are associated with cell resistance to the drugs used in chemotherapy (Oesterreich, et al., 1993; Lamson & Brignall, 2000).

Quercetin also demonstrates an important role in the chemoprevention of colorectal carcinogenesis by inhibiting the expression of the p21-ras oncogene in colon cancer cell lines and primary colorectal tumors (Hansen, et al., 1997; Oesterreich, 1997). Mutations in this gene make it an active oncogene and trigger uncontrolled cell proliferation, and this mutation is present in 50% of colon cancer and other types of tumors (Lamson & Brignall, 2000).

Another protein related to the most common genetic abnormalities in human cancers is the p53 protein, and quercetin is also involved in the reduction of p53 expression. As this protein is involved in cell proliferation, the cell becomes "trapped" in the G1 phase of the cell cycle due to alterations in the dynamics of cell division (Lamson & Brignall, 2000; Ranelletti; et al., 1992; Hall, 1997; Avila, et al., 1994).

Another study evaluated the activity of quercetin on the cell cycle and revealed a significant increase in the proportion of cells in the G2/M phase (Choi & Ahn, 2008) and the subG0/G1 phase (corresponding to apoptotic cells). In addition, quercetin glucuronides increased the expressions of cyclin B, Cdc25c-ser-216-p and Wee1 proteins, indicating the arrest of cell-cycle at G2/M. There are also decreases in the mitochondrial membrane potential, the release of cytochrome c, the upregulation of Bax and downregulation of Bcl-2, the activation of caspase-3, and subsequently, the cleavage of poly(ADP-ribose) polymerase. Notwithstanding, a broad-spectrum caspase inhibitor completely blocked the apoptosis induced by chemotherapy with quercetin (Yang, et al., 2006).

The exposure of gastric cancer cells to quercetin resulted in a pronounced pro-apoptotic effect through activating the mitochondrial pathway. Meanwhile, treatment with this substance induced the appearance of autophagic vacuoles, the formation of acidic vesicular organelles (AVO), the conversion of LC3-I to LC3-II, and the recruitment of LC3-II to autophagosomes, as well as the activation of autophagy genes, features suggesting that quercetin initiates an autophagic progression in gastric cancer cells. Quercetin also activated autophagy by modulation of Akt-mTOR (an intracellular signaling pathway) signaling and hypoxia-induced factor 1α (HIF-1α) signaling. Therefore, quercetin may induce autophagy and apoptosis in tumor cells (Wang, et al., 2011).

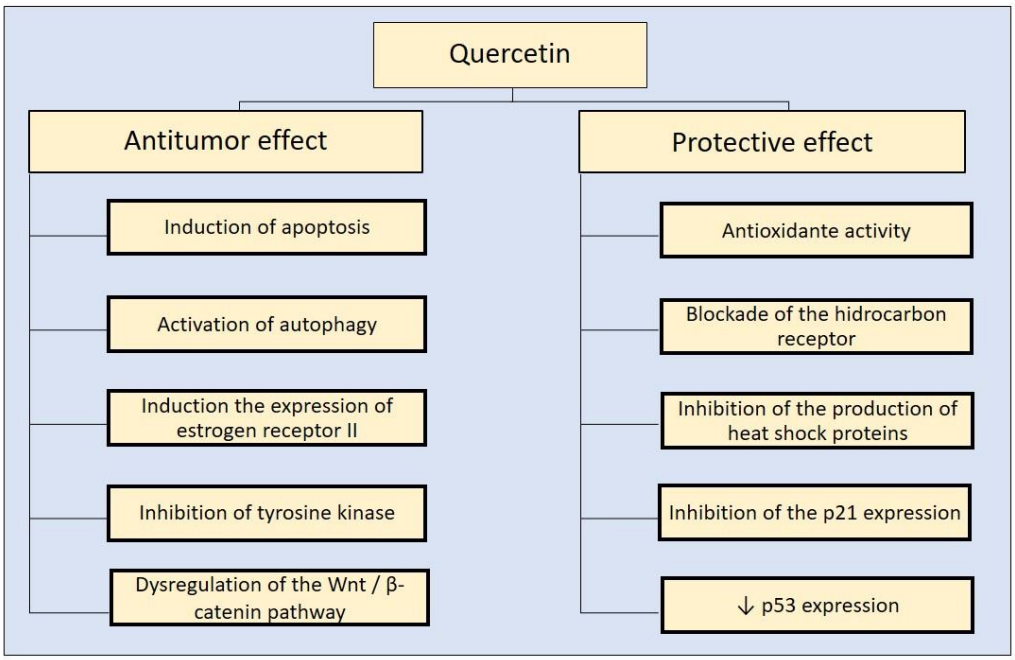
Moreover, quercetin has been shown to induce the expression of estrogen (ER) II in ER type I receptors in human breast cancer cells. The induction of ER II allows greater inhibition in the growth of cells that have ER (Hansen, et al., 1997; Oesterreich, et al., 1993; Ranelletti, et al., 1992; Hall, 1997; Avila, et al., 1994; Choi & Anh, 2008; Yang, et al., 2006). Quercetin's effects on the proliferation of HT-29, COLO 201, LS-174T human colon cancer cell lines and WiDr[2], a derivative of another colon adenocarcinoma cell line (HT-29 derivate), were also evaluated. The results showed that this metabolite exerted a dose-dependent reversible inhibition of cell proliferation. Cell-cycle analysis revealed that the growth-inhibitory effects of quercetin were due to a blocking action at the G0/G1 phase. Quercetin and other flavonoids (3,7-4′-trimethoxyquercetin, 3,7,3,4′-tetramethoxyquercetin, kaempferol, morin, and rutin) inhibit type-1 estrogen binding sites (type II EBS). Therefore, when binding to II EBS, quercetin can regulate the growth of cancer cells (Ranelletti, et al., 1992).

[2] Although deposited with the ATCC as a colon adenocarcinoma line established from a 78-year-old female, DNA fingerprinting has shown this line to be a derivative of HT-29.

Indeed, quercetin was the first tyrosine kinase inhibitor compound tested in a phase I trial. Intravenous administration of quercetin led to the inhibition of tyrosine kinase in patients with advanced cancer (Lamson & Brignall, 2000; Renelletti, et al., 1992; Hall, 1997; Avila, et al., 1994; Choi & Ahn, 2008; Yang, et al., 2006; Wang, et al., 2011; Ferry, et al., 1996). Protein kinases play a crucial role in signal transduction and in cell proliferation, cell differentiation and various regulatory mechanisms (Scambia, et al., 1993; Traxler, 2003). Inhibition of growth-related kinases, especially tyrosine kinases, may provide new therapies for diseases such as cancer. Therefore, the inhibition of this pathway is a promising target for the treatment of this disease (Klohs & Fry, 1997).

A study was conducted to investigate whether quercetin modulates β-catenin/Tcf (T-cell transcription factor) signaling in human colon cancer cells, SW480, and HEK293 (transiently transfected with wild-type β -catenin genes). Figure 5 summarizes the main mechanisms involved in quercetin's protective anticancer and antitumor activities.

Figure 5. Some mechanisms involved in the antitumor and protective effects of quercetin.



Wnt/β catenin- signaling pathway of the Wnt family of secreted glycolipoproteins; p21, oncogene; p53, tumor protein. Source: Authors

The results showed that quercetin is an excellent inhibitor of β-catenin/Tcf signaling in SW480 cells and that the reduced transcriptional activity of β-catenin/Tcf was due to a decrease of nuclear proteins, beta-catenin and Tcf-4 proteins. Importantly, the deregulation of the Wnt/β-catenin pathway plays a central role in the early stages of colorectal carcinogenesis,

and quercetin has been shown to inhibit the signaling of this pathway (Park, et al., 2005).

4. Conclusion

Species of Apocynaceae used in folk medicine of the Amazon region for the treatment of cancer are *Asclepias curassavica*, *Himatanthus articulates*, and *Macoubea spruce. A. curassavida* and *H. articulates* present phytochemical studies with isolation of substances: iridoids, flavonoids, steroids, terpenes, and glycosylated cardenolides. Studies involving the antitumor activity of some isolated constituents (Asclepin, New cardenolide, Curassavoside A) and extract obtained from these species demonstrated antitumor activity against several cell lines.

In summary, Apocynaceae species evaluated in this study are promising as anticancer agents, however, there is currently a lack of scientific research on the species used in the Amazon for the treatment of cancer. We advise in vivo experimental scientific studies and invitro anticancer with the plants mentioned here.

Acknowledgments

The authors acknowledge the *Universidade Federal do Pará* (Belém, Brazil) for providing structure for the development of this review.

References

Abdel-Karder, M. S., Wisse, J., Evans, J. W., van-der.Werff, H. & Kingston, D. G. I. (1997). Bioactive iridoids and new lignan from *Allamanda carthatica* and *Himatanthus falax* from the Suriname rainforest. *J Nat Prod*, 60(12), 1924-1927. https://doi.org/10.1021/np970253e

Agra, M. F., Freitas, P. F. & Barbosa-Filho, J. M. (2007). Synopsis of the plants known as medicinal and poisonous in Northeast of Brazil. *Brazilian Journal of Pharmacognosy*, 17(1), 114-140. https://doi.org/10.1590/S0102-695X2007000100021

Agra, M. F., Silva, K. N., Basílio, I. J. L. D., Freitas, P. F, Barbosa-Filho, J. M. (2008). Survey of medicinal plants used in the region Northeast of Brazil. *Brazilian Journal of Pharmacognosy*, 18(3), 472-508. https://doi.org/10.1590/S0102-695X2008000300023

Aimi, N., Uchida, N., Ohya, N., Hosokawa, H., Takayama, H., Sakai, S., Mendonza, L. A., Polz, L. & Stöckigt, J.(1991). Novel indole alkaloids from cell suspension cultures of *Aspidosperma quebracho blanco* Schlecht. *Tetrahedron Lett*, 32(37), 4949-4952

Allen, J. R. F. & Holmstedt, B. R. (1980). The simple β-carboline alkaloids, *Phytochemistry*, 19(8), 1573-1582. https://doi.org/10.1016/S0031-9422(00)83773-5

Al-Snafi, A. E. (2015). Chemical constituents and pharmacological effects of Asclepias curassavica - A review. *Asian Journal of Pharmaceutical Sciences*, 5(1), 83-87. Retrieved from https://www.academia.edu/11581129/CHEMICAL_CONSTITUENTS_AND_PHARMACOLOGICAL_EFFECTS_OF_ASCLEPIAS_CURASSAVICA_A_REVIEW

Amaro, M. S., Filho, M. S., Guimarães, R. M. & Teófilo, E. M. (2006). Morfologia de frutos, sementes e de plântulas de janaguba (*Himatanthus drasticus* (Mart.) Plumel - Apocynaceae). *Rev Bras Sementes*, 28(1), 63-71. https://doi.org/10.1590/S0101-31222006000100009

Ariazi, E. A., Clark, G. M., & Mertz, J. E. (2002). Estrogen-related receptor a and estrogen-related receptor g associate with unfavorable and favorable biomarkers, respectively, in human breast cancer. *Cancer research*, 62(22), 6510-6518. Retrieved from https://cancerres.aacrjournals.org/content/62/22/6510.

Avila, M. A., Velasco, J. A., Cansado, J. & Notario, V. (1994). Quercetin mediates the down regulation of mutant p53 in the human breast cancer cell line MDA-MB468. *Cancer research*, 54(9), 2424-2428. Retrieved from https://pubmed.ncbi.nlm.nih.gov/8162591/.

Barreto, A. S., Carvalho, M. G., Nery, I. A., Gonzaga, L. & Kaplan,cM. A. C. (1998). Chemical constituents from *Himatanthus articulata. J. Braz. Chem. Soc*, 9(5), 430-434. https://doi.org/10.1590/S0103-50531998000500004

Behling, E. B., Sendão, M. C., Francescato, H. D. C., Antunes, L. M. G. & Bianchi, M. L. P. (2004). Flavonóide quercetina: aspectos gerais e ações biológicas. *Alimentos e Nutrição*, 15(3), 285-292. Retrieved from http://serv-bib.fcfar.unesp.br/seer/index.php/alimentos/article/viewFile/89/102

Boots, A. W., Balk, J. M., Bast, A. & Haenen, R. M. M. (2005) The reversibility of the glutathionyl-quercetin adduct spreads oxidized quercetin-induced toxicity. *Biochem Biophys Res Commun*, 338(2), 923-929. doi: 10.1016/j.bbrc.2005.10.031

Boots, A. W., Kubben, N., Haenen, G. R. M. M. & Bast, A. (2003). Oxidized quercetin reacts with thiols rather than with ascorbate: implication for quercetin supplementation. *Biochem Biophys Res Commun*, 308(3), 560-565. doi: 10.1016/s0006-291x(03)01438-4

Boots, A. W., Li, H., Schins, R. P. F., Duffin, R., Heemskerk, W. M., Bast, A. & Haenen, G. R. M. M. (2007).The quercetin paradox. *Toxicol Appl Pharmacol*, 222(1), 89-96. doi: 10.1016/j.taap.2007.04.004.

Brandão, H. N., David, J. P., Couto, R. D., nascimento, J. A. P. & David, J. M. (2010). Química e farmacologia de quimioterápicos antineoplásicos derivados de plantas. *Quim Nova*, 33(6), 1359-1369. doi.org/10.1590/S0100-40422010000600026

Brandão, M. G. L., Cosenza, G. P., Moreira, R. A. & Monte-Mor, R. L. M. (2006). Medicinal plants and other botanical products from the Brazilian Official Pharmacopoeia. *Rev Bras Farmacogn*, 16(3), 408-420. http://dx.doi.org/10.1590/S0102-695X2006000300020

Cavallini, A., Notarnicola, M., Giannini, R., Montemurro, S., Lorusso, D., Visconti, A., Minervini, F. & Caruso, M. G. (2005). Oestrogen receptor-related receptor alpha (ERRα) and oestrogen receptors (ERα and ERβ) exhibit different gene expression in human colorectal tumour progression. *Eur J Cancer*, 41(10), 1487-1494. doi: https://doi.org/10.1016/j.ejca.2005.04.008

Chang, Y. C., Chou, F. P., Huang, H. P., Hsu, J. D. & Wang, C. J. (2004). Inhibition of cell cycle progression by penta-acetyl geniposide in rat C6 glioma cells. *Toxicol Appl Pharmacol*, 198(1), 11-20. https://doi.org/10.1016/j.taap.2004.03.004

Cheung, C. P., Yu, S., Wong, K. B., Chan, L. W., Lai, F. M. M., Wang, X., Suetsugi, M., Chen, S. & Chan, F. L. (2004). Expression and functional study of estrogen receptor-related

receptors in human prostatic cells and tissues. *J Clin Endocrinol Metab*, 90(3), 1830-1844. doi: 10.1210/jc.2004-1421

Chierrito, T. P., Aguiar, A. C. C., Andrade, I. M., Ceravolo, I. P., Gonçalves, R. A. C., Oliveira, A. J. B. & Krettli, A. U. (2014). Anti-malarial activity of indole alkaloids isolated from Aspidosperma olivaceum. *Malar J*, 13(142), 2-10. Retrieved from http://www.malariajournal.com/content/13/1/142

CHOI, E. J. & AHN, W. S. (2008). Kaempferol induced the apopitosis via cell cycle arrest in human breast cancer MDA-MB-453 cells. *Nutr Res Pract*, 2(4), 322-325. doi: 10.4162/nrp.2008.2.4.322

Choi, E. J. & Ahn, W. S. (2008). Kaempferol induced the apoptosis via cell cycle arrest in human breast cancer MDA-MB- 453 cells. *Nutr. Res. Pract*, 2(4), 322-325. doi: 10.4162/nrp.2008.2.4.322

Cragg, g. m. & Newman, D. J. (2005). Plants as a source of anti-cancer agents, *J Ethnopharmacol*, 100(1-2), 72-79. doi: 10.1016/j.jep.2005.05.011

Elia, G., Amici, C., Rossi, A. & Santoro, M. G. (1996). Modulation of prostaglandin A1-induced thermotolerance by quercetin in human leukemic cells: role of heat shock protein 70. *Cancer research*, 56(1), 10-217. Retrieved from https://pubmed.ncbi.nlm.nih.gov/8548766/

El-Sayed, A., Handy, G. A. & Cordell, G. A. (1980). Catharanthus alkaloids XXIII. 21'-oxo-leurosine from Catharanthus roseus (Apocynaceae). *J Nat Prod*, 43(4), 157-161. https://doi.org/10.1021/np50007a016

Endo, Y., Hayashi, H., Sato, T., Moruno, M., Ohta, T. & Nozoe, S. (1994). Confluentic acid and 2'-O-methylperlatolic acid, monoamine oxidase B inhibitors in a Brazilian plant, Himatanthus sucuuba. *Chem. Pharm. Bull*, 42(6), 1198-201. doi: 10.1248/cpb.42.1198

Endress, M. E., Liede-Schumann S. & Meve, U. (2014). An updated classification for Apocynaceae. *Phytotaxa*, 159(3), 175-194. Retrieved from https://www.biotaxa.org/Phytotaxa/article/view/phytotaxa.159.3.2/0

Ferraresi, R., Troiano, L., Roat, E., Lugli, E., Nemes, E., Nasi, M., Pinti, M., Fernandez, M. I. G., Cooper, E. L. & Cossarizza, A. (2005). Essential requirement of reduced glutathione (GSH) for the anti-oxidant effect of the flavonoid quercetin. *Free Radic Res*, 39(11), 1249-1258. doi: 10.1080/10715760500306935

Ferry, D. R., Smith, A., Malkhandi, J., Fyfe, D. W., Takats, P. G., Anderson, D., Baker, J. & Kerr, D. (1996). Phase I clinical trial of the flavonoid quercetin: pharmacokinetics and evidence for in vivo tyrosine kinase inhibition. *Clin cancer res*, 2(4), 659-668. Retrieved from https://pubmed.ncbi.nlm.nih.gov/9816216/

Flora do Brasil 2020 em construção (2017). Jardim Botânico do Rio de Janeiro, "specimen of Asclépias curassavica. Retrieved from http://floradobrasil.jbrj.gov.br/

Galvéz, M., Martin-Cordero, C. & Ayuso, M. J. (2005). Iridoids as DNA topoisomerase I poisons. *J Enzyme Inhib Med Chem*, 20(4), 389-392. https://doi.org/10.1080/14756360500141879

Gibellini, L., Pinti, M., Nasi, M., Montagna, J. P., Biasi, S. D. Toat, E., Bertoncelli, L., Cooper, E. L. & Cossarizza, A. (2011). Quercetin and Cancer Chemoprevention. *Evid Based Complement Alternat Med*, 2011 591356. doi: 10.1093/ecam/neq053

Hall, E. J. (1997). Etiology of cancer: physical factors. In: V.T DeVita Junior; S Hellman, S.A Rosenberg, eds. *Principles & Practice of Oncology*. (5a ed.) Philadelphia: Lippincortt- Raven, 203-218.

Hamdi, H. K. & Castellon, R. (2005). Oleuropein, a non-toxic olive iridoid, is an anti-tumor agent and cytoskeleton disruptor. *Biochem Biophys Res Commun*, 334(3), 769-778. https://doi.org/10.1016/j.bbrc.2005.06.161

Hanahan, D., & Weinberg, R. A. (2011) Hallmarks of cancer: the next generation. *Cell*, 144 (5), 646-74. doi: 10.1016/j.cell.2011.02.013

Hanahan, D., & Weinberg, L. A. (2000). The hallmarks of cancer. *Cell*, 100(1), 57-70. doi: 10.1016/s0092-8674(00)81683-9

Hansen, R. K., Oesterreich, S., Lemieux, P., Sarge, K. D. & Fuqua, S. A. W. Quercetin inhibits heat shock protein induction but not heat shock factor DNA-binding in human breast carcinoma cells. *Biochem Biophys Res Commun*, 239(3), 851-856. https://doi.org/10.1006/bbrc.1997.7572

Hartwell, J. L. (1982). *Plants used against cancer*. Lawrence, MA: Quarterman publication, 34(4), 438-439

Henrique, M. C., Nunomura, S. M. & Pohlit, A. M. (2010). Alcalóides indólicos de cascas de *Aspidosperma vargasii* e *A. Desmanthum. Quim Nova*, 33(2), 284-287. https://doi.org/10.1590/S0100-40422010000200010

Huss, J. M., Kopp, R. P. & Kelly, D. P. Peroxisome proliferator activated receptor coactivator-1alpha (PGC-1alpha) coactivates the cardiac-enriched nuclear receptors estrogen-related receptor-alpha and -gamma. Identification of novel leucinerich interaction motif within PGC-1alpha. *J Biol Chem*, 277(43), 40265-40274. Retrieved from https://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.123.9210&rep=rep1&type=pdf

Kamei, Y., Ohizumi, H., Fujitani, Y., Nemoto, T., Tanaka, T., Takahashi, N., Kawada, T., Miyoshi, M., Ezaki, O. & Kakizuka, A. (2003). PPAR gamma coactivator 1beta/ERR ligand 1 is an ERR protein ligand, whose expression induces a high-energy expenditure and antagonizes obesity. *Proc Natl Acad Sci U S A*, 100(21), 12378-12383. doi: 10.1073/pnas.2135217100

Kardono, L. B., Angerhofer, C. K., Tsauri, S., Padmawinata, K., Pezzuto, J. M. & Kinghorn, A. D. (1991). Cytotoxic and antimalarial constituents of the roots of Eurycoma longifolia. *J Nat Prod*, 54(5), 1360-1367. doi: 10.1021/np50077a020

Kim, G. N. & Jang, H. D. (2009). Protective mechanism of quercetin and rutin using glutathione metabolism on H_2O_2-induced oxidative stress in hepg2 cells. *Natural Compounds*

and Their Role in Apoptotic Cell Signaling Pathways, 1171, 530-537. doi: 10.1111/j.1749-6632.2009.04690.x

Kim, H. K., Park, H. R., Lee, J., Chung, T. S., Chung, H. & Chung, J. (2007). Down-regulation of iNOS and TNF-α expression by kaempferol via NF-ķB inactivation in aged rat gingival tissues. *Biogerontology,* 8(4), 399-408. Retrieved from https://www.semanticscholar.org/paper/Down-regulation-of-iNOS-and-TNF-alpha-expression-by-Kim-Park/91ede4414a1c25b710907fc34b8097540445b8d0

Kim, S. H. & Choi, K. C. (2013). Anti-cancer effect and underlying mechanism(s) of kaempferol, a phytoestrogen, on the regulation of apoptosis in diverse cancer cell models. *Toxicol Res,* 29(4), 229-234. doi: 10.5487/TR.2013.29.4.229

Klohs, W. D., Fry, D. W., & Kraker, A. J. (1997). Inhibitors of tyrosine kinase. *Curr Opin Oncol*, 9(6), 562-568. doi: 10.1097/00001622-199711000-00012

Koishi, M., Hosokawa, N., Sato, M., Nakai, A., Hirayoshi, K., Hiraoka, M., Abe, M. & Nagata, K. (1992). Quercetin, an inhibitor of heat shock protein synthesis, inhibits the acquisition of thermotolerance in a human colon carcinoma cell line. *Cancer research*, 83(11), 1216-1222. doi: 10.1111/j.1349-7006.1992.tb02748.x

Kumar, A., Patil, D., Rajamohanan, P. R. & AHMAD, A. (2013). Isolation, purification and characterization of vinblastine and vincristine from endophytic fungus Fusarium oxysporum isolated from Catharanthus roseus. *PLoS One,* 8(9), 1-10. https://doi.org/10.1371/journal.pone.0071805

Kuo, W. H., Chou, F. P., Young, S. C., Chang, Y. C. & Wang, C. J. (2005). Geniposide activates GSH S-transferase by the induction of GST M1 and GST M2 subunits involving the transcription and phosphorylation of MEK-1 signaling in rat hepatocytes. *Toxicol Appl Pharmacol*, 208(2), 155-62. https://doi.org/10.1016/j.taap.2005.02.013

Kupchan, S. M., Knox, J. R., Kelsey, J. E. & Renauld, J. A. S. (1964). Calotropin, a cytotoxic principle isolated from Asclepias curassavica L. *Science*, 146(3652) 1685-1686. DOI: 10.1126/science.146.3652.1685

Lamson, D. W. & Brignall, M. S. (2000). Antioxidants and Cancer III: Quercetin. *Altern Med Rev*, 5(3), 196-208. Retrieved from https://pubmed.ncbi.nlm.nih.gov/10869101/.

Laphookhieo, S., Maneerat, W. & Koysomboon, S. (2009). Antimalarial and cytotoxic phenolic compounds from Cratoxylum maingayi and Cratoxylum cochinchinense. *Molecules*, 14(4), 1389-1395. doi: 10.3390/molecules14041389

Li, C., Zhao, Y., Yang, D., Yu, Y., Guo, H., Zhao, Z., Zhang, B. & Yin, X. (2014). Inhibitory effects of kaempferol on the invasion of human breast carcinoma cells by downregulating the expression and activity of matrix metalloproteinase-9. *Biochem Cell Biol*, 93(1), 16-27. https://doi.org/10.1139/bcb-2014-0067

Li, J. Z., Liu, H. Y., Lin, I. J., Hao, X. J., Ni, W. & Chen, C. X. (2008). Six new C21 steroidal glycosides from *Asclepias curassavica* L. *Steroids*, 73(6), 594-600. https://doi.org/10.1016/j.steroids.2008.01.015

Li, J. Z., Qing, C. & and Chen, C. X. "Cytotoxicity of cardenolides and cardenolide glycosides from Asclepias curassavica", *Bioorg Med Chem Lett*, 19(7), 1956-1959, 2009.

Lorenzi, H. & Souza, H. M. S. (2008) *Plantas Ornamentais no Brasil: Arbutivas, Herbaceas e Trepadeiras,* Nova Odessa, SP: Editora Plantarum, 3ed.

Lübeck, W. (2001). *O Poder Terapêutico do Ipê Roxo – a árvore divina dos xamãs da América do Sul***.** 1ed. São Paulo: Madras.

Luo, H., Rankin, G. O., Li, Z., DePriest, L. & Chen, Y. C. (2011). Kaempferol induces apoptosis in ovarian cancer cells through activating p53 in the intrinsic pathway. *Food Chem*, 128(2), 513-519. doi: 10.1016/j.foodchem.2011.03.073

Luo, H., Rankin, Rankin, G. O., Liu, L., Daddysman, M. K., Jiang, B. H. & Chen, Y. C. (2009). Kaempferol inhibits angiogenesis and VEGF expression through both HIF dependent and independent pathways in human ovarian cancer cells. *Nutr Cancer*, 61(4), 554-563. doi: 10.1080/01635580802666281

Mena-Rejon, G., Caamal-Fuentes, E., Cantillo-Ciau, Z., Cedillo-Rivera, R., Flores-Guido, J. & Moo-Puc, R. In vitro cytotoxic activity of nine plants used in Mayan traditional medicine. *J Ethnopharmacol*, 121(3), 462-465. doi: 10.1016/j.jep.2008.11.012

Metodiewa, D., Jaiswal, A. K., Cenas, N., Dickancaité, E. & Segura-Aguilar, J. (1999). Quercetin may act as a cytotoxic prooxidant after its metabolic activation to semiquinone and quinoidal product. *Free Radic Biol Med*, 26(1-2), 107-116. doi: 10.1016/s0891-5849(98)00167-1

Milliken, W. (1997). Traditional antimalarial medicine in Roraima, Brazil. *Econ Bot*, 51(3), 212-237. Retrieved from. https://link.springer.com/article/10.1007/BF02862091.

Moreno, P. R. H., Heijden, R. &. Verpoorte, R. (1995). Cell and tissue cultures of Catharanthus roseus: A literature survey. *Plant Cell Tissue Organ Cult*, 42(1), 1-25. Retrieved from https://link.springer.com/article/10.1007/BF00037677

Mousinho, K. C., Oliveira, C. C., Ferreira, J. R. O., Carvalho, A. A., Magalhães, H. I. F., Bezerra, D. P., Alves, A. P. N. N., Costa-Lotufo, L. V., Pessoa, C., Matos, M. P. V., Ramos, M. V. & Moraes, M. O. (2011). Antitumor effect of laticifer proteins of *Himatanthus drasticus* (Mart.) Plumel – Apocynaceae. *J Ethnopharmacol*, 137(1), 421-426. doi: 10.1016/j.jep.2011.04.073

Murakami, A., Ashida, H. & Terao, J. (2008). Multitargeted cancer prevention by quercetin. *Cancer Lett*, 269(2), 315-325. doi:10.1016/j.canlet.2008.03.046

Myers, N., Mittermeier, R. A., Mittermeier, C. G., Fonseca, G. A. B. & Kent, J. (2000). Biodiversity hotspots for conservation priorities. *Nature*, 403, 853-858. Retrieved from https://www.nature.com/articles/35002501

Nazar, n., Goyder, D. J., Clarkson, J. J., Mahmood, T. & Chase, M. W. (2013) The taxonomy and systematics of Apocynaceae: where we stand in 2012. *Biol J Linn Soc Lond*, 171(3), 482-490. https://doi.org/10.1111/boj.12005

Neto, C. C., Owens, C. W., Langfield, R. D., Comeau, A. B., Onge, J. S., Vaisberg, A. J. & Hammond, G. B. (2002). Antibacterial activity of some medicinal plants from the Callejon de Huaylas. *J Ethnopharmacol*, 79(1), 133-138. https://doi.org/10.1016/S0378-8741(01)00398-1

Newman, D. J., Cragg, G. M. & Snader, K. M. (2003). Natural products as sources of new drugs over the period 1981-2002, *J Nat Prod*, 66(7), 1022-1037.doi: 10.1021/np030096l.

Nguyen, T. T. T., Tran, E., Ong, C. K., Lee, S. K., Do, P. T., Huynh, T. T., Lee, J. J., Tan, Y., Ong, C. S & Huynh, H. (2003). Kaempferol-induced growth inhibition and apoptosis in A549 lung cancer cells Is mediated by activation of MEK-MAPK, *J Cell Physiol*, 197(1), 110-121. doi: 10.1002/jcp.10340

Oesterreich, S., Hilsenbeck, S. G., Ciocca, D. R., Allred, D. C., Clark, G. M., Chamness, G. C., Osborne, C. K. & Fuqua, S. A. The small heat shock protein HSP27 is not an independent prognostic mark in axillary lymph node-negative brest cancer patients. *Clin Cancer Res*, 2(7), 1199-1206. Retrieved from https://pubmed.ncbi.nlm.nih.gov/9816288/

Oliveira, V. B., Freitas, M. S. M., Mathias, L., Braz-Filho, R. & Vieira, I. J. C. (2009). Atividade biológica e alcalóides indólicos do gênero *Aspidosperma* (Apocynaceae): uma revisão. *Rev Bras Pl Med Botucatu*, 11(1), 92-99. http://dx.doi.org/10.1590/S1516-05722009000100015

Pang, J.L., Ricupero, D. A., Huang, S. Fatma, N., Singh, D. P., Romero, J. R. & Chattopadhyay, N. (2006). Differential activity of kaempferol and quercetin in attenuating tumor necrosis factor receptor family signaling in bone cells. *Biochem Pharmacol*, 71(6), 818-826. doi: 10.1016/j.bcp.2005.12.023

Park, C. H., Chang, J. Y., Hahm, E. R., Park, S., Kim, H. K. & Yang, C. H. (2005). Quercetin, a potent inhibitor against b-catenin/Tcf signaling in SW480 colon cancer cells. *Biochem Biophys Res Commun*, 328(1), 227-234. https://doi.org/10.1016/j.bbrc.2004.12.151

Patnaik, G. K. & Köhler, E. (1978). Pharmacological investigation on asclepin--a new cardenolide from Asclepias curassavica. Part II. Comparative studies on the inotropic and

toxic effects of asclepin, g-strophantin, digoxin and digitoxin. *Arzneimittelforschung*, 28(6), 1368-1372, 1978. Retrieved from https://pubmed.ncbi.nlm.nih.gov/380581/

Peng, C. H., Tseng, T. H., Huang, C. N., Hsu, S. P. & Wang, C. J. (2005) Apoptosis induced by penta-acetyl geniposide in C6 glioma cells is associated with JNK activation and Fas ligand induction. *Toxicol Appl Pharmacol*, 202(2), 172-179. doi: 10.1016/j.taap.2004.06.016.

Perdue, G. P. &. Blomster, R. N. (1978). South American plants III: Isolation of fulvoplumierin from *Himatanthus sucuuba* (M. Arg.) Woodson (apocynaceae). *Brazilian Journal of Pharmaceutical Sciences*, 67(9), 1322-1323. https://doi.org/10.1002/jps.2600670936

Pereira, A. S., Shitsuka, D. M., Pereira, F. J. & Shitsuka, R. (2018). *Metodologia da pesquisa científica.* Santa Maria: UFSM,NTE. Retrieved from https://repositorio.ufsm.br/bitstream /handle/1/15824/Lic_Computacao_Metodologia-Pesquisa-Cientifica.pdf

Pereira, A. S. S., Simões, A. O. & Santos, J. U. M. Taxonomy of Aspidosperma Mart. (Apocynaceae, Rauvolfioideae) in the State of Pará, Northern Brazi. *Biota Neotrop,* 16(2), 1-23. http://dx.doi.org/10.1590/1676-0611-BN-2015-0080

Pereira, M. M., Jácome, R. L. R. P., Alcântara, A. F. C., Alves, R. B. & Raslan, D. S. (2007). Alcalóides indólicos isolados de espécies do gênero *Aspidosperma* (Apocynaceae). *Quim Nova*, 30(4), 970-983. https://doi.org/10.1590/S0100-40422007000400037

Pungitore, C. R., Ayub, M. J., García, M., Borkowski, E. J., Sosa, M. E., Ciuffo, C., Giordano, O. S. & Tonn, C. E. (2004). Iridoids as allelochemicals and DNA polymerases inhibitors. *J. Nat. Prod*, 67(3), 357-361. https://doi.org/10.1021/np030238b

Quinet, C. G. P. & Andreata, R. H. P. (2005). Estudo taxonômico e morfológico das espécies de Apocynaceae Adans. na reserva Rio das Pedras, Município de Mangaratiba, Rio de Janeiro, Brasil. *Rev Bras Bot*; 56, 13-74. Retrieved from http://www.anchietano.unisinos.br/publicacoes/botanica/botanica56/a02.pdf.

Ranelletti, F. O., Ricci, R., Larocca, L. M., Maggiano, N., Capelli, A., Scambia, G., Benedetti-Panici, P., Mancuso, S., Sumi, C. & Piantelli, M. (1992). Growth-inhibitory effect of quercetin and presence of type-II estrogen-binding sites in human colon-cancer cell lines and primary colorectal tumors. *Int J Cancer*, 50(3), 486-492. doi: 10.1002/ijc.2910500326

Rebouças, S. O., Grivicich, I., Santos, M. S., Rodrigues, P., Gomes, M. D., Oliveira, S. Q., Silva, J & Ferraz, A. B. F. (2011). Antiproliferative effect of a traditional remedy,*Himatanthus articulates* bark, on human cancer cell lines. *J Ethnopharmacol*, 137(1), 926-929. doi: 10.1016/j.jep.2011.06.006

Santos, A. C. B., Silva, M. A. P., Santos, M. A. F. & Leite, T. R. (2013). Levantamento etnobotânico, químico e farmacológico de espécies de Apocynaceae Juss. ocorrentes no Brasil. *Brazilian journal of medicinal plants*, 15(3), 442-458. https://doi.org/10.1590/S1516-05722013000300019

Scambia, G., Ranelletti, F. O., Panici, P. B., Piantelli, M., Vincenzo, R., Ferrandina, G., Bonanno, G., Capelli, A. & Maancuso, S. (1993). Quercetin induces type-II estrogen-binding sites in estrogen-receptor-negative (MDA-MB231) and estrogen-receptor-positive (MCF-7) human breast-cancer cell lines. *Int J Cancer*, 54(3), 462-466. doi: 10.1002/ijc.2910540318

Serra, M., Shanley, P., Melo, T., Fantini, A., Medina, G., &. Vieira, P. From the forest to the consumer: the ecology, local management and trade of amapá amargoso Parahancornia fasciculata (Poir) Benoist in the state of Pará. Recent developments and case studies. In: Albuquerque, U. P., Hanazaki. N. eds. (2010) *Recent developments and case studies in ethnobotany*. Recife: Sociedade Brasileira de Etnobiologia/Núcleo de Publicações em Ecologia e Etnobotânica Aplicada, 213-231

Shi, L. M., Myers, T. G., Fan, Y., O'Connor, P. M., Paull, K. D., Friende, S. H. & Weinstein, J. N. (1998). Mining the national cancer institute anticancer drug discovery database: Cluster analysis of ellipticine analogs with p53-inverse and central nervous system-selective patterns of activity. *Mol Pharmacol*, 53(2), 241-251. doi: 10.1124/mol.53.2.241

Siegelin, M. D., Reuss, D. E., Habel, A., Herold-Mende, C. & Deimling, A. (2008). The flavonoid kaempferol sensitizes human glioma cells to TRAIL-mediated apoptosis by

proteasomal degradation of surviving. *Mol Cancer Ther*, 7(11), 3566-3574. doi: 10.1158/1535-7163.MCT-08-0236

Silva, J. R. A., Amaral, A. C. F., Silveira, C. V., Rezende, C. M. & Pinto, A. C. (2007). Quantitative determination by HPLC of irioids in the bark and latex of Himatanthus sucuuba. *Acta Amazon*, 37(1), 119-122. https://doi.org/10.1590/S0044-59672007000100014

Silva, J. R. A., Rezende, C. M., Pinto, A. C., Pinheiro, M. L. B., Cordeiro, M. C., Tamborini, E., Young, C. M. & Bolzani, V. S. (1998). Ésteres Triterpênicos de Himatanthus sucuuba (Spruce) Woodson. *Quim. Nova*, 21(6), 702-704. http://dx.doi.org/10.1590/S0100-40421998000600005

Silva, M. S., Fantini, A. C. & Shanley, P. (2011) Látex de amapá *(Parahancornia fasciculata (Poir)* Benoist, Apocynaceae*):* remédio e renda na floresta e na cidade. Boletim do Museu Paraense Emílio Goeldi. Ciências Humanas, 6(2), .287-305

Silva, R. A. D. (1929) Pharmacopeia dos Estados Unidos do Brasil. São Paulo, SP: Companhia Editora Nacional

Sousa, E. L., Grangeiro, A. R. S., Bastos, I. V. G. A., Rodrigues, G. C. R., Silva, M. J., Anjos, F. B. R., Souza, I. A. & Sousa, C. E. L. (2010). Antitumor activity of leaves of Himatanthus drasticus (Mart.) Plumel-Apocynaceae (Janaguba) in the treatment of sarcoma 180 tumor. *Brazilian Journal of Pharmaceutical Sciences*, 43(2), 1-5. http://dx.doi.org/10.1590/S1984-82502010000200005

Spina, A. P. (2004). *Estudos taxonômicos, micro-morfológico e filogenético do gênero Himatanthus Willd. Ex Schult. (Apocynaceae: Rauvolfioideae-Plumerieae)*. 197f. Tese (Doutorado em Biologia Vegetal), Campinas, SP: Universidade Estadual de Campinas

Suffredini, I. B., Paciencia, M. L. B., Varella, A. D. & Younes, R. N. (2006). *In vitro* prostate cancer cell growth inhibition by Brazilian plant extracts. *Pharmazie*, 61(8), 722-724. Retrieved from https://pubmed.ncbi.nlm.nih.gov/16964718/

Suffredini, I. B., Paciencia, M. L. B., Varella, A. D. & Younes, R. N. (2007). *In vitro* cytotoxic activity of Brazilian plant extracts against human lung, colon and CNS solid cancers and leukemia. *Fitoterapia*, 78(3), 223-226, doi: 10.1016/j.fitote.2006.11.011

Sun, P., Sehouli, J., Denkert, C., Mustea, A., Könsgen, D., Koch, I., Wei, L. & Lichtenegger, W. (2005). Expression of estrogen receptor-related receptors, a subfamily of orphan nuclear receptors, as new tumor biomarkers in ovarian cancer cells. *J Mol Med*, 83(6), 457-467. Retrieved from https://link.springer.com/article/10.1007/s00109-005-0639-3

Suzuki, T., Miki, Y., Moriya, T., Shimada, N., Ishida, T., Hirakawa, H., Ohuchi, N. & Sasano, H. (2004). Estrogen-related receptor a in human breast carcinoma as a potent prognostic factor. *Cancer research*, 64(13), 4670-4676. doi: 10.1158/0008-5472.CAN-04-0250

Thorburn, A. (2004). Death receptor-induced cell killing. *Cell Signal*, 16(2), 139-144. https://doi.org/10.1016/j.cellsig.2003.08.007

Tokarnia, C. H., Döbereiner, J. & Peixoto, P. V. (2000) "*Plantas Tóxicas do Brasil".* Rio de Janeiro, RJ: Helianthus, 2 ed

Traxler, P. (2003). Tyrosine kinases as targets in cancer therapy – successes and failures. *Oncologic*, 7(2), 1472-8222. doi: 10.1517/14728222.7.2.215

Trópicos®.org, (2017). internal research and world's scientific community, "nomenclatural, bibliographic, and specimen of Asclépias curassavica. Retrieved from http://www.tropicos.org/

Tundis, R., Loizzo, M. R., Menichini, F., Statti, G. A. & Menichini, F. (2008). Biological and pharmacological activities of iridoids: Recent developments. *Mini Rev Med Chem*, 8(4), 399-420. doi: 10.2174/138955708783955926

Vale, V. V., Vilhena, T. C., Trindade, R. C. S., Ferreira, M. R. C., Percário, S., Soares, L. F., Pereira, W. L., Brandão, G. C., Oliveira, A. O., Dolabela, M. F. & Vasconcelos, F. (2015). Anti-malarial activity and toxicity assessment of *Himatanthus articulatus*, a plant used to treat

malaria in the Brazilian Amazon. *Malar J*, 14(132), 2-10. Retrieved from https://malariajournal.biomedcentral.com/articles/10.1186/s12936-015-0643-1

Wang, J., Fang, F., Huang, Z., Wang, Y., & Wong, C. (2009). Kaempferol is an estrogen-related receptor a and g inverse agonist. *FEBS Lett*, 583(4), 643-647. https://doi.org/10.1016/j.febslet.2009.01.030

Wang, K., Liu, R., Li, J., Mao, J., Lei, Y., Wu, J., Zeng, J., Zhang, T., Wu, H., Chen, L., Huang, C. & Wei, Y. Quercetin induces protective autophagy in gastric cancer cells: Involvement of Akt-mTOR- and hypoxia-induced factor 1α-mediated signaling. *Autophagy*, 7(9), 966-978. doi: 10.4161/auto.7.9.15863

Wang, W., Li, L., Lin, W. L., Dickson, D. W., Petrucelli, L., Zhang, T., & Wang, X. (2013). The ALS disease-associated mutant TDP-43 impairs mitochondrial dynamics and function in motor neurons. *Hum Mol Genet*, 22(23), 4706-4719. doi: 10.1093/hmg/ddt319

Yang, J. H., Hsia, T. C., Kuo, H. M., Chao, P. D. L., Chou, C. C., Wei, Y. H. & Chung, J. G. (2006). Inhibition of lung cancer cell growth by quercetin glucuronides via G2/M arrest and induction of apoptosis. *Drug Metab Dispos*, 34(2), 296-304. doi: 10.1124/dmd.105.005280

Percentage contribuition of each author in the manuscript

Mirian Letícia Carmo Bastos – 20%

Rosana Moura Sarmento – 20%

Marcelo de Oliveira Bahia – 10%

Jaqueline da Silva Rodrigues – 10%

Valdicley Vieira Vale – 10%

Sandro Percário – 10%

Maria Fâni Dolabela – 20%