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Chapter

Anticancer Activity of Uncommon Medicinal Plants from the Republic of Suriname: Traditional Claims, Preclinical Findings, and Potential Clinical Applicability against Cancer

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Abstract

Despite much progress in our understanding of the essence of cancer, remarkable advances in methods for early diagnosis, the expanding array of antineoplastic drugs and treatment modalities, as well as important refinements in their use, this disease is among the leading causes of morbidity and mortality in many parts of the world. In fact, the next decade is anticipated to bring over 20 million new cases per year globally, about half of whom will die from their disease. This indicates a need for better strategies to deal with cancer. One way to go forward is to draw lessons from ancient ethnopharmacological wisdom and to evaluate the plant biodiversity for compounds with potential antineoplastic activity. This approach has already yielded many breakthrough cytotoxic drugs such as vincristine, etoposide, paclitaxel, and irinotecan. The Republic of Suriname (South America), renowned for its pristine and highly biodiverse rain forests as well as its ethnic, cultural, and ethnopharmacological diversity, could also contribute to these developments. This chapter addresses the cancer problem throughout the world and in Suriname, extensively deals with nine plants used for treating cancer in the country, and concludes with their prospects in anticancer drug discovery and development programs.

Keywords: cancer, Suriname, medicinal plants, traditional uses, phytochemistry, pharmacology, anticancer activity

1. Introduction

1.1 Generalities

Cancer is a generic term to describe over 200 distinct disease forms that, nonetheless, share three distinguishing characteristics, namely uncontrolled cellular proliferation, invasion of the abnormal cells into adjacent tissues, and their spread to distant organs via blood and lymph vessels [1]. The biological events fundamental to the development of cancer involve the transformation of normal cells

to a precancerous lesion which subsequently progresses to a malignant tumor in a multistage process [1]. These changes are the result of the interaction between an individual's genetic make-up and external agents including physical, chemical, and biological carcinogens [2].

Recognized physical carcinogens are ultraviolet and ionizing radiation which have been linked to skin cancer as well as leukemia and a number of solid tumors, respectively [2]. Well-studied chemical carcinogens are asbestos that has mainly been associated with lung cancer and mesothelioma; components of tobacco smoke which have been linked not only to breast and lung cancer but also to a host of other malignancies; aflatoxins produced by certain molds in improperly stored staple commodities which have been related to liver cancer; and the drinking water contaminant arsenic that has particularly been associated with lung, bladder, and kidney cancer [2]. Examples of biological carcinogens are the human papillomavirus, the hepatitis B virus, the hepatitis C virus, and the Epstein-Barr virus, the causative factors of cervical cancer, liver cancer, and certain lymphomas, respectively; the stomach bacterium *Helicobacter pylori* that has been implicated in the development of stomach cancer; and certain fish-parasitic flatworms associated with cholangiocarcinoma and urinary bladder cancer [2].

Molecular insights have revealed that the development of cancer—including its capacity to proliferate in an uncontrolled fashion, escape apoptosis, invade neighboring tissues, and disseminate to distant organs—involves aberrations in molecular networks that include oncogenes, tumor suppressor genes, and repair genes [1]. These changes occur in a multistep manner and often take place over many years [1]. This is an important reason that cancer usually manifests at older age, when sufficient carcinogenic mutations have accumulated to cause cancer and innate defense and cellular repair mechanisms have become less effective [1].

1.2 Worldwide epidemiology

According to GLOBOCAN 2018 estimates of cancer incidence and mortality produced by the International Agency for Research on Cancer, cancer will represent the leading cause of death throughout the world in the twenty-first century [3]. In 2018, there were an estimated 18.1 million new cancer cases and 9.6 million cancer deaths globally [3]. Lung cancer and female breast cancer were the most commonly diagnosed malignancy (each 11.6% of total overall cases), followed by cancer of colon and rectum (10.2%), prostate (7.1%), stomach (5.7%), and liver (4.7%) [3]. The most deadly cancers in that year were lung, colorectal, stomach, liver, and breast cancer accounting for 18.4, 9.2, 8.2, 8.2, and 6.6%, respectively, of the total number of cancer fatalities [3]. The most frequent cancers in males were lung, prostate, colorectal, stomach, and liver cancer with incidence rates of 14.5, 13.5, 10.9, 7.2, and 6.3%, respectively, and mortality rates of 22.0, 6.7, 9.0, 9.5, and 10.2%, respectively [3]. And in females, the most common cancers were those of the breast, colon and rectum, lung, and cervix uteri, with incidence rates of 24.2, 9.5, 8.4, and 6.6%, respectively, and mortality rates of 15.0, 9.5, 13.8, and 7.5%, respectively [3].

There were substantial variations among countries with respect to the most frequently diagnosed cancers and the leading causes of cancer death [3]. For instance, for many cancers, incidence rates were generally two- to threefold higher in industrialized countries than in transitioning economies [3]. However, differences in mortality were smaller, as relatively more patients in developing countries died from their disease, probably because of low screening rates as well as less advanced screening services and diagnostic methods in these regions [3]. Furthermore, cancers related to a westernized lifestyle such as lung, breast, and colorectal cancer were (much) more common in industrialized regions than in developing/

transitioning regions, even though these neoplasms were among the most common malignancies in both regions [3]. On the other hand, oral cancer and cervical cancer were much more frequent in (certain) developing/transitioning countries than in industrialized countries [3]. These differences are probably for an important part attributable to differences in associated risk factors and screening facilities, respectively, resulting in the former malignancy accounting for almost 50% to the burden of cancer in south-central Asia [4] and the latter occurring at incidence rates between 13.0 and 43.1 per 100,000 in Central America, South America, and the Caribbean, as well as in the parts of Africa [5].

1.3 Treatment modalities

The treatment modalities for cancer depend on the type of cancer as well as its stage and grade [6]. Some cases require only one form of treatment, but most patients need a combination of therapeutic modalities such as surgery with chemotherapy and/or radiation therapy. Surgery is applied for removing localized solid tumors or debulking large solid tumors in order to improve the efficacy of, for instance, chemotherapy [6]. Radiation therapy—external beam radiation therapy, brachytherapy, or systemic radioisotope therapy—uses high doses of radiation to kill cancer cells by damaging their DNA [6]. Chemotherapy is a systemic treatment with mostly combinations of antineoplastic drugs and is intended to kill cancer cells by stopping or slowing their growth or division, but it is also applied as an adjuvant to prevent disease recurrence after surgery or radiation therapy and as a neoadjuvant therapy to decrease the size of a tumor before surgery or radiation therapy [6].

Other cancer treatment modalities are immunotherapy, hormonal therapy, and angiostatic therapy. Immunotherapy can make use of adoptive cell transfer involving the infusion of engineered autologous or allogeneic T cells into a patient which can attack the cancer directly; monoclonal antibodies directed at cancer cell-specific antigens; or immunomodulating substances such as cytokines and Bacillus Calmette-Guérin vaccine which stimulate the immune system in a more general way [6]. Hormonal therapy slows or stops the growth of hormone-dependent tumors such as breast and prostate cancers, or reduces or prevents the symptoms in patients suffering from these cancers who do not qualify for surgery or radiation therapy [6]. Hormonal therapy can also be used in the adjuvant or neoadjuvant setting [6]. Angiostatic or antiangiogenic therapy interrupts the angiogenic signals that a tumor emits to its surroundings for recruiting a blood supply and causes tumors to shrink [6].

Despite this respectable array of antineoplastic agents and therapeutic modalities most cancers remain fatal, particularly when detected at an advanced stage. This implies a need for more efficacious forms of treatment of neoplastic disease. Many efforts are being dedicated to this goal, including improved early diagnosis, the development of highly specific targeted therapies, and the identification of more efficacious antineoplastic drugs. It is generally agreed that the application of ancient wisdom and folk medicine represents an important strategy to discover and develop new anticancer drugs [7–10]. This approach has led to breakthrough anticancer drugs such as the tubulin-interfering agents vincristine from the periwinkle plant *Catharanthus roseus* (L.) G. Don (Apocynaceae) [11] and paclitaxel from the Pacific yew *Taxus brevifolia* Peattie 1950 (Taxaceae) [12]; the topoisomerase I and II inhibitors irinotecan [13] and etoposide [14], respectively, from *Podophyllum* plant species (Berberidaceae) and the Chinese happy tree *Camptotheca acuminata* Decne. (Nyssaceae), respectively; as well as a host of other plant-derived compounds [7, 10]. Notably, almost half of the anticancer drugs that have been granted approval in the United States of America between 1981 and 2014 were from natural origin [9].

So far, only a relative handful of the plant kingdom has been evaluated for pharmacologically active plant substances with potential efficacy against cancer. Therefore, it is likely that further exploration of the rain forests along with other less explored environments such as deserts, tundras, as well as freshwater and marine ecosystems [15], will help identify many structurally novel and mechanistically unique compounds for fighting cancer. This chapter first reviews a few aspects of cancer throughout the world, then focuses on cancer in the Republic of Suriname, subsequently addresses in detail nine medicinal plants that are used for treating cancer in the country, and concludes with some remarks about their potential usefulness against this disease.

2. Background on Suriname

2.1 Geography, population, demographics, and economy

The Republic of Suriname is situated in the north-eastern part of South America adjacent to the Atlantic Ocean and has a land area of roughly 165,000 km² (**Figure 1**). The population of about 570,000 is among the ethnically most varied in the world, comprising Amerindians, the original inhabitants; Maroons, the immediate descendants of enslaved Africans shipped from western Africa between the seventeenth and the nineteenth century; Creoles, a generic term referring to anyone having one or more African ancestors; the descendants from indentured laborers attracted from China, India, and Java (Indonesia) between the second half of the nineteenth century and the first half of the twentieth century; as well as immigrants from various European, South American, and Caribbean countries [16].



Figure 1. Location of Suriname with respect to its neighboring countries French Guiana, Brazil, and Guyana, as well as its position in South America (insert) (from: <https://goo.gl/images/F77jgS>).

Suriname can be characterized as a demographically transitioning country with declining mortality and infertility rates as well as a growing and aging population. These changes are for an important attributable to considerable progress in health care, nutrition, sanitation, and drinking water quality; the eradication of various infectious diseases; as well as improvements in average living and working conditions, education, and income [17, 18]. The result was a decline of the death rate from 24 per 1000 in 1923 to 6 per 1000 in 2011 and the attainment of an average life expectancy of 70 years in 2011 [17].

The country's most important economic means of support are crude oil drilling as well as gold and bauxite mining [19]. These activities, together with agriculture, fisheries, forestry, and ecotourism, have substantially contributed to Suriname's gross domestic income (GDI) in 2014 of USD 5.21 billion and the average *per capita income* in that year of USD 9325 [19]. This positions Suriname on the World Bank's list of upper-middle income economies [20].

2.2 Health care

Suriname spends about 5.7% of its GDI—which amounted to USD 589 *per capita* in 2014—to health care [21]. This sum covers the health costs for the economically weakest individuals; insurance for government employees and employees of government-related companies; import and distribution of essential pharmaceuticals; vaccination programs; maternal and child health care; programs to fight parasitic and microbial diseases; dental care for schoolchildren; services for dermatological diseases, sexually transmitted diseases, and HIV/AIDS; as well as a Kidney Dialyses Center and a Blood Bank [21].

Primary health care in Suriname is offered by the government-subsidized Regional Health Services and Medical Mission, as well as approximately 250 general practitioners. The Regional Health Services run 43 community health centers staffed with physicians and nurses, covers the entire coastal area, and offers basic laboratory testing as well as curative and preventive services including cervical cancer screening and dental, prenatal, and obstetric care. The Medical Mission is a nongovernmental organization that provides health services to people living in Suriname's hinterland. The clinics are staffed with community health workers who are supervised by general practitioners who travel back and forth on a regular basis.

Secondary care is provided by two private and two government-supported hospitals in Paramaribo and one public hospital in the western district of Nickerie. Medical emergencies can turn around-the-clock to the First-aid Stations of the Academic Hospital Paramaribo and the Saint Vincentius Hospital Suriname. The Academic Hospital Paramaribo also functions as training facility for both general practitioners and medical specialists. All hospitals have modern clinical laboratory facilities as well as radiology services at their disposal. There are, in addition, four private clinical laboratories and three private radiology clinics. Diagnostic imaging including computed tomography and magnetic resonance imaging is possible at two private clinics and the Academic Hospital Paramaribo. This hospital also provides tertiary care at a Thorax Center, a Neurology High-Care Unit, a Neonatal Care Unit, and a Radiotherapy Center.

3. Cancer in Suriname

3.1 Epidemiology

As in many other low- and middle-income countries, there is no population-based cancer registry in Suriname. The occurrence of cancer in the country is

estimated from data on the histopathologically confirmed cases at the Pathologic Anatomical Laboratory of the Academic Hospital Paramaribo that functions as the country's cancer-based registry. This institution reported for 2014 a crude incidence rate of 133 per 100,000 population with the most common cancers being breast, colorectal, prostate, and cervical cancer [22]. An earlier publication [23] mentioned an average of 70 per 100,000 population for the period 1980–2000, suggesting an almost twofold increase in the occurrence of cancer in Suriname since the turn of the century.

Cancer mortality in Suriname has been registered since 1958. In the period between 1962 and 1970, the average death rate due to cancer was 60 per 100,000 per year [24]. This figure had risen to approximately 72 in 2011, ranking cancer as the second most common cause of mortality in the country, after cardiovascular diseases [25]. The top five causes of cancer mortality in that year were prostate, lung, rectum-sigmoid, female breast, and cervical cancer [25]. Most of the fatalities in females were attributable to breast and cervical cancer, while prostate cancer was the leading cause of cancer death in males [25].

3.2 Allopathic forms of cancer treatment in Suriname

Suriname has no national guidelines for the screening, diagnosis, and treatment of cancer, and structured screening programs for breast, cervical, and colon cancer are nonexistent. For these reasons, a comprehensive national cancer control plan has been developed [22] that will be executed in the short term by the Ministry of Health.

Still, primary prevention programs such as mandatory vaccination against the hepatitis B virus (since 2011) and the availability of a HPV vaccine for young girls (implemented in 2013) may help reduce the cancer burden in the country. This may also be achieved by early detection services such as screening for cervical and breast cancer, even though these facilities are in general utilized on an *ad hoc* basis. Cervical cancer screening occurs upon referral and is done at the Lobi Foundation, a nongovernmental organization for reproductive preventive services, using cytology (Pap smear) or visual inspection with acetic acid. Unfortunately, the coverage of this program is below 20% and thus has probably little impact on cervical cancer mortality [26]. Mammography, breast ultrasound, and fine needle aspiration for the assessment of breast lesions are since 2009 possible at two private clinics and two hospitals. Stereotactic (mammogram-guided) breast biopsy has been available since 2018 at the Academic Hospital Paramaribo. Cancer-specific evaluations such as testing for hormone receptors and tumor markers, are carried out at the Pathologic Anatomical Laboratory of this hospital.

Surgery, radiation therapy, and chemotherapy as standard therapeutic modalities for cancer are all available in Suriname. Surgical treatment is offered by all four hospitals in Paramaribo. Radiation therapy has been available since 2012 and is performed by two radiation oncologists. Chemotherapy is delivered by two oncologists and two gynecologic oncologists. If diagnostic or therapeutic services are not available in Suriname, patients can be transferred to health centers abroad provided that they have a good prognosis and are younger than 70 years. More than half of the selected patients are treated in Bogotá, Columbia. All costs are covered by the Surinamese Ministry of Health through the State Health Foundation [21].

3.3 Traditional forms of cancer treatment in Suriname

All ethnic groups in Suriname have preserved their own specific identity including their particular forms of traditional medicine, probably as a means of

strengthening the ethnic identity after their relocation to their new homeland [27, 28]. Not surprisingly, the use of various traditional medicinal systems—involving, among others, Indigenous, African, and Chinese traditional medicine, Indian Ayurveda, as well as Indonesian Jawa—is deeply rooted in Suriname [27, 28]. Furthermore, Suriname's large biodiversity provides ample and readily available raw material that can be processed into ethnopharmacological plant-based preparations [29]. As a result, many diseases including cancer are often treated with such medications instead of, or in conjunction with, allopathic forms of treatment [30] despite the availability of affordable and accessible modern health care throughout the entire country.

This holds true for, for instance, patients who are motivated by aversion of “chemical” drugs with attendant adverse or side effects and those whose philosophy about life is not compatible with the use of allopathic medicine or who have reservations about the viewpoints of allopathic medicine [31]. Others prefer traditional treatments because these modalities would improve conventional therapies and represent gentler means of managing their disease when compared to allopathic medicines [32]. Still other patients, particularly those with advanced disease or cancer that, from a medical standpoint, can no longer be treated, resort to traditional medicines as an ultimate means to improve their situation [33]. And cultural beliefs, traditional values, and certain perceptions of health and disease may entice some people to choose for a familiar traditional therapy rather than a “western” therapy [34, 35].

4. Plants for treating cancer in Suriname

Hereunder, nine plants that are used in Suriname for treating cancer have in detail been assessed for their presumed activity against this disease. The plants have been selected after consulting a number of comprehensive publications describing various aspects of medicinal plants in the country [36–43]. Several of these plants such as the graviola *Annona muricata* L. (Annonaceae), *Aloe vera* (L.) Burm.f. (Asphodelaceae), the bitter melon *Momordica charantia* L. (Cucurbitaceae), the neem tree *Azadirachta indica* A.Juss., 1830 (Meliaceae), *Moringa oleifera* Lam. (Moringaceae), several subspecies and varieties of the black nightshade *Solanum nigrum* L. (Solanaceae), as well as the noni *Morinda citrifolia* L. (Rubiaceae) have elaborately been dealt with in the literature. This led us to decide to leave these plants out of the current chapter and address a number of less well-known plants, which *prima facie* may not qualify for evaluation for their anticancer potential (Table 1).

4.1 Annonaceae—*Annona squamosa* L.

The sugar apple *A. squamosa* (Figure 2) is probably native to the tropical parts of South America and the Caribbean but is now widely cultivated for its flavorful fruit in many other tropical and subtropical regions throughout the world. Unripe fruits as well as seeds and leaves contain toxic alkaloids with effective vermifugal and insecticidal properties [44]. For these reasons, the seed oil is commonly used to treat head lice [44]. *A. squamosa* preparations are also used against gastrointestinal ailments, urinary tract infections, irregular menstrual flow, and cancer [42, 43, 45]. The therapeutic efficacy of some of these applications may be attributed to acetogenins, terpenes and terpenoids, as well as alkaloids [45, 46].

The seed oil as well as the essential oils from the pericarp, the leaves, and the stem bark of *A. squamosa* displayed anticancer activity against a broad range of human cancer cell lines [47–62] as well as H22 hepatoma implanted into laboratory

Family	Species (vernacular names in English; Surinamese)	Part(s) used	Active constituent(s)	References
Annonaceae	<i>Annona squamosa</i> L. (sugar-apple; kaner'apra)	Oil from seed, pericarp, leaf, stem bark	Annonaceous acetogenins, terpenes/ terpenoids, alkaloids	[47–67]
Asteraceae	<i>Cyanthillium cinereum</i> (L.) H. Rob. (little ironweed; doifiwiwiri)	Whole plant	Sesquiterpene lactones	[74–79]
Asteraceae	<i>Eclipta prostrata</i> (L.) L. (false daisy; luwisa wiwiri)	Leaf, aerial parts, whole plant	Terthiophenes/ thiophenes, saponins, triterpenoids, coumestans, flavonoids	[84–94]
Fabaceae	<i>Abrus precatorius</i> L., 1753 (crab's eye; kokriki)	Seed, leaf	Abrin, phenolics, flavonoids	[100–110]
Fabaceae	<i>Tephrosia sinapou</i> (Buch.) Chev. (Surinam poison; bumbi)	Root, leaf, aerial parts, stem	Benzil derivatives, coumestan derivatives, flavones/flavonoids, phenols	[118–131]
Loranthaceae	<i>Phthirusa stelis</i> (L.) Kuijt (bird vine; pikin fowru doti)	Whole plant, stem, leaf	Peptides, alkynic fatty acids, lectins, triterpenes, glycosides, flavonoids	[135–148]
Rubiaceae	<i>Uncaria guianensis</i> (Aubl.) J.F. Gmel. (cat's claw; popokainangra)	Stem bark	Oxindole alkaloids	[157–162]
Simaroubaceae	<i>Quassia amara</i> L. (bitterwood; kwasibita)	Stem, leaf	Quassinoids, canthin alkaloids	[171–178]
Zingiberaceae	<i>Zingiber officinale</i> (ginger; gember, dyindya)	Rhizome	Gingerols, shogaols	[187–203]

Table 1.

Plants with anticancer activity addressed in this chapter, parts preferentially used, presumed constituents with anticancer and chemoprotective activity, and references supporting these activities.

**Figure 2.**

The sugar apple *Annona squamosa* L. (Annonaceae) (from: <https://goo.gl/images/Lh5g7Z>).

mice [51, 60–63]. The anticancer effects have particularly been attributed to annonaceous acetogenins in the seed oil [47–53, 59] as well as annonaceous acetogenins, terpenes, and terpenoids, and alkaloids in pericarp, leaves, and stembark [56–58, 60–62]. Interestingly, the acetogenin squamoxinone-D displayed selective cytotoxicity against the (drug-resistant) SMMC 7721/T cell line [59], and annonaceous acetogenins were highly active in H22 hepatoma-bearing laboratory mice [64].

The antitumor activities have in some cases been associated with cycle arrest effects and apoptotic events [54, 60–62] as indicated by the increased caspase-3 activity, the downregulation of antiapoptotic genes, and the fragmentation of the nuclear DNA [54, 60]. The mechanism underlying these events presumably involves the generation of oxidative stress [54]. This supposition is based on the enhanced generation of intracellular reactive oxygen species and the decreased levels of intracellular glutathione species noted in cultured human cells undergoing apoptosis following exposure to *A. squamosa* seed oil [54, 60].

Notably, leaf and stembark extracts protected Swiss albino mice and Syrian golden hamsters from the mutagenic effects of the alkylating agent cyclophosphamide [65] or the potent laboratory carcinogen 7, 12 dimethylbenz(a) anthracene (DMBA) [66], respectively. Furthermore, aqueous and ethanolic stembark extracts decreased lipid peroxidation and potentiated antioxidant activities in an animal model of oral carcinogenesis [67]. These observations suggest that *A. squamosa* also possesses chemopreventive properties.

4.2 Asteraceae—*Cyanthillium cinereum* (L.) H. Rob.

The little ironweed *C. cinereum*, also known as *Vernonia cinerea* (L.) Less. (Figure 3), is native to the tropical parts of Africa and Asia but has become naturalized in various other tropical regions including those in South America and the Caribbean. The plant is traditionally used for treating genitourinary disorders, gastrointestinal complaints, and respiratory ailments; to stimulate perspiration in malaria patients; against childhood conditions including bed-wetting; and to fight cancer [42, 43, 68]. *C. cinereum* seeds yield vernonia oil that contains vernolic acid [69], a natural epoxy fatty acid that may serve as a renewable starting material for manufacturing adhesives, paints, dyes, coatings, composites, and plastics [70].

Pharmacological and phytochemical studies have shown a wide range of bioactive compounds such as (a) sesquiterpene lactone(s), which may lend credit to the traditional uses [68]. Two clinical trials found *C. cinereum* preparations efficacious in smoking cessation [71], while one study reported encouraging results with a



Figure 3.
The little ironweed *Cyanthillium cinereum* (L.) H. Rob. (Asteraceae) (from: <https://goo.gl/images/Lh5g7Z>).

herbal *C. cinereum*-containing preparation in patients with type 2 diabetes mellitus [72]. However, the clinical evidence available at this moment is insufficiently sound to support these applications [73].

Support for anticancer activity of *C. cinereum* came from the potent cytotoxicity of an extract from the whole plant against various drug-sensitive and multidrug-resistant human tumor cell lines [74–76]. The whole-plant extract caused the cells to apoptose and sensitized them to common cytotoxic drugs [76]. Furthermore, such an extract as well as the sesquiterpene lactone vernolide A stimulated the activity of cytotoxic T lymphocytes and natural killer cells and enhanced antibody-dependent cellular cytotoxicity and antibody-dependent complement-mediated cytotoxicity in tumor-bearing BALB/c mice by increasing the secretion of interleukin-2 and interferon- γ [77]. This suggests that (this) sesquiterpene lactone may play an important role in the anticancer activity of *C. cinereum* [68, 78].

Other indications for anticancer activity of *C. cinereum* preparations were the inhibitory effects of a 70%-methanol whole-plant extract on the *in vitro* proliferation, invasion, migration, and matrix metalloproteinase activation of B16F-10 murine melanoma cells [79]. The extract also prevented the formation of lung metastases by the B16F-10 cells in C57BL/6 mice, lowered vascular-endothelial growth factor (VEGF) levels in the animals, and substantially increased their life span when compared to untreated controls [79]. Together, these observations raise the possibility that *C. cinereum* may exert its anticancer activity by boosting the immune system, suppressing angiogenesis, and inhibiting drug transport mechanisms in addition to direct cytotoxicity.

4.3 Asteraceae—*Eclipta prostrata* (L.) L.

The false daisy *E. prostrata*, also known as *E. alba* (L.) Hassk. or *E. erecta* L. (**Figure 4**), is probably native to either Asia or the Americas but is now commonly encountered in subtropical and tropical regions throughout the world. It has become an invasive weed in many parts of the tropics, which is particularly due to its ability to grow fast and flower early. The tender leaves and young shoots are consumed as a vegetable but may also serve as a source for the synthesis of titanium dioxide nanoparticles (nano-TiO₂) [80]. Nano-TiO₂ is widely employed to provide whiteness and opacity to paints, plastics, papers, inks, food colorants, and tooth-pastes; for the production of cosmetics and skin care products such as sun blocks because of its ability to protect the skin from UV rays while remaining transparent on the skin; and as an additive in antifogging coatings and self-cleaning windows because of its photocatalytic sterilizing properties [81].



Figure 4.
The false daisy *Eclipta prostrata* (L.) (Asteraceae) (from: <https://goo.gl/images/YGw37Z>).

E. prostrata is an important herb in Indian traditional medicine and is used for treating a host of conditions such as skin wounds and certain skin disorders; toothache; hair loss and graying hair; gastrointestinal complaints; uterine disorders; microbial infections; as well as cancer [42, 43, 82]. Some of these claims may be attributable to the presence in the plant of various bioactive constituents including coumestans, thiophene derivatives, terthiophenes, flavonoids, as well as triterpenoids and their glycosides such as eclalbasaponins [82, 83].

Converging lines of evidence suggest that *E. prostrata* preparations and some of their constituents may elicit anticancer activity through multiple mechanisms including direct cytotoxicity, angiostatic activity, and chemoprevention. The former possibility is supported by the growth inhibitory effects of crude extracts of the plant in a variety of drug-sensitive and drug-resistant cell lines [84–87] while causing apoptosis in some cases [87, 88]. Also, an orally administered methanolic leaf extract exerted encouraging anticancer activity against Ehrlich ascites carcinoma in Swiss albino mice [89], and a hydroalcoholic extract reversed multidrug resistance in an animal model of liver cancer induced by diethylnitrosamine and 2-acetylaminofluorene [86]. Furthermore, terthiophenes, thiophenes, saponins, triterpenoids, coumestans, and flavonoids isolated from the aerial parts exhibited cytotoxicity against cultured SKOV3 human ovarian cancer cells [90]; an eclalbasaponin I-containing fraction from the aerial parts and the saponin dasyscyphin-C isolated from the leaves inhibited the *in vitro* proliferation of SMMC-7721 human hepatocarcinoma and HeLa human cervical carcinoma cells, respectively [85, 91]; and eclalbasaponin II induced cytotoxicity as well as apoptotic and autophagic cell death in human ovarian cancer cell lines [92].

That *E. prostrata* may also exhibit angiostatic activities can be derived from the inhibitory effect of the juice from the whole plant on invasion, migration, and adhesion of a variety of cancer cell types and endothelial cells in the chick chorioallantoic membrane assay [93]. And indications for chemopreventive actions of this plant were provided by the growth inhibitory effect of a coumestan-containing methanolic whole-plant extract in an experimental skin cancer in mice [94]. This presumably occurred by restoring endogenous antioxidant defense mechanisms, enhancing immunosurveillance, silencing cell cycle progression signals, and inducing stable expression of p53 [94].

4.4 Fabaceae—*Abrus precatorius* L., 1753

The crab's eye or rosary pea *A. precatorius* (Figure 5) is a slender, woody, climbing plant that grows twisting around trees, shrubs, and hedges and probably originates from India. However, due to its severely invasive capacity, this plant is now commonly encountered in many tropical and subtropical parts of the world. Its deep roots are very difficult to remove, and its aggressive growth, hard-shelled seeds, and ability to sucker make it very difficult to eradicate and to prevent re-infestation. The brightly red colored seeds are used to make necklaces and other ornaments as well as percussion instruments in various cultures. However, they are very toxic because of their high content of the toxalbumin abrin, and ingestion of a single well-chewed seed can be fatal [95].

The sweet-tasting leaves of the plant are used in West Tropical Africa to sweeten foods [96]. These parts of the plant along with the seeds (after denaturing abrin at high temperatures [97]) are also used in various traditional medicinal systems for treating or preventing tetanus, inflammation, snake bites, rabies, and leukoderma; as aphrodisiacs; as oral contraceptives and abortifacients; and for treating cancer [42, 98].



Figure 5.
The crab's eye *Abrus precatorius* L., 1753 (*Fabaceae*) (from: <https://goo.gl/images/8VobSd>).

Pharmacological studies with preparations from *A. precatorius* seeds and leaves revealed that many of their biological activities may be attributable to abrin [98]. This compound consists of a dimer with a B subunit that facilitates its entry into cells by binding to plasma membrane-associated transport proteins, after which the A subunit inactivates the 26S subunit of ribosomes, preventing protein synthesis [99]. One molecule of abrin is able to inactivate up to 1500 ribosomes per second [95], indicating its powerful inhibitory effect on protein synthesis. On the other hand, this mechanistic feature of abrin presents the opportunity of inhibiting the proliferation of cancerous cells which characteristically have a higher metabolic turnover when compared to normal cells.

Indeed, protein-rich extracts or peptide fractions from *A. precatorius* seeds and ethanol, ethyl acetate, and water extracts from the leaves potently inhibited the proliferation of several tumor cell lines [100–104] without affecting the growth of normal murine peritoneal macrophages [102]. The cytotoxic effects were accompanied by upregulation of particularly p21 and p53 levels [104] and clear signs of apoptosis occurring through the mitochondrial pathway [101]. The seed preparations also inhibited the growth of several tumor types implanted into laboratory rodents [105–108]. And direct injection of abrin into a murine Meth-A sarcoma growing in syngeneic BALB/c mice led to regression of the tumor [109]. The anticancer effects might be related to the antioxidant activities of phenolics and flavonoids in the extracts [102, 104].

Importantly, administration of Meth-A tumor cells which had been treated *in vitro* with abrin, induced strong antitumor immunity of the mice [109]. This suggests that the antitumor effects of abrin were also produced by boosting the immune system. Support for this presumption came from the immunopotentiating and immunostimulatory properties of abrin [107, 110] and the behavior of *Abrus* agglutinin as a B cell and T cell stimulator [111].

4.5 Fabaceae—*Tephrosia sinapou* (Buchholz) A.Chev.

The Surinam poison *T. sinapou*, also known as *T. toxicaria* (Swartz) Pers. (**Figure 6**), is native to parts of Central America, the Caribbean, and tropical South America. The plant is mainly known for its high content of the isoflavonoids rotenone and tephrosin in its black roots and seeds, which are used as a fish poison by the Amazon Indigenous peoples [112, 113]. Particularly rotenone is also highly toxic to insects and pests [112, 113]. For this reason, Guyana hinterland peoples use the root sap or the leaf juice externally against head lice [112]. These preparations are also used to ward off evil spirits and for treating eczema, snakebites, syphilis,



Figure 6.
The Suriname poison Tephrosia sinapou (Bucholz) A.Chev. (Fabaceae) (from: <https://goo.gl/images/q6BZZN>).

and gonorrhoea, as well as skin ulcers associated with AIDS and cancer [42, 43, 114]. These health benefits have particularly been ascribed to the rotenoids and other flavonoids in roots, leaves, and aerial parts of the plant [115–117].

Indications for anticancer activity of *Tephrosia* preparations were provided by the cytotoxic effects of extracts from parts of *T. calophylla* Bedd., *T. persica* Boiss., *T. purpurea* (L.) Pers., *T. villosa* (L.) Pers., and *T. vogelii* Hook F. against human carcinoma cell lines and brine shrimp cultures [118–124]. In some cases, the cytotoxic effects were accompanied by signs of apoptotic cell death [118]. Comparable anticancer effects were produced by benzil and coumestan derivatives from a *T. calophylla* root extract [125]; flavonoids from parts of *T. calophylla*, *T. pulcherrima* (Baker) Gamble, and *T. pumila* (Lam.) Pers. [126]; phenol- and flavonoid-rich methanolic extracts from the leaves of *T. purpurea* and the aerial parts of *T. apollinea* (Delile) DC. [124, 127]; and a prenylated flavone from the aerial parts of *T. apollinea* [128]. Notably, the high flavonoid content of the aerial parts of *T. apollinea* has also been associated with potent anti-angiogenic activity in an *ex vivo* rat aortic ring assay [127].

There are also indications for cancer chemopreventive activity of *Tephrosia* preparations. Thus, flavonoids from an ethyl acetate-soluble extract of *T. sinapou* stem selected for potential cancer chemopreventive properties in an *in vitro* assay for quinone reductase induction, inhibited the formation of preneoplastic lesions induced by DMBA in a mouse mammary organ culture [129]. Furthermore, *T. purpurea* extracts substantially reduced the formation of skin lesions in Swiss albino mice treated with the potent tumor promoter phorbol 12-myristate 13-acetate (PMA) following treatment with DMBA [130]. The extract also inhibited the development of hepatocellular carcinoma in Wistar rats treated with the carcinogenic and mutagenic compound N-nitrosodiethylamine [131].

4.6 Loranthaceae—*Phthirusa stelis* (L.) Kuijt

The bird vine *P. stelis* (Figure 7) is, like many of its relatives in the plant family Loranthaceae (commonly known as mistletoes), a small flowering plant that grows



Figure 7.

The bird vine *Phthirusa stelis* (L.) Kuijt (Loranthaceae) (from: <https://goo.gl/images/J9D1zG>).

hemiparasitically on the branches of trees and shrubs. It is encountered in various Southern and Middle American countries between Costa Rica and Bolivia where it often constitutes a serious pest on cultivated trees of economic importance such as rubber, orange, cocoa, and bread fruit trees [132]. *P. stelis* is mostly spread by bird droppings, hence the abovementioned Surinamese vernacular name of “*pikin fowru doti*” meaning small birds’ excrement.

None of the parts of the plant have edible uses. However, the viscous layer of its fruits has been suggested to represent a potential source of natural rubber [133]. *P. stelis* preparations are traditionally used to treat oral candidiasis in children; leukorrhea; problems of the female reproductive system; tonsillitis; and skin problems such as scabies [42, 43, 134]. The plant is also used as a chemopreventive substance and by cancer patients for whom no other options are available, presumably because of its hemiparasitic, cancer-like lifestyle, which would signal its usefulness for these purposes [43].

Indications for anticancer activity of *P. stelis* are scant, being limited to the cytotoxic effects of small polypeptides of 3–5 kDa isolated from dried dichloromethane or ethanol whole-plant extracts in cultured U-937 GTB human histiocytic lymphoma cells [135]. This finding is in line with the identification of (larger) cytotoxic peptides in the Loranthaceae species *Helicanthus elastica* (Desr.) Dans. [136] and *Ligaria cuneifolia* (Ruiz & Pav.) van Tiegh. [137]. Other phytochemicals in Loranthaceae species with *in vitro* anticancer activity are alkynic fatty acids in *Scurrula atropurpurea* (BL.) Dans. [138]; lectins in *Viscum album coloratum* Kom. [139]; the triterpene moronic acid in *Phoradendron reichenbachianum* (Seem.) Oliv. [140]; glycosides in *Macrosolen globosus* (Roxb.) Tiegh. [141], *Loranthus tanakae* Franch. & Sav. (Loranthaceae) [142], and *Viscum coloratum* (Kom.) Nakai [143]; and flavonoids in *L. cuneifolia* [144].

Crude extracts from stem or leaves of *Scurrula oortiana* (Korth.) Danser [145], leaves of *Dendrophthoe pentandra* (L.) Miq. [146], and stem of *Elytranthe parasitica* (L.) Danser [147] also exerted cytotoxic effects. In addition, the alkynic fatty acids from *S. atropurpurea* potently inhibited *in vitro* tumor cell invasion [148], and extracts from the stem or leaves of *S. oortiana* increased tumor cell sensitivity to TNF- α -mediated lysis [145].

4.7 Rubiaceae—*Uncaria guianensis* (Aubl.) J.F. Gmel.

The cat's claw *U. guianensis* (**Figure 8**) is indigenous to the Amazonian parts of Paraguay, Brazil, Bolivia, Peru, Ecuador, Colombia, Venezuela, and the Guyanas. Preparations from its stem bark and leaves have a long history of traditional medicinal use and are particularly employed for treating osteoarthritis and rheumatoid arthritis [42, 43, 149]. Pharmacological studies with extracts from *U. guianensis*—and with those from other closely related species, mainly *U. tomentosum* (Willd. ex Schult.) DC—indeed showed anti-inflammatory activities [150]. These effects have primarily been attributed to pentacyclic oxindole alkaloids [149–152]. Clinical studies with an *U. guianensis* stem bark extract or a highly purified pentacyclic oxindole alkaloids fraction from *U. tomentosum* reported some benefits in patients with osteoarthritis of the knee [153–155]. However, the overall clinical data are insufficient to draw a firm conclusion about the anti-inflammatory efficacy of *Uncaria* preparations [156].

No studies have been carried out on the anticancer activity of *U. guianensis*. However, studies with the oxindole alkaloids from *U. tomentosa* stem bark showed notable anticancer activity against human cancer cell lines [157–160] and a mouse model [159] which was in some cases accompanied by apoptosis [157]. In addition, *Uncaria* preparations may possess immunomodulatory and chemopreventive properties besides direct cytotoxic activity. The former assumption is supported by the involvement of anti-inflammatory processes rather than cytotoxic events in the antitumor activity of a hydroethanolic *U. guianensis* stem bark extract in 4 T1 mammary tumor-bearing BALB/c mice [161]. The latter supposition stems from the changes in expression patterns of critical proto-oncogenes and tumor suppressor genes in DMBA-treated CBA/Ca mice following administration of Claw of Dragon tea (CoD™ tea), a mixture of the stem barks from *U. guianensis*, *U. tomentosa*, and the trumpet-tree *Tabebuia avellanedae* Lorentz ex Griseb. (Bignoniaceae) [162].

A clinical trial with a dried extract of *U. tomentosa* stem bark reported improved overall quality of life, social functioning, and fatigue in patients with advanced solid tumors, but there were no improvements in biochemical and inflammatory markers or tumor responses [163]. Another trial found a decrease in the occurrence of neutropenia caused by the 5-fluorouracil-doxorubicin-cyclophosphamide combination in patients with breast cancer [164]. However, a third study found no effect of oral tablets containing a dried ethanolic *U. tomentosa* stem bark on the most prevalent adverse events caused by the 5-fluorouracil-oxaliplatin regimen in colorectal cancer patients [165].



Figure 8. The cat's claw *Uncaria guianensis* (Aubl.) J.F. Gmel. (Rubiaceae) (from: <https://goo.gl/images/7ezTTN>).

4.8 Simaroubaceae—*Quassia amara* L.

The bitterwood *Q. amara* (**Figure 9**) is native to South and Central America but is now also cultivated in various other tropical and subtropical regions throughout the world. In Suriname, the plant has been named “kwasibita” (Kwasi’s bitter) after the freedman Kwasi or Quassi (1692–1787) who was the first to broadly apply the remarkable medicinal properties of the hardwood for treating malaria fevers [28]. The plant contains triterpene quassinoids, secondary metabolites that are among the bitterest in nature [166]. These compounds are almost exclusively encountered in members of the Simaroubaceae and are a taxonomic marker of this plant family [166]. They constitute basic ingredients of Angostura bitters, concentrated alcoholic preparations produced by the House of Angostura in Trinidad and Tobago, which are key ingredients of cocktails such as gin-based drinks.

The quassinoids quassin, neoquassin, bruceantin, and similikalactones D and E have been associated with a host of pharmacological activities including antimalarial, insecticidal, anti-inflammatory, antimicrobial, and antianorectic activities [166–168]. Other *Q. amara* phytochemicals with a broad pharmacological spectrum are canthin-6-one alkaloids, which displayed antiviral, antiparasitic, antibacterial, anti-inflammatory, and cytotoxic activities [166, 168, 169]. Notably, a 4% *Quassia* cream containing both groups of phytochemicals has been found safe and effective in the management of rosacea [170].

There is ample evidence that *Q. amara* preparations and some of its constituents also possess anticancer activity. For instance, crude stem or leaf extracts, quassamarin- and/or similikalactone-enriched fractions, partially purified quassinoid-containing fractions, as well as quassamarin, similikalactones, and canthin alkaloids displayed substantial cytotoxicity against human carcinoma cell lines [171–174] as well as P-388 lymphocytic leukemia inoculated into laboratory mice [171]. Importantly, the quassinoids did not affect the viability of nontumorigenic African green monkey Vero kidney cells [173] and produced anticancer effects at lower concentrations than those required for antimalarial effects [172, 173]. Comparable results were found with quassinoids and/or canthin alkaloids from other members of the Simaroubaceae family [175–178]. Markedly, the quassinoids and canthin alkaloids also prevented the activation of Epstein-Barr virus early antigen by PMA [175] and inhibited the activity of CYP1A1, a cytochrome P450 isoform with presumed carcinogen-activating properties [179]. These observations suggest that these compounds may also possess chemopreventive properties.

Based on this large body of preclinical data, several *Q. amara* constituents have undergone clinical evaluation in patients with advanced solid and hematological



Figure 9.
The bitterwood *Quassia amara* L. (Simaroubaceae) (from: <https://goo.gl/images/d5ZqEd>).

malignancies. Unfortunately, the results from phase 1 and phase 2 studies with bruceantin—as well as Fructus bruceae oil obtained from the dried ripe fruits of *Brucea javanica* (L.) Merr.—were uniformly disappointing, showing no meaningful anticancer activity but substantial toxicity [180–182].

4.9 Zingiberaceae—*Zingiber officinale* Roscoe

The ginger *Z. officinale* (**Figure 10**) is presumably native to the Indian subcontinent and other Southern Asian regions. This plant was probably introduced in Suriname by Javanese indentured laborers around the beginning of the twentieth century [28, 38]. The rhizome is extensively used as a hot and fragrant kitchen spice in many cuisines and to prepare various hot and cold beverages. This part of the plant also has many long-standing traditional uses [43, 183]. The essential oil from the rhizomes is topically applied as an analgesic, while preparations from powdered fresh or dried rhizomes are orally or topically used for treating, among others, respiratory complaints; obesity; microbial infections; vertigo, travel sickness, morning sickness, as well as nausea and vomiting associated with surgery and chemotherapy; and cancer [43, 183].

These claims are supported by the pharmacological activities displayed by particularly gingerols (such as zingerone and zingerol) and shogaols in the rhizomes. Gingerols are the main compounds in the volatile oil of fresh ginger rhizomes and are responsible for their characteristic fragrance [184]. They are thermally labile and easily undergo dehydration reactions to form the corresponding shogaols, which convey the typical pungent taste of dried ginger during cooking [184]. Both gingerols and shogaols exhibited pharmacological activities which supported the traditional uses of *Z. officinale* [185, 186].

A host of data supports that gingerols and shogaols possess both anticancer and chemopreventive activities. Evidence for the former suggestion came from their inhibitory effects on the proliferation, cell cycle progression, and viability of human carcinoma cell lines [187–197] and tumors implanted into laboratory animal [198, 199]. Suggestions for chemopreventive activities of these compounds came from their inhibitory effects on the development of cancer in animals treated with laboratory carcinogens [199–203]. Both activities may be mediated by multiple mechanisms including inhibition of invasion through activation of the nuclear receptor peroxisome proliferator-activated receptor γ (PPAR- γ) [197]; downregulation of matrix metalloproteinase 9 transcription [204]; suppression of tumor angiogenesis [191, 194]; deactivation of aberrant cell cycle-regulating elements [189, 200]; and interference with microtubule integrity [190, 196].



Figure 10.
The ginger *Zingiber officinale* Roscoe (Zingiberaceae) (from: <https://goo.gl/images/Tr2fgV>).

All these observations have led to the consideration of *Z. officinale* preparations for treating cancer as well as cancer-related complications such as chemotherapy-induced nausea and vomiting. So far, however, there is no scientific proof of clinical efficacy against either cancer [205] or nausea and vomiting resulting from chemotherapy or surgery [206].

5. Concluding remarks

The nine plants addressed in this chapter have a long traditional use in Suriname against various conditions including neoplastic disease and indeed showed some evidence of anticancer activity. However, in all cases, the evidence was limited to preclinical models and was not sufficient to support claims of clinical efficacy. However, this does not necessarily mean that these plants and their active constituents should be discarded as failed compounds. Some may constitute useful parts of an integrative medical approach for treating or preventing cancer. Others—including many mentioned in this chapter—may boost the immune system or improve overall health, well-being, and quality of life. And still others may help relieve some of the symptoms of cancer such as fatigue or reduce the side effects of chemotherapy and radiotherapy.

Converging lines of evidence lend support to these suppositions. Firstly, several phenolic compounds such as curcumin from the turmeric *Curcuma longa* L. (Zingiberaceae) and apigenin from the celery *Apium graveolens* L. (Apiaceae) may directly or indirectly exert cytotoxic and apoptotic effects by stimulating autophagy [207, 208]. Other plant phenols such as luteolin in celery, thyme, green peppers, and chamomile tea; epigallocatechin-3-gallate in Chinese green tea; and resveratrol in the skin of grapes, blueberries, raspberries, and mulberries have shown promise in the treatment and prevention of cancer [209–211]. These compounds are able to inactivate molecular signals and transcription pathways essential for cancer cells, scavenge harmful free radicals, and inhibit tumor angiogenesis, respectively [209–211].

Secondly, mistletoe extracts may alleviate cancer-related fatigue [212]; preparations from the holy basil *Ocimum sanctum* L. (Lamiaceae) may avert radiation-induced clastogenesis [213]; those based on *A. vera* may prevent or treat radiation-induced oral mucositis [214]; and the gingerols and shogaols in *Z. officinale* may reduce the cardiotoxicity of doxorubicin [215]. These compounds may exercise their protective effects through their anti-inflammatory, immunomodulating, free radical-scavenging, antioxidant, and/or metal-chelating properties [212–215].

Furthermore, recent advances in analytical and computational techniques as well as the introduction of innovative technologies such as predictive computational software may help employ apparently “useless” anticancer compounds in novel ways. For instance, the rejected tubulin-binding maytansines from *Maytenus* species (Celastraceae) may have found a new use as “warheads” attached to specific antitumor monoclonal antibodies in order to precisely attack tumor tissues while causing little toxicity [216]. And the discarded topoisomerase I inhibitor lapachol from the stem bark of the Surinam greenheart *Handroanthus serratifolius* (Vahl) S.O. Grose—also known as *Tabebuia serratifolia* (Vahl) G. Nicholson (Bignoniaceae)—is attracting renewed attention following reports that its inhibitory effect on melanoma cell proliferation may involve interference with glycolysis and decreasing ATP levels [217].

Likewise, the therapeutic index of gingerols in the treatment of breast cancer may improve when formulated as a PEGylated nanoliposomal form, allowing for high specificity, improved bioavailability, slow release, and low systemic toxicity [218]. And structural modifications of quassinoids on the basis of, for instance,

(quantitative) structure-activity relationships, may produce more potent and less toxic analogues [219, 220]. These and many other examples support continued assessment of the plants and their bioactive compounds dealt with in the current chapter for their usefulness against cancer. If only one of these compounds would reach the clinic, the efforts invested in their evaluation would have been worthwhile.

Conflict of interest

The authors declare that no conflict of interest exists.

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