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Traditional Plant-Based Forms of Treatment of Fungal Infections in Suriname

Phytochemical and Pharmacological Rationale

Authored by Dennis R.A. Mans

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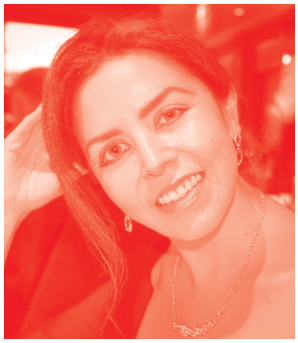

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Meet the author

Dennis R.A. Mans graduated in 1984 as a Medical Biologist in Utrecht, The Netherlands. He received his Ph.D. in 1991 at the Free University of Amsterdam, The Netherlands, with a thesis on the mechanism of action of etoposide. From 1992 to 2000, he was the head of the Preclinical Units of the South-American Office for Anticancer Drug Development and the Integrated Center for Cancer Research, both in Brazil. In 2000, he accepted an academic position at the Anton de Kom University of Suriname. In 2001, he became the head of the Pharmacology Department at the same university, where he is currently a full professor with a chair in Pharmacognosy.

Contents

Preface

Human beings have probably used naturally derived substances, particularly plant-derived substances, since their existence for managing and preventing disease. As a result, the ancient ethnopharmacological knowledge of the many forms of traditional medicine throughout the world has been recognized as an important source for obtaining new lead compounds for drug development programs. Indeed, important life-saving allopathic medicines such as cardiac glycoside digoxin, the oral hypoglycemic agent metformin, the antineoplastic agent paclitaxel, and artemisinin-derived antimalarials have been developed by scientifically exploring medicinal plants that have long been used in various traditional medical systems.

Similarly, the exploration of plants that are traditionally used in Suriname (South America) for treating fungal infections may well yield novel, more efficacious, and less toxic mainstream antifungal medicines. This information may also help validate the antifungal efficacy of traditional medicines in settings where allopathic drugs are not available. This book discusses nine plants that are commonly used in the Republic of Suriname against fungal infections.

Before discussing these plants, the book provides background information about fungi and Suriname. Section 1 outlines a few general features of the Fungi Kingdom. Section 2 describes the most prominent biological characteristics of fungi, including their cell structure (with an inner plasma membrane and an outer cell wall), body organization (comprising a single cell or multiple cells), mode of acquiring nutrition (through saprophytism, parasitism, or symbiosis), and means of reproduction (asexually, sexually, or both). It also addresses the current subdivision of the Fungi Kingdom into the phyla Microsporidia, Chytridiomycota, Blastocladiomycota, Neocallimastigomycota, Glomeromycota, Ascomycota, and Basidiomycota as well as the significance of fungi to humans. In the latter case, one should consider the contribution of fungi to medicine as well as modern households and industrial processes, for instance, in the form of β-lactam antibiotics and the use of baker's yeast for winemaking, baking, and brewing, respectively.

Section 3 discusses fungal infections and their differentiation into superficial, cutaneous, subcutaneous, and systemic (deep) lesions. Examples are pityriasis versicolor, tineas, sporotrichosis and intertriginous candidiasis, and opportunistic infections in immunocompromised individuals, respectively. This section furthermore addresses the worldwide occurrence of fungal infections and the number of fatalities they claim, as well as the five main classes of drugs for treating fungal infections, namely, the polyenes, azoles, allylamines, echinocandins, and the antimetabolite flucytosine.

Section 4 focuses on Suriname, providing some generalities about the country, its healthcare structure, and its most important health issues, before focusing on the fungal infections in the country. The main body of the book is presented in Section 5, where nine plants that are traditionally used in Suriname against fungal infections are extensively reviewed. The plants are *Colocasia esculenta* (taro), *Euphorbia hirta* (milkweed), *Ocimum tenuiflorum* (holy basil), *Persea americana* (avocado),

Punica granatum (pomegranate), *Virola surinamensis* (baboonwood), *Psidium guajava* (common guava), *Nigella sativa* (black caraway), and *Aegle marmelos* (bael tree). Section 6 concludes the book with an evaluation of the scientific status of the antifungal substances prepared from these plants and the potential of developing them into mainstream antifungal formulations.

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Chapter

Traditional Plant-Based Treatments of Fungal Infections in the Republic of Suriname (South America): Phytochemical and Pharmacological Rationales

Dennis R.A. Mans

Abstract

Fungi are unicellular or multicellular thick-walled eukaryotic organisms that are not capable of photosynthesis and are placed in a biological kingdom of their own. They are ubiquitous in our environment, and include tens of thousands, perhaps even millions of species of yeasts, rusts, smuts, mildews, molds, and mushrooms. Together with bacteria, fungi are the principal decomposers of plant materials such as cellulose and lignin, fulfilling vital ecological functions in all terrestrial habitats. Some species of fungi are also of major importance in households (for instance, as foods such as edible mushrooms), medicine (for instance, as producers of antibiotics such as penicillin), and industry (for instance, for making bread, wine, and cheese). About 300 fungal species cause infections in humans, varying from relatively harmless skin complaints such as pityriasis versicolor to potentially life-threatening systemic syndromes such as candidiasis. Fortunately, a broad armamentarium of efficacious antifungal drugs has been developed, ranging from topical nystatin to parenteral amphotericin B. In addition, most, if not all traditional medical systems throughout the world have identified a large assortment of plant-based remedies for treating these infections. This also holds true for the multi-ethnic and multicultural Republic of Suriname (South America), where plant-based traditional medicines are abundantly used, either alone or in conjunction with allopathic medications. This monograph extensively addresses nine plants that are traditionally used for treating fungal infections in Suriname, and explains the phytochemical and pharmacological rationales for these applications. These sections are preceded by some general observations about the Fungal Kingdom; a few words about the characteristics of fungi, their taxonomy, and their significance to humans; information about fungal infections as well as the available forms of treatment; and some details about Suriname including health aspects, the health care structure, and the main fungal infections in the country. The monograph is concluded with an evaluation of the status of the Surinamese herbal antifungal substances and the previsions of developing them into mainstream antifungal formulations.

Keywords: fungal infections, Suriname, medicinal plants, traditional uses, phytochemistry, pharmacology, antifungal activity

1. Introduction

The Fungal Kingdom encompasses a diverse and broad group of organisms that includes microscopic yeasts, as well as rusts, smuts, mildews, molds, and mushrooms. These organisms are neither plants nor animals and have been placed in a group of their own because of the distinct chemical composition of their plasma membrane and cell wall, their existence as unicellular and complex multicellular organisms, their heterotrophic lifestyle involving the intake of nutrients from other organisms for their metabolism, and their ability to reproduce both asexually and sexually [1]. Fungi are eukaryotic organisms believed to have descended from an ancestor they shared with animals that lived roughly a billion years ago [2]. The earliest fungal fossils are from the Ordovician, 460–455 million years ago [3], but some scientists believe that fungi may even be 3.5 billion years old [3]. Notably, the first vascular land plants only appeared approximately 425 million years ago, and fungi may have played an essential role in the colonization of land by these early plants [3].

Since their emergence, fungi have evolved into a major taxonomic kingdom. So far, about 150,000 species of fungal organisms have been described [4]. However, studies using molecular methods have estimated that the number of fungal species on Earth may amount to 3.5–5.1 million [5]. This number is probably comparable to that of all animal species on our planet and substantially more than that of all plant species in our biodiversity [5]. Fungi thrive in almost all habitats and are only surpassed by bacteria in their ability to withstand and adapt to extreme environmental conditions [6]. Tropical regions have the highest diversity of fungi [7], and finds of novel, unusual species in these regions are regularly reported. An example is the discovery of the ascomycete *Pseudotulostoma volvata* in the Guiana Shield described in 2001 [8]. In addition, exploration of deserts and arctic regions has yielded an unexpectedly large fungal diversity [9, 10].

Most fungi are free-living in nature, where they function—together with bacteria—as decomposers in the energy cycle, breaking down organic matter such as leaf litter, animal excrements, wood, and dead animals, and releasing carbon, oxygen, nitrogen, and phosphorus into the soil and the atmosphere to be used by other organisms [11]. This makes fungi vital for the health of ecosystems and the entire biodiversity. Furthermore, various fungal species were at the basis of commercially successful drugs. The common indoor fungus *Penicillium chrysogenum* produced penicillin, the first of a series of β-lactam antibiotics that revolutionized the medical world [12]. *Tolypocladium inflatum* parasitizes on insects and gave cyclosporine that is commonly used as an immunosuppressant after bone marrow and organ transplants [13]. And the specific HMG-CoA reductase-inhibiting statins were first discovered as secondary metabolites in the soil-borne fungus *Aspergillus terreus* and became important LDL-lowering compounds that reduce the risk of arterial blockage and developing a heart attack, stroke, and diabetes mellitus [14].

Other fungi such as the baker's or brewer's yeast *Saccharomyces cerevisiae*, along with various mushrooms, have been found useful as food. *Saccharomyces cerevisiae* converts carbohydrates into carbon dioxide and alcohols through fermentation. The products of this reaction have been used in baking and the production of alcoholic beverages for thousands of years [15]. *Saccharomyces cerevisiae* has also served as a model organism for studying human genetics including DNA sequences involved in disease and aging [16]. Notably, this fungal species was the first eukaryotic organism to have its genome completely sequenced [17]. Another landmark model fungal species for scientific research was the pink mold *Neurospora crassa*. Studies with this organism revealed for the first time that genes control the expression of enzymes and that one gene regulates one enzyme [18].

On the other hand, many fungi—such as molds on food or pathogenic spores—are less desirable. Currently, over 8000 fungal species are known to be detrimental to plants, causing, among others, smut and rust, and routinely destroying crops and plants such as beans, barley, and pine trees [4]. And around 300 fungi cause disease in humans [4]. Some, like yeast species in the genus *Malassezia* cause relatively harmless superficial infections such as pityriasis versicolor [19]. Others, however—like several yeast species in the genus *Candida*—are the causative agents of potentially fatal infections in immunocompromised individuals [20]. And certain species in the genus *Aspergillus* produce aflatoxins on improperly stored staple commodities such as peanuts, maize, rice, and cassava, which have been associated with liver cancer [21].

This monograph first presents some important characteristics and the taxonomy of fungi, clarifies the significance of fungi to humans, then deals with the different types of mycoses and their treatment; subsequently focuses on Suriname and elaborately addresses nine plants used for treating fungal infections in Suriname; and concludes with a few remarks on the importance of these plants for medicine.

2. Characteristics of fungi, their taxonomy, and their significance to humans

As mentioned above, fungi are eukaryotic, non-vascular, non-motile and heterotrophic organisms that include yeasts, rusts, smuts, mildews, molds, and mushrooms [22]. These organisms are classified under the Kingdom Fungi, next to the Kingdoms of bacteria, protists, plants, and animals [22]. Fungi are among the most widely distributed organisms on Earth [22]. Many are free-living in soil or water, performing essential ecological functions, while others form parasitic or symbiotic relationships with plants or animals [22]. A considerable number of species is also of great economic and medical importance [22]. Hereunder, a few notable characteristics of fungi are addressed, as well as some aspects of their taxonomy and their significance to humans.

2.1 Characteristics

Although, the numerous fungal species on Earth have widely diverse habitats and characteristics, they have some key aspects in common which make them sufficiently distinct from other organisms to place them in their own biological kingdom [22]. The main differences with the other kingdoms are differences in cell structure, body organization, mode of acquiring nutrition, and means of reproduction. The most important characteristics of the fungal kingdom have elaborately been reviewed in reference [22].

Firstly, fungi are eukaryotes and have their cells surrounded by an inner plasma membrane and an outer cell wall, similarly to bacterial cells and plant cells [23, 24]. However, in fungal cells, both these cellular constituents have a unique composition and distinct properties when compared to the members of the other biological kingdoms. The fungal cell wall contains adhesins and receptors which mediate the interactions of the organisms with the external environment [24]. Furthermore, it helps the organisms to maintain their structure, to protect the cells from various types of stress (particularly osmotic changes), and to guard the integrity of the cellular content [24]. Importantly, the fungal cell wall is mainly made up of glucans, chitin, and glycoproteins instead of cellulose as is the case with plant cells [24]. These ingredients are not present in human cells, providing the opportunity of selective antifungal therapies [24].

The plasma membrane of fungi contains, among others, transport proteins and proteins involved in signal transduction, cell wall and cytoskeleton synthesis, as well as various glycerophospholipids, sphingolipids, and sterols [23]. The main component of the fungal plasma membrane is the unique sterol ergosterol instead of cholesterol which is the major sterol in animal cells [23]. This distinction has therapeutically been exploited by identifying antifungal drugs that target ergosterol synthesis, perturbing the integrity of the fungal cell membrane [23].

Secondly, fungi can consist of a single cell as in the case of yeasts, or multiple cells as in the case of, for instance, mushrooms [22]. Yeasts such as the baker's or brewer's yeast *Saccharomyces cerevisiae* are estimated to constitute 1% of all described fungal species [25]. They have probably evolved from multicellular ancestors [26], and some species can develop multicellular characteristics by forming strings of connected budding cells known as pseudohyphae or false hyphae [27]. Yeast species typically measure 3–4 μm in diameter, but some can reach a size of 40 μm [28].

The majority of fungal species are multicellular and is generally known as molds. A few well-known species are those in the genera *Aspergillus* (commonly found on compost and other decaying vegetable matter as well as stored grain [29]), *Penicillium* (of major importance in food spoilage and food and drug production [30]), *Rhizopus* (found on decaying fruit and vegetables, animal feces, and old bread [31]), and *Trichophyton* (the causative agents of tineas such as athlete's foot, ringworm, jock itch, and similar infections of the nail, beard, skin and scalp [32]).

The cells of multicellular fungal species are grouped to form tubular, elongated, and filamentous structures called hyphae of 2–10 μm in diameter and up to several centimeters in length, and may contain multiple nuclei [22]. They extend by branching at their tips, and several hyphae mesh together to form the fungal body or mycelium [22]. There are in general specialized hyphal structures for nutrient uptake from living hosts such as the haustoria in most fungal phyla and the arbuscules of several mycorrhizal fungi [33]. Of note, some fungal species can exist as unicellular and multicellular forms, depending on the temperature [34]. An example of such a dimorphic fungus is *Talaromyces marneffei*, an important cause of opportunistic infections in individuals with HIV/AIDS-related immunodeficiency that grows as a mold at room temperature and as a yeast at human body temperature [35].

Furthermore, fungi lack chlorophyll and cannot conduct photosynthesis, acquiring food by absorbing nutrients from organic substances around them which they break down outside their body by digestive enzymes secreted from the tips of their hyphae [22]. Depending on the species, this occurs through saprophytism, parasitism, or symbiotic relationships. Saprophytic fungi feed on dead organic substances. Examples are species in the genera *Aspergillus* [29], *Penicillium* [30], and *Rhizopus* [31]. Parasitic fungi obtain their nutrition by living on other living organisms (plants or animals) and absorbing nutrients from their host. Examples are *Taphrina* which causes deformities in flowering plants such as leaf curl disease [36] and witches' brooms [37], as well as *Puccinia* that causes leaf rust in, among others, wheat [38]. And symbiotic fungi such as lichens and mycorrhiza have an interdependent relationship with other species in which both are mutually benefited. Lichens are the symbiotic association between algae and fungi [39]. A mycorrhiza is a symbiotic association between a green plant and a fungus. The plant makes organic molecules such as sugars by photosynthesis and supplies them to the fungus, and the fungus provides the plant with water and minerals from the soil such as phosphorus [40].

Lastly, fungi are capable of reproducing by both asexual and sexual means. Relatively simple, single-celled fungi like *Saccharomyces cerevisiae* reproduce vegetatively by budding [22, 41]. Other forms of vegetative reproduction in fungi are by fission or fragmentation [22, 41]. The majority of multicellular fungal species

reproduce asexually through the formation of diploid spores formed by mitosis and called conidia or zoospores or sporangiospores [22, 41]. However, in most mushrooms, puffballs, and toadstools, sexual reproduction takes place by spores (ascospores, basidiospores, and oospores) formed through meiosis [22, 41]. The haploid spores germinate into primary mycelia which form secondary mycelia when they come into contact with each other, after which the nuclei fuse and give rise to cells with the original number of chromosomes [22, 41]. On the other hand, in some fungi, the fusion of two haploid hyphae does not result in the formation of a diploid cell but first in the formation of an intermediate stage called the dikaryophase, which is followed by the formation of diploid cells [22, 41].

Sexual reproduction is an important source of genetic variability, allowing fungi to adapt to new environments. Another strategy of some fungi to generate genetic diversity—often because of stress such as antifungal therapy—is the formation of polyploid/aneuploid nuclei. Dimorphic fungi can switch between a yeast phase and a hyphal phase in response to environmental conditions. An example is the above-mentioned species *Talaromyces marneffei* [35], probably one of the world's most feared fungi that can cause potentially lethal talaromycosis [42]. This is a systemic opportunistic infection in immunocompromised individuals that is characterized by fever, skin lesions, anemia, generalized lymphadenopathy, and hepatomegaly [42].

2.2 Taxonomy

The taxonomy of fungi is regularly revised as novel molecular data and DNA comparisons allow for phylogenetic analyses that replace older classifications that mainly use morphological features and reproductive characteristics. Primarily based on the characteristics of sexual reproductive structures, the Fungal Kingdom is currently subdivided into seven phyla: the Microsporidia, the Chytridiomycota, the Blastocladiomycota, the Neocallimastigomycota, the Glomeromycota, the Ascomycota, and the Basidiomycota [43]. The Microsporidia are spore-forming unicellular endobiotic fungi of 1–40 μm that parasitize on animals and humans. Roughly 1500 of the known fungal species belong to this phylum. Several species such as members of the genera *Enterocytozoon* and *Encephalitozoon* can cause microsporidiosis in immunocompromised individuals, an opportunistic infection characterized by diarrhea and wasting [44].

The Chytridiomycota, commonly known as chytrids, encompasses approximately 900 identified species that can be encountered in a wide range of aquatic and terrestrial habitats throughout the world. They produce zoospores that are capable of active movement through aqueous phases with a single flagellum. Chytrids are saprobic, feeding on decayed organic matter. Some, like *Batrachochytrium dendrobatidis*, parasitize on animals. *Batrachochytrium dendrobatidis* is the causative agent of chytridiomycosis, an infectious disease that is responsible for dramatic declines and even extinctions in amphibian populations in many countries [45].

The Blastocladiomycota are also posteriorly uniflagellated zoosporic fungi that live as saprotrophs primarily in freshwater and soil, and they parasitize on all eukaryotic groups. At this moment, less than 200 species have been described. Whereas their close relatives, the chytrids, mostly exhibit zygotic meiosis (*i.e.*, meiosis of the zygote immediately after karyogamy, resulting in the production of several haploid cells), the blastocladiomycetes undergo sporic meiosis (*i.e.*, meiosis resulting in the production of haploid spores that can develop directly into new, haploid, individuals). A well-known species is *Paraphysoderma sedebokerense*, a highly destructive pathogen of algae grown in mass cultures for biofuels and pharmaceuticals [46].

The Neocallimastigomycota are anaerobic organisms that live in the digestive system of larger herbivorous mammals [47] as well as that of humans [48] where they play an essential role in the digestion of fibre. They are also closely related to chytrids and form zoospores that are posteriorly uniflagellate or polyflagellate. However, neocallimastigomycetes lack mitochondria but contain hydrogenosomes of mitochondrial origin. This phylum consists of about 20 species that are grouped in only one family, the Neocallimastigaceae. The type species is *Neocallimastix frontalis* that has been studied as a means of large-scale cellulase production [49].

The Glomeromycota include only one class, the Glomeromycetes, and contain approximately 230 described terrestrial species that are widely distributed in soils worldwide. All known Glomeromycota species reproduce asexually. Many form highly branched arbuscular mycorrhizas with the thalli of bryophytes and the roots of vascular land plants [50, 51]. These mutualistic relationships are beneficial for both participants, because the fungus acquires carbohydrates formed by the plant, and the plant acquires nitrogen, phosphorous, and other minerals produced by the fungus [50, 51]. One of the most distinctive features of glomeromycetes is the arbuscules, the points of exchange between fungus and plants [50, 51].

The Ascomycota, commonly known as sac fungi or ascomycetes, is the largest phylum in the fungal kingdom, harboring over 64,000 species. Members of this phylum reproduce sexually or meiotically via the production of non-motile ascospores inside a microscopic sac-like structure called an ascus, the defining feature of this group of fungi. Because the products of meiosis—the ascospores—are retained within the ascus, ascomycetes such as *Neurospora crassa* have been used—as mentioned before—for elucidating the principles of genetics and heredity [18]. Many species of Ascomycota also (or exclusively) produce spores called conidia through an asexual or mitotic process [52]. The Ascomycota include fungal species that are of particular importance as sources of antibiotics and for a variety of industrial applications, but also because of their pathogenicity towards humans, animals, and/or plants (see, for instance, references [53, 54]). A few examples are fission yeasts in the genus *Schizosaccharomyces*, the unicellular yeast genera *Saccharomyces* and *Candida*, as well as morels, some edible mushrooms, truffles, and various filamentous ascomycetes in the genera *Aspergillus*, *Penicillium*, *Fusarium*, and *Claviceps* [53, 54].

The Basidiomycota, also known as the club fungi or basidiomycetes, include mushrooms (such as the champignon mushroom *Agaricus bisporus*; **Figure 1**), puffballs, stinkhorns, bracket fungi, other polypores, jelly fungi, boletes, chanterelles, earth stars, smuts, bunts, rusts, mirror yeasts, and the human pathogenic yeast genus *Cryptococcus*. With over 31,500 species described species, this group is the second largest of the Fungal Kingdom and constitutes, together with the Ascomycota, the subkingdom Dikarya (often referred to as the 'higher fungi'). Well-known basidiomycetes are species in the genus *Puccinia* that cause rust in many economically important crops [55], *Ustilago maydis* that causes smut on maize [56], *Malassezia* yeasts that are mainly associated with certain skin conditions in humans [57], as well as the opportunistic human yeast *Cryptococcus neoformans* that usually infects the lungs or the central nervous system but sometimes also other parts of the body [58]. All Basidiomycota are filamentous fungi composed of hyphae (except for basidiomycota-yeast), and reproduce sexually via the formation of specialized club-shaped end cells called basidia that produce meiospores called basidiospores [59]. Another distinctive anatomical feature of this fungal phylum is the presence of clamp connections, hook-like structures which ensure that each hyphal cell or segment of hypha receives a set of different nuclei obtained through the mating of hyphae of differing sexual types to create genetic variation [60].

Figure 1.
The champignon mushroom Agaricus bisporus *(from: https://images.app.goo.gl/Ahbf55DQRixrBZfw6).*

2.3 Significance of fungi to humans

Humans have been aware of the existence of fungi—albeit indirectly in some cases—since they learned to prepare wine from grapes and bake bread. Ancient peoples were also familiar with the devastating effects of fungi on their crops but attributed these ravages to the wrath of the gods. The Romans had even designated a particular deity, Robigus, as the god of blight and wheat rust, and sacrificed a dog during the Robigalia, a festival held in his honor on April 25 to appease him and protect their grain fields from the disease [61]. Later, many devastating plant pathogenic fungal species have been identified. Examples are *Glomerella cingulata* that causes anthracnose (plant canker) and fruit rotting diseases on, among others, cereals, grasses, legumes, fruits, vegetables, perennial crops, and trees [62] (**Figure 2**); *Botrytis cinerea*, a necrotrophic fungus that is responsible for botrytis bunch rot or grey mould on wine grapes [63]; *Gibberella pulicaris*, a fungal pathogen that infects, among others, potato, strawberry, hop, and alfalfa [64]; and *Podosphaera fuliginea*, that causes powdery mildew on cucurbits [65].

Several fungal species also cause disease in humans. These are dealt with in the next section. On the other hand, various fungi have a long medicinal use and have been at the basis of many important therapeutics. For instance, 'Ötzi the ice man', who had lived between 3400 and 3100 BC during the Copper Age and had been found frozen in the Ötztal Alps (Austria) in 1991, carried pieces of fungus among his personal effects which he presumably had used to treat the parasites in his gastrointestinal tract [66]. Later, fungi made breakthrough contributions to medicine. A few notable examples have been given above and include the β-lactam antibiotics from *Penicillium chrysogenum* [12], the immune-suppressant drug cyclosporine

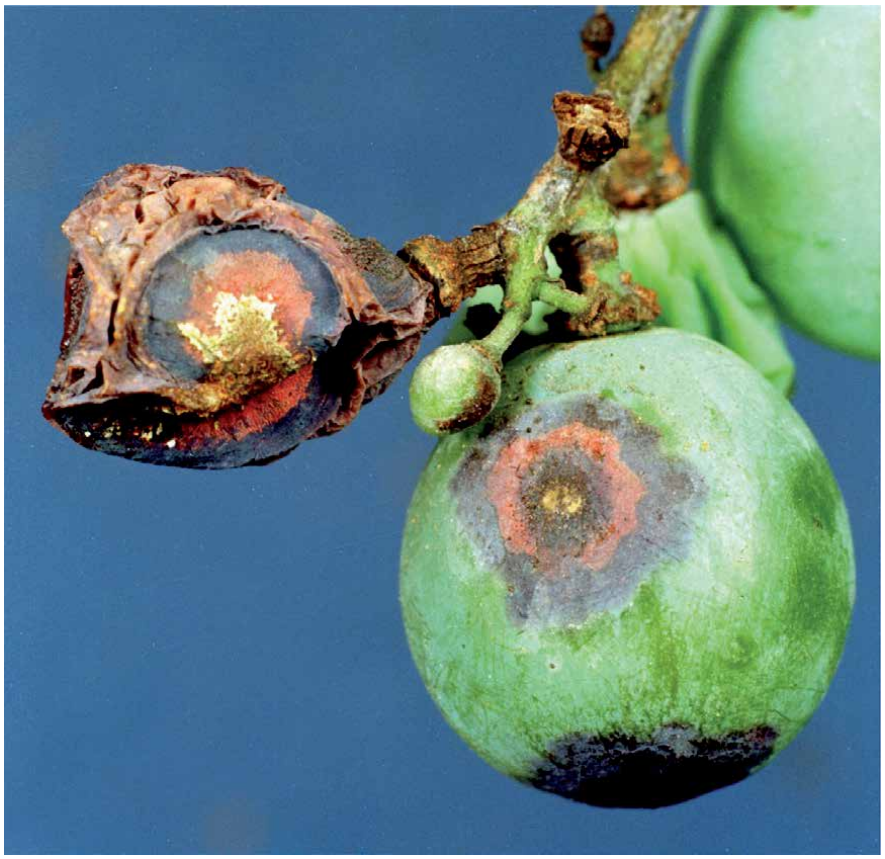

Figure 2.
Anthracnose on grapes caused by the plant pathogenic fungus Glomerella cingulata *(from: https://images.app.goo.gl/rBcDiAFTKCBwLQXH8).*

from *Tolypocladium inflatum* [13], and the blood cholesterol-lowering statins from *Aspergillus terreus* [14].

Other drugs of fungal origin are the oral antifungal agent griseofulvin from *Penicillium griseofulvum* that is efficacious against fungal infections of the skin, nails, and scalp [67]; micafungin, a synthetic analogue from a lead compound produced by *Coleophoma empetri* for treating invasive fungal infections including candidemia, abscesses, and esophageal candidiasis [68]; and sordarin and its analogues isolated from *Sordaria araneosa* that target protein synthesis and are active against yeasts and yeast-like fungi [69]. *Penicillium griseofulvum* occurs on cereals, nuts, and stored fruits [70], *Coleophoma empetri* causes cranberry fruit rot disease [71], and *Sordaria* species are commonly found in the feces of herbivores [72]. Furthermore, the polyketide zaragozic acid also known as squalestatin produced by common soil fungi in the genus *Phoma*—that includes species causing heart rot and blight of beets, and dry rot of sweet potato [73]—potently inhibited mammalian squalene synthase, the rate-limiting enzyme in sterol biosynthesis, thereby blocking cholesterol production to a comparable extent as statins [74].

As well, the sympathicomimetic ergot alkaloids produced by the ergot fungus *Claviceps purpurea* can constrict the blood vessels around the brain and are therefore very efficacious in relieving migraine headaches [75]. However, these compounds were responsible for dreadful epidemics of poisoning in the Middle Ages, when many individuals developed ergotism after the consumption of bread made from rye or wheat contaminated with this fungal species [76]. The syndrome

was popularly known as 'St. Anthony's fire' because it caused intensely painful burning sensations in the limbs and extremities, along with painful seizures and spasms, diarrhea, mental effects including mania or psychosis, headaches, nausea and vomiting, and eventually gangrene, neurological diseases, and death [76]. Due to its specific uterotonic activity, *Claviceps purpurea* was also used to speed up child deliveries but it claimed instead many additional fatalities [76].

Several 'domesticated' fungi have become essential in modern households and industrial processes. As mentioned above, *Saccharomyces cerevisiae* is instrumental in winemaking, baking, and brewing [15]. The trichocomaceous family members *Penicillium roqueforti* and *Penicillium camemberti* are indispensable for the proper ripening of the blue-veined sheep's milk cheese Roquefort and the cow's milk cheese Camembert, respectively [77]. The champignon mushroom *Agaricus bisporus* is one of the most widely consumed mushrooms in the world [78]. The morel mushroom *Morchella esculenta* and several species of truffles in the genus *Tuber* are highly appreciated items in haute cuisine [79]. And the mycoproteins derived from the mycelia of the filamentous soil fungus *Fusarium venenatum* serve as the starting materials for high-protein and high-fiber foods as alternatives to meat and substitutes for fat in dairy products and cereal in breakfast cereals and snacks [80].

Furthermore, to meet the increasing worldwide demands of citric acid, malic acid, and lactic acid, these compounds are currently produced by fermentation with *Aspergillus niger* and several species in the genera *Candida* [81], *Aspergillus* [82], and *Rhizopus* [83], respectively. Certain fungi are also industrially used to produce enzymes on a large scale. A few examples are lipases for the food, detergent, and pharmaceutical sectors [84]; cellulase for the production of cellulose as veterinary foods, wood and paper, fibers and clothes, cosmetics, and pharmaceutical excipients [85]; and amylases for the food, textile, paper, and detergent industries [86].

3. Fungal infections, epidemiology, and treatment

As mentioned before, there are tens of thousands if not millions of different species of fungus [1, 5]. Many live in air, soil, water, and plants, but some live naturally in the human body [1, 5]. And indeed, only a relative minority—about 300—is pathogenic to humans, and this usually occurs when the invading fungus takes over an area of the body and cannot be effectively dealt with by the immune system [20, 21]. Examples of common types of fungal infections in humans are athlete's foot, vaginal yeast infections, *Candida* toenail infections and diaper rash, jock itch, and ringworm [20, 21]. Familiar symptoms of many fungal infections include skin changes, redness, itching, and cracking or peeling skin [20, 21]. Fortunately, these infections are usually not very serious if treated promptly and properly [22, 23], often with over-the-counter or prescription creams [22, 23]. On the other hand, fungal infections are more severe in individuals with a weakened immune system [22, 23]. The same holds for fungal infections in people taking antibiotics [22, 23], undergoing treatment for cancer [22, 23], or suffering from diabetes mellitus [22, 23]. These infections may require additional methods of treatment [5, 6].

3.1 Types of fungal infections

Fungal infections or mycoses can be classified on the basis of the route of acquisition of the pathogen, the degree of virulence exhibited by the fungus, and the site of the infection [20, 21]. The route of acquisition of a fungal infection may either be exogenous or endogenous, i.e., resulting from airborne, cutaneous, or percutaneous fungi, or colonization by a member of the normal flora or reactivation of a previous

infection [20, 21]. With regards to the classification based on virulence, primary pathogens can establish infections in normal hosts while opportunistic pathogens cause disease in individuals with compromised host defense mechanisms [20, 21]. More often, fungal infections are classified by the site of the infection, *i.e.*, as superficial, cutaneous, subcutaneous, or systemic (deep) infections depending on the type and degree of tissue involvement and the host response to the pathogen [20, 21].

Superficial mycoses are fungal infections of the skin, hair, and nails that invade only the stratum corneum and the superficial layers of the skin and neither invade living tissue nor provoke an immune response by the host. A well-known superficial fungal infection is pityriasis versicolor, a condition characterized by light spots on the chest, back, upper arms, and legs that are usually caused by *Malassezia globosa*, a yeast species that normally lives in the pores of the skin [19].

Cutaneous mycoses (also referred to as dermatophytoses or dermatomycoses) are fungal infections of skin, hair, and nails that extend deeper into the epidermis and may evoke host immune responses that result in pathologic changes in the deeper layers of the skin. Common cutaneous mycoses are tinea corporis (ringworm of the body), tinea unguium or onychomycosis (fungal infection of the fingernails, toenails, and the nail bed; **Figure 3**), tinea pedis (athlete's foot), tinea cruris (jock itch), and tinea capitis (fungal infection of the scalp and hair) [87]. These conditions are rather common and are mostly caused by parasitic dermatophytes in the genus *Trichophyton*, in addition to the genera *Epidermophyton* and *Microsporum* [87]. Other widespread cutaneous fungal infections are oropharyngeal candidiasis (oral thrush) and vulvovaginal candidiasis, common fungal infection of the mouth and vagina caused by the opportunistic pathogenic yeast *Candida albicans* [88, 89]. A less frequent but distinctive fungal skin infection that is prevalent in tropical regions is caused by the yeast-like fungus *Lacazia loboi*, which is transmitted by direct contact with contaminated water, soil, vegetation, or an infected dolphin,

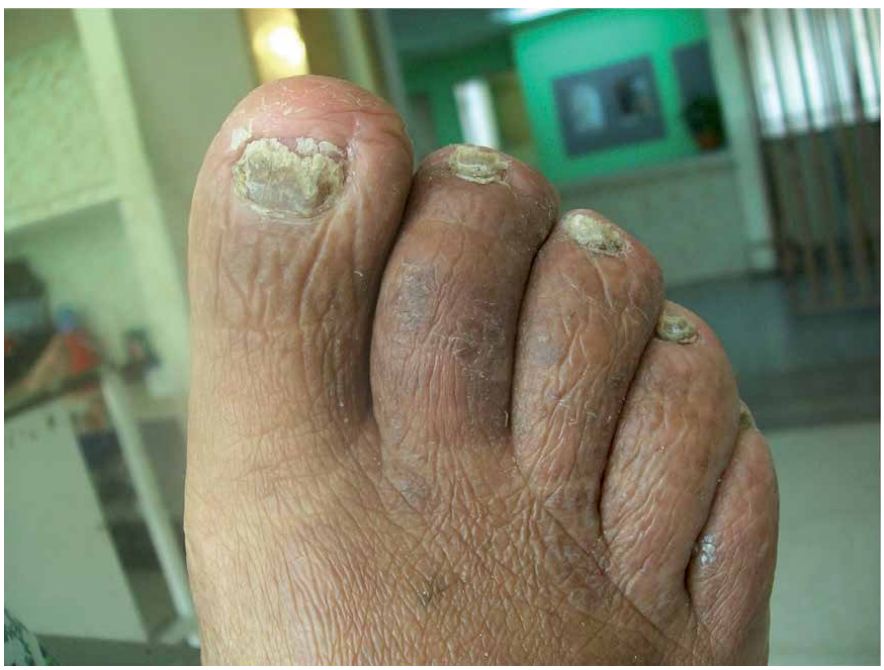

Figure 3.
Tinea unguium or onychomycosis mostly caused by dermatophytes in the genus Trichophyton *(from: https://upload.wikimedia.org/wikipedia/commons/5/57/Onychomycosis.JPG).*

and usually presents with bumps in the skin, firm swellings, deep skin lesions, or even malignant tumors [90].

Subcutaneous mycoses are chronic, localized fungal infections of the dermis, subcutaneous tissues, muscle, and fascia. These lesions are caused by a variety of soil saprophytes following trauma to the skin which allows the fungi to enter the body. Common subcutaneous mycoses are sporotrichosis (rose gardener's disease) caused by *Sporothrix schenkii* in soil and decomposing plant material [91], and intertriginous candidiasis, an opportunistic infection of the skin characterized by dermatitis, localized rashes, and/or yellowing of the nails caused by yeasts in the genus *Candida* [92]. Subcutaneous fungal infections are in general difficult to treat and may require surgical interventions such as debridement [20].

Systemic infections can be caused by primary pathogens or opportunistic pathogens. As mentioned above, systemic mycoses due to primary pathogens can occur in people with a normal immune system [20, 21]. They generally originate in the lungs, tend to develop at a slow rate, and may spread to the brain, heart, lungs, liver, spleen, and/or kidneys [20, 21]. Fungi that cause systemic mycoses are often dimorphic, inherently virulent, and can cause serious health problems. Examples of primary fungal infections are paracoccidioidomycosis (characterized by asymptomatic lung infection preceding in 5% of cases acute or subacute forms in children and young adults, and the chronic form in adults), coccidioidomycosis, and histoplasmosis, caused by soil fungi in the genera *Paracoccidioides* [93], *Coccidioides* [94], and *Histoplasma capsulatum* [95], respectively. These conditions primarily affect the respiratory organs, may remain asymptomatic, but may cause acute, subacute, or chronic infections [20, 21].

Systemic mycoses due to opportunistic pathogens are infections of patients with immunocompromising conditions who would otherwise not be infected [20, 21, 96]. Patients with a high risk of developing such invasive fungal infections are those suffering from HIV/AIDS, those with an altered flora caused by antibiotics, those suffering from diabetes mellitus, those undergoing chemotherapy for metastatic cancer or organ transplantation, and those undergoing major surgical procedures [20, 21, 96]. Common opportunistic mycoses are candidiasis, cryptococcosis, and aspergillosis [20, 21, 96]. Candidiasis is caused by species in the genus *Candida* (particularly *Candida albicans*) which normally live on the skin as well as in the mouth, throat, gut, and vagina, without causing any problems in healthy individuals [88, 89]. Cryptococcosis is a pulmonary or disseminated infection acquired by inhalation of soil or dried bird's feaces (particularly pigeon's) contaminated with the encapsulated yeasts *Cryptococcus neoformans* or *Cryptococcus gattii* [97]. And aspergillosis is caused by species in the ubiquitous genus of *Aspergillus* and also affects the respiratory system [98]. These fungal infections are in general rather aggressive, often rapidly spread to other organs, and can be life-threatening, while early diagnosis and efficacious treatment are in general difficult [20, 21, 96].

3.2 Epidemiology

Despite the astonishing number of fungal species, only some 300 are known to cause illness in humans. Nevertheless, the number of individuals on Earth having a fungal infection is astonishing [99]. Fortunately, many cases are aymptomatic to mild mucocutaneous infections rather than potentially life-threatening systemic infections [99]. Even so, nearly a billion people on our planet have skin, nail and hair fungal infections; tens of millions suffer from mucosal candidiasis; and more than 150 million fall victim to debilitating and potentially serious fungal diseases [99–102].

Among the latter conditions are roughly 3,000,000 cases of chronic pulmonary aspergillosis, about 223,100 cases of cryptococcal meningitis complicating HIV/AIDs, about 700,000 cases of invasive candidiasis, about 500,000 cases of

pneumocystis pneumonia, about 250,000 cases of invasive aspergillosis, about 100,000 cases of disseminated histoplasmosis, over 10,000,000 cases of fungal asthma, and about 1,000,000 cases of fungal keratitis per year [99–102]. Notably, over 1.6 million people die each year from their disease, which is comparable to the mortality due to tuberculosis and more than three-fold that caused by malaria [99]. These disturbingly high numbers are important causes of the emergence of the HIV/AIDS pandemic as well as the increasing incidence of chronic obstructive pulmonary disease and cancers, conditions that promote the virulence of opportunistic and potentially pathogenic fungi [103–105].

3.3 Treatment

The five main classes of drugs for treating fungal infections are polyenes, azoles, allylamines, echinocandins, and the antimetabolite flucytosine [22, 23]. Polyene antimycotics are macrolides derived from certain species of *Streptomyces* bacteria. These compounds bind to ergosterol in the fungal plasma membrane, perturbing membrane integrity and causing leakage of K^+ and Na^+ ions [106]. Well-known examples are nystatin from *Streptomyces noursei*, amphotericin B from *Streptomyces nodosus*, and natamycin from *Streptomyces natalensis* [106]. Nystatin is mainly used for the topical, oral, or intravaginal treatment of *Candida* infections including diaper rash, oral thrush, esophageal candidiasis, and vaginal yeast infections [106]. Amphotericin B is parenterally given against a broad range of invasive fungal infections such as aspergillosis, candidiasis, coccidioidomycosis, and cryptococcosis [106]. Natamycin is mainly used topically as cream and in eye drops for treating fungal infections of the eyelids, conjunctiva, and cornea [106].

Antifungal azoles are synthetic five-membered heterocyclic compounds that can be distinguished into imidazoles and triazoles. Imidazoles have two atoms of nitrogen in the azole ring, triazoles have three. The primary mechanism of action of these compounds is inhibition of lanosterol 14-α-demethylase, an enzyme required for the biosynthesis of ergosterol [107]. Imidazoles such as miconazole, ketoconazole, and clotrimazole are topically used for treating fungal infections of the skin and mucous membranes such as ringworm, pityriasis versicolor, vaginal yeast infections, oral thrush, dandruff, and diaper rash [107]. 'First-generation' triazoles such as fluconazole and itraconazole can be given both orally and intravenously against a range of superficial infections, but also against invasive fungal infections such as candidiasis, coccidiodomycosis, cryptococcosis, histoplasmosis, dermatophytosis, aspergillosus, and/or pityriasis versicolor [107]. 'Second-generation' triazoles such as voriconazole, posaconazole and ravuconazole have broad-spectrum activity against yeasts and molds including *Aspergillus* species, and are more potent and more active against resistant fungi when compared to their first-generation counterparts [107].

Allylamine antifungal compounds inhibit squalene epoxidase (one of the rate-limiting enzymes in sterol biosynthesis), resulting in the intracellular accumulation of toxic concentrations of squalene, depletion of ergosterol, and fungal cell death [108]. The two most important representatives of this class of antifungal compounds are naftifine and terbinafine. Naftifine is mainly used for the topical treatment of athlete's foot, jock itch, and ringworm [108]. Terbinafine, either taken by mouth or applied to the skin as a cream or ointment, is used to treat pityriasis versicolor, ringworm including jock itch and athlete's foot, as well as fungal nail infections [108]. Of note, terbinafine is the treatment of choice for fungal infection of the nails but is only efficacious in this condition when taken as oral tablets, not when used as a topical cream or ointment [108].

A more recent class of antifungal drugs is that of the semisynthetic echinocandin derivatives caspofungin, micafungin, and anidulafungin [109]. These

compounds act by inhibiting the synthesis of β-glucan in the fungal cell wall, preventing cross-linking of the cell wall components, perturbing the integrity of the cell wall [109]. Because of this mechanism of action, toxicity associated with echinocandins is infrequent (glucan is not found in mammalian cells) [109]. Furthermore, they are not metabolized by cytochrome P450 enzymes, which virtually excludes drug-drug interactions [109]. Echinocandins are administered intravenously, and are effective for treating (drug-resistant) mucosal and systemic *Candida* and *Aspergillus* infections [109].

The fluorinated cytosine analog 5-fluorocytosine or flucytosine is an antimetabolite that, following penetration through the fungal cell via cytosine permease, is intracellularly converted into 5-fluorouracil that perturbs DNA and RNA synthesis, resulting in the death of the fungus [110]. It was initially developed as an antineoplastic agent, but is now indicated in combination with amphotericin B for the treatment of septicemia, endocarditis and urinary system infections caused by *Candida* spp., as well as meningitis and pulmonary infections due to *Cryptococcus* spp. [110]. It can be used singly or with other antifungals for chromomycosis [109] and can be given orally or intravenously [110]. Chromomycosis (also known as chromoblastomycosis) is a chronic fungal infection that mainly occurs in subtropical and tropical areas and that is caused by traumatic inoculation of pigmented fungi (generally the ascomycetous soil saprotroph *Fonsecaea pedrosoi*) and is characterized by slow-growing, raised, crusted small nodular to papillary-like lesions of the skin and subcutaneous tissues [111].

4. Suriname: the country profile, health and health care, and fungal infections

Suriname is a presidential republic located on the northeast coast of South America, bordering the Atlantic Ocean to the north, French Guiana to the east, Brazil to the south, and Guyana to the west (**Figure 4**). Although, situated in South America, Suriname is considered a Caribbean country rather than a Latin American country [112]. The climate is tropical moderated by trade winds, with dry and rainy seasons [113]. The average daily temperature throughout the year varies between 21 and 32°C (70–90°F), the average annual percentage of humidity is 72.0%, and the yearly rain average is 2200 mm [113]. The capital city Paramaribo lies roughly 15 km from the Atlantic Ocean along the Suriname River. Paramaribo's historical center has been designated a World Heritage status by the United Nations Educational, Scientific, and Cultural Organization (UNESCO) in 2002 [114].

The country's land area of about 165,000 km^2 is divided into ten administrative districts [113, 115], and can be distinguished into northern urban-coastal and rural-coastal plains consisting of sandbanks and mudbanks as well as swampland, and a southern rural interior with mostly savanna grassland, rolling hills that rise to over 1000 m [113, 115], and dense, pristine, tropical rain forest with a great diversity of flora and fauna [116]. The relatively narrow urban-coastal area—that includes Paramaribo and its suburbs—harbors approximately 80% of the population of over 600,000 [113, 115]. The hinterland encompasses more than three-quarters of Suriname's land surface and is home to the remaining 20% of Suriname's inhabitants [113, 115]. The urban areas are characterized by a "western" lifestyle, modern health-care facilities, and an economy that is mainly based on commerce, services, and industry [113]. The rural societies have a more traditional way of living, lack comprehensive public health services, and have agriculture, forestry, crude oil drilling, bauxite and gold mining, as well as ecotourism as major economic activities [113].

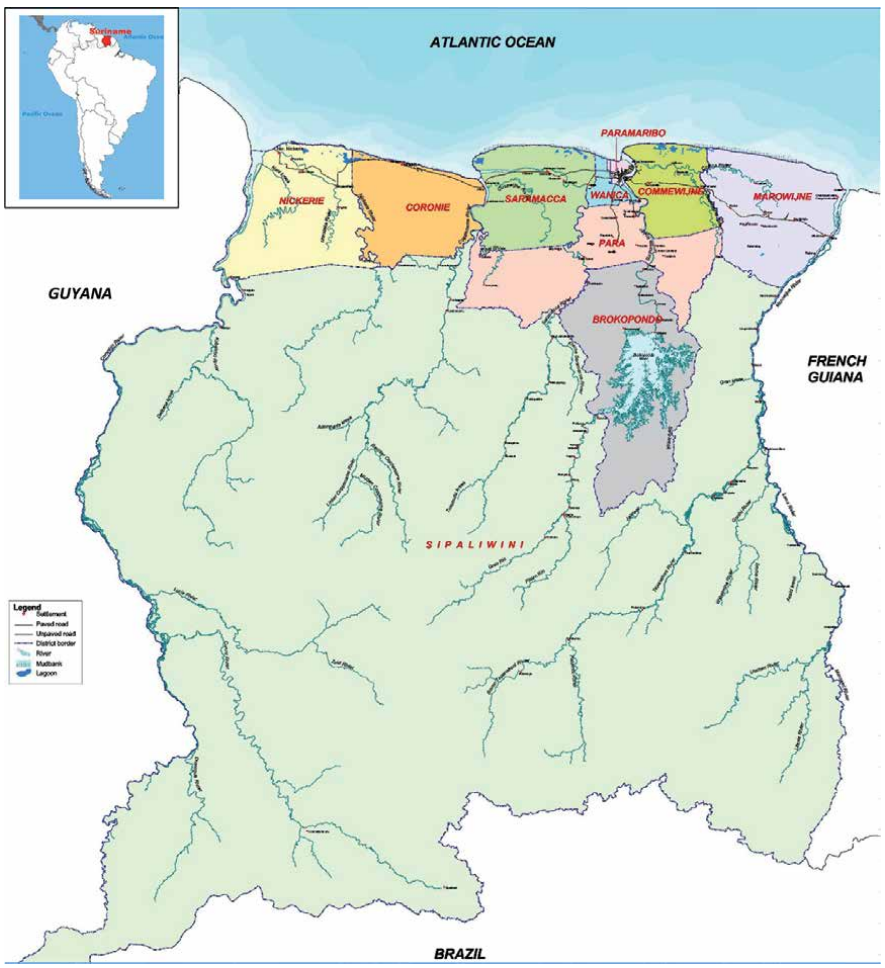

Figure 4.
Map of Suriname (from: https://images.app.goo.gl/nEEqreFZcJy1XHJz8). Insert: location of Suriname in South America (from: https://images.app.goo.gl/75w3iEDBm44i3W259).

The official language of government, business, media, and education is Dutch, reminiscent of the nearly 300 years Suriname was a colony under Dutch rule [117]. The common language is Surinamese or Sranantongo has evolved from an English- and Portuguese-based lingua franca in the seventeenth century to a language with its own official orthography [117]. Suriname's economy is dominated by the mining industry, with oil and gold accounting for approximately 85% of exports and 27% of government revenues [118]. Other means of sustenance are agriculture, fisheries, forestry, and ecotourism [118]. These activities have led to a gross domestic product (GDP) in 2019 of USD 4221 billion and an average gross national income per capita in that year of USD 6340 [118, 119]. This positions Suriname on the World Bank's list of upper-middle-income economies [119].

Suriname's population is among the most varied in the world, comprising the Indigenous Amerindians, the original inhabitants; descendants from enslaved Africans imported between the seventeenth and the nineteenth century (called Maroons and Creoles); descendants from indentured workers from China, India (called Hindustanis), and the island of Java, Indonesia (called Javanese) who had been attracted between the second half of the nineteenth century and the first half of the twentieth century; descendants from settlers from several European and Middle Eastern countries; and more recently, immigrants from various Latin

American and Caribbean countries including Brazil, Guyana, French Guiana, Haiti, and Cuba [115, 120, 121]. According to the 2012-census, the largest groups are represented by the Hindustanis, Maroons, Creoles, and Javanese, making up roughly 27, 22, 17, and 16%, respectively, of the total Surinamese population [115, 122].

4.1 Health and health care in Suriname

Like most other South American and Caribbean countries [123], Suriname can be characterized as a demographically transitioning country with declining mortality and infertility rates as well as a growing and aging population [124, 125]. These changes are for an important part attributable to considerable progress in health care, nutrition, sanitation, and drinking water quality; the eradication of various infectious diseases including malaria; as well as improvements in average living and working conditions, education, and income [124, 125]. The result was a decline of the death rate from 24 per 1000 in 1923 to 8 per 1000 in 2017 and the attainment of an average life expectancy of 72 years in 2019 [126]. The latter estimate is slightly below those for the rest of South America [126].

On the other hand, as also seen in many demographically transitioning countries [123], during the past decades, non-communicable diseases (NCDs) have largely replaced infectious diseases as the most important causes of morbidity and mortality in Suriname [127, 128]. According to estimates of the World Health Organization, cardiovascular ailments, cancer, and diabetes mellitus, along with their complications, were among the leading causes of morbidity and mortality in Suriname in 2014 [127]. Notably, 68% of the total number of deaths in the country in that year were attributable to these NCDs [127], and the probability of dying from these conditions between age 30 and 70 years was estimated at 14% [127]. These NCDs were also among the main causes of mortality in 2012–2013, accounting for almost 1000 cases or about one-third of the total number of 3260 deaths in that period [127, 128]. Nevertheless, Suriname is not entirely free from infectious diseases, important ones being bacterial and protozoal diarrhea, hepatitis A, and typhoid fever; vector-borne diseases such as dengue fever and chikungunya; and more recently, HIV/AIDS and covid-19 [129, 130]. The fungal infections in Suriname are addressed further in this section.

The responsibility of all aspects of health care in Suriname is in the hands of the Minister of Health and the Director of Health (the Chief Medical Officer) [131]. About 6% of the country's GDP is available for this purpose [119]. This sum covers, among others, the health costs for the economically weakest individuals, insurance for government employees and employees of government-related companies, as well as import and distribution of essential pharmaceuticals [131]. Specialized institutions under the responsibility of the Ministry of Health are the Regional Health Services and the Medical Mission [131]. The Regional Health Services run about forty community health centers in Suriname's coastal area and are, together with approximately 250 general practitioners, responsible for primary care in that part of Suriname [131]. The Medical Mission is a non-governmental organization that provides health services to people in the country's hinterland through a network of almost fifty clinics spread over the interior [131].

These institutions are supported by the Dermatology Services, the Office of Public Health, and Stichting Lobi Health Center [19]. The Dermatology Services is a governmental institution that specifically deals with dermatological diseases, sexually transmitted diseases, and HIV/AIDS [131]. The Office of Public Health is also government-owned and is principally involved in programs to prevent and fight parasitic and microbial diseases [131]. Stichting Lobi Health Center is a non-governmental organization for Sexual and Reproductive Health Services [131].

Secondary care is provided by two private and two government-supported hospitals in Paramaribo and one public hospital in the western district of Nickerie [131]. All hospitals have modern clinical laboratory facilities at their disposal including a microbial culture laboratory at the Academic Hospital Paramaribo [131]. There are, in addition, four private clinical laboratories and three private radiology clinics in Suriname [131]. The Academic Hospital Paramaribo also functions as a training facility for both general practitioners and medical specialists, and provides tertiary care at, among others, a Thorax Center, a Neurology High-Care Unit, and a Neonatal Care Unit [131].

4.2 Fungal infections in Suriname

Until now, there is no registry of fungal and other infections in Suriname, and only a relative handful of scientific papers have addressed these topics. As a result, there are no accurate data available about either the prevalence and incidence of, and mortality due to mycoses in the country. Still, according to several general practitioners, dermatologists, gynecologists, infectologists, and epidemiologists, rather prevalent mycoses in Suriname are infections of the skin and mucous membranes caused by *Malassezia* spp., those due to *Candida* spp., as well as tineas caused by dermatophytic fungi in the genera *Trichophyton*, *Epidermophyton*, and *Microsporum*. These infections mainly include pityriasis versicolor (called '*lota*' in Suriname); infections of the mouth, throat, gut, and vagina; ringworm; infections of fingernails, toenails, and nail bed; athlete's foot; jock itch; as well as infections of scalp and hair [132, 133], and are treated according to the standard medical protocols addressed in the previous section of this monograph [134, 135].

In addition, a relatively recent overview of infectious diseases of Suriname [136] has mentioned the occurrence in the country of chromomycosis, cryptococcosis, dermatophytosis, histoplasmosis, lobomycosis, as well as invasive fungal infections. As mentioned before, chromomycosis or chromoblastomycosis is a chronic fungal infection of the skin and subcutaneous tissues that is caused by traumatic inoculation of pigmented fungi (often *Fonsecaea pedrosoi*) [111]; cryptococcosis is a pulmonary or disseminated infection acquired by inhalation of soil or dried pigeon feces contaminated with the encapsulated yeasts *Cryptococcus neoformans* or *Cryptococcus gattii* [97]; dermatophytoses are tineas that affect hair, skin, or nails and are most commonly caused by the dermatophytic mold *Trichophyton* genus [87]; histoplasmosis is caused by inhaling spores of the dimorphic fungus *Histoplasma capsulatum* that is often found in bird and bat droppings [95]; and lobomycosis is a skin infection that is caused by the yeast-like fungus *Lacazia loboi* and is transmitted by direct contact with contaminated water, soil, vegetation, or an infected dolphin [90].

Invasive fungal infections reported in Suriname are those involving major syndromes such as candidiasis, blastomycosis, and histoplasmosis [136]. These conditions are often life-threatening and are in general seen in critically ill, aged patients as well as immunosuppressed individuals such as those suffering from AIDS and recipients of transplanted abdominal organs [137]. Invasive candidiasis occurs when endogenous *Candida* organisms that are normally found in the digestive tract, enter the bloodstream, spread through the body, and damage the heart, brain, eyes, bones, and other parts of the body [138]. Blastomycosis is mainly caused by the thermally dimorphic fungi *Blastomyces dermatitidis* and *Blastomyces gilchristii* which cause pneumonia and disseminated disease following inhalation of mycelial fragments and spores [139]. Disseminated histoplasmosis occurs—as indicated in the preceding alinea—after inhaling the spores of *Histoplasma capsulatum* from droppings of birds and bats, and develops progressively, spreading from the lungs to other organs through the bloodstream, and affecting multiple organs [140]. This syndrome is

not uncommon in Suriname, where it has particularly been associated with immunocompromised patients suffering from HIV/AIDS [141]. These infections are also treated as mentioned before in this monograph. Incidentally, an assessment of six families and fifteen genera by the Zoological Collection of Suriname suggested that the amphibian skin disease chytridiomycosis, caused by the pathogenetic fungus *Batrachochytrium dendrobatidis*, is not present in the country [142].

5. Traditional herbal treatments of fungal infections in Suriname

Despite the availability of affordable and accessible health care [131], traditional medicines are abundantly used in Suriname [143]. The various ethnic groups of Suriname have largely preserved their beliefs, values, behaviors, language, religion, ancestry, and other characteristics, including much of their specific ethnopharmacological traditions [120, 131]. This probably was a means of strengthening the ethnic identity during the secluded lifestyle the former colonial authorities had forced them into [120, 131]. As a result, the use of various forms of traditional medicine is deeply rooted in the entire Surinamese population [143]. Consequently, many diseases are often treated with traditional plant-based medicines instead of, or together with prescription drugs [143]. This also holds for several fungal infections, particularly the relatively mild superficial and cutaneous mycoses.

All ethnic groups in Suriname have made important contributions to the traditional treatment of mycoses. The Indigenous Trio Amerindians recognize various skin infections including those from the fungal origin, and have identified medicinal plants for treating these conditions [144]. Maroon and Creole females regularly use genital steam baths for their personal hygiene [145], but presumably also to prevent and treat vaginal candidiasis [145]. Chinese traditional healers have prescribed curcumin, the yellow-colored secondary metabolite in the turmeric *Curcuma longa* L. (Zingiberaceae), for centuries against fungal infections [146]. Practitioners of Indian Ayurveda, Unani, and Siddha are for over two millennia familiar with the antifungal properties of the neem tree *Azadirachta indica* A. Juss., 1830 (Meliaceae) [147]. And Javanese Jamu has recognized centuries ago the apparent efficacy of the rhizomes from the blue ginger *Alpinia galanga* (L.) Willd. (Zingiberaceae) against pityriasis versicolor [148].

The next sections address nine plants that have less thoroughly been evaluated in the scientific literature but are commonly used in Suriname for treating fungal infections. The plants have been selected from several comprehensive publications describing various aspects of medicinal plants in the country [148–155]. Their relevant aspects have been summarized in **Table 1**. Hereunder, the plants have in detail been assessed for their phytochemical and pharmacological properties, to support their traditional use against fungal infections.

5.1 Araceae—*Colocasia esculenta* (L.) Schott

The taro *Colocasia esculent*a (L.) Schott. is believed to originate from south-eastern Asia (hence its Surinamese vernacular name '*snesi taya*' meaning 'Chinese taro'), but is now grown in many tropical regions including Suriname for its edible, starchy corm. The plant bears characteristic large green leaves which resemble elephant ears (**Figure 5**) and have long, erect petioles of 40–200 cm tall growing in clusters from a large, tuberous rootstock. *C. esculenta* is presumably one of the earliest plants human beings have started to cultivate and has become one the most extensively grown members of the plant family Araceae. Similarly to yam, *C. esculenta* corm is an important food staple in many African, Oceanic, and South Asian cultures. The

Plant family	**Plant species (vernacular name in English; Surinamese)**	**Part(s) Used**	**Presumed active constituent(s)**	**Antifungal activity [references]**
Araceae	*Colocasia esculenta* (L.) Schott. (taro; snesi taya)	Leaf Corm	Flavonoids Phytosteroids	*Aspergillus niger*, *Candida albica*ns [156] *Athelia rolfsii* [157]
Euphorbiaceae	*Euphorbia hirta* L. (milkweed; sabana merkiwiwiri)	Leaf Flower Root Shoots Stem, stem latex Aerial parts Whole plant	Tannins Flavonoids Alkaloids Glycosides Proteins Sterols Saponins	*Aspergillus* spp., *Fusarium* spp., *Trichophyto*n spp. [158–163] *Saccharomyces cerevisia*e [164] *Colletotrichum capsici*, *Lasiodiplodia theob*romae, *Phomopsis caricae-papaya*e [160] *Rhizopus oryza*e [161, 163] *Candida albicans* [165, 166]
Lamiaceae	*Ocimum tenuiflorum* L. (holy basil; tulsi)	Leaf, leaf essential oil Root	Eugenol; linalool	*Alternaria* spp. *Aspergillus* spp., *Penicillium chrysogenu*m [167–169]. *Candida* spp. [169, 170] *Trichophyton* spp., *Microsporum* spp., *Epidermophyton floccosum* [171] *Fusarium oxysorum*, *Cochliobolus lunatus*, *Rhizoctonia solani* [169]
Lauraceae	*Persea americana* Mill. (avocado; afkati)	Seed, epicarp Flesh of unripe fruit, peel Leaf	Persin 1-acetoxy-2,4-dihydroxy-n-heptadeca-16-ene and 1-acetoxy-2-hydroxy-4-oxo-heneicosa-12,15-diene	*Candida* spp. [172–174] *Cryptococcus neoformans* [175, 176] *Malassezia pachydermatis* in dogs [177] *Zygosaccharomyces bailii* [178] *Rhizopus stolonifera*, *Botryodiploidia theobromae*, *Fusarium oxysporum*, *Geothricum candidum* [179] *Aspergillus* spp. [179, 180] *Colletotrichum gloeosporioides* [181–183]

Plant family	Plant species (vernacular name in English; Surinamese)	Part(s) Used	Presumed active constituent(s)	Antifungal activity [references]
Lythraceae	*Punica granatum* L. (pome granate; granaatappel)	Fruit, fruit peel, fruit juice Seed	Phenolic compounds	*Aspergillus fumigatus* [184] *Candida* spp. [184, 185] including *Candid*a associated with denture stomatitis [186] *Mucor indicus*, *Penicillium citrinum*, *Rhizopus oryzae*, *Trichoderma rees*ei [187] Various dermatophytic fungi [188] *Botrytis cinerea* [185, 186, 188–192] *Pyricularia oryzae*, *Colletotrichum falcatum*, *Dreschlera rostrata*, *Curvularia lunata* [188] *Penicillium digitatum* [190] *Fusarium sambucinum* [193]
Myristicaceae	*Virola surinamensis* (Rol. ex Rottb.) Warb. (baboonwood; babunudu)	Root Stembark Leaf Seed	Flavonoids; (neo)lignans; capric acid	*Cladosporium cladosporioides* [194] *Candida* spp. [195, 196] *Microsporum gypseum* [197]
Myrtaceae	*Psidium guajava* L. (common guava; guyaba)	Leaf Ripe fruit Bark Twigs	Phenolic compounds (tannins, coumarins, flavonoids), terpenoids	*Candida* spp., *Saccharomyces* spp., *Cryptococcus* spp., *Trichosporon* spp., *Aspergillus* spp., *Sporothrix* spp., *Microsporum* spp., *Trichosporon* spp. [198–205] *Arthrinium sacchari*, *Chaetomium funicol*a [206]
Rananculaceae	*Nigella sativa* L. black caraway; zwarte komijn	Seed, seed essential oil	Peptidergic defensins Ns-D1 and Ns-D2	*Aspergillus* spp., *Curvularia* spp., *Microsporum* spp., *Penicillium* spp., *Trichoderm*a spp., *Candid*a spp., *Chaetomium* spp., *Fusarium* spp., *Trichophyton* spp., *Chrysosporium* spp. [207–216] Various dermatophytic fungi [217, 218]

Plant family	Plant species (vernacular name in English; Surinamese)	Part(s) Used	Presumed active constituent(s)	Antifungal activity [references]
Rutaceae	*Aegle marmelos* (L.) Corrêa (golden apple; bel	Leaf, leaf essential oil Fruit	Terpenoids	Various dermatophytic fungi [219–227] *Fusariu*m spp. [227, 228] *Trichophyton* spp., *Microsporum* spp., *Epidermophyton* spp. [181, 229–233]. *Pythium deharyanum* [183] *Aspergillu*s spp., *Epidermophyton floccosum*, *Candida albicans* [229–233]

References are placed between [ ].

Table 1.
Plants with antifungal activity addressed in this section, parts preferentially used, presumed antifungal constituents, and proven antifungal activity.

corm can be roasted, baked, or boiled, and is also used for baby food. Furthermore, the nutritious young leaves and stems are eaten after the pungent flavor and the stinging and burning calcium oxalate- or calcium carbonate-containing raphides [234] have been removed by boiling twice or by steeping overnight in cold water.

C. esculenta corm, leaf, leaf sap, and stem are traditionally used for treating a variety of conditions such as parasitic infections; asthma; diabetes mellitus;

Figure 5.
The taro Colocasia esculenta *(L.) Schott. (Araceae) (from: https://images.app.goo.gl/HH8Zt3mnRgyfVqhSA).*

hypertension; neurological disorders; arthritis and other inflammatory disorders; body ache; amenorrhea; stomach problems and liver ailments; internal haemorrhages; cysts, boils, and wounds; baldness; as well as bacterial infections including conjunctivitis [235, 236]. In Suriname, a raw peeled corm is eaten with salt against jaundice [153]; the grated whole plant is made into an ointment for treating skin conditions including acute dermatitis that may be caused by *Malassezia* yeasts [237]; the stem is rubbed between the toes to treat fungal infections such as tinea pedis after the raphides have been broken down by heating [148]; and the corm is used as an ingredient of genital steam baths to recuperate the uterus post-partum and treat vulvovaginal candidiasis [155].

The results from several pharmacological studies provided support for some of these traditional uses. Aqueous and ethanolic leaf extracts decreased blood glucose levels in alloxan-induced diabetic rats to a comparable degree as the oral hypoglycemic medication metformin [238]. Cooked corm decreased tissue cholesterol and triglycerides in cholesterol-fed rats [239]. Ethanolic leaf extracts exerted anti-inflammatory activity, inhibiting carrageenan-induced hind paw edema, carrageenan-induced pleurisy, and cotton pellet-induced granuloma in Wistar rats [240]. Ethanolic corm extracts elicited hepatoprotective effects in paracetamol- and carbon tetrachloride-treated laboratory rats [241] while ethanolic leaf extracts had similar effects in precision-cut liver slices from rats [242]. And aqueous and ethanolic leaf extracts showed anthelmintic activity against earthworms [243].

Several studies also reported antimicrobial activity of *C. esculenta* including antifungal activity. For instance, an aqueous extract of the leaves displayed remarkable *in vitro* activity against various bacterial strains as well as the common food contaminant *Aspergillus niger* and the opportunistic pathogenic gastrointestinal yeast *Candida albicans* when compared to the reference compounds chloramphenicol and rifampicine [156]. Incidentally, a chloroform extract of *C. esculenta* leaf also showed antibacterial activity in an evaluation of fifteen coastal medicinal plants for antibacterial activity against bacterial fish pathogens [244]. Furthermore, comparing 130 ethanol extracts of lyophilized vegetables for inhibitory activity on recombinant human lanosterol synthase activity in a cell-free assay, a *C. esculenta* corm preparation showed the highest activity [245]. This is of relevance when considering the key role of lanosterol synthase in the viability of fungi [246].

A wide range of chemical compounds including flavonoids, β-sitosterol, and steroids have been isolated from *C. esculenta* [235, 236]. Still, there are no clear indications about the biochemical identity of the antifungal compound in this plant. However, in a study with the phytopathogenic crust fungus *Athelia rolfsii*—the causative agent of southern blight in many crops including tomato, onion, snapbean, and pea—the antifungal activity could be related to a phytocystatin in the corm that potently inhibited cysteine protease [157]. The phytocystatin inhibited mycelium growth and lyzed sclerotia by acting against the endogenous cysteine proteinase in the mycelia [157]. Notably, the inhibition of exogenous proteinases by phytocystatins have been suggested to represent a defense mechanism of plants against, among others, pathogenic fungi [247].

5.2 Euphorbiaceae—*Euphorbia hirta* L

The milkweed *Euphorbia hirta* L. (**Figure 6**) is a pantropical weed that is presumably native to India but is now encountered in many tropical parts of the world in gardens, abandoned estates, open grasslands, and along roadsides. It can grow up to 60 cm tall and has a solid, hairy stem. The vernacular name 'milkweed' stems from the white latex the stem produces when damaged, a characteristic shared by most plants in the genus *Euphorbia* [248]. This distinctive feature is also reflected by

Figure 6.
The milkweed Euphorbia hirta *L. (Euphorbiaceae) (from: https://images.app.goo.gl/1HjVzdfUghX9AyiH7).*

the Surinamese vernacular name '*sabana merkiwiwiri*' that means 'the herb from the savanna that emits a milky substance'. The latex is believed to represent a deterrent to herbivores, is rather toxic, and is used as an ingredient of arrow poisons and antimicrobial substances [249].

E. hirta has also been named 'asthma-plant' because of the traditional use of preparations from the leaf against asthma, bronchitis, and hay fever [250]. Preparations from various parts of the plant are, furthermore, traditionally used for treating, among others, gastrointestinal disorders; worm infestations; hypertension; genito-urinary conditions including kidney stones; diabetes mellitus; lactation insufficiency; conjunctivitis; several skin diseases as well as swellings and boils; and as a gargle for oral thrush [155, 251, 252]. In Suriname, *E. hirta* is used, in addition, as an essential ingredient of vaginal steam baths, in herbal baths to make child delivery proceed smoothly, and as an ingredient of cleansing baths to protect against evil forces [155].

Pharmacological studies with various laboratory models supported the traditional claims of *E. hirta* preparations against asthma [251], diarrhea [253], bowel cramps [254], hypertension [255], and diabetes mellitus [256], and as a diuretic [257]. There was also preclinical evidence for sedative and anxiolytic activity [258]; analgesic, antipyretic, and anti-inflammatory effects [259, 260]; as well as anti-amoebic [254] and antimalarial actions [261, 262]. Several of these effects have been associated with the presence in the plant of polyphenolic compounds such as quercitin [253, 254, 263, 264]. In addition, preparations from several of its parts exhibited meaningful and broad antibacterial activity in laboratory assays (see, for instance, references [158, 164, 165] including some activity against *Helicobacter pylori* [265].

There is also ample evidence for antifungal activity of *E. hirta*. For instance, aqueous extracts from the leaf inhibited aflatoxin contamination of rice, wheat, maize, and mustard crops by the cosmopolitan saprotrophic and pathogenic fungus *Aspergillus flavus* [159] and the growth of *Saccharomyces cerevisiae* in culture [164]. Ethanolic leaf extracts displayed meaningful activity against the plant pathogenic molds *Colletotrichum capsici*, *Fusarium pallidoroseum*, *Lasiodiplodia theobromae*, and *Phomopsis caricae-papayae* [160] as well as *Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus flavus*, and *Rhizopus oryzae* [161]. Importantly, some combinations of a methanol extract of the leaf and nystatin exhibited synergistic activity against clinical isolates of *Candida albicans* [266].

A preparation from the whole plant also inhibited aflatoxin production by *Aspergillus flavus* [162], while methanolic and acetonic extracts from the whole plant and the latex from the stem showed meaningful activity against *Aspergillus flavus*; *Fusarium incarnatum* that affects crops such as sorghum, rice, and maize; as well as *Trichophyton* spp., the causative agents of athlete's foot, ringworm, jock itch, and similar infections of nail, beard, skin and scalp [158]. Furthermore, ethanolic extracts of the aerial parts of the plant were active against *Aspergillus niger*, *Aspergillus fumigatus*, *Aspergillus flavus*, and *Rhizopus oryzae* [163]; methanolic extracts of leaf, flower, stem, and root were active against *Candida albicans* [166]; and water extracts of the root and shoots were active against a clinical isolate of *Candida albicans*, although not against *Penicillium* spp., *Aspergillus* spp., and *Microsporum* spp. [165].

So far, only a few studies have assessed the ingredient(s) and/or the mechanism(s) involved in the antifungal activity of *E. hirta* preparations. For instance, the antimicrobial activity of the crude plant extract has been attributed to tannins, flavonoids, alkaloids, glycosides, proteins, sterols, and/or saponins [163]. Nevertheless, these observations support the use of *E. hirta* in traditional medicine against certain fungal infections, providing a possible explanation for the use of a decoction of fresh leaves as a treatment for oral thrush [251] and in genital steam baths for cleansing the vagina from, among others, fungal infections [155].

5.3 Lamiaceae—*Ocimum tenuiflorum* L

Ocimum tenuiflorum L. (**Figure 7**), commonly known as holy basil or *tulsi* in Surinamese-Hindi or *Sarnami*, is a perennial plant growing between 30 and 100 cm tall that is particularly valued for its strong-scented and sharp-tasting but edible leaves. It is native to India but has spread throughout the south-eastern parts of Asia as a cultivated plant, and is also grown in various other tropical parts of the world with an Indian diaspora such as Suriname. As indicated by the vernacular 'holy basil', it is a sacred plant in Hinduism and is widely grown around Hindu houses and temples for its perceived protective influence [267]. Leaf preparations are regarded as 'elixirs of life' and believed to promote longevity [267], and the flowers are used as a holy cleanser for food offerings during prayers.

O. tenuiflorum leaf essential oil and seed extracts contain antimicrobial, insecticidal, and antifeedant compounds and have for centuries been added to stored grains to repel insects [268]. The seeds also yield an essential oil containing pleasantly scented monoterpes, sesquiterpenes, and phenols which are used in the cosmetic industry and food technology [269]. In addition, preparations from all parts of the plant have a myriad of traditional medical applications. A few indications are asthma and bronchitis; fevers, colds, influenza, sinusitis, and headaches; inflammatory conditions such as rheumatism and arthritis; pains, cramps, and spasms; diabetes mellitus; hypertension; convulsions; stress and a disturbed homeostasis; parasitic infections such as leishmaniasis; as well as antibacterial and antifungal infections such as ringworm [153, 155, 270]. Some of these activities have been attributed to eugenol, the major compound in the essential oil, as well as other terpenoids such as β-elemene, β-caryophyllene, and germacrene [271, 272].

Several pharmacological investigations supported some of the traditional claims for *O. tenuiflorum*. For instance, in line with its presumed usefulness against asthma and related conditions, a leaf extract displayed anti-anaphylactic, antihistaminic, and mast cell-stabilizing activities in laboratory rodents [273]. Indications for its anti-inflammatory, analgesic, and antipyretic activities came from the inhibitory effects in laboratory animals of the non-volatile oil from leaf and seed on formaldehyde-, carrageenan-, inflammatory mediators-, or turpentine oil-induced arthritis, paw edema, and joint edema [274–276]; acetic acid-induced tail flicking,

Figure 7.
The holy basil Ocimum tenuiflorum *L. (Lamiaceae) (from: https://images.app.goo.gl/F1HdJrRmdGUcjxZM6).*

tail clipping, tail immersion, and writhing [277]; and typhoid-paratyphoid A/B vaccine-provoked pyrexia [277].

Furthermore, oral administration of an ethanolic leaf extract led to marked lowering of blood sugar in animal and laboratory models of diabetes mellitus [278, 279], and the *O. temuiflorum*-containing polyherbal Ayurvedan supplement Diabecon® seemed efficacious and safe in helping control blood sugar levels in diabetics [280]. In addition, ethanol and chloroform leaf and stem extracts protected rats to a comparable extent as phenytoin from tonic convulsions induced by transcorneal electroshock [281]. And ethanolic leaf extracts led to normalization of stress hormone and neurotransmitter levels in animals which had been exposed to noise stress [282, 283].

As well, both the essential oil from *O. tenuiflorum* leaf and purified eugenol showed potent anthelmentic activity against *Caenorhabditis elegans* [284]. Aqueous extracts, several organic extracts, and the essential oil of the leaf and the root of the plant also exerted meaningful antibacterial activity *in vitro* against a broad range of bacterial strains (see, for instance, references [167, 285]. *O. tenuiflorum* preparations were also active against isolates of various bacterial strains from urine, stool,

and sputum from infected individuals [286], and attacked both Gram-positive and Gram-negative pathogenic bacteria [287] as well as methicillin-resistant *Staphylococcus aureus* [288].

There are also several studies reporting antifungal activity of *O. temuiflorum*. Aqueous leaf extracts and the leaf essential oil were active against cultures of *Candida albicans* and *Candida tropicalis* [170] as well as those of *Aspergillus flavus* [168]. The fractions obtained after successive extraction of the crushed and dried leaf with hexane, benzene, chloroform, ethyl acetate, methanol, and water were active against five different clinical isolates of dermatophytic fungi, namely *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Microsporum canis*, *Microsporum gypseum*, and *Epidermophyton floccosum* [171]. Hexane, acetone, and ethanol extracts of leaf and root were active against the plant pathogenic fungal strains *Alternaria alternata*, *Fusarium oxysorum*, *Cochliobolus lunatus*, and *Rhizoctonia solani*, as well as *Aspergillus flavus* and *Candida albican*s [169]. And a methanol leaf extract was active against cultures of the fungal species *Alternaria porri*; *Aspergillus flavus*, *Aspergillus niger*, and *Aspergillus oryzae*; as well as *Penicillium chrysogenum* [167]. Some investigators attributed the antifungal activity of the essential oil to eugenol [168], but others to linalool [170]. Markedly, both the leaf essential oil and eugenol not only inhibited the growth of *Aspergillus flavus* but also completely inhibited aflatoxin B_1 production by the fungus [168].

5.4 Lauraceae—*Persea americana* Mill

The avocado *Persea americana* Mill. is a large, spreading, evergreen tree that can reach a height of approximately 30 m and bears large fruits (**Figure 8**) that are surrounded by a leathery peel and contain a single large seed. The plant presumably originates from south-central Mexico but is now cultivated in various tropical and subtropical areas for the commercially valuable and very nutritious fruit [289]. The dried or fresh leaves are prepared as a tea but also used as a spice in stews, giving a flavor that resembles that of anise.

Figure 8.
The avocado Persea americana *Mill. (Lauraceae) (from: https://images.app.goo.gl/LoRCDzk7Z8bW61A28).*

The fresh fruit pulp is massaged into the hair and scalp as a vitamin-rich hair tonic and restorer, and the cosmetic industry uses the fruit oil as an ingredient of soaps and skin moisturizer products [290]. Avocado oil has a favorable lipid composition and is very suitable for cooking due to its high smoke point [290, 291], but is relatively expensive when compared to common salad and cooking oils. Leaf and seed contain cyanide and the fatty acid fungicidal compound persin in amounts that can cause intoxications in small animals but at too low concentrations to be hazardous to humans [292]. However, more recent studies showed that methanolic extracts of fruit and leaf caused chromosomal aberrations in cultured human peripheral lymphocytes [293].

Almost all parts of *P. americana* are medicinally used in many traditional systems including those in Suriname. Conditions treated with preparations from this plant are, among others, dysentery, gut parasites, gastritis, gastroduodenal ulcers, and diarrhea; liver and bilious disorders; anemia; hypertension and hypercholesterolemia; coughing; menstrual problems; cystitis; exhaustion; nervousness; to evoke abortion; against scabies, purulent wounds, lesions of the scalp, dandruff, and hair loss; as well as various microbial infections [149, 152, 153, 155, 289]. Some of these applications may be related to the presence in the plant of certain aliphatic acetogenins such as persin, avocadenols, 1,2,4-trihydroxyheptadec-16-ene, and 1,2,4-trihydroxynonadecane; terpenoid glycosides such as glycosylated abscisic acid derivatives; furan ring-containing derivatives called 'avocadofurans'; flavonoids such as quercetin, catechin, and epicatechin; as well as the plant coumarin scopoletin [294].

The results from pharmacological studies support some of the ethnomedical uses of *P. americana*. Aqueous leaf and seed extracts displayed vasorelaxant and blood pressure-lowering activities in laboratory rats and isolated rat aortic rings precontracted with KCl or norepinephrine [295–297]. Aqueous and/or methanolic leaf and/or seed extracts reduced plasma glucose levels in alloxan-treated rats [298, 299] and influenced lipid metabolism in normal or hypercholesterolemic rats [297, 298, 300]. The fruit extract exerted hepatoprotective effects in rats which might be attributed to certain constituents in the oil such as the fatty acid acids [301]. A methanol leaf extract also exerted hepatoprotective activity in rats [302], while aqueous leaf extracts showed analgesic and anti-inflammatory [303] as well as anticonvulsant effects in laboratory mice [304].

Furthermore, chloroformic and ethanolic extracts of the seed were active against *Giardia lamblia* and *Entamoeba histolytica*, the causative agents of giardiasis and amoebic dysentery, respectively [305]. Seed preparations also showed *in vitro* activity against the trophozoites of *Trichomonas vaginalis* (that is responsible for trichomoniasis) [305], the epimastigotes of *Trypanosoma cruzi* (the etiological agent of Chagas' disease) [306], and the larvae of *Aedes aegypti* (that spreads, among others, yellow fever, dengue fever, chikungunya, and Zika fever viruses) [172]. The antitrypanosomal activity was tentatively localized to 1,2,4-trihydroxyheptadecane and 1,2,4-trihydroxynonadecane derivatives [306].

Evidence for antibacterial activity of *P. americana* came, among others, from the *in vitro* activity of organic seed extracts against both Gram-positive and Gram-negative bacteria (except *Escherichia coli*) [307], and drug-sensitive as well as mono-resistant and multidrug resistant strains of *Mycobacterium tuberculosis* [305]; and that of a petroleum ether root extract against several bacterial strains including methicillin-resistant *Staphylococcus aureus* [175]. Some of the antibacterial effects might be due to the high phenolic content of the plant parts tested [173] and/or to avocadenols, 1,2,4-trihydroxyheptadec-16-ene, and 1,2,4-trihydroxynonadecane in the (unripe) fruit pulp [308].

There is also abundant evidence supporting that *P. americana* has antifungal activity. Hexane, chloroform, and methanol seed extracts displayed *in vitro* activity

against yeast species including *Cryptococcus neoformans* [175, 176], *Malassezia pachydermatis* in dogs [177], and strains of *Candida* [172]. Ethanolic extracts from the epicarp and seed of several *P. americana* cultivars were active against the yeast *Zygosaccharomyces bailii* that is responsible for the spoilage of many normally shelf-stable acidic and/or high-sugar products such as fruit concentrates, wine, soft drinks, syrups, ketchup, mayonnaise, pickles, and salad dressings [178], but not against *Penicillium* spp. and *Aspergillus flavus* [307]. Seed extracts also showed *in vitro* activity against the black bread mold *Rhizopus stolonifer* as well as the plant pathogenic fungi *Aspergillus flavus*, *Botryodiploidia theobromae*, *Fusarium oxysporum*, and *Geothricum candidum* [179]. In addition, a hydroethanol leaf extract and ethyl acetate and butanol fractions derived therefrom, and an acetonic leaf extract showed substantial activity against both drug-sensitive and drug-resistant strains of *Candida glabrata* [173] and *Candida albicans* [174] as well as *Aspergillus fumigatus*, *Aspergillus niger*, and *Aspergillus flavus* [180].

The compounds responsible for the antifungal activities have not conclusively been identified. However, persin isolated from *P. americana* idioblast cells inhibited spore germination of *Colletotrichum gloeosporioides* that causes anthracnose and fruit rotting diseases in many economically important plants [181]. And 1-acetoxy-2,4-dihydroxy-n-heptadeca-16-ene and 1-acetoxy-2-hydroxy-4-oxo-heneicosa-12,15-diene in peel and flesh of unripe avocado fruits may act synergistically to prevent *Colletotrichum gloeosporioides* of infecting and causing bitter rot in *P. america* fruit and various other economically valuable crops [182, 183].

5.5 Lythraceae—*Punica granatum* L

The pomegranate *Punica granatum* L. is a slow-growing, deeply rooting, drought-tolerant, fruit-bearing deciduous shrub or small tree that grows to an average height of 5 meters, and is originally from the region extending from modern-day Iran to northern India. It is presumably one of the first fruit trees to be domesticated in the eastern Mediterranean region (around the fifth millennium BC), and is now cultivated in warm temperate to subtropical and tropical zones as an economically highly valued fruit crop (**Figure 9**). The inner, spongy mesocarp of the fruit houses around six hundred seeds, each surrounded by a juicy, deep red- or purple-colored sour-tasting pulp, the edible part of the fruit. The red color is attributable to anthocyanins such as delphinidin, cyanidin, and pelargonidin glycosides, the sour notes are from the acidic ellagitannins [229].

P. granatum has a history of traditional medical use that dates back more than 3000 years, and is still abundantly used today in various traditional medical systems. Indications are, among others, worm infestations, diarrhea and jaundice; throat infections, colds, fevers, cough, and a runny nose; nose bleeds; mouth sores and bleeding gums; tuberculosis and shortness of breath; hypertension; diabetes mellitus; syphilis; menstrual problems and vaginal discharge including leucorrhoea; and various other microbial and viral infections [149, 150, 152, 230, 231].

The results from phytochemical and pharmacological studies supported some of the traditional uses. For instance, leaf, stem bark, and peel extracts exerted both *in vitro* and *in vivo* activity against the gastrointestinal parasites *Schistosoma mansoni* [232], *Ascaris suum* [233], and *Giardia lamblia* [309]. These effects might be due to pelletierine alkaloids, unusual alkaloids which, among others, paralyze tapeworms so that they are easily expelled from the body by using a laxative [310]. Other compounds isolated from the fruit such as the phenolics gallagic acid and punicalagins exhibited *in vitro* activity against the malaria parasite *Plasmodium falciparum* [184].

As well, orally administered *P. granatum* juice or seed or flower extracts led to a significant reduction of blood glucose levels as well as those of blood lipids and

Figure 9.
The pomegranate Punica granatum *L. (Lythraceae) (from: https://images.app.goo.gl/4bBBQ5FahGprBx4FA).*

lipoproteins in streptozotocin- or alloxan-induced diabetic rats [311, 312] and type II diabetic patients with hyperlipidemia [313]. These effects have been attributed to oleanolic, ursolic, and gallic acids [314], and might be associated with inhibition of the reabsorption of glucose in the proximal tubuli of the kidneys [315], an increased utilization of glucose by the peripheral tissues [311], and/or improved sensitivity of the insulin receptor [314]. Furthermore, *P. granatum* fresh, fermented or concentrated fruit juice as well as cold-pressed seed oil elicited meaningful anti-inflammatory activities *in vitro* and in experimental mouse and rat models of colitis and osteoarthritis [316, 317].

There are many pharmacological indications for the antimicrobial activity of *P. granatum*. Extracts from leaves, roots, bark, rhizomes, seeds, fruit peels, fruit juice, whole fruit, as well as flowers prepared with solvents of different polarities, showed broad and strong activity against various bacterial strains (see, for instance, references [184, 187, 189, 318, 319]), including multidrug-resistant pathogenic bacteria [184, 318]. The antibacterial activity was more pronounced against Gram-positive than against Gram-negative bacteria [319], was often highest in the methanol extracts or fractions [246], and has also been attributed to several phenolic compounds [184, 189, 318, 319].

There is ample evidence for antifungal activity of *P. granatum*. For instance, extracts of various parts of the plant were active against dermatophytic fungi [188]. An extract of the fruit formulated as a gel elicited antifungal activity in individuals with candidosis associated with denture stomatitis [186]. Extracts from the fruit peel, seed, juice, and whole fruit were active against industrially important fungi such as *Mucor indicus*, *Penicillium citrinum*, *Rhizopus oryzae*, and *Trichoderma reesei* [187]. Furthermore, several fractions of the fruit juice obtained by column chromatography, as well as purified ellagic acid, gallagic acid, punicalins, and punicalagins exerted *in vitro* activity against the common pathogens *Candida albicans* and *Candida neoformans* as well as *Aspergillus fumigatus* [184]. Punicalagin isolated from the fruit peel also showed strong *in vitro* activity against *Candida albicans* and *Candida parapsilosis*, and acted synergistically with fluconazole [185].

In addition, extracts from various parts of the plant were active against the plant pathogenic fungi *Pyricularia oryzae*, *Colletotrichum falcatum*, *Dreschlera rostrata*, and *Curvularia lunata*, completely inhibiting spore germination of the latter two species [188]. Particularly the fruit peel seemed to possess potent activity against plant pathogenic fungi. Preparations from this part of the plant were active against the plant pathogenic fungi *Penicillium digitatum* [190], *Botrytis cinerea* [185, 186, 188–192], and *Fusarium sambucinum* [193], both *in vitro* and *in vivo*. These fungal species are responsible for green rot in citrus fruit, bunch rot in grapes, and dry rot on potato tubers, respectively. Again, methanolic extracts seemed to be more effective than water extracts [191], and the main antifungal constituents of *P. granatum* seemed to be phenolic compounds such as ellagic acid derivatives like punicalagin, castagalagin, and granatin; gallotannins and procyanidins; cyanidin 3-glucoside and pelargonidin 3-glucoside; as well as catechins, kaempferol, and quercetin [187, 190, 192, 318].

5.6 Myristicaceae—*Virola surinamensis* (Rol. ex Rottb.) Warb

Virola surinamensis (Rol. ex Rottb.) Warb, commonly known as baboonwood or (white) ucuba is probably native to the tropical and subtropical parts of northern Brazil, Venezuela, Guyana, French Guiana, Suriname, Panama, Costa Rica, and the West Indies, where it can be found in moist lowland forests, swamps, and heavily degraded former forests. It is an evergreen tree that grows 25–35 m tall and has a straight, widening cylindrical trunk that is free of branches for 15–18 m (**Figure 10**). *V. surinamensis* is called '*babun udu*' in Suriname, because the reddish-brown-color of the hardwood ('*udu*' in Surinamse) resembles the fur color of the red howler monkey called '*babun*' in the country [145]. The tree is much in demand for its light-weight wood and is listed as globally 'endangered' on the IUCN Red List of Threatened Species [320].

V. surinamensis produces grey seeds of about 2 cm long and 1.5 cm wide which are surrounded by a brilliant red nutritious aril that attracts several species of birds and monkeys which function as its primary seed dispersers. The seeds contain 60–70% fat (consisting of, among others, 69% myristic acid, 13% lauric acid, and 7% palmitic acid), as well as vitamins A and C and traces of oleic acid and linoleic acid [321]. The fat is called ucuúba seed butter ('*ucuúba*' is the indigenous name of the tree, '*ucu*' meaning 'grease' and '*yba*' meaning 'tree') and is edible, but is also used in a wide assortment of skin-conditioning products [322].

Leaf, fruit, stembark, and root of *V. surinamensis* are extensively used for preparing traditional medicines, particularly by the Indigenous peoples of the Amazon including those from Suriname. Some of the many indications are rheumatism, arthritis, and inflammation; coughing and other symptoms of respiratory disease; aphthae, mouth sores, and abscessed teeth; conjunctivitis; skin problems including rash caused by scabies, infected wounds and bacterial infections such as erysipelas; gastrointestinal troubles such as dyspepsia, ulcers, gastritis, intestinal worms, and bloody diarrhea; hemorrhoids and piles; malaria; bladder problems; infertility; and fungal infections [145, 151, 323, 324]. Interestingly, several Amazonian tribes process the red sap from the inner bark into a hallucinogenic snuff or an intoxicating paste [325]. This substance contains psychoactive substances including hallucinogenic tryptamines such as N, N-dimethyltryptamine and 5-methoxy-N, N-dimethylpritmamine, and psychedelic β-carbolines such as harmine, harmaline, and tetrahydroharmine [325]. The sap would also be efficacious against ringworm, oral thrush, and jock itch [323].

Pharmacological studies have shown substantial activity of *V. surinamensis* preparations against the cercaria of the parasitic flatworm *Schistosoma mansoni* that causes bilharzia [326]; the tripomastigote forms of *Trypanosoma cruzi*, the causative

Figure 10.
The baboonwood Virola surinamensis *(Rol. ex Rottb.) Warb. (Myristicaceae) (from: https://images.app.goo.gl/kjANY1chTGChw2DF6).*

agent of Chagas disease [327, 328]; cultured promastigotes and/or amastigotes of several species of *Leishmania* that are responsible for the severe forms of leishmaniasis including kala-azar [329, 330]; the larvae of *Aedes aegypti*, a known factor of dengue fever, chikungunya, Zika fever, and yellow fever viruses [331]; those of the oriental latrine fly *Chrysomya megacephala* that can cause accidental myiasis [332]; and the trophozoite stages of *Plasmodium falciparum* that causes malaria [324]. These activities might be attributable to various lignans and neolignans such as grandisin in the leaf and twig of the plant and/or constituents in the leaf essential oil such as the sesquiterpenoid nerolidol [327–332]. Grandisin also elicited anti-inflammatory and antinociceptive effects in laboratory mice [333]. And an ethanolic extract of the resin stem bark (that contains the antioxidant flavonoid epicatechin) prevented the development of ethanol-, indomethacin-, stress-, or pylorus ligature-induced ulcers in laboratory mice [334].

Pharmacological support for the folkloristic claims of antifungal effects of *V. surinamensis* is scant. A dichloromethane extract from the root and the fractions obtained from this extract, were active against cultures of *Cladosporium cladosporioides* that can cause fruit rot disease in red wine grapevine but also allergies and asthma in humans [194]. Furthermore, an ethanol extracts from the stembark was active against several species of *Candida* [239]. The antifungal activity has been attributed to the flavonoids 7-hydroxyflavanone and 7-hydroxy-4′-methoxyisoflavone and was ten times greater than that found for nystatin [194], but also to (neo)lignans in leaf and seed of the plant [335]. In the latter case, the antifungal activity has been associated with the inhibition of the polymerization or assembly of the fungal cell wall [336]. Interestingly, the saturated fatty acid capric acid (or decanoic acid) in *V. surinamensis* seed, leaf, and bark elicited meaningful activity against the parasitic dermatophyte *Microsporum gypseum* [197] and forty isolates of *Candida* [196]. Capric acid also displayed synergism with fluconazole and nystatin against drug-resistant *Candida* isolates from oral thrush in neonates [196].

However, the amounts of this compound in at least *V. surinamensis* seed (around 1%) [321] seem too low to be responsible for the antifungal activity.

5.7 Myrtaceae—*Psidium guajava* L

The common guava *Psidium guajava* L. is an evergreen tree that grows to a height of 3–10 m and is native to South America, Central America, and the Caribbean. It is widely cultivated for its edible fruit in many tropical and subtropical regions. Depending on the cultivar, the fruit can be ovoid or pear-shaped; have a green, yellow, or red skin and white-, pink-, or red-colored fleshy pulp; and range in size from as small as an apricot to as large as a grapefruit (**Figure 11**). Edible oil is obtained from the seeds [337], and extracts from the fruit are included in various cosmetic products such as shampoos to confer a pleasantly fresh scent [338].

Preparations from the young and ripe fruit as well as leaf, stem, stembark, and rootbark from *P. guajava* are used in many traditional medical systems in Africa, Asia, Central America, and the Caribbean. A few indications are diarrhea, constipation, spasms, and ulcers; colds, sore throat, coughs, laryngitis, and bronchitis; menstrual disorders; gonorrhea; inflammatory disorders such as rheumatism; diabetes mellitus; hypertension; sprains and pains; vertigo, epilepsy, and convulsions; a wide variety of skin complaints; as well as parasitic and microbial infections including those causing vaginal discharge and ringworm [339, 340]. In Suriname, *P. guajava* preparations are, in addition, used in genital steam baths for cleansing the vagina and preventing microbial infections [155].

Some of the traditional uses of *P. guajava* have been validated by phytochemical and pharmacological studies (see, for instance, references [341, 342]). Aqueous and ethanolic leaf extracts elicited antidiarrheal activity in mice and rats treated with Castor oil [343] that was comparable to that caused by loperamide and might occur through inhibition of gut motility [343]. The leaf essential oil was efficacious in diarrhea associated with infantile rotaviral enteritis [344]. And the polyphenolic fraction of an aqueous leaf extract displayed spasmolytic activity in an isolated guinea-pig ileum preparation precontracted with acetylcholine and/or KCl [345].

Figure 11.
The guava Psidium guajava *L. (Myrtaceae) (from: https://images.app.goo.gl/Cdw93GHRJaJ2jHYg7).*

Notably, a double-blind clinical study with a phytodrug called QG5 developed from *P. guajava* leaf, produced a decrease in the duration of abdominal pain, presumably due to the antispasmodic activity of quercetin in the preparation [346].

The presumed efficacy of *P. guajava* against respiratory disorders was supported by the antitussive activity of leaf extracts in rats and guinea pigs exposed to a capsaicin aerosol [347]. Evidence for anti-inflammatory and antinociceptive activity of the plant was provided by the inhibitory effects of an aqueous leaf extract on fresh egg albumin-induced paw edema in rats and thermally and chemically induced nociceptive pain in mice [348]. And indications for central modulatory effects of *P. guajava* came from the suppression of central nervous system activity and the prolongation of pentobarbital-induced sleeping time in mice that had been given methanol leaf extracts or non-polar fractions therefrom [349, 350]. These observations have been attributed to terpenes and possibly also flavonoids in the extracts [349, 351].

Studies with both laboratory animals and human subjects also supported the antihypotensive and antidiabetic activities of *P. guajava*. Leaf preparations produced vasorelaxation in spontaneously-contracting portal veins as well as rat aortic ring preparations of normotensive rats [352]. Importantly, randomized clinical studies found that the consumption of the fruit led to small but statistically significant positive effects on blood pressure, total blood cholesterol and triglyceride levels, as well as HDL cholesterol in hypertensive patients [353, 354]. And intraperitoneal administration of an aqueous extract of the unripe fruit or from the fruit peel led to clear hypoglycemic and antidiabetic activities in streptozotocin-treated diabetic rats [355]. The ripe fruit without peel was more efficacious in diabetic patients when compared to the fruit with peel [356].

Evidence for antiparasitic activity of *P. guajava* was provided by the *in vitro* inhibitory effect of a polyphenolic fraction of an aqueous leaf extract on the growth of *Entamoeba histolytica* (that causes amoebic dysentery) [345]; the potent activity of an aqueous stembark extract against the malaria parasite *Plasmodium falciparum* in a lactate dehydrogenase assay [357]; and the meaningful anticestodal efficacy of an aqueous leaf extract against experimental *Hymenolepis diminuta* (tapeworm) infection in rats [358].

Support for antibacterial effects of *P. guajava* came from the activity of aqueous and organic extracts from the leaf and the stembark against the main causative agent of acne lesions, *Propionibacterium acnes*, and other organisms isolated from these lesions [359]; two clinical isolates of the gastrointestinal tract, *Escherichia coli* and *Staphylococcus aureus* [360]; a wide variety of clinically important bacterial strains (see, for instance, references [198, 361]); as well as multidrug-resistant clinical isolates of *Staphylococcus aureus* [362] and a multidrug-resistant strain of *Vibrio cholera* [363]. The antibacterial activity might be associated with inhibition of adherence by certain lectins in the fruit [364] or phenolic compounds including flavonoids in the leaves [198, 361].

Most studies on the antifungal activity of *P. guajava* have been carried out with preparations of the leaf from the plant. Thus, extracts from this part of the plant obtained with various organic solvents or hot water elicited broad and meaningful activity against species in the genera *Candida*, *Saccharomyces*, *Cryptococcus*, *Trichosporon*, *Aspergillus*, *Sporothrix*, and *Microsporum* [198–203]. The antifungal activities in the leaf preparations potentiated that of fluconazole [203, 204] and have been attributed to phenolic compounds including tannins, coumarins, and flavonoids such as quercetin, and/or terpenoids [198, 201, 203, 361]. The former supposition is supported by the activity of tannic and flavonoid fractions from the leaf against several species of *Candida* [204] and the inhibitory effects of plant phenolic compounds on the biosynthesis of ergosterol for assembling the fungal plasma membrane [365].

As well, a methanolic extract from the ripe fruit was active against strains of *Arthrinium sacchari* that can cause damping-off disease of wheat (collapse and overgrowth of emerging seedlings), as well as the melanin-containing 'black yeast' *Chaetomium funicola* that can cause pheohyphomycosis, a dark-brown-colored infection of skin and subcutis, paranasal sinuses, or central nervous system [206]. Furthermore, a tincture of *P. guajava* bark effectively killed various dermatophytes in the genera *Trichophyton* and *Microsporum* [205], while organic extracts from the twigs inactivated *Candida albicans* and *Aspergillus niger* [204].

5.8 Rananculaceae—*Nigella sativa* L

The black caraway (or black cumin) *Nigella sativa* L. is an annual flowering plant that is native to a large region that includes eastern Mediterranean, northern Africa, the Indian Subcontinent, and western Asia. It grows 20–30 cm tall, and bears relatively large fruits made up of an inflated capsule composed of three to seven united follicles, each containing numerous black seeds. The plant is mainly cultivated for the edible seeds (called 'black cumin seeds'; **Figure 12**) which have a pungent, bitter taste and smell, and are used as a spice, flavoring, and food preservative [366].

In addition, the seeds and the seed oil (called 'black seed oil') are widely used for treating, among others, inflammatory conditions such as rheumatism, as well as respiratory conditions, gastrointestinal problems, diabetes mellitus; elevated blood cholesterol levels, a weakened immune system, parasitic infections, and microbial infections such as athlete's foot, nail infections, ringworm, and thrush [367–369]. Relatively recently, Ayurvedic supplements of *N. sativa* seed oil in capsule or softgel form have been promoted in various countries including Suriname as a remedy for several of these conditions including skin, hair, and nail problems.

Some of the therapeutic properties of *N. sativa* have been attributed to the monoterpene thymoquinone, a major bioactive component of the seed essential oil [207] that is virtually non-toxic to humans [208]. For instance, exposure of cultured pancreatic cancer cells to thymoquinone led to a reduction in markers of

Figure 12.
The black caraway Nigella sativa *L. (Rananculaceae) (from: https://images.app.goo.gl/s29DmisCFu30pVT78).*

inflammation [209]. This was consistent with the inhibitory effects of a ground seed extract on inflammation in the cerebellum and medulla of a rat model of multiple sclerosis [210] and with the improvement of inflammation markers in the serum of patients with rheumatoid arthritis who had received the seed oil [211]. Furthermore, *N. sativa* seed oil protected rats from developing stomach ulcers following exposure to acetylsalicylic acid [370] and from liver damage caused by aflatoxin B_1 [212], and caused a decrease in levels of blood sugar [213], serum triglycerides and LDL [214]. *N. sativa* seed preparations and seed oil also elicited meaningful antimicrobial activity. Antibacterial effects were seen with a topical formulation against a staphylococcal skin infection in children [215] and against many cultured bacterial strains including methicillin-resistant *Staphylococcus aureus* isolates from the wounds of diabetic patients [216, 371].

Support for antifungal activity of *N. sativa* was provided by the inhibitory effects of diethyl ether, methanol, and aqueous seed extracts on the growth of *Candida albicans in vitro* [372] and on the infestation of liver, spleen, and kidneys of mice inoculated with the fungus [373]. The extracts also inactivated various dermatophytic fungi [217, 218], albeit to a lesser extent when compared to griseofulvin [217]. However, another study only found an inhibitory effect of organic seed extracts on the formation of *Candida albicans* colonies in the organs of experimental animals, not of aqueous extracts [374]. Thymoquinone also inhibited the growth of dermatophytes [217] as well as that of intravaginally administered *Candida albicans* in mice immunosuppressed by subcutaneously injected methyl prednisolone [375]. The antifungal activities of thymoquinone (that is rather lipophilic) presumably occurred as a result of the perturbation of fungal plasma membrane proteins [375].

Furthermore, the seed essential oil of *N. sativa* exerted excellent and broad activity against various species of *Aspergillus*, *Curvularia*, *Microsporum*, *Penicillium*, *Trichoderma*, *Candida*, *Chaetomium*, *Fusarium*, *Trichophyton*, and *Chrysosporium* [376–380]. However, in another study, the oil did not affect the growth of *Aspergillus flavus* and *Aspergillus parasiticus in vitro*, but inhibited the production of aflatoxin B_1 by at least one-third [381]. The antifungal activity of *N. sativa* seeds has been hypothesized to be attributable to (an) ingredient(s) that kill(s) fungi by stimulating the production of nitric oxide by host granulocytes and monocytes [382]. A subsequent study reported two peptides called defensins and designated Ns-D1 and Ns-D2 that displayed strong activity against phytopathogenic fungi, presumably by interacting with specific sphingolipids in the fungal plasma membrane [383].

5.9 Rutaceae—*Aegle marmelos* (L.) Corrêa

The bael tree or *Aegle marmelos* (L.) Corrêa is a slow-growing deciduous tree that can reach a height of 10–15 m and is native to the northern parts of India. It is mainly cultivated for its edible aromatic, sweet-tasting, yellow-colored fruit (**Figure 13**) in that country as well as in other south-eastern Asian countries such as Sri Lanka, Thailand, and Malaysia. Young leaves and shoots of *A. marmelos* are eaten as salad greens and contain the alkaloid aegeline (N-[2-hydroxy-2 (4-methoxyphenyl) ethyl]-3-phenyl-2-propenamide) that would reduce appetite, produce weight loss, improve athletic performance, and increase energy [384]. For these reasons, aegeline has been incorporated in dietary supplements that have been marketed for weight loss and muscle building [385], even though there is no sound scientific evidence to support these uses. More importantly, aegeline has been associated with potentially fatal liver damage [386], and the more than fifty cases of acute hepatitis including several instances of fatal, acute liver failure have led to the withdrawal from the market of an aegeline-based slimming product called OxyElite Pro® [386].

Figure 13.
The Indian bael tree Aegle marmelos *(L.) Corrêa (Rutaceae) (from: https://images.app.goo.gl/BkkX6CZgxx1q5Whv7).*

Nevertheless, *A. marmelos* is extensively used in the traditional medical systems of the Indian subcontinent [387] and those of the Indian diaspora in Suriname [155]. Preparations from leaf, stembark, root, fruit, and seed are used against, among others, stomach pain, peptic ulcers, diarrhea, amoebic dysentery, constipation, and jaundice; rheumatoid arthritis, gout, and swollen joints; diabetes mellitus; high blood pressure; asthma; anemia; bone fractures; agitation and insomnia; wounds; skin problems such as leucoderma; as well as microbial infections [387, 388].

Pharmacological studies have validated many of the ethnomedicinal uses of *A. marmelos* (see, for instance, references [388, 389]). Thus, a chloroform root extract was effective against castor oil-induced diarrhea in laboratory rodents and inhibited the *in vitro* growth of various cultured diarrhea-causing species of bacteria—particularly *Vibrio cholerae*, *Escherichia coli*, and *Shigella* spp.—at a comparable degree as the fluoroquinolone antibiotic ciprofloxacin [390]. A methanolic leaf extract elicited considerable anti-inflammatory, antinociceptive, and antipyretic activities in rats and mice [391]. And leaf, callus, and fruit extracts displayed notable hypoglycemic and antihyperlipidemic effects in alloxan- and streptozotocin-treated mice, rats, and rabbits [392–394]. This was presumably due to the stimulation of glucose uptake by the peripheral tissues [392] and/or insulin secretion from the pancreatic β-cells [392, 393].

A methanolic leaf extract formulated as an ointment or an injectable preparation for intraperitoneal administration, stimulated the healing of excision and incision wounds in rats to a comparable degree as the topical nitrofuran antimicrobial compound nitrofurazone [395]. Preparations from *A. marmelos* leaf, fruit, seed, and root also displayed antibacterial and antifungal activity. The antibacterial activity was directed against a broad range of Gram-positive as well as and Gram-negative bacteria (see, for instance, references [219, 220, 396]) including multidrug resistant strains [396]. Some of the pharmacological activities of *A. marmelos* have been attributed to the presence of coumarins, monoterpenoids (such as cuminaldehyde),

phenolic compounds (such as flavonoids and eugenol), alkaloids, tannins, and essential oils in the plant [221, 222].

Evidence for antifungal properties of *A. marmelos* was provided by the meaningful activity of the leaf essential oil against a variety of yeast-like and filamentous fungal species including clinical isolates of dermatophytic fungi such as those causing ringworm [219–227]. Furthermore, the essential oil of the plant completely inhibited spore germination of dermatophytic and plant pathogenic *Fusarium* fungal species *in vitro*, including that of a highly resistant species, *Fusarium udum*, the causative agent of wilt disease in the pigeon pea (characterized by the disruption of the flow of water in the xylem transport tissue of the plant) [227]. In addition, water, methanol, and ethanol leaf extracts as well as fractions from them, exerted potent antifungal activity against clinical isolates of dermatophytic fungi in the genera *Trichophyton*, *Microsporum*, and *Epidermophyton* [397].

As well, fractions from chloroform leaf and fruit extracts showed substantial activity in pot cultures against the plant pathogenic fungi *Fusarium oxysporum* f.sp. *ciceris* [228] and *Pythium debaryanum* [398], the causative agents of wilt of chickpea, and damping-off in peanut, beet, and tobacco, respectively. Notably, the addition of the leaf methanol extract to the bio-agents *Trichoderma viride* and/or *Pseudomonas fluorescens* suppressed chickpea wilt disease more when compared to either substance alone [228]. Preparations from *A. marmelos* seed also exhibited considerable *in vitro* activity against various species of *Trichophyton* and *Aspergillus*, as well as *Epidermophyton floccosum* (that causes skin and nail infections in humans) and *Candida albicans* [399–402]. And an ethanolic extract of the root showed activity against *Aspergillus fumigatus* and *Trichophyton mentagrophytes* [403]. The antifungal activity of the leaf essential oil has been attributed to certain terpenoids that inhibited spore germination by interfering with Ca^{2+}-dipicolonic acid metabolism [220, 227], a metabolic pathway involved in the regulation of the resilience of macromolecules including DNA to stressors such as heat [404].

6. Concluding remarks

Since their emergence on Earth, humans have explored the biodiversity to improve their well-being [405]. For this purpose, various plants, animals, and micro-organisms have been used as food, spices, shelter, poisons on arrow- and spearheads for hunting and warfare, cosmetics, stimulants, as well as medicines. Insight into the latter uses has provided unlimited opportunities for new drug leads because of nature's enormous chemical diversity and the production of a myriad of drugs that became an essential part of health care systems throughout the world. For instance, the antineoplastic agents vincristine and paclitaxel have first been identified in the periwinkle plant *Catharanthus roseus* [406] and the Pacific yew *Taxus brevifolia* [407], respectively. The angiotensin-converting enzyme inhibitor captopril and its derivatives for treating hypertension and some types of congestive heart failure, have been developed from the venom of the Brazilian viper *Bothrops jararaca* [408]. And exenatide for treating type 2 diabetes mellitus was originally isolated from the venom of the Gila monster *Heloderma suspectum* [409].

The bacterial species *Saccharopolyspora erythraea* and *Streptomyces nodosu*s gave the antibacterial agent erythromycin [410], and the antifungal and antileishmanial agent amphotericin B [411], respectively. And as mentioned throughout this monograph, the fungal species *Penicillium chrysogenum*, *Tolypocladium inflatum*, and *Aspergillus terreus* were at the basis of identifying β-lactam antibiotics such as the penicillins [12], the immunosuppressive agent tacrolimus [13], and the specific

LDL-lowering HMG-CoA reductase-inhibiting statins that reduce the risk of arterial blockage, a heart attack, a stroke, and diabetes mellitus [14].

This monograph has presented data about the antifungal activities of nine plants that are traditionally used for treating mycoses in Suriname. The plants were the taro *Colocasia esculenta* (Araceae), the milkweed *Euphorbia hirta* (Euphorbiaceae), the holy basil *Ocimum tenuiflorum* (Lamiaceae), the avocado *Persea americana* (Lauraceae), the pomegranate *Punica granatum* (Lythraceae), the baboonwood *Virola surinamensis* (Myristicaceae), the guava *Psidium guajav*a (Myrtaceae), the black caraway *Nigella sativa* (Rananculaceae), and the golden apple *Aegle marmelos* (Rutaceae). Preparations from these plants showed good and broad antifungal properties *in vitro*. In addition, most of the samples also displayed various other pharmacological activities including antiparasitic, antibacterial, and antiviral activity. An extract of *P. granatum* fruit formulated as a gel even elicited antifungal activity in individuals with candidosis associated with denture stomatitis [186]. And there are in most cases also valuable indications about the pharmacologically active compound(s) and the mechanism(s) of action.

These data are encouraging, providing preliminary indications of the usefulness and potential toxicity of the plant samples, but do not reflect their clinical efficacy and usefulness. It is therefore imperative to properly evaluate the plant preparations for their chemical stability, spectrum of antifungal activity in the clinical setting, susceptibility to efflux pumps, bioavailability and degree of protein binding and inactivation by serum and hepatic enzyme systems, and many other pharmacokinetic and pharmacodynamics aspects. This is all the more important because of two reasons. First, the development of resistance to available antifungal drugs including the spread of multidrug-resistant fungal strains, is becoming a growing problem in many parts of the world [412]. Second, despite the availability of modern allopathic antifungal drugs, about 80% of the world population residing in the developing world rely on herbal medicinal products as a primary source of healthcare [413]. It is just and fair to provide sound scientific evidence on the clinical efficacy of these products for treating fungal infections.

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Plant-based traditional medicines are abundantly used in the Republic of Suriname (South America) for treating a wide variety of conditions including fungal infections. This book reviews nine plants with antifungal potential and explains the phytochemical and pharmacological support for their apparent usefulness against fungal infections. These data are placed within the context of some health aspects and the healthcare structure of Suriname, following observations about the characteristics and taxonomy of fungi and their significance to humans and information about fungal infections and their allopathic forms of treatment. The book concludes with a section about the significance of these Surinamese herbal antifungal substances to mainstream antifungal treatments.

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