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Contents

1	Introduction	3776
1.1	Structural Diversity and Natural Occurrence of the Quassinoids	3776
1.2	From Kwasi to Quassin, or How a Traditional Pharmacological Application Led to a New Promising Family of Molecules	3781
1.3	Pharmacological Activities: A Focus on Cancer and Malaria	3783
2	Pharmacological Applications	3784
2.1	Historical Perspective and In Vitro Cytotoxic Activities	3784
2.2	In Vivo Anticancer Assays with Quassinoids, Clinical Trials	3785
2.3	Historical Perspective and In Vitro Antiplasmodial Activities	3786
2.4	In Vivo Antimalarial Activity of Quassinoids in Murine Models	3787
3	Mechanisms of Action	3789
4	Other Biological Activities and Ethnopharmacological Relevance	3791
5	Conclusion	3796
	References	3796

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Abstract

Quassinoids were initially isolated as bitter principles of plants of the Simaroubaceae family. These natural products are formed by oxidative degradation of triterpene derivatives. Since the 1970s, these molecules have attracted attention because of their promising biological activities, especially in the context of research regarding active anticancer and antimalarial principles. In this chapter, the structural diversity of quassinoids and their botanical and geographical occurrence are described, combining a historical perspective from the literature references regarding these two major biological activities and focusing on the results obtained *in vivo* with the most promising compounds; *in vitro* studies are less relevant and have already been extensively reviewed in the literature. The biological activities with respect to the uses of the corresponding Simaroubaceae in traditional medicine are also analyzed.

Species names have been transcribed according to the nomenclature system used by The Plant List (<http://www.theplantlist.org>). Full names of species with determinant are given when cited for the first time only.

Keywords

Anticancer • Antimalarial • Ethnopharmacology • Simaroubaceae • Quassinoids

Abbreviations

ED ₅₀	Drug dose inducing 50% response
SkD	Simalikalactone D
SkE	Simalikalactone E

1 Introduction

1.1 Structural Diversity and Natural Occurrence of the Quassinoids

Quassinoids are natural products formed by oxidative degradation of triterpene derivatives; their biosynthetic precursors are similar to those of limonoids but the biosynthetic pathways of quassinoids have not been established so far [1]. At least 351 different natural quassinoids have been described in the literature (Fig. 125.1), and a large number of semisynthetic and synthetic analogues have been prepared for synthesis or medicinal chemistry purposes, mostly in last 30 years [see, for example, 2–4]. Several base skeletons have been described in the literature, and these can be classified into five distinct groups according to the number of atoms of the main chain (Fig. 125.1).

The C₁₈ quassinoids comprise laurycolactones A and B, eurycolactone B-D, and samaderin A and derivatives. Here, the lactone linkage between carbon atoms C-15

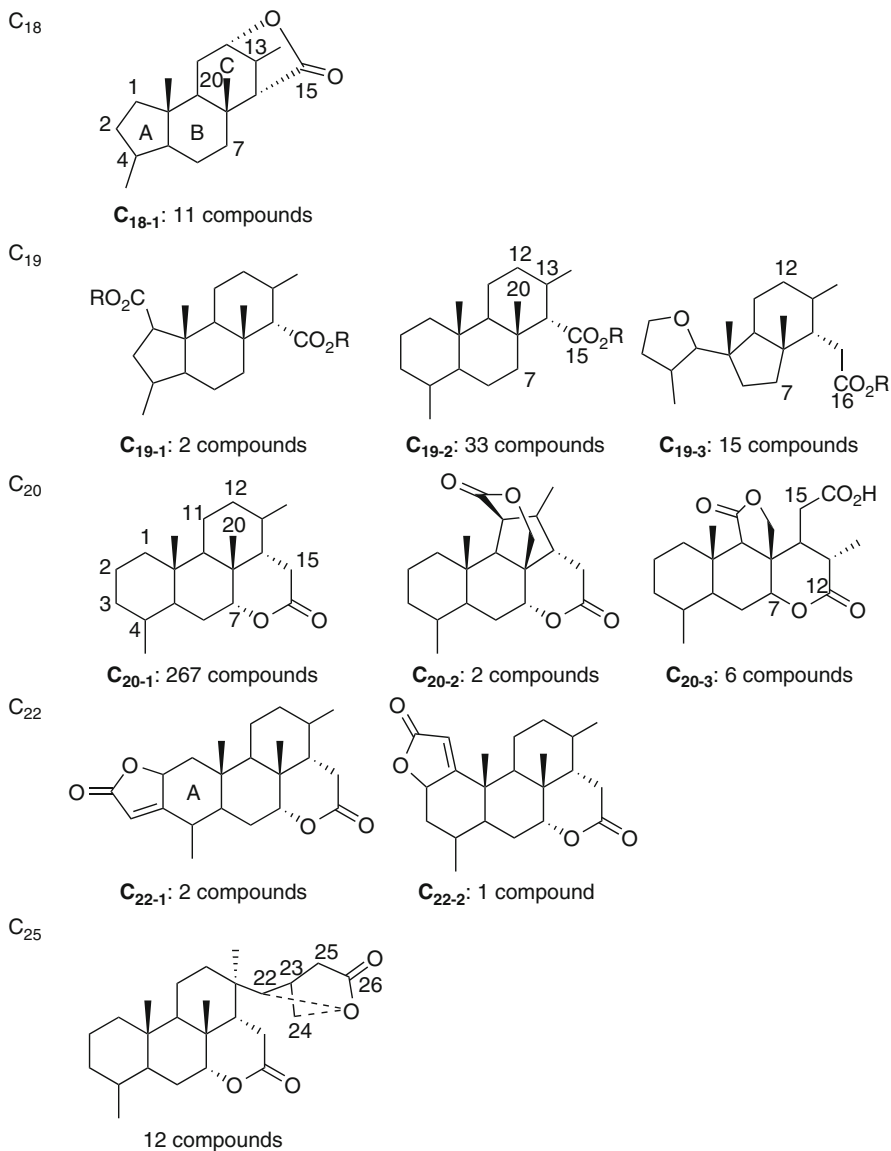


Fig. 125.1 Natural quassinoids: base skeletons and occurrence

and C-12 is always present, and rings A and B are oxidized with carbonyl groups at positions 1 and 7. In samaderin A, carbon atoms C-20 and C-13 are interconnected with an ether moiety.

The C₁₉ quassinoids can be subdivided into three structural groups (Fig. 125.2). The first includes eurycolactone A and samaderolactone A. The second is more diverse, with 33 compounds, including eurycomalactone, eurycomalide, and

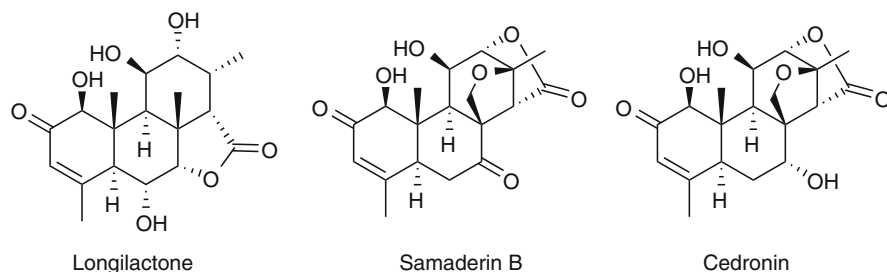


Fig. 125.2 Examples of C₁₉ quassinoids

longilactone derivatives, more samaderin derivatives and eurycolactones E and F, indaquassin A, and cedronin. The first representatives of this series were the samaderins B and C, isolated and characterized in 1962 from *Quassia indica* (Gaertn.) Noot. by Polonsky [5].

In this series, longilactones have a lactone linkage between C-15 and C-7, while all others have a lactone ring closure between carbon atoms C-15 and C-12. The only exceptions are eurycolactone F and eurycomaaside, which should have been named after longilactone. In addition, cedronin and samaderins have an ether linkage between C-20 and C-13. The third group of C₁₉ quassinoids is smaller. It is composed of 15 different compounds with a contracted B ring. In general, C-16 is linked to C-7, forming a six-membered lactone ring. The A ring is always a γ -butyrolactone and is almost always unsaturated.

More than 75 % of all natural quassinoids described in the literature have a C₂₀ skeleton. In the first type of C₂₀ quassinoids, a lactone is usually formed between C-16 and C-7 (as represented here), although some members of this group are lactonized between C-16 and C-12. All positions can be oxidized with double bonds or oxygenated functional groups, and again, an ether moiety linking C-20 to C-13 and sometimes C-11 can be encountered. When the C-15 atom is hydroxylated, the hydroxyl group is often esterified with small lipophilic side chains. Quassin, the first isolated quassinoid, belongs to this C₂₀ group, and most in vivo studies and clinical trials with quassinoids were conducted on compounds of that group. Quassin is used as natural insecticide and bitter food flavoring. The C₂₀ quassinoids that have attracted most attention in the literature for their pharmacological interest are ailanthone and its analogues (ailanthinone, glaucarubinone, chaparrinone, 15-desacetylundulatone, and peninsularinone), bruceins, brusatol, bruceolide, bruceantin, and simalikalactones D and E (Fig. 125.3).

The second group of C₂₀ quassinoids with a contracted C ring is represented by shinjudilactone and ailantinol D, and the third group with a cleaved C ring is composed of vilmorinines A-F isolated from *Ailanthus vilmoriniana* (Dode) [6].

The three C₂₂ natural quassinoids known in the literature have a butenolide moiety attached to the A ring, presumably originating from the aldol cyclization of a α -acetoxycarbonyl moiety from the normal C₂₀ skeleton. In this series, sergeolide has attracted much attention due to its very good antimalarial potential (Fig. 125.4) [7].

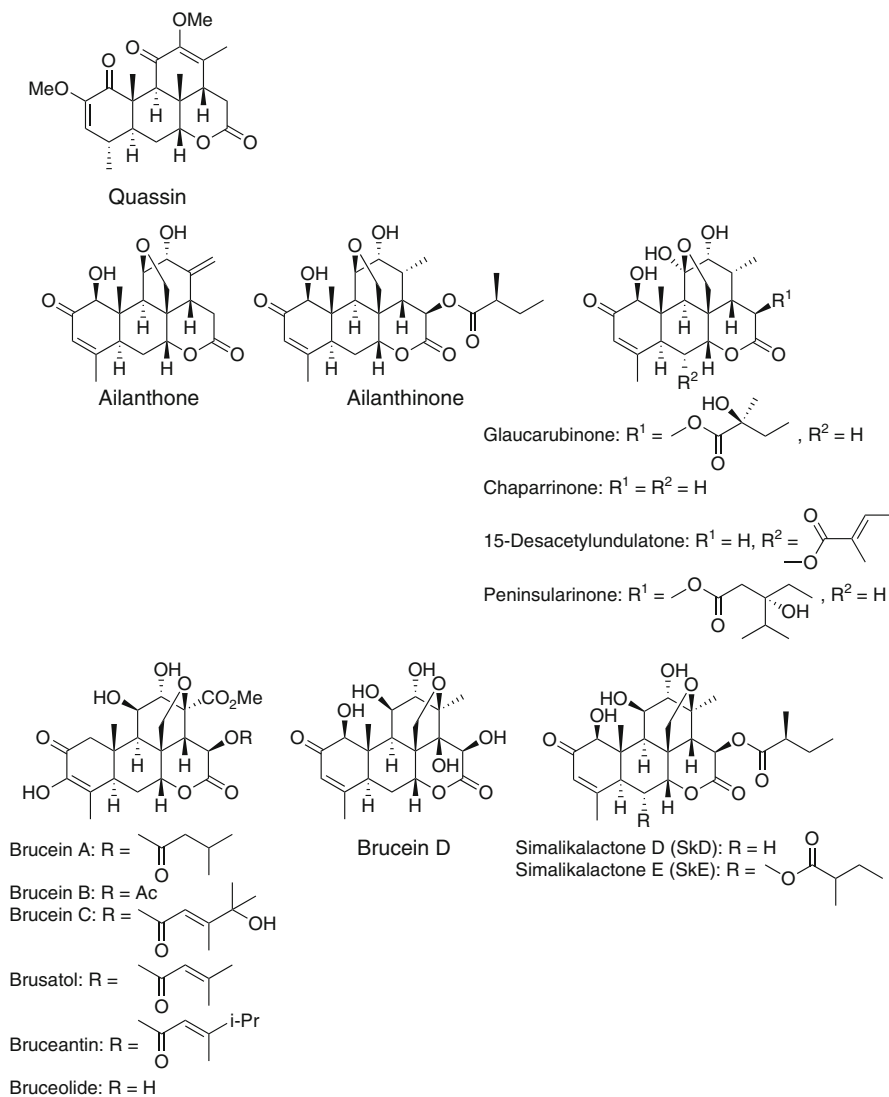
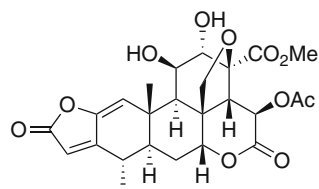


Fig. 125.3 Examples of naturally occurring C_{20} quassinoids

Fig. 125.4 Structure of sergeolide



C₂₅ quassinoids are rather rare. Simarolide was the first member of this group to be isolated and characterized by Polonsky in the early 1960s [8, 9]. The side chain consisting of carbon atoms C-22 to C-26 is always lactonized, either forming an O–C-22 or a O–C-24 bond. In this series, the C-15 position is never hydroxylated so the side chain that seems to impact on the biological activity of the C₂₀ quassinoids is absent. Also, C-20 is always a methyl group, whereas, the A ring of soulameolide and indaquassin F does bear the α,β -unsaturated ketone with the carbonyl functional group on C-2.

Quassinoids are natural products occurring in the Simaroubaceae family and are known as the bitter principles of these plants. The Simaroubaceae belong to the Sapindales order and are considered as emerging from a protorutaceous stock because of the presence of tryptophan-derived alkaloids (canthinones and β -carbolines) common to the Rutaceae and the Simaroubaceae. The major metabolic difference with Rutaceae species originates from the presence of limonoids in Rutaceae, whereas the Simaroubaceae generate quassinoids [10–12]. The correlation between the presence of alkaloids and quassinoids and the geographical distribution of the species has also been studied to clarify the phylogenetic relationships within the Simaroubaceae family [11].

Nevertheless, some exceptions to this rule must be highlighted, with the examples of the genera *Samadera* and *Harrisonia*. In 1997, the first example of joint occurrence of quassinoids and limonoids was uncovered in a new Australian Simaroubaceae species SAC-2825, tentatively assigned as aff. *Samadera bidwillii* Oliv. [12]. The genus *Harrisonia* was also shown to contain both families of molecules [13]. However, with the evolution of botanical nomenclature, *Samadera bidwillii* is considered unresolved and some *Samadera* species have been placed in synonymy with *Quassia* species, whereas the genus *Harrisonia* is now included in the Rutaceae family. These examples of species containing simultaneously limonoids and quassinoids could illustrate the chemistry of primitive Rutes, before the metabolic separation between the two families, and quassinoids therefore appear to be of chemotaxonomic relevance.

Currently, the Simaroubaceae family includes 16 genera divided into 102 species exclusively distributed in tropical and subtropical areas, with the exception of the *Ailanthus* and *Picrasma* genera, the distribution area of which extends to temperate Asia. The most species-rich genera are *Quassia* (37 species), followed by *Castela* (17), *Simaba* (12), and *Brucea* (10). *Armorica*, *Gymnostemon*, *Iridosma*, *Leitneria*, and *Simarouba* are monospecific. Some genera have distribution areas restricted to Asia (*Eurycoma*) or southwest Africa (*Odyendyea* and *Hannoa*). *Brucea* is present in East Africa and Asia, *Picrasma* and *Quassia* are considered cosmopolitan, and *Castela* is essentially neo-tropical [14]. A biogeographic study of the Simaroubaceae family suggested that this family may originate from North America with a migration through the Bering Strait by ancestral taxa [15].

Morphologically, species of this family are trees of medium to small size, or branched and bushy shrubs, sometimes spiny. The leaves are alternate, compound, rarely simple, without stipules. The bitter taste of all parts of the plants of this family is also a criterion for botanic identification. The scientific names and even



Fig. 125.5 Young leaf (left) and mature leaf and flower (right) of *Quassia amara* L. (Picture: G. Bouchon)

more the vernacular names of these species bear witness to this feature. For example, *Quassia africana* (Baill.) Baill., an African Simaroubaceae, is known in Congo under the name of “simalikali” which means “bitter than everything else” [16].

1.2 From Kwasi to Quassin, or How a Traditional Pharmacological Application Led to a New Promising Family of Molecules

The history of quassinoids began in the mid-eighteenth century, after the discovery in 1760 of the febrifuge properties of a Simaroubaceae, *Quassia amara* L. (Fig. 125.5). The medicinal property of the roots of this species was revealed to Carl G. Dahlberg, a Dutch army officer, by a Suriname slave and famous healer named Kwasi. This recipe was subsequently made public by Daniel Rolander, a Swedish naturalist. Linnaeus, excited by the discovery of this plant and its uses, named it in honor of the healer. The botanist, however, committed an error in its description, corrected in 1763 by his disciple C.M. Blom [17–20].

Under the name of “quassia” or “quassia wood” (*Quassiae lignum*), two indiscriminate species were then sold in Europe: *Quassia amara* (mainly root, wood and stems) and *Picrasma excelsa* (Sw.) Planch. (formerly *Picraena excelsa* (Sw.) Lindley) or Jamaican quassia (trunk wood) [17, 18, 20]. Quassia wood was initially used as an antiseptic, for meat preservation and as antipyretic. But because of its bitter principles its main recommendation was as a digestive and tonic [17, 21]. *Q. amara* was rapidly registered in various European pharmacopoeias, alone or with other Simaroubaceae species with the same reputation, such as *Picrasma excelsa* or *Simarouba amara* Aubl. [22–25]. The reputation of quassia wood then spread to the United States, where the medicinal use of cups mostly made of *Q. amara* wood became popular [26]. Meanwhile, a few Simaroubaceae were registered in North American official pharmaceutical documents, such as the King’s American Dispensatory [27] or the United States Dispensatory [28].



Fig. 125.6 Left: *Middags Markt* stall, Paramaribo, Suriname, with a choice of bitter-cups (Picture: G. Odonne) – Right: close-up view of a bitter-cup (Picture: E. Deharo)

These cups, called tonic- or bitter-cups, are still in use for their tonic properties in Suriname today (Fig. 125.6), where they are also known under the name “Kwasibita beker” [29].

The bitter substances of *Quassia amara* were first named quassin by Thompson in the beginning of the nineteenth century [17, 21] and were obtained in crystalline form by Winckler in 1835 [30]. It was more than a century later that a method for preparation and purification of quassin and neoquassin was described, highlighting that the crude extract was, in fact, a mixture of these two components [31, 32]. Studies on quassinoids from *Quassia amara* and *Picrasma excelsa* – mainly quassin, neoquassin, and isoquassin, the latter initially named picrasmine – then continued until the 1950s [33–36]. In particular, their structures were partially determined by Robertson et al. based on physical and chemical observations. The authors also synthesized norquassin, isolated thereafter and named simalikalactone B or picrasine B [37]. The complete structure of these molecules (quassin and neoquassin) and their stereochemistry, however, were only fully established in the early 1960s, when nuclear magnetic resonance techniques could be applied to them [38, 39]. This step marked the beginning of many studies leading to the isolation of quassinoids from natural sources.

Technical advances in structural analysis also initiated subsequent advances in synthesis of quassinoids, leading in particular to the first total synthesis of quassin

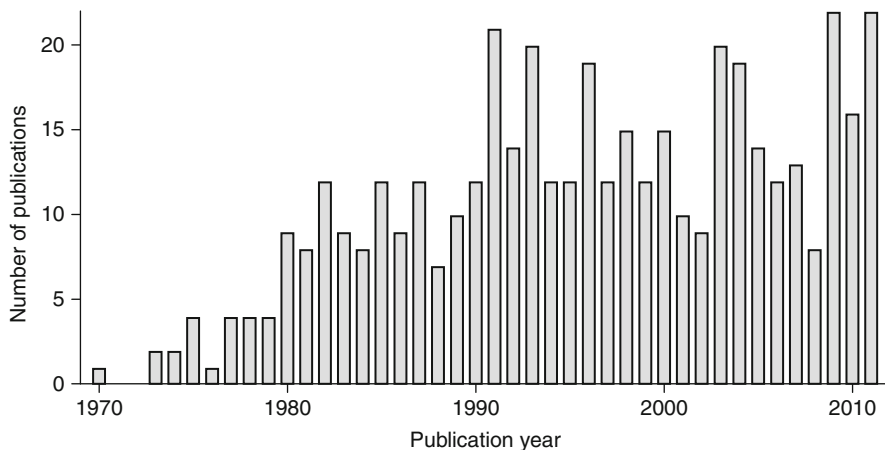


Fig. 125.7 Yearly number of publications related to quassinoids between 1970 and 2011 (Source Scopus + Science Direct)

by Grieco et al. in 1980 [40]. This milestone contribution to the study of quassinoids and the marked antileukemic activity of some of them – especially quassinoids with the C_{20} skeleton – initiated a considerable increase in publications related to quassinoids in the 1980s [41].

A literature search conducted for the terms “quassinoid” and “simaroubolide” (a term used in the 1970s to designate these molecules isolated from plants of the Simaroubaceae family) on the search engines Scopus and Science Direct provided a total of 453 references from 1970 to 2011; Fig. 125.7 illustrates the yearly profile.

This graph highlights the growing interest in quassinoids between the 1970s and 1980s. This trend could be explained simply by the increasing number of scientific publications at the time, but a study of the literature shows clearly that it is also correlated with the discovery of the anticancer properties of these molecules. Since 1990, the number of articles on this family of molecules has remained stable.

1.3 Pharmacological Activities: A Focus on Cancer and Malaria

The quassinoids are renowned for two major pharmacological activities: their anticancer and their antiplasmodial potential. Looking more closely at the evolution of publications on these two major classes of biological activities, we obtained the curves shown in Fig. 125.8. The linear regressions represented here demonstrate an early interest in their anticancer activities (1970–1985) and the increasing interest in their antimalarial potential (since 1990). Subsequent sections will therefore focus on these two pathologies.

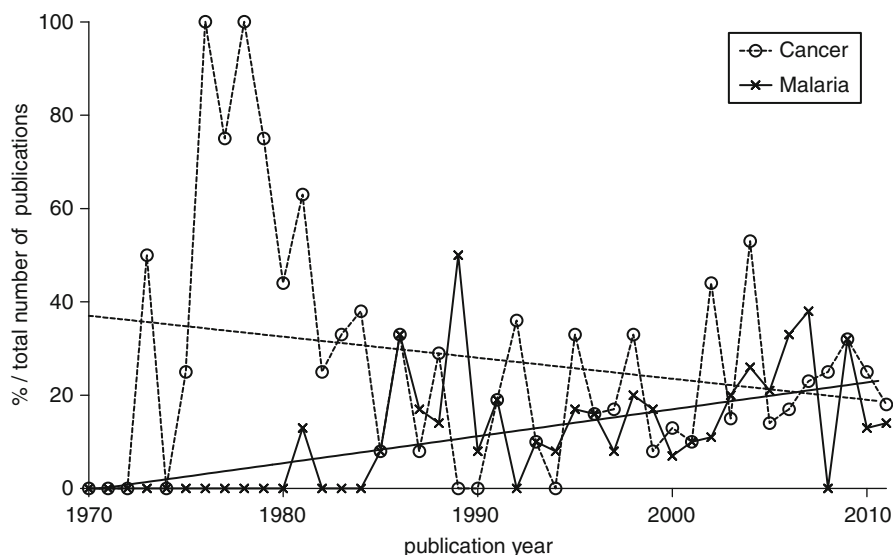
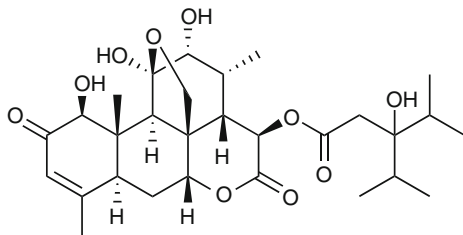


Fig. 125.8 Trends in numbers of publications on anticancer and antimalarial activities of quassinoids from 1970 to 2011

2 Pharmacological Applications

2.1 Historical Perspective and In Vitro Cytotoxic Activities

The decade that followed the discovery of the antileukemic activity of bruceantin is marked with a strong interest of the scientific community for the study of the anticancer properties of quassinoids. Bruceantin was isolated in 1973 by Kupchan from the stem bark of *Brucea antidysenterica* Mill. and identified as the active ingredient of this tree used against cancer in Ethiopia [41]. Following this discovery, many plants of the Simaroubaceae family were studied, and more than twenty molecules with high in vitro cytotoxic activity were isolated between 1973 and 1985, including dehydroailanthinone from *Pierreodendron kerstingii* (Engl.) Little [42], quassamarin extracted from *Quassia amara* [43], bruceoside A from *Brucea javanica* (L.) Merr. [44], samaderine E from *Samadera indica* Gaertn. (syn. *Quassia indica*) [45], and sergeolide from *Picrolemma pseudocoffea* Ducke (syn. *Picrolemma sprucei* Hook.f.) [7]. Quassinoids' in vitro anticancer activity has been broadly compiled in excellent reviews [46, 47]. Bruceantin was the first quassinoid introduced in clinical trials (see Sect. 2.2), but the unsatisfactory results obtained led to a decline in interest in research on anticancer activity of quassinoids. Since 2000, new results on bruceantin have suggested that the activity of this molecule towards certain types of cancer (leukemia, lymphoma, myeloma) deserves further investigation [48]. To date, the quassinoids therefore remain a family of molecules with potential in the context of the search for anticancer compounds.

Fig. 125.9 NBT-272

2.2 In Vivo Anticancer Assays with Quassinoids, Clinical Trials

Quassinoids have been widely studied for their anticancer activity *in vitro*, however, only a few of them have shown interesting activity. Bruceantin was active in animal models against melanoma, colon cancer and leukemia [41, 48]. According to Cuendet et al. (2004), male mice seemed to be more sensitive to bruceantin than females, independent of the age of the treated mice. It was claimed that doses of 2.5 and 5.0 mg kg⁻¹ promote the regression of earlier and advanced tumors (multiple myeloma, RPMI 8,226 cells) without apparent toxicity [49]. Phase I and II clinical trials were conducted with this compound. Unfortunately, no objective regression of the proliferative process was observed in humans, whereas a relative toxicity was noticed (hypotension, nausea, and vomiting at low dose, thrombocytopenia at higher dose) [50–53].

NBT-272, a semisynthetic analogue of bruceantin (Fig. 125.9), was found to be two to tenfold more potent than the original compound in inhibiting the cellular proliferation of a variety of cancer cell lines [54]. It also prevented tumor progression in a xenograft model of neuroblastoma cells with coinciding reduction of MYC expression and ERK activation in treated tumors [55].

Peninsularinone extracted from *Castela peninsularis* Rose, has been shown to be very active against pancreatic adenocarcinoma at 4.3 mg kg⁻¹ and against colon adenocarcinoma (3.2 mg kg⁻¹) in animal models. The most surprising observation was that a lethal dose of peninsularinone could be administered safely in previously treated animals with low non-toxic concentrations a few days before the injection of the lethal dose. Interestingly, this molecule could be synthesized from glaucarubolone (isolated from *Castela polyandra* Moran & Felger) [56], which also showed activity in this model. Chapparinone, a related compound, also showed potential clinical application according to National Cancer Institute standards in the treatment of colon adenocarcinoma due to its activity against C38 cells implanted in mice [56].

15-desacetylundulatone, isolated from *Hannoa klaineana* Pierre & Engl root bark, which has free hydroxyl functions at C-1, C-11, and C-12 and an ester chain at C-6, was active against P388 leukemia in mice at doses up to 100 mg kg⁻¹. Remarkably, when the carbonyl group in C-2 was reduced, the activity dropped dramatically [57].

Administration of simalikalactone E (SkE) to nude mice implanted with K562-luc human leukemia cells resulted in leukemia regression at 1 mg kg⁻¹

SkE [58]. New assays against leukemia should be conducted with quassinoids as SkE and/or bruceantin are strongly active against leukemia cell lines in which Ras/Raf/MEK/Erk and c-MYC are activated.

2.3 Historical Perspective and In Vitro Antiplasmodial Activities

The emergence of resistance of the human malaria parasite *Plasmodium falciparum* to all commercialized antimalarials is of great concern for mankind. The wide use of Simaroubaceae species against malaria in areas of endemism stimulated the study of quassinoids and derivatives against *Plasmodium species*. As early as 1930, a quassinoid glycoside isolated from the seeds of *Simaba cedron* Planch. demonstrated an interesting potential for the treatment of malaria via the parenteral route, but renal secondary effects at high doses were recorded [59]. In 1947, the pharmaceutical company Merck screened around six hundred plant extracts on bird malaria models in vivo to find new antimalarials [60]. From the Simaroubacea family many plants were found to have excellent activity against *Plasmodium gallinaceum* in chickens: *Castela spinosa* Cronquist, *Castela tortuosa* Liebm., *Castela tweediei* Planch., *Mannia africana* Hook. f. (syn. *Pierreodendron africanum* (Hook.f.) Little), *Picrolemma sprucei*, *Simaba cedron*, *Simaba cuneata* A.St.-Hil. & Tul., *Simaba insignis* A.St.-Hil. & Tul., *Simarouba amara*, *Simarouba berteroa* Krug & Urb., *Simarouba glauca* DC., *Simarouba tulae* Urb. Unfortunately, at the end of the World War II, the company stopped the project and no further study was conducted on these plants.

The investigation of the antimalarial properties of quassinoids then restarted at a significant rate in the mid-1980s and has remained relatively constant since then. Review articles on the antimalarial activity of quassinoids were published by Muhammad and Samoylenko in 2007 [59] and Guo et al. in 2005 [47].

The discovery of antiparasitic activities of quassinoids (see Sect. 4) prompted some authors to study the antimalarial potential of these molecules [61]. Among the quassinoids highlighted as potential antimalarials by Trager and Polonsky were simalikalactone D, identified as the most active molecule with complete inhibition of parasite growth at a dose of $2 \mu\text{g ml}^{-1}$, as well as glaucarubinone and soularubinone. Other compounds, such as sergeolide [62] and bruceantin [63], also showed significant antiplasmodial activity.

Studies based on traditional use of Simaroubaceae continued in the 1980s, especially by Phillipson et al. [63–67]. Many articles on this subject followed, with, for example, the reisolation of simalikalactone D and the isolation and characterization of gutolactone from the bark of *Simaba guianensis* Aubl., a species used by people in the Amazon Basin [68]. Also, cedronin was isolated from the bark of *Simaba cedron*, a species used in Central and South America for the treatment of malaria [69], and samaderines B, E, X, and Z were isolated from *Quassia indica* branches used in the Indonesian traditional pharmacopeia [70]. In our work, it was chosen to test the traditional remedies as prepared by local people. This approach highlighted the remarkable activity of a decoction made from the

leaves of *Quassia amara* [71, 72]. Later, it was shown that the antimalarial activity of this remedy could originate from the presence of two quassinoids: simalikalactone D (SkD) isolated from an optimized young leaf tea and simalikalactone E (SkE) isolated from a mature leaf decoction [73–76]. SkD was shown to be responsible for both the antimalarial activity and the cytotoxicity of the young leaf preparation. Overall, these studies take all their importance within the framework of the World Health Organization's recommendations on the evaluation of traditional medicines.

2.4 In Vivo Antimalarial Activity of Quassinoids in Murine Models

We will focus herein on compounds harboring antimalarial activity in vivo in a mouse model. Because that model requires more facilities than culture and larger amount of compound, only a few quassinoids have been studied against murine malaria. Among them, less than 20 quassinoids showed interesting activity. They were isolated from six species (*Ailanthus altissima*, *Brucea javanica*, *Hannoa chlorantha* Engl. & Gilg. (syn. *Quassia undulata* (Guill. & Perr.) D. Dietr.), *Picrolemma pseudocoffea*, *Quassia amara*, *Simaba cedron*) or were semisynthesized from quassinoids extracted from *B. javanica* (Table 125.1).

They can be separated into the following two classes derived from a core C₂₀ carbon skeleton as suggested by Muhammad and Samoylenko [59]:

- Class A: quassinoids with the C-8(13)-oxymethylene bridge in the C ring isolated from *Brucea*, *Quassia*, *Simaba*, *P. pseudocoffea*, and semisynthetic bruceolide derivatives.
- Class B: quassinoids with the C-8(11)-oxymethylene bridge reported from *Ailanthus* and *Hannoa*.

The authors claimed that the quassinoids with a C-8(13)-oxymethylene group were five to tenfold more potent than C-8(11)-oxymethylene analogs in vitro. In vivo, this scheme does not appear so clear.

In class B derivatives, the activity seems to be influenced by the presence or absence of a hydroxyl group or a side chain at the C-15 position. Hence, 15-hydroxy-ailanthone isolated from *A. altissima* is very active (ED₅₀ 0.76 mg kg⁻¹ day⁻¹ when administered orally); while chaparrine, which lacks function in the C-15 position, is inactive [66]. Interestingly, carbonyl group in C-2 is also important; when position 2 is occupied by a hydroxyl substituent (chaparrine) instead of a ketone (chapparione) the activity disappears. The difference between in vivo activity of glaucarubin (with a C-2 hydroxyl group) inactive and glaucarubinone (=O) very active (ED₅₀ 0.86 mg kg⁻¹ day⁻¹ upon oral administration) is another example. It seems that the length of the C-15 substituent does not influence the antimalarial activity because ailanthone, ailanthinone, and glaucarubinone present the same antimalarial potential. Montjour et al. [77] showed that glaucarubinone was ineffective against *P. berghei* when administrated once by oral route at 2.5 mg kg⁻¹ and was effective by intraperitoneal route at 0.5 mg kg⁻¹ day⁻¹ for

Table 125.1 In vivo antimalarial activity of natural and semisynthetic quassinoids against murine *Plasmodium*

Origin	Molecule	<i>Plasmodium</i> species	Route	ED ₅₀ mg kg ⁻¹ day ⁻¹	Ref
<i>Ailanthus altissima</i> (Mill.) Swingle (stem)	Ailanthone	<i>P. berghei</i>	Oral	0.76	[66, 77]
	Ailanthinone			1.25	
	Glaucarubinone			0.86	
<i>Brucea javanica</i> (L.) Merr. (fruits)	Brucein A	<i>P. berghei</i>	Oral	3.36	[65]
	Brucein B			0.9	[79]
	Brucein C			Inactive	[80]
	Brucein D			2.79	
	Brusatol			1.27	
	Bruceolide			0.46	
Semisynthetic from bruceolide	3,15-Di- <i>O</i> - ethylcarbonyl	<i>P. berghei</i>	Intraperitoneal	0.49	[80]
	3,15-Di- <i>O</i> - isopropylcarbonyl			1.4	
	3,15-Di- <i>O</i> - methylcarbonyl			1.3	
	3,15-Di- <i>O</i> -acetyl			0.46	
	3,15-di- <i>O</i> -acetyl			0.46	[79]
<i>Hannoa chlorantha</i> Engl. & Gilg. (syn. <i>Quassia undulata</i> (Guill. & Perr.) D.Dietr.) (seeds & roots)	Chaparrinone	<i>P. berghei</i>	Subcutaneous	<50	[78]
	14- Hydroxychaparrinone			<50	
	15- Desacetylundulatone			<50	
<i>Picrolemma</i> <i>pseudocoffea</i> Ducke (syn. <i>P. spruce</i> Hook. f.) (roots)	Sergeolide	<i>P. berghei</i>	Subcutaneous	0.2	[62]
<i>Quassia amara</i> L. (leaves)	Simalikalactone D	<i>P. yoelii</i>	Oral	3.7	[73, 76]
	Simalikalactone E	<i>P. vinckeii</i>	Subcutaneous	0.5	
			Oral	1	
<i>Simaba cedron</i> Planch. (Stem bark)	Cedronin	<i>P. vinckeii</i>	Intraperitoneal	1.8	[71]

12 days. The authors also observed toxicity at doses > 2.5 mg kg⁻¹ (oral) and 0.5 mg kg⁻¹ (intraperitoneal). According to François et al. [78] among the quassinoids isolated from *Hannoa chlorantha*, the most active one was 15-desacetylundulatone but the EC₅₀ was not calculated. Nevertheless, the administered doses (50 mg kg⁻¹) were high and close to the toxic range. Authors proposed to split the treatment in several lower doses, but further such experiments have not been described so far. Interestingly, 15-desacetylundulatone is functionalized in position C-6 as SkE, a very active class A compound (see below).

In class A, brucein derivatives are almost all equally potent; the presence of either a hydroxyl or a short acyloxy substituent in C-15 does not influence the antimalarial activity. Nevertheless, with a too long/bulky acyloxy group, the activity drops dramatically (brucein A vs brucein C) [65]. Semisynthetic derivatives of bruceolide [79] were found more potent than chloroquine, increasing by four times the life span of treated mice without noticeable signs of toxicity even at doses of 3 mg kg^{-1} . For example, ED_{50} for 3,15-*O*-diacetylbruceolide was 0.46 mg kg^{-1} , but this compound was unable to remove malaria parasites in the blood stream of infected mice completely [80]. Authors suggested that the 15-acetoxy substituent was critical to the *in vivo* antimalarial efficiency. Nevertheless, to the best of our knowledge, no other semisynthetic quassinoid derivative has been studied for antimalarial purposes.

SkE seems to be almost four times more active *in vivo* than SkD [73, 76], but the *Plasmodium* species used for the test were different: *P. vinckei* for SkE and *P. yoelii* for SkD, *P. vinckei* being usually almost ten times more sensitive to treatment than *P. yoelii* [81].

Sergeolide isolated from roots of *Picrolemma pseudocoffea* had an original structure with a butenolide function attached to the ring A. It had been shown to be active *in vivo* against *P. berghei* ($\text{ED}_{50} 0.2 \text{ mg kg}^{-1} \text{ day}^{-1}$), unfortunately with a poor therapeutic index (median lethal dose $\text{LD}_{50} 1.8 \text{ mg kg}^{-1}$) [62].

Compared with the plethora of studies on antiplasmodial activity against *P. falciparum* *in vitro*, *in vivo* antimalarial assays dedicated to quassinoids are scarce and hardly comparable. Nevertheless, the excellent antimalarial activities highlighted in those studies should open the way to complementary studies of their pharmacokinetics and toxicity. Association with other antimalarials should also be investigated in order to define new therapeutic schemes and to lower the administered doses, increasing drugs' tolerability.

3 Mechanisms of Action

Anticancer activity is one of the most striking biological properties of quassinoids. It has been particularly well documented and is still a source of discoveries. Many mechanisms of action have been proposed, including inhibition of phosphoribosyl pyrophosphate aminotransferase of the *de novo* purine synthesis pathway [82], inhibition of aerobic respiration [83], mitochondrial membrane depolarization, activation of caspase-3 [84], and alteration of microtubules [85]. It is also generally well accepted that quassinoids restrain protein synthesis, inhibiting the polypeptide chain elongation that prevents the first round of peptide bond establishment prior to polysome formation [86–88], this inhibition being reversible [87]. In particular, bruceantin binds to the peptidyl transferase center on ribosomes [89]. Brusatol has been claimed to decrease c-MYC oncoprotein expression at the post-transcriptional level [90] and to up-regulate mRNA levels of transcription factor NF- κ B [91] and phosphorylate NF- κ B inhibitors promoting NF- κ B translocation into the nucleus. On the contrary, brucein D has been shown to inhibit NF- κ B,

increasing the protein level of I κ B- α , known to sequester NF- κ B in the cytoplasm and prevent its nuclear translocation. It has also been shown to generate oxidative stress depleting GSH and to activate p38-MAPK pathway. Some authors suggested that discrepancies between these related molecules are due to different methodologies [46].

Quassinoids also impair the protein synthesis mediated by the translation initiation factor 4E [92]. A lipophilic extract of *Nothospondias staudtii* Engl. inhibited Activator Protein-1 (AP-1), a transcription factor found in cellular nucleus, known to promote tumoral progression under certain conditions [93]. A quassinoid analogue, NBT-272, was reported to induce down-regulation of c-MYC in medulloblastoma-derived cells [54]. Castelletti et al. [55] showed that this molecule interferes with AKT and MEK/extracellular signal-regulated kinase pathways. The authors suggested that the depleting effect of NBT-272 on MYC protein expression occurred via indirect mechanisms, rather than selective inhibition. Crude extract and fractions of *Eurycoma longifolia* have been shown to induce apoptosis via a caspase-9-independent pathway in MCF-7 breast cancer cells [94]. This finding was corroborated by Zakaria et al. [95], who showed that an eurycomanone-enriched fraction was able to induce apoptosis via the p53 pathway in HepG2 liver cancer cells. More recently, Wong et al. [96] found that eurycomanone reduced the abundance expression of the following lung cancer cells markers: heterogeneous nuclear ribonucleoprotein A2/B1, p53 tumor suppressor protein and other cancer-associated genes including prohibitin, annexin 1, and endoplasmic reticulum protein 28 but not the housekeeping genes. Another bruceantin analog has been shown to inhibit the phosphorylation of upstream elements of HIF-1 α (ERK1/2, MNK1 and eIF4E), a clue mediator of cellular responses to low oxygen, over-expressed in certain cancers [97]. It has been suggested that its effect was the consequence of the inhibition of this dependent MAPK cascade (HIF-1 α upstream elements) and/or the inhibition of the phosphorylation of eIF4E, which inhibits HIF-1 α translation.

In the case of *Plasmodium*, the main accepted mechanism of action is that quassinoids target plasmodial protein synthesis [98]. Arnot and Gull [99] showed that throughout *P. falciparum* growth inside the red blood cell, protein synthesis increases rapidly while the DNA synthesis peaks between the 20 and the 38 h of its blood cycle. Afterwards, DNA, RNA, and protein synthesis decrease dramatically at the schizont stage announcing the end point of the cycle. Interestingly, when SkE was pulsed every 6 h in a *Plasmodium falciparum* synchronous culture, it was found more effective at stages when DNA synthesis occurs [76]. This finding was corroborated by Bertani et al. [100], who showed that when SkD was pulsed every 4 h, the half-inhibitory concentration (IC₅₀) dropped to 10 nM at the 30 h, when the production of plasmodial DNA is maximal and rate of protein synthesis still elevated. SkD targets a very particular moment of *Plasmodium* growth. It is almost inactive on young and old stages while it is strongly active on mature cells at the DNA replication stage. Mata-Greenwood et al. [101] showed in 2001 that some quassinoids are able to inhibit DNA synthesis with greater efficacy when these molecules possess a C-15 ester side chain; that is the case for SkD.

Bertani et al. [100] also showed that SkD was inactive against heme biomineralization process and did not affect permeability pathways induced by a parasite in the host erythrocyte membrane. They also showed that SkD enhanced the activity of atovaquone on *Plasmodium* mitochondrial membrane potential, while it had an additive effect when combined with other commercial antimalarials.

4 Other Biological Activities and Ethnopharmacological Relevance

An extensive search for antimalarial compounds among the quassinoids was inspired by the discovery in the 1950s of the antiparasitic properties of these compounds, especially towards *Entamoeba histolytica* [61]. Glaucarubine's amoebicide property, isolated from *Simarouba glauca*, had been discovered a few years earlier [102]. Many antiparasitic activities would later be identified for extracts and molecules from the Simaroubaceae: amoebicidal (bruceantin [103], *Castela texana* (Torr. & A. Gray) Rose (syn. *Castela tortuosa*) [104]), nematicide (chaparrinone, klaineaneone, and glaucarubolone [105], samaderins B and E [106]), antibabesial (*Brucea javanica* extract, and brusatol, bruceantin, brucein, abruceantinol, dehydrobrusatol, and dehydrobrucein A isolated from this species [107, 108]).

Many other activities were also recorded for quassinoids: insecticidal, antiviral, anti-inflammatory, and so on. These were extensively reviewed by Guo et al. and Almeida et al. [47, 109], thus justifying the interest in drawing parallels between the biological activities identified *in vitro* or *in vivo* for these molecules and the traditional uses of species from which they come.

Species belonging to the Simaroubaceae family are widely referenced in the pharmacopoeias of different medical systems around the world, whether they be of contemporary or ancient use, transmitted orally, or from written sources. For example, *Ailanthus altissima*, the area of natural distribution of which extends from Manchuria to Malaysia, is one of the most cited species in ancient Chinese medical treatise for a wide range of indications. One of the oldest recipes for this species has been recorded in a book in China dating back to 732 AD for the treatment of mental illness [110]. Its bark is still registered in actual Chinese and Asian pharmacopoeias, and it is traded across China. The same applies to *Brucea javanica* fruits in Southeast Asia and to *Ailanthus excelsa* Roxb. bark, mentioned in ancient and contemporary ayurvedic medicine books [111]. The use of *Brucea antidysenterica* bark has also been documented since the sixteenth century in ancient Arabic medical pharmacopoeias [112].

Moreover, some species have been introduced, naturalized, cultivated, and marketed outside their original distribution area with respect to their therapeutic value. This is the case for *Simarouba amara*, introduced in India; *Ailanthus altissima*, introduced as an ornamental and medicinal plant in North America, then in Europe; *Brucea javanica*, now cultivated in Africa; and *Quassia amara*, a few specimens of which were introduced in Africa and India. In their country of

origin, *Ailanthus altissima*, *Ailanthus excelsa*, *Brucea javanica*, *Castela tortuosa*, *Eurycoma longifolia*, *Picrasma excelsa*, *Quassia amara*, *Quassia indica*, *Simaba cedron*, and *Simarouba amara*, among others, are still prepared under more or less advanced galenic forms and some are even for sale on the Internet.

Within the 102 Simaroubaceae species, an exhaustive bibliographic investigation (Table 125.2) highlights about twenty of most used species in traditional medicine. The most cited genera worldwide are *Ailanthus*, *Brucea*, *Castela*, *Eurycoma*, *Hannoa*, *Picrasma*, *Picrolemma*, *Quassia*, *Simaba*, and *Simarouba*. Despite the multiplicity of species, their geographic distribution range, and therefore the extreme cultural diversity that underlies their use, there is a marked homogeneity in the uses made of these species. Much of the uses of Simaroubaceae are first centered on the gastrointestinal sphere and the corresponding organs (stomach, liver, small intestine, colon). *Ailanthus triphysa* (Dennst.) Alston, *Brucea antidysenterica*, *Eurycoma longifolia*, *Picrasma excelsa*, *Quassia amara*, and *Simarouba amara* are recommended for their invigorating “tonic” and stimulating effect and used to increase appetite, in cases of dyspepsia, and for indigestion. *Ailanthus altissima*, *A. excelsa*, *Hannoa klaineana*, *Picrasma crenata* Engl. in Engl. & Prantl., *Picrasma quassioides* (D. Don) Benn., *Quassia africana*, *Q. gabonensis* Pierre, *Simaba cedron*, and *Simarouba amara* are prescribed as intestinal antispasmodics and in cases of acute colic with or without diarrhea.

Simple diarrhea, without blood, can be treated with *Ailanthus altissima*, *A. excelsa*, *Brucea antidysenterica*, *B. javanica*, *Castela coccinea* Griseb., *Eurycoma longifolia*, *Quassia amara*, *Q. undulata*, and *Simarouba amara*; bloody dysenterical diarrhea is treated by the administration of *Ailanthus altissima*, *A. excelsa*, *A. triphysa* (Dennst.) Alston., *Castela coccinea*, *C. erecta* Turpin, *C. tortuosa*, *Eurycoma longifolia*, *Picrasma excelsa*, and *Simaba cedron*. The most widely used species, the effectiveness of which has been demonstrated for this indication, is *Simarouba amara* (bark and seeds), together with the fruits of *Brucea antidysenterica* and *Brucea javanica*. Stomach pains are treated with *Brucea antidysenterica*, *Castela tortuosa* (syn. *Castela texana*), *Picrasma excelsa*, *Picrolemma sprucei*, *Quassia amara*, *Q. gabonensis*, *Q. indica*, *Q. undulata*. The seed kernels of *Simaba cedron* have an effect on hepatic colic and liver tropism. This is justified in the context of traditional medicine by their bitterness. Indeed, most Simaroubaceae are extremely bitter [72], as it is the case for *Brucea antidysenterica*, *Castela tortuosa*, *Eurycoma longifolia*, and *Quassia amara*, used in cases of jaundice and other chronic liver diseases. Antidiabetic and/or lipolytic remedies *Castela tortuosa*, *Picrasma crenata*, *Picrolemma sprucei*, *Quassia amara*, and *Simaba orinocensis* Kunth. may also target liver.

Ailanthus altissima, *Brucea antidysenterica*, *Picrasma excelsa*, *Quassia africana*, *Quassia undulata*, *Simaba cedron*, and *Simarouba amara* are also used as anthelmintics.

Simaroubaceae are broadly used against dermatological conditions from bacterial origin (furuncles, superinfected wounds, erysipelas, acne, abscesses), parasitic origin (leishmaniasis), related to the presence of dermatophytes (ringworm), to those described as warts or “cancerous tumors of the skin,” tropical ulcers, and

Table 125.2 Medicinal uses of Simaroubaceae species (Part of plant used: *AP* aerial part, *Bd* bud, *Ft* fruit, *L* leaf, *Bk* bark, *RBk* root bark, *R* root, *Res* resin, *S* seed, *SBk* Stem bark, *St* stem, *Wd* wood)

Species and main geographic distribution of registered uses	Uses (part of plant used)
<i>Ailanthus altissima</i> (Mill.) Swingle (China, South east Asia)	Anthelmintic (Bk), cutaneous parasitic ulcers (L, Bk, Rbk), kala azar (Bk), intestinal hemorrhage (Bk, RBk), spermathorrea (Bk) [113]; Cardiovascular disease (L), asthma (Bk, R), epilepsy (L), antispasmodic (gastro-intestinal) (L) [114]; Dysentery (Bk, L, RBk) [113–115]; Diarrhea (Bk, RBk) [113, 115]; Leucorrhea (Bk) [115, 116]; Menstrual disorders (Bk, RBk) [113, 116]; Uterine hemorrhage (Bk, RBk) [115]
<i>Ailanthus excelsa</i> Roxb. (India)	Asthma (SBk), antispasmodic (gastro-intestinal) (SBk) [117]; Affection of the mouth (L), cough (L), leucorrhea (L), skin ulcers (BK, L), uterine hemorrhage (L) [116]; Contraceptive effect (L, SBk) [118]; Diarrhea (Bk, L), dysentery (BK, L), menstrual disorders (Bk, L) [111, 116]
<i>Ailanthus integrifolia</i> subsp. <i>calcynia</i> (Pierre) Noot. (Nepal, North India)	Furunculosis (Res) [119]
<i>Ailanthus triphysa</i> (Dennst.) Alston (South East Asia)	Dysentery, dyspepsia, bronchitis (Bk, Res) [113]
<i>Brucea antidysenterica</i> J.F.Mill. Southern and Eastern Africa, Tropical Africa	Asthmatic disorders (L, R), digestive (Bk, Ft, L, R, S), cancerous tumor of the skin (L, S) [120]; Diarrhea (Bk, Ft, L, R, S) [112, 114, 120]; Dysentery (Bk, Ft, R) [114, 120, 121]; Fever (Bk, Ft, R) [114, 120]; Hepatitis (AP, Ft) [121, 122]; Leprosy (L) [112]; Ringworm (L) [122]; Skin disease (L, St), wounds (L, St) [112, 120]; Snake bite (Ft), teeth problem (Ft) [121]; Stomachic (Bk, Ft, L, R, S) [120, 122]
<i>Brucea javanica</i> (L.) Merr. China, South East Asia	Animal bites (L), diarrhea (Ft), furunculosis (L), dysentery (Bk, Ft, RBk), intestinal hemorrhage (Bk, Rbk), piles (Ft), poison (antidote) (R) [113] ; Malaria (Ft, L) [113, 123, 124]; Ringworm (L) [113, 125]; Skin corn (Ft), wart (Ft), wounds, skin ulcers (Ft) [124]
<i>Castela coccinea</i> Griseb. Bolivia	Dysentery, diarrhea (Fr, L) [126]
<i>Castela emoryi</i> (A.Gray) Moran & Felger	Skin disease (Bd) [127]
<i>Castela erecta</i> Turpin Central America	Skin disease, dysentery, fever [128]

(continued)

Table 125.2 (continued)

Species and main geographic distribution of registered uses	Uses (part of plant used)
<i>Castela tortuosa</i> Liebm. Mexico	Diabetes (Bk, L, St) [129, 130]; Dysentery, fever (AP), stomachic (AP) [129]; Liver problem (L, St) [130]
<i>Eurycoma longifolia</i> Jack South East Asia	Aphrodisiac (R) [131]; Diarrhea, (Rbk, R), dropsy (R), dysentery (Fr), fever (RBk, R), hepatitis (R, Rbk), indigestion (Bk), antidote (poison) (R), skin disease (L) [113]; Malaria (R, Rbk) [113, 123]
<i>Hannoa klaineana</i> Pierre et Engl. Tropical Africa	Antispasmodic (gastro-intestinal) (R) [132]; Cough (Bk) [133] Intestinal disease, malaria (R) [134]
<i>Hannoa undulata</i> <i>Picrasma crenata</i> Engl. in Engl. & Prantl	Cf. uses under <i>Q. undulata</i> . Antidote (poison), malaria (Bk), wound (L) [113]
Tropical America	Anthelmintic, cardiovascular disease, diabetes, digestive, dysentery, fever, intestinal disease, malaria, tonic (Wd), syphilis (St) [20]
<i>Picrasma excelsa</i> (Sw.) Planch. Caribbean islands	Alcohol weaning (Wd) [27]; Anthelmintic, digestive, dysentery, fever, malaria, stomachic, tonic (Wd) [20]
<i>Picrasma javanica</i> Blume South East Asia	Antidote (poison), malaria (Bk), wound (L) [113]
<i>Picrasma quassioides</i> (D. Don) Benn. Nepal, South East Asia	Skin disease (L) [135]; Fever, stomachic (Bk) [113]
<i>Picrolemma sprucei</i> (Hook.) f. Tropical South America	Diabetes, malaria (L, St) [136]; Stomach pain [137]
<i>Quassia africana</i> (Baill.) Baill. Tropical Africa	Anthelmintic (Bk, L), wounds, skin ulcers (RBk), menstrual disorders (L) [132]; Intestinal disease, antispasmodic (gastro-intestinal) (Bk, L), sexually transmitted disease (Bk), bronchitis (R), fever (Rbk) [132, 133]; Malaria (L, R) [138]
<i>Quassia amara</i> L. Tropical America	Anthelmintic, cholagogue (StBk), snake bite (R) [136]; Diabetes (L, StBk, Wd), stomach pain (L, Wd) [20] ^a ; Diarrhea (Wd) [20]; Liver, tonic (StBk, Wd) [20, 136]; Malaria (L) [71]

^aBourdy G. 2003, unpublished data from French Guiana

other skin diseases (psoriasis, eczema, pruritus, rash), together with affections of the oral mucosa. Seventeen species are applied locally to treat these conditions: *Ailanthus altissima*, *A. excelsa*, *A. integrifolia* subsp. *calcyntia* (Pierre) Noot., *Brucea antidysenterica*, *B. javanica*, *Castela emoryi* (A.Gray) Moran & Felger,

C. erecta, *Eurycoma longifolia*, *Picrasma javanica* Blume, *P. quassioides*, *Quassia africana*, *Q. amara*, *Q. gabonensis*, *Q. indica*, *Q. undulata*, *Simaba cedron*, and *Simarouba amara*.

The Simaroubaceae find their field of election in the treatment of malarial fevers, which makes these species a major therapeutic recourse in places where the disease is endemic. The species most used against malaria worldwide are *Brucea javanica*, *Eurycoma longifolia*, *Hannoa klaineana*, *Picrasma excelsa*, *Picrasma javanica*, *Picrolemma sprucei*, *Quassia africana*, *Q. amara*, *Q. indica*, *Simaba cedron*, and *Simarouba amara*. As a corollary to the antibacterial and antiparasitic activities of quassinoids, the Simaroubaceae *Brucea antidysenterica*, *Castela erecta*, *C. tortuosa*, *Eurycoma longifolia*, *Picrasma excelsa*, *P. quassioides*, *Quassia africana*, *Q. amara*, *Q. indica*, *Q. undulata*, *Simaba cedron*, and *Simarouba amara* in particular are widely used against febrile illnesses of various etiologies.

Another major indication of the Simaroubaceae also focuses on the respiratory system, and *Ailanthus altissima*, *A. excelsa*, *A. triphysa*, *Brucea antidysenterica*, *Hannoa klaineana*, *Quassia africana*, *Q. gabonensis*, and *Q. undulata* are prescribed in case of serious pulmonary infections (bronchitis, asthma, cough, emphysema, bronchopneumonia).

Some Simaroubaceae also display therapeutic actions on the male or female reproductive system: *Simaba cedron* and *Simarouba amara* are used during childbirth and in the postpartum period; *Ailanthus altissima* and *Simarouba amara* are known to stop uterine bleeding; *Ailanthus excelsa* is contraceptive; and *A. altissima*, *A. excelsa*, *Quassia indica*, *Q. africana*, *Picrasma crenata*, and *Simarouba amara* regulate menstruation and are sometimes used in cases of vaginal leucorrhea, some of which may be due to the presence of vaginal parasites. For the male reproductive tract, *Ailanthus altissima* cures spermatorrhea; *Eurycoma longifolia* and *Quassia undulata* are reportedly aphrodisiacs; and *Picrasma crenata* and *Quassia africana* are used against syphilitic venereal diseases.

Lastly, three Simaroubaceae species are described as antivenom (*Brucea antidysenterica*, *Quassia amara*, and *Simaba cedron*, with a very strong convergence of use for the cotyledons of *Simaba cedron* seeds in South America). *Brucea antidysenterica*, *Brucea javanica*, *Eurycoma longifolia*, *Quassia undulata*, and *Picrasma javanica* are known as antidotes to food poisoning or other types poisoning. Central nervous system troubles, such as dementia, nervousness, and epilepsy, and alcohol addiction are treated with preparations of *Ailanthus altissima*, *Quassia undulata*, *Simarouba amara*, or *Picrasma excelsa*.

Used for centuries to treat frequent, sometimes life-threatening, medical tropical conditions (malaria, amoebic dysentery, infectious diarrhea in young children), the Simaroubaceae have demonstrated a real therapeutic interest with remarkable convergence of practice undoubtedly linked to the strong antiparasitic, antibacterial, and antiproliferative activities of quassinoids. Moreover, functional activities justifying organotropisms also contribute to the effectiveness of Simaroubaceae medicinal plants, making them an invaluable resource and justifying their inscription in national pharmacopoeias.

5 Conclusion

Quassinoids are a family of molecules with a broad range of remarkable pharmacological activities (anticancer, antimalarial, ameobicide, nematocidal, anti-inflammatory, antiviral, and so on), the most of which is being made through the still active use of the Simaroubaceae in traditional medicines. Quassinoids' pharmacological potential has been largely demonstrated in the laboratory both in vitro and in vivo. Nevertheless, no drug has been developed so far from these substances. With respect to their anticancer activity, these compounds have not been up to expectations against cancers for which they were tested (breast cancer and melanoma). They are likely to be more efficient against hematological cancers but this remains to be demonstrated. Also, the antimalarial activity seems to be associated with some toxicity, and these compounds have never been placed into clinical trials for their antimalarial potential. However, the results described in the literature speak in favor of the search for new active and less toxic quassinoids and the parallel development of further structure-activity relationship studies aiming at improving the antimalarial selectivity of these natural products. The discovery of synergistic interactions between quassinoids and other clinical antimalarial drugs can also contribute to circumvent the obstacle of their toxicity. Finally, considering the structural complexity of these highly oxygenated molecules containing multiple stereocenters, quassinoids' total synthesis also remains an interesting challenge.

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