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1. Introduction

Since a long time ago health sciences and natural products have been linked by the use of remedies and poisons, and nowadays there is little doubt that humans used natural drugs long before the emergence of written history [1,2]. The Ebers Papyrus dating from about 1600 BC, is one of the oldest medical treatise, which documents natural product-derived drugs used by the Sumerians and Akkadians in the 3rd century BC. Today there is information on medicinal plants dating back over about 500 years, as documented in herbaria. Laboratory studies of medicinal natural products started only about 200 years ago, with the isolation of morphine, an alkaloid, from opium (Papaver spp.) [2,3].

Aspidosperma genus (Apocynaceae) species are trees of a great diversity of sizes that grow in different habitats and are distributed mainly among the Americas; In Brazil about 50 species of this genus have been catalogued [4–6]. There are several reports in the literature concerning the folk utilization of plants of this genus, as in treatment of malaria, dysentery, appendicitis, wounds, fever, dyspnea, asthma, scabies, stomachache, cough, constipation, boils, rheumatism, leishmaniasis, toothache, urinary tract inflammation and dermatitis. However several studies show that some plants of the genus are not recommended for pregnant women because of their potential abortifacient and teratogenic effects [7–28].

Given the diversity of popular uses of plants of the genus Aspidosperma as well as the predominance of terpenoid-alkaloids production in this genus and the importance of these substances for organic synthesis, medicinal chemistry and for knowledge of the biosynthetic
pathways used by plants to produce them, we propose to review the literature concerning the aspidosperma-type terpenoid-alkaloids chemical synthesis and their biological potential.

2. Biosynthesis of Aspidosperma terpenoid alkaloids

The isolation of alkaloids from species of *Aspidosperma* trees and their structural elucidation give rise to theories that attempt to explain their biosynthetic origin. In the field of indole-type alkaloids, one of the earliest theories to explain its biosynthesis arose in 1933, proposing that this type of alkaloid has origin in the reaction between tryptophan, phenylalanine and glycine (although at the time the proposed structures do not represent exactly the known reality today) [29]. Revisions of this theory lead to a new biosynthetic route, proposing that the indole-type alkaloids are derived from shikimic and prephenic acids and their interactions with seco-prephenate-formaldehyde units and aromatic aminoacids as tryptamine and tryptophan (figure 1) [30,31]. As Aspidosperma type alkaloids were isolated theories that tried to explain their biosynthetic origin began to emerge, which, at this moment, were based on the chemical synthesis of such alkaloids, as done by several research groups [32].

![Figure 1. Early propositions for indole alkaloid precursors.](image)

Early work on proof of terpenoid alkaloid biosynthesis were based on administration of deuterium-labelled precursors of alkaloids to the plants tested and analysis of the metabolites produced to confirm a proposed biosynthetic way. The earliest proposition for the biosynthesis of Aspidosperma terpenoid alkaloids was the synthesis via mevalonate pathway, demonstrated in 1966 by the administration of 1-[^2]H₂-geraniol and 2-[^14]C-geraniol to *Vinca rosea* and mass spectrometry detection of labeled vindoline, what allowed the proposition of the biosynthetic route showed in figure 2 [33,34]. This biosynthetic way was refined two years later with the demonstration that administration of [^{14}C]-labelled loganin (produced by the administration of 2-[^{14}C]-geraniol to *Meyanthes trifoliata*) to *V. rosea* and *Rauwolfia serpentina* allowed the isolation of [^{14}C]-labeled catharanine, serpentine, ajmalicine, vindoline and perivine [35], whose biosynthetic mechanism was detailed elsewhere [36–47].
3. Chemical synthesis of Aspidosperma terpenoid alkaloids

Since the structure elucidation of the first isolated Aspidosperma alkaloids, various alternatives and techniques have emerged, due mainly to the great structural complexity of this family of alkaloids. One of the earliest syntheses of an Aspidosperma alkaloid was published by a group from Harvard University in 1959, which obtained the recently-isolated alkaloid ellipticine from condensation of indole with 3-acetylpyridine followed by reduction and pyrolysis, as shown in figure 3 [48].

Many years later, a new synthesis of aspidosperma-type skeleton was published, in a very simple way using four steps (figure 4) [49]. Another example is the synthesis of quebrachamine, one way published in 1966, and another three ways, one of them based on alkylation of cyclic enamines, other starting with 1,3-propanediol and another based on the cleavage of a thioketal group (figure 5) [50–53].
Despite the many synthetic routes described for obtaining quebrachamine, none was obtained with enantiomeric purity until the problem was addressed in 1980, with the development of a synthetic route to (+)-quebrachamine using L-glutamic acid as a chiral template (figure 6) [54].

Figure 5. Total synthesis of quebrachamine.

Figure 6. Enantioselective total synthesis of quebrachamine
Enamines were also utilized in the synthesis of aspidospermine, as showed in 1971 by a group from Rice University (figure 7) and other groups [55,56].

In 1978 was published a work that introduced a conceptually new approach to the synthesis of Aspidosperma-type alkaloids, the photocyclization-rearrangement or heteroatom directed photoarylation of anilinocyclohexanones, exemplified by the synthesis of the indolines A and B shown in figure 8 [57], this concept being expanded many years later, with the demonstration of different techniques of photo-induced reactions [58–60].

Given the biosynthetic route proposed by Wenkert [30], a group from Yale University developed a synthetic route for obtaining the alkaloid minovine in a biogenetically modeled way (figure 9), refined many years later by the same group [61,62].
Based on the fact that the Aspidosperma alkaloids share common structural features, a group from the Chinese Academy of Synthesis developed a strategy to aspidophytine enantioselective and stereo-controlled synthesis that could be applied to the synthesis of several other alkaloids of this family by simply varying the initial aniline (figure 10) [63].

Another powerful technique for the Aspidosperma alkaloids skeleton is the utilization of aza-Cope rearrangements, utilized for the first time in 1981 for the stereoselective synthesis of 9a-arylhydrolilolidines precursors of vindoline (figure 11) and later expanded to other alkaloids [64–66].

Based on the premise that Heck reaction is a powerful method for the construction of quaternary carbon centers, researchers from Kyoto University decided to apply this methodology to the entantioselective synthesis of (-)-epieburnamonine (figure 12) [67].
Exploiting the possibilities of C-H bond functionalization on the pyrrole ring, a group from Cambridge University recently proposed the total synthesis of rhanizilam-type alkaloids as precursors to Aspidosperma-type alkaloids, as shown in figure 13 [68].

3.1. Aspidosperma alkaloid precursors

Another field of great interest is in synthesis of precursors which can serve to the achieve greater structural diversity from common structures. Various approaches have been utilized in this field, such as ketone annelation of endocyclic enamines [69] (figure 14) and the utilization of photochemistry with the one pot synthesis of a 9-membered ring system that could be
applied not only in the synthesis of Aspidosperma-type alkaloids, but also Strychnos, Schizozygane and Eburnamine-types, as shown in figure 15 [70].

Another approach relied on the conversion of para-substituted anisoles into 4,4-dissubstitued cyclohexenones via cyclohexadiene-Fe(CO)₃ complexes, to obtain the tetrasubstituted carbon of Aspidosperma-type alkaloids, as demonstrated by the synthesis shown in figure 16 [71]. The iron complexes were also utilized in the synthesis of limaspermine derivatives, as shown in figure 17 [72]. Iron [73] and others metals were also utilized in Aspidosperma alkaloids synthesis, such as rhodium [74–77], copper [75,78], ruthenium and molybdenum [79], titanium [80] and palladium [81,82].

Another precursor of Aspidosperma type alkaloids was synthesized in 1978, from azocetones or iminomalonates via acid-catalysed and Birch reduction reactions (figure 18) [83].
One of the main concerns of chemists worldwide is the development of more efficient and “green” procedures in organic synthesis procedures. Among the procedures developed we can cite the so-called domino synthesis, where several bonds are formed in sequence, without isolation of intermediates, addition of reagents or changes in reaction conditions, so that the subsequent reaction result as a consequence of the functionality formed in the previous step [84]. One example of domino synthesis application to Aspidosperma alkaloids synthesis was recently published, where the alkaloids (-)-aspidospermidine, (-)-tabersonine and (-)-vinca-diformine were synthesized in an asymmetric domino Michael/Mannich/N-alkylation sequence, as shown in figure 19 [85].

The majority of synthetic strategies employed to obtain natural products are based on the construction of a single target skeleton, in contrast with the strategy utilized by plants, where
divergent molecular cyclizations of a polyunsaturated common intermediate produce different scaffolds, as recently demonstrated in two different papers, by the synthesis of different Aspidosperma alkaloids [81] and diverse indole alkaloids skeletons [86] from a common intermediate in a biogenetically-inspired way, as shown in figure 20 [86].

4. Biological importance of Aspidosperma terpenoid alkaloids

One of the research interests of our group is the isolation of alkaloids from Aspidosperma species with pharmacological potential. From a chemotaxonomic point of view, alkaloids are substances of great potential in malaria treatment [87,88]. In this perspective, we decided to study the alkaloids produced by A. pyrifolium, resulting in the isolation of the alkaloids 15-deme-
thoxypyrifoline, aspidofractinine and N-formylaspidofractinine [89]. We have identified in A. pyrifolium insecticidal [90], antibacterial [91] and hypotensive activities [92]. Another plant studied by our group was A. tomentosum, which showed great anti-hypertensive [93,94], antinociceptive, anti-inflammatory and analgesic [95–98] and A. macrocarpum, which showed anti-hypertensive activity in spontaneously hypertensive mice [99].

Some species have been the subject of research in order to identify its pharmacological properties and other biological activities. In vitro assay with aqueous extracts of the aerial parts and roots of A. pachypterum against Staphylococcus aureus and the Human Immunodeficiency Virus (HIV), respectively, showed that this species exhibited a moderate activity [100,101]. The methanolic extract of the aerial parts of A. ramiflorum was active in vitro against gram-negative bacterium Escherichia coli [102] and against the fungus Cryptococcus neoformans (causing opportunistic infections in humans) [103] while the methanol extract of the stem bark of the same species was found to be moderately active against gram-positive bacteria and inactive against gram-negatives ones [104]. Studying tailings from the processing of hardwoods in Paraná (Brazil), it was found that the methanol extract of the wood of the plant identified as Peroba pink (Aspidosperma sp.) had a composition rich in phenols and alkaloids as well as strong activity against gram-negative bacteria Proteus mirabilis [105]. In two trials conducted with various plant species, among them five from Aspidosperma genre, it was observed that the ethanol extract of the stem bark of A. excelsum, A. megalocarpon, A. oblongum and A. marcvgraviaum were active against gram-positive bacteria Bacillus subtilis and that the same extracts and also the ethanol extract of the stem bark of A. album were active against gram-positive S. aureus [106,107]. In a study of Peruvian plants, it was reported that the extract of the bark of A. rigidum showed antibacterial activity against B. subtilis [108].

Another reported activity for species was the anti-Leishmania, where in vitro assay for Leishmania amazonensis promastigotes ahead and L. braziliensis, the fraction rich in alkaloids obtained from the stem bark proved to be active, with the highest activity observed against the first species [109]. Yet in order to find alternatives for the treatment of neglected diseases, the methanol extract of the bark of A. megalocarpon was tested against the D2 and F32 Plasmodium falciparum strains, being active [110]. The dichloromethane extract of the roots of A. tomentosum was active front P. falciparum (strain FcB1/Colombia) with a selectivity index of 67.5 compared with the activity front NIH-3T3 cells. In relation to substances with antifungal properties, it was seen that the ethanol extract of the stem of A. polyneuron was capable of inhibiting Cladosporium herbarum (pathogen of plants) [111].

In order to find alternatives for the treatment of cancer, the dichloromethane extract of the aerial parts of A. tomentosum was capable of inhibiting the proliferation of cell lines MCF-7 (breast cancer), UACC62 (melanoma), NCIADR (breast cancer phenotype with resistance to multiple drugs and NCI460 (lung cancer), and we observed that the activity was concentrated in fractions rich in terpenes and species of high polarity [112].

In vivo assay of the ethanol extract of the stem of A. nitidum showed significant anti-inflammatory activity when evaluated in the trial of edema induced by carrageenan in mice. Prospecting for sources of antioxidant compounds, the hot aqueous extract of A. quebracho-
blanco was tested for oxidation power / ferric reduction, showing a low activity and is therefore not considered as potential producer of antioxidant compounds [113].

It was observed that administration of a fraction rich in alkaloids obtained from the root bark of *A. uleí* exerted pro-erectile effect in rats and suggested a mechanism of action via blocking presynaptic α2-adrenergic receptors, the activation of the dopaminergic system and release of nitric oxide [114]. When the same fraction was tested in corpus cavernosum penis obtained from rabbit, its ability to cause relaxation was observed and the proposed mechanism blocking the influx of calcium into the cells [115]. In assay using α-adrenergic receptors isolated from human penis, it was shown that the crude extract and four fractions obtained from the bark of *A. quebracho-blanco* were able to block them, and the magnitude of interaction directly proportional to the content of the alkaloid yohimbine [116].

Despite reports of low toxicity associated with the use of plants of the genus *Aspidosperma* [109,110,117–119], some studies show a contrary position regarding the species *A. pyrifolium* [89,120]. In a study of the species *A. pyrifolium* cases of abortion in goats were reported due to ingestion of parts of the plants and when the ethanol extract of the leaves was administered to pregnant rats reduced fetal weight and maternal toxicity was observed, as well as hemolysis and toxicity test the front microcrustacean *Artemia salina* [120]. In a toxicity study with the microcrustacean *A. franciscana* with several species found in the Brazilian Amazon, among them seven species of *Aspidosperma*, it was reported that the bark extracts of *A. marcgravianum*, *A. vargasii*, *A. nitidum* and *A. sprucenaum* led to mortality of 100, 94, 70 and 65% of the crustaceans, whilst extracts from the bark of *A. desmanthum*, *A. sandwithianum* and *A. shultesii* led to a mortality rate of 6, 0 and 0% crustaceans, showing the potential toxicity of some species gender [121]. In another test with brine shrimp, both the dichloromethane extract and the methanol extract of the bark of *A. excelsum* showed toxicity [14].

5. Conclusion

The present literature review shows the importance of the study of Aspidosperma type alkaloids due to the widespread usage of plants that produce these substances in folk medicine and the great array of potential biomedical applications that these substances exhibit. Beyond this it is clear the importance of developments in synthetic organic chemistry to obtain these substances without the necessity of extraction from natural sources.

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