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Review

Comprehensive Review of the Components in Cat's Claw (*Uncaria tomentosa*) and Their Antibacterial Activity

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Abstract: Cat's claw (*Uncaria tomentosa* (Willd. ex Schults) DC.), a plant that is exceptionally rich in phytochemicals, has been used for centuries by the indigenous people of South and Central America as a therapeutic and is currently widely exported for medicinal purposes. Extracts and individual components have shown considerable potential as antibacterials in the literature. The purpose of this review is twofold: first, to provide a substantiated, comprehensive collection of the known chemical constituents of *U. tomentosa*, including their detailed structures; second, to identify those components that offer some promise as antibacterials based on the research to date. Bacterial resistance to currently available antibiotics continues to increase and is widely recognized as an impending, potentially catastrophic, problem. There is research to suggest that *U. tomentosa* components may have antibacterial potential individually or synergistically with established antibiotics against microbes, including *Borrelia burgdorferi*, the causative agent of Lyme disease. It is our intention that this review will provide a valuable resource to investigators in search of new antimicrobials to meet the daunting challenge of antibiotic resistance.

Keywords: cat's claw; antibacterial; phytochemicals; *Borrelia burgdorferi*; Lyme disease; alkaloids; polyphenols; terpenoids; medicinal plants; *Uncaria tomentosa*

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1. Introduction

Medicinal plants and their natural products have been a source of important drug discoveries for decades. Since 1981, of the 1394 small-molecule drugs approved by the FDA, 930 of them were derived, to some extent, from a natural product, with fourteen being direct isolates from medicinal plant sources [1]. Many of these medicinal plants continue to be a primary therapeutic source for a large portion of the population in developing countries in Asia, South America, and Africa. The family Rubiaceae contains many of these plants, of which the genus *Uncaria* is prominent. This review focuses on *Uncaria tomentosa* (Willd. Ex Schults) DC., commonly referred to as "cat's claw", a plant that is native to South and Central America. The name of this woody vine was derived from the long, cat claw-like thorns protruding from the stem at its leaf junctions. The phytochemical composition of the plant has been the subject of many studies that pre-date this review [2–12], with one of these studies purporting more than 50 phytochemicals originating from the plant [13].

The interest in the specific phytochemical composition of *U. Tomentosa* comes from the plant's long history of medicinal use by indigenous people in the region. Peruvian tribes such as the Ashaninka, Aguarurna, Cashibo, and Shipibo have used the plant for centuries to treat a multitude of ailments. Documentation from these cultures have indicated its use as a therapeutic for allergies, arthritis, asthma, diabetes, cancer, bacterial and viral infections, and other medicinal uses [14]. Scientific investigations into *U. tomentosa* extracts and constituents have uncovered a range of biological activities, such as antioxidant, anti-inflammatory, antimicrobial, antiviral, and immunomodulating activity [11–13].

Of the biological activities and potential medicinal purposes, this review focuses on its antibacterial properties. As a traditional medicine, *U. tomentosa* has been documented in wound treatment, indicating potential as an antibacterial agent [14]. Recent investigations of the plant and its extracts have produced in vitro evidence of antibacterial activity [15–19]. Antimicrobial activity has been observed against both the latent and active forms of the bacterium *Borrelia burgdorferi*, the bacterium responsible for Lyme disease [20,21]. Lyme disease is a tick-borne ailment brought on by the introduction of *Borrelia burgdorferi* to a host through a tick bite. Recent Centers for Disease Control (CDC) investigations have indicated that as many as 300,000 Americans are affected by Lyme disease every year [22,23]. Improved antibiotic therapies capable of not only treating the initial symptoms of *B. burgdorferi* infections, but also preventing and treating persistent infections are needed. The in vitro anti-borrelia efficacy demonstrated by *U. tomentosa* warrants an investigation into the possibility of identifying the constituent or a combination of constituents responsible for this effect.

To date, several reviews have been published providing general information on the genus *Uncaria*, including *U. tomentosa*, which contain focused, but limited, information on constituents and/or bioactivity [11–13]. In addition, none of these reviews have focused specifically on *U. tomentosa* constituents and their applications as antibacterial agents. The purpose of this review is to present a comprehensive collection of molecular structures from *U. tomentosa*, as well as consolidate research and literature regarding these components' potential as antibacterial candidates. The information provided in this review will hopefully highlight promising candidates for the possible development or isolation of antibacterial agents from the species *U. tomentosa*, and specifically those related to anti-borrelia efficacy.

2. Methodology

This review focuses on reporting a comprehensive list of all known phytochemical structures of *U. tomentosa*, while also providing relevant information on antibacterial activity. Structures were sourced and verified from the literature, Reaxys, PubChem, Google Scholar, and SciFinder. A number of existing reviews were referenced citing the entire or multiple plant species within the *Uncaria* genus [11,12,14,24–31], and one recent review focused directly on *U. tomentosa* constituents and bioactivity [13]. The information in these reviews were corroborated before being reported here, and minor errors in which constituents were wrongly assigned to the species *U. tomentosa* are also noted in this review. Antibacterial activity was investigated via a literature search for every identified phytochemical component. Few examples of antibacterial activity exist from compounds directly sourced from *U. tomentosa*. As a result, instances where the same constituents were extracted from other natural products are included. The phytochemical constituents of *U. tomentosa* were divided into three classes: alkaloids, polyphenols, and terpenoids (Supplementary Materials). The compounds identified in these classes were then further divided into groups and subclasses, based on structural commonality.

3. Alkaloids

Alkaloids are heterocyclic compounds that contain one or more nitrogen atoms in the structure. They are secondary metabolites generally derived from amino acids and found in a wide range of plants, with an estimated 12,000 molecules identified from natural sources [32]. The structural definition of alkaloids allows for the inclusion of structurally diverse compounds in the class, resulting in a wide range of bioactivities [33].

There are various systems of nomenclature used to discuss the structural diversity found in alkaloids. Biological sources, structural motifs, and biogenesis pathways are a few ways to classify alkaloids [34,35]. In this review, the grouping and discussion of alkaloids focus on using a method of chemo-molecular classification based on the structural motifs surrounding the nitrogen-containing heterocyclic portion of the molecule. The alkaloids of *Uncaria tomentosa* contain a variety of structures that were classified into two groups: indole alkaloids and oxindole alkaloids. These groups were further classified into subclasses defined as tetracyclic and pentacyclic indoloquinolizidine, β-carboline-type, and tetracyclic and pentacyclic oxindole alkaloids.

3.1. Indole Alkaloids

Indole alkaloids contain an indole group, a heterocyclic structure that consists of a five-member pyrrole ring fused to a benzene ring, within the heterocyclic structure of the molecule. The indole alkaloids of *U. tomentosa* were classified into three subclasses: tetracyclic indoloquinolizidine, pentacyclic indoloquinolizidine, and β-carboline. The indole alkaloids are biosynthesized from the precursor compounds tryptophan and tryptamine [32,36]. These indole alkaloids are known for possessing a range of bioactivity, which includes antimicrobial activity [37]. The indole moiety is present in twenty alkaloid constituents identified in *U. tomentosa* (Figures 1 and 2).

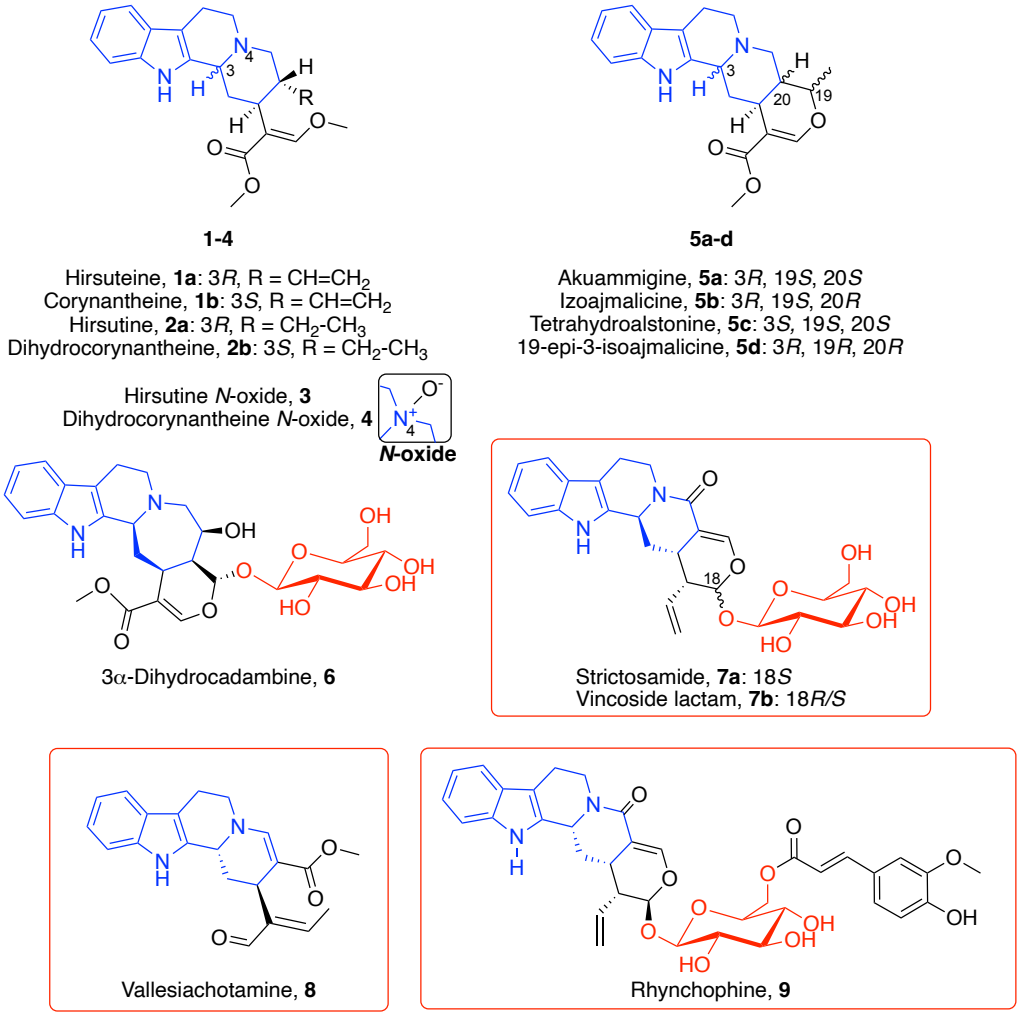


Figure 1. Structures of indole alkaloids, specifically indoloquinolizidine (**1**–**5d**). Structures boxed in red indicate compounds mistakenly attributed to *U. tomentosa* in previous sources. Sugars in red are β-D-glucose.

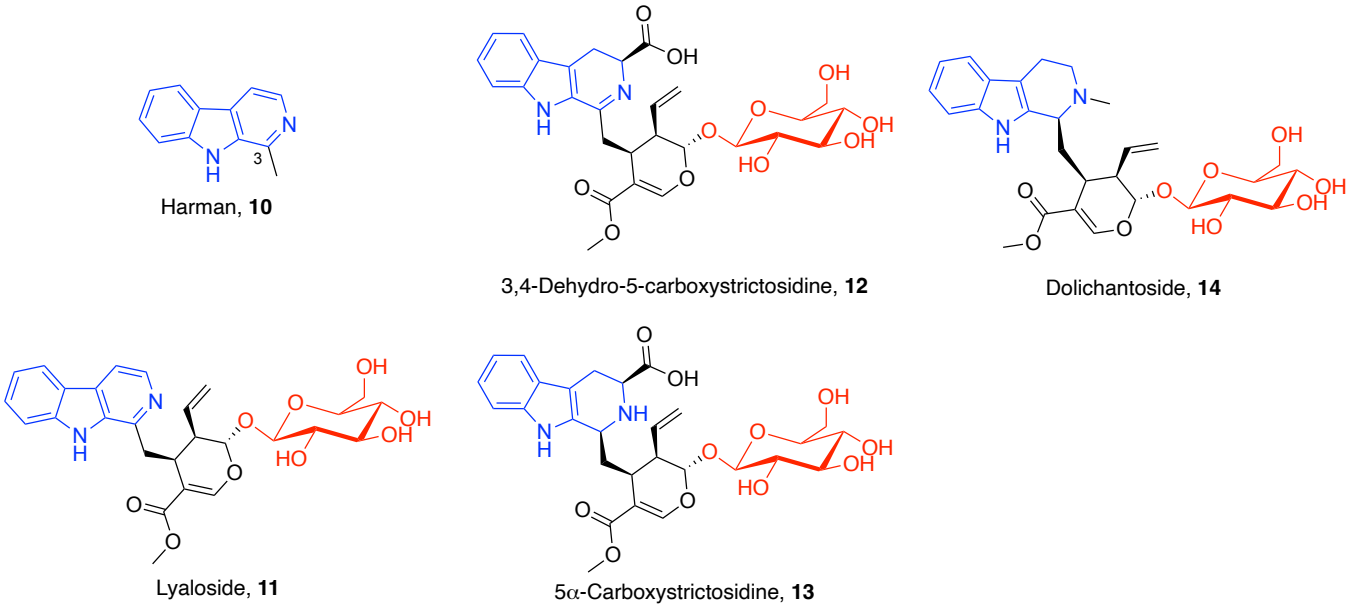


Figure 2. Structure of β-carboline alkaloids (**10**–**14**). Sugars in red are β-D-glucose.

3.1.1. Tetracyclic Indoloquinolizidine Alkaloids

There are six tetracyclic indoloquinolizidine alkaloids that have been identified in *U. tomentosa* (Figure 1, **1**–**4**). These compounds are distinguished by a quinolizidine ring fused to an indole to form a tetracyclic indoloquinolizidine highlighted in blue in Figure 1. These alkaloids are commonly identified as corynanthe-type monoterpenoid alkaloids in other literature sources [38].

The six compounds share several similar structural motifs besides the tetracyclic indoloquinolizidine structure. An alkoxy and carboxylate ester within the monoterpene skeleton exists for all compounds within this subclass. Compounds **1a**–**2b** were isolated and quantified in a study of sixteen plant samples utilizing high-performance liquid chromatography (HPLC) retention times, mass spectrometry (MS), proton (^{1}H) and carbon (^{13}C) nuclear magnetic resonance (NMR) spectroscopy, and ultraviolet-visible (UV–Vis) spectroscopy, with **2b** reported in trace amounts [10]. Of the citations from this source that reference structural determination of compounds **1**–**4**, a single chromatographic method utilizing retention time and mass spectroscopy is the only report that confirmed structural identification of these molecules [39]. Molecules **1a**–**2b** are structurally related. Hirsuteine **1a** and corynantheine **1b** are epimers with a vinyl group at C-20, while the compounds hirsutine **2a** and dihydrocorynantheine **2b** are epimers with ethyl substitutions at C-20. The structural determination of these compounds was completed utilizing—chromatographic method with the addition of MS [39].

N-oxide derivatives of alkaloids are known to naturally occur in plants [40]. Two *N*-oxide tetracyclic indoloquinolizidine compounds have been identified from the leaves of *U. tomentosa* [41]. The *N*-oxide tetracyclic indoloquinolizidine alkaloids **3** and **4** possess a structure identical to **1a** and **2b**, respectively, with the addition of an oxygen atom bound to the nitrogen atom of the quinolizidine structure. Heterocyclic *N*-oxides are currently being investigated as an emerging class of therapeutic agents with antibacterial activity [42,43]. However, antibiotic data for **3** and **4** have not been reported to date. Examples of *N*-oxides exhibiting antibacterial activity are the quinoxaline 1,4-di-*N*-oxide derivatives [42]. The exact mechanism of antibacterial activity is unknown; however, it has been established that the *N*-oxide moiety improves antibacterial activity [44], and that the mechanism proceeds though oxidative damage of bacterial DNA [45].

3.1.2. Pentacyclic Indoloquinolizidine Alkaloids

Pentacyclic indoloquinolizidine alkaloids contain one additional heterocyclic ring (Figure 1, **5a**–**d**). Like tetracyclic indoloquinolizidine alkaloids, these compounds are also referred to as monoterpene alkaloids (i.e., heteroyohimbine alkaloids, a type of corynanthe-type alkaloid) [46,47]. Four of the pentacyclic indoloquinolizidine alkaloids are stereoisomers. Compound **6** is structurally related to both the tetracyclic and pentacyclic indoloquinolizidine subclasses but does not contain the indoloquinolizidine moiety. Instead, **6** contains a hydroxy substituted 7-membered ring in addition to a β-linked glucose molecule. The glycosylated indole alkaloid **6** has been identified from root cells grown under oxidative stress alongside the production of oxindole alkaloids [48–50]. This compound possesses biological activity including hypotensive, lipid lowering, and antioxidant activity; however, no antibacterial evidence has been tested or implicated [48,49].

While investigating literature sources, it was discovered that several compounds within this subclass were incorrectly described as being constituents of *U. tomentosa* [12]. In a 2005 review, compounds **7a**, **7b**, **8**, and **9** were incorrectly attributed to *U. tomentosa* via a study on constituents from *Uncaria rhynchophylla* (Miq.) Miq. ex Havil. a separate species of *Uncaria*, native to Southeast Asia (Figure 1) [51]. These structures are highlighted in red in Figure 1, and to date, this is the first correction of the error.

3.1.3. β-Carboline Alkaloids

Indole alkaloids possessing the β-carboline subclass have been more recently isolated from *U. tomentosa*, with the first study identifying and structurally determining their presence in plant extracts established by Kitajima and colleagues in 2000 [4,5]. This group of indole alkaloids have a tricyclic structure highlighted in blue in Figure 2. This characteristic scaffolding is composed of an indole structure fused to a pyridine ring, where primary structural differences within the subclass arise from the saturation of this pyridine-type ring. In all cases, a carbon skeleton branches from C-3.

The simplest of these alkaloids found in *U. tomentosa* is harman (**10**). This molecule represents the core scaffolding of the β-carboline alkaloid subclass, with a fully aromatic ring system and a simple methyl substitution at C-3. Compound **10** was first isolated by Kitajima and colleagues along with other β-carboline structures **11**, **12**, and **13** [4]. Compound **10** has demonstrated antibacterial activity against both Gram-negative and Gram-positive bacteria, exhibiting minimum inhibitory concentration (MIC) values of 500 μg/mL against *Escherichia coli* and *Bacillus subtilis*, and 1000 μg/mL for *Staphylococcus aureus* [52]. Compound **10** has also been utilized as a scaffold for the development of antibacterial candidates, with some analogues exhibiting MIC values below 10 μg/mL for *S. aureus*, methicillin-resistant *Staphylococcus aureus* (MRSA), *B. cereus*, *B. subtilis*, and *Ralstonia solanacearum* [53]. Substitutions of the harman structure that improve antibacterial activity include substituting C-6 with a methoxy group, C-1 with a benzo[d][1,3]dioxle group, and the quaternization of N-2 with a *para*-substituted benzyl group and a complexed bromine anion [53].

The gluco-β-carboline-type alkaloids **11**–**13** were also isolated by Kitajima and colleagues in a previous study [5]. The structures were determined utilizing UV, ^{1}H and ^{13}C NMR spectroscopy, and MS, with the absolute configuration of compound **12** solved through a total synthesis based upon the biosynthetic precursors *L*-tryptophan and secologanin [4,5,7]. Compounds **12** and **13** differ only by the bond between C-3 and N-4, which is saturated in **13** and unsaturated in **12**. The saturation of this bond produces a stereocenter at C-3 for **13**, in the *S* configuration. Compound **11** possesses both the same skeletal structure and β-linked glucose molecule as **12** and **13**, with the fully conjugated β-carboline core, but lacks the carboxylic acid.

There is only one study confirming the isolation of an additional glycosylated *β*-carboline alkaloid **14** from micropropagated plantlets and root cultures [50]. This structure possesses some unique features, including a methyl-substituted nitrogen and a stereocenter at C-3 in the *S* configuration. The glycosyl portion of the molecule is identical to that of compounds **11**–**13**. Compound **14** and a derivative of compound **13** have been identified as precursor molecules in the biosynthesis of tetracyclic indoloquinolizidine and pentacyclic indoloquinolizidine alkaloids [47]. Antibacterial activity has been noted for compound **13**. When isolated from *Psychotria nuda* (Cham. and Schltdl.) Wawra, **13** exhibited in vitro antimycobacterial activity against *Mycobacterium tuberculosis* strain H37Rv with a reported MIC value of 26.3 µg/mL [54].

3.2. Oxindole Alkaloids

The first extraction of an oxindole derivative from a natural source was acquired from *U. tomentosa* [55]. Oxindole alkaloids, like indole alkaloids, are derived from *L*-tryptophan [34,56]. The biogenesis of these compounds has been studied using molecular and isotopic labeling in *Uncaria guianensis* (Aubl.) J.F.Gmel. It was determined that the formation of the oxindole moiety proceeds along a pinacol-pinacolone rearrangement reaction from an indole precursor [57]. The oxindole moiety is comprised of a benzene ring fused with a pyrrole ring, substituted at C-2 with a carbonyl [55]. Oxindole derivatives have been shown to have biological properties that are useful in drug development. There are several positions on the oxindole molecule that can be selectively modified to enhance antibacterial activity. Oxindole derivatives with substitutions at the N-1, C-3, C-4, and C-5 positions have exhibited antibacterial activity. For a comprehensive review of these compounds, please refer to references [58–60].

3.2.1. Tetracyclic Oxindole Alkaloids

Tetracyclic oxindole alkaloids contain a tetracyclic structure linked to the methyl 3-methoxyacrylate skeleton (Figure 3, **15**–**20**). The structures depicted in Figure 3 were isolated from *U. tomentosa* and were reported in several research papers focused on structural determination [10,41,50,61]. The structural differences in the compounds reside in the substitution of an ethyl or vinyl group on the indolizidine ring. Additional structural differences exist at the spiro carbon stereocenter. The presence and verification of these compounds were established through HPLC methods employing reference material and comparison of UV–Vis absorbance curves and retention time [62,63]. Other studies validated the structural identification of these compounds only through HPLC-MS analyses [39].

Two *N*-oxide variations have also been reported [41]. Structures **17** and **18** represent the *N*-oxide versions of compounds **15a** and **15b**, respectively. The *N*-oxide moiety resides on the nitrogen at position 4 on the indolizine. Compound **19** was isolated and characterized as a minor alkaloid during an investigation into the phenolic composition of *U. tomentosa* [2]. This compound contains an ethyl substitution at C-20 in the *R* configuration. In addition, another unique structural characteristic is located on the methyl 3-methoxyacrylate, where the ester group has undergone demethylation into a carboxylic acid. The structure of this compound was confirmed via ^{1}H and ^{13}C NMR spectroscopy [64].

Compounds **20a** and **20b** are diastereomers with ethyl substitutions at C-20; however, their distinguishing feature is the presence of a hydroxy group on the oxindole ring. These compounds are attributed to *U. tomentosa* through older work contributed by Hemingway and Phillipson [39,65]. More recent investigations into the alkaloid components of *U. tomentosa*, such as those reported by Laus and coworkers, have not identified these compounds as present [10,27].

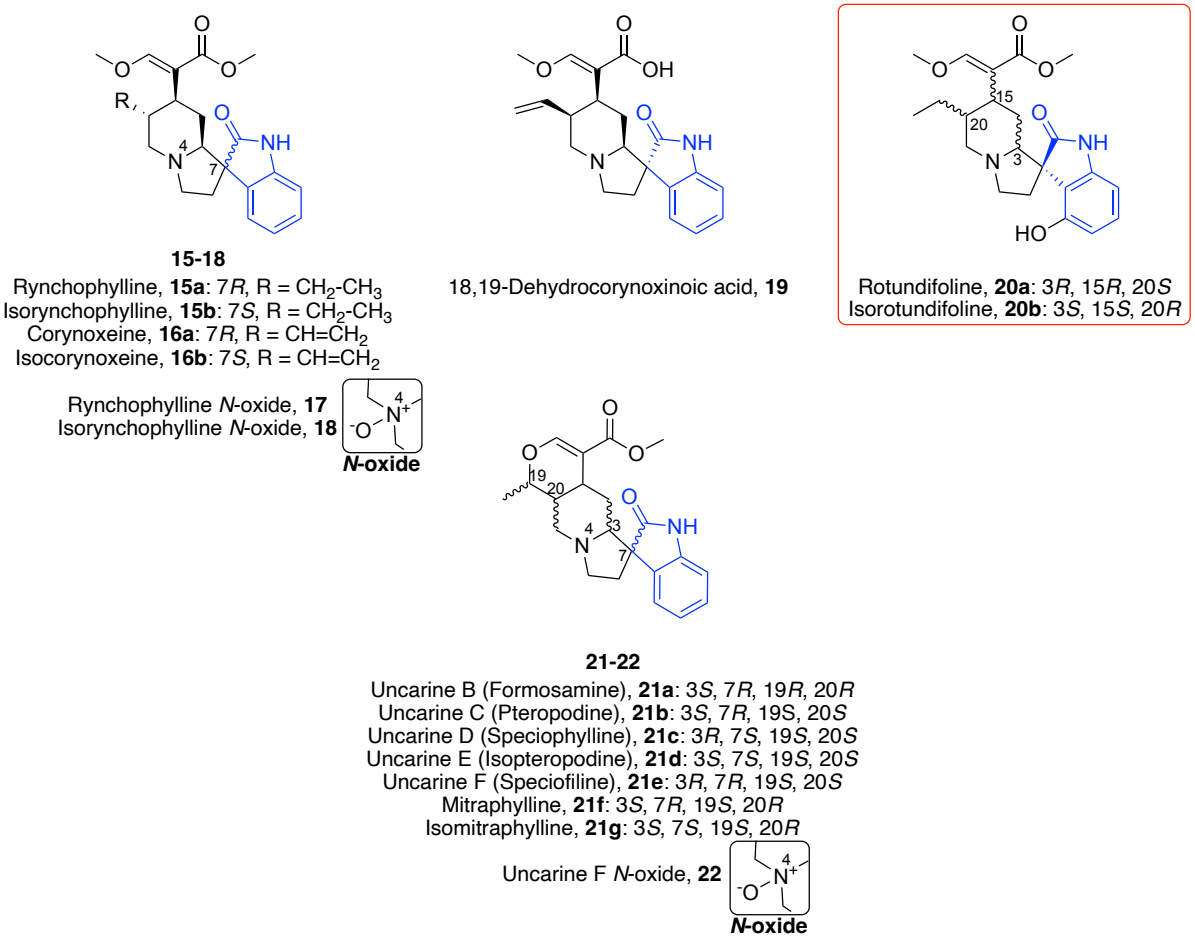


Figure 3. Structures of oxindole alkaloids (**15**–**22**). Structures boxed in red indicates compounds mistakenly attributed to *U. tomentosa* in previous sources.

3.2.2. Pentacyclic Oxindole Alkaloids

The pentacyclic oxindole alkaloids present in *U. tomentosa* are shown in Figure 3 (**21**–**22**). These compounds possess the identical oxindole group linked to an indolizidine with an additional di-hydropyran structure fused to the six-member ring of the indolizidine structure. This ring structure is substituted with a methyl group at C-19 and an acetyl group branching from the unsaturated bond from the pentacyclic heterocycle. These compounds have been identified in alkaloid studies of *U. tomentosa* [10,50]. Structural determinations were established by comparison with NMR datasets [66,67]. A single *N*-oxide exists from these groups of compounds, Uncarine F *N*-oxide (**22**), which is like other *N*-oxides of *U. tomentosa* (**17** and **18**).

The bioactivity of these compounds has been the focus of many investigations. A recent review focusing on the bioactivity of components and extracts from *Uncaria tomentosa* cites a number of sources [13]. A few of the bioactivities referenced include anticancer activity for compound **21e** [68], antineoplastic activity for **21c** [69], antioxidant activities for **21f** and **21g** [70,71], anti-inflammatory activity for **21f**, and immunomodulating properties for **21b** [72]. The antimicrobial activity of these compounds has not been as thoroughly investigated as other bioactivities, although a few examples of antibacterial evidence were found during the literature search and are presented below.

The stereoisomers **21f** and **21g** demonstrated in vitro activity against two tuberculosis causing mycobacteria strains resistant to the antibacterial medication isoniazid. Isolated from the leaves of *Hallea rubrostipulata* (K.Schum.) J.-F.Leroy and tested using a broth microdilution method, the results indicated moderate antimycobacterial activity. Compound **21f** demonstrated MIC values of 800 and 400 µg/mL against *Mycobacterium madagascariense* and *M. indicus pranii*, respectively. Compound **21g** demonstrated MIC values of 800 µg/mL for both *M. madagascariense* and *M. indicus pranii* [73].

One of the few examples of compounds directly isolated from *Uncaria tomentosa* displaying antibacterial activity was reported by Garcia and colleagues. The oxindole **21d** isolated from a methanolic extraction of *U. tomentosa* demonstrated moderate in vitro antibacterial activity against Gram-positive bacteria *Staphylococcus aureus* and Gram-negative *B. subtilis*, with MIC values of 150 and 250 µg/mL [74].

4. Polyphenols

The term polyphenol is a broad term that encompasses a large range of compounds. Structurally, all polyphenols contain hydroxyl groups attached to aromatic rings; however, the number of hydroxyl groups as well as the size of these compounds could range from a single benzene ring to a series of fused rings up to 4000 Daltons. This class of compounds is structurally diverse with a variety of carbon skeletal arrangements that make up several different groups of compounds including flavonoids, proanthocyanidins, and phenolic acids.

Polyphenols are found in all types of plants and can vary widely in structure and content. These compounds are all bio-generated through the shikimate/phenylpropanoid or the acetate/malonate secondary metabolic pathways [75]. The role of these compounds range from defensive functions such as antimicrobial and antifungal activities to cell wall strengthening and repair [76]. Polyphenols exhibit antioxidative capabilities as well as solubility in water [75]. As a result, these compounds have a diverse array of bioactivities and are generally considered key components to a healthy diet when consumed from natural plant sources [77,78]. The polyphenol fraction of *U. tomentosa* includes a variety of compounds. The compounds will be categorized and discussed in relation to antibacterial activity in the following subsections.

4.1. Flavonoids

Flavonoids make up a large portion of the polyphenols present in *U. tomentosa*. Flavonoids are a group of secondary metabolites found in an array of natural plant materials including fruits, vegetables, grains, bark, roots, stems, and flowers [79]. Flavonoids contain a simple skeleton consisting of three rings commonly referred to as rings A, B, and C depicted in Figures 4–6. Flavonoids can be divided into several subclasses based on the saturation, linkage, and substitution of these ring moieties. The subclasses identified in *U. tomentosa* include flavone, flavonol, and flavan-3-ol structures.

4.1.1. Flavones

The structural composition of flavones can be seen highlighted in structures **23**–**27** in Figure 4. The key structural components of flavones are localized to the aromatic C ring, also characterized by a ketone substitution at C-4. The position of hydroxy groups can vary; however, the flavones present in *U. tomentosa* have been noted to contain hydroxy groups in C-5 and C-7 of ring A and C-3′, -4′, -5′, and -6′ of ring B. Flavones putatively identified from *U. tomentosa* are apigenin (**26**) and luteolin (**27**). These compounds were identified upon analysis of an ethanol extraction of *U. tomentosa* using UV absorption peaks and retention time compared to standard references; however, no efforts were made to spectroscopically characterize the compounds [80]. These basic structures contain the same components of flavones coupled with hydroxy groups at C-5 and -7 of ring A and C-4′ of ring B (highlighted in blue in Figure 4), with an additional hydroxy group at C-3′ for compound **27**.

Three additional flavones—artochamin C (**23**), 5′-hydroxycudraflavone A (**24**), and dihydrocudraflavone B (**25**)—were identified via a bioactivity-guided isolation of a methanol extract of *U. tomentosa*. They were identified utilizing MS and ^{1}H and ^{13}C NMR spectroscopy [81]. These compounds possess additional substitutions when compared to the previously discussed flavones.

Compound **23** contains a dimethyl 2H-pyran structure fused to the A ring via C-7 and -8, with an additional hydroxy on C-3′ of ring B. Compounds **24** and **25** are structurally related, where **24** contains a dimethyl substituted 2-H pyran structure fused at C-6 and -7 of ring A, while **25** contains a saturated pyran. Structures **24** and **25** also contain an oxygen bound to C-6′ of the B ring. In **25**, the oxygen is present as a hydroxy moiety, while **24** has an ether that links to the 2 methylpent-2-ene group emanating from C-3 of ring C, forming a 2H-pyran heterocycle.

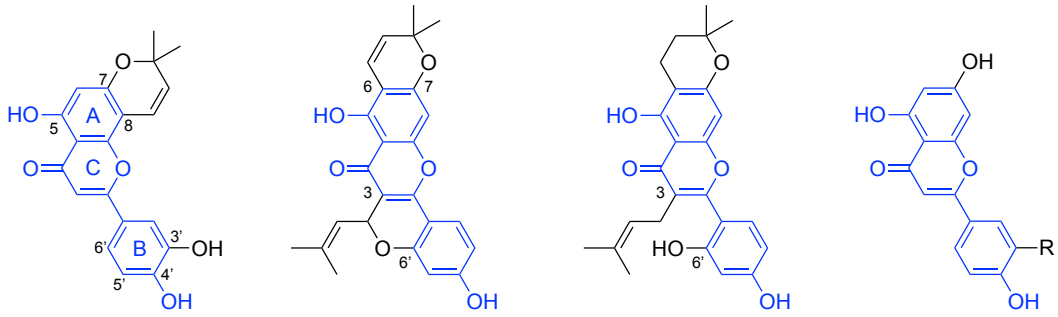


Figure 4. Flavones (**23**–**27**) are characterized by aromaticity of the three A, B, and C rings and a ketone substitution on the C ring.

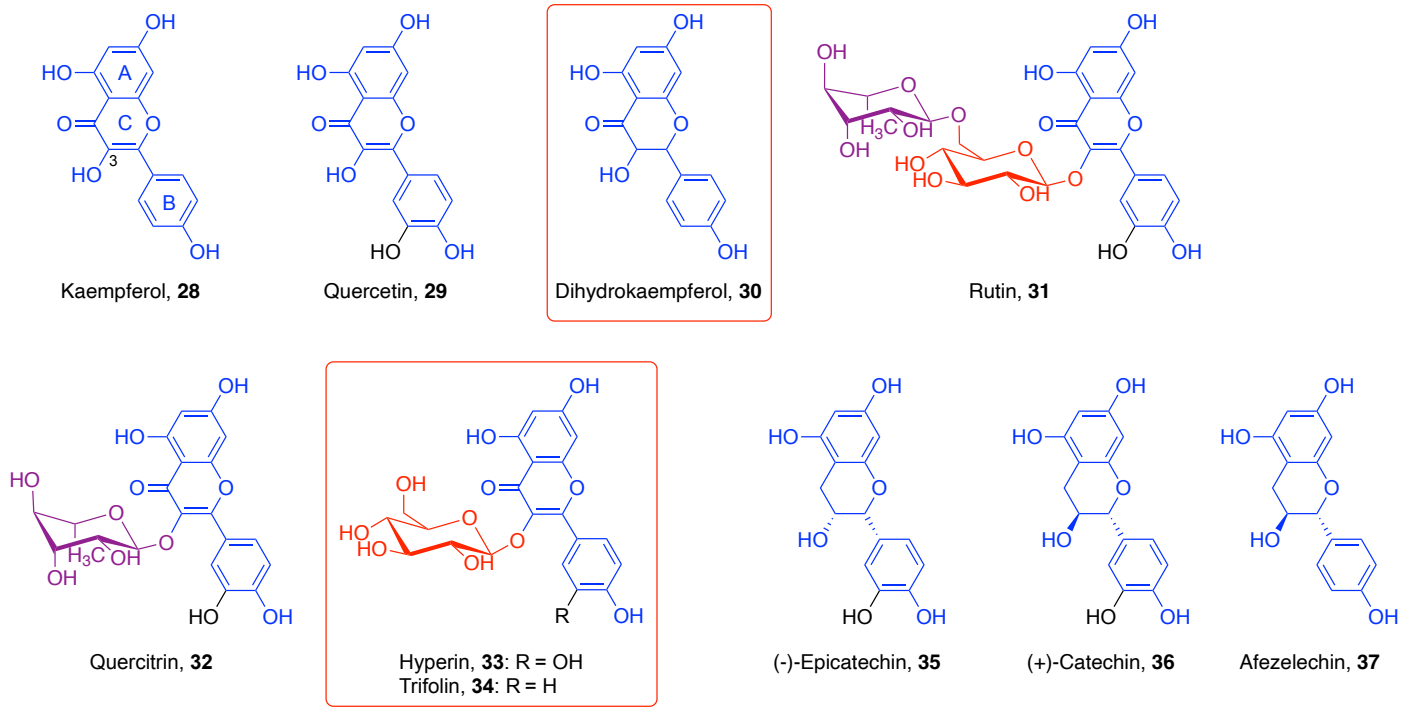


Figure 5. Flavonols (**28**–**34**), with flavan-3-ols below (**35**–**37**). Sugars in red are β-D-glucose and α-L-rhamnose sugars are depicted in purple. Structures boxed in red indicates compounds mistakenly attributed to *U. tomentosa* in previous sources.

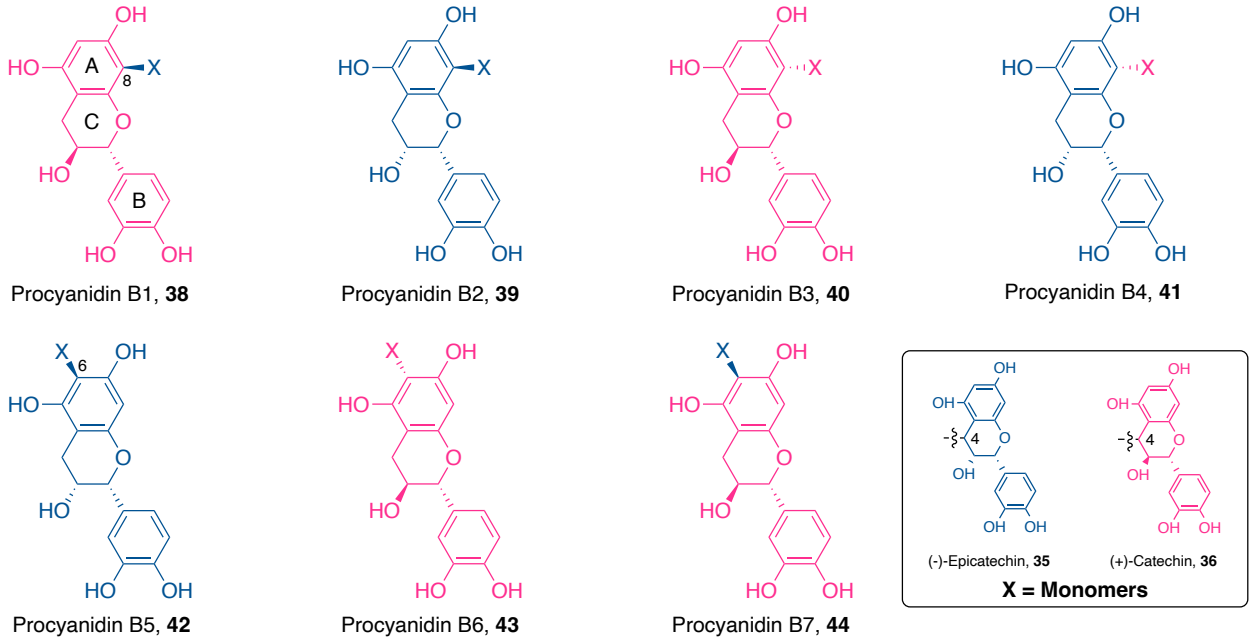


Figure 6. Procyanidin dimers (**38**–**44**) color-coded based on their monomeric composition, with **35** and **36** depicted in blue and pink, respectively.

The compounds **23**–**25** exhibited antibacterial activity when isolated via a methanol extraction. They were analyzed to determine MIC values for *S. aureus*, *B. subtilis*, *E. coli*, and *Klebsiella pneumoniae*. Of the compounds tested, **23** produced the best results with MIC values ranging from 4.1 to 6.7 µg/mL, indicating an antibacterial effect on both Gram-positive and Gram-negative bacteria. The MIC values of **25** ranged from 5.1 to 8.3 µg/mL and **24** was found to be least efficacious with values ranging from 9.8 to 16.9 µg/mL [81].

4.1.2. Flavonols

Like flavones, flavonols also have an aromatic C ring with a C-4 ketone; however, they also contain a hydroxy group at C-3 on the C ring (Figure 5, **28**–**34**). Several constituents of *U. tomentosa* have been identified that possess these characteristics. The simple structures are kaempferol (**28**) and quercetin (**29**). Both these compounds possess the structural characteristic of the flavonol subclass, with additional hydroxy substitutions at C-5 and C-7 of ring A (highlighted in blue in Figure 5). Differences in their structures are localized to ring B, which is monosubstituted in **28** and disubstituted in **29**. These compounds were identified in an ethanol extraction of *U. tomentosa* bark utilizing a HPLC with diode-array detection setup to compare retention times and spectral analysis to stock standards [80]. Larger structures have been identified that are products from biosynthetic pathways involving **29** [80,82,83]. Rutin (**31**) and quercitrin (**32**) are both glycosides of **29**. These three related structures have been identified and structurally characterized in several studies [80,82,83].

When isolated from other plant sources, such as *Dicranopteris linearis* (Burm.f.) Underw., **31** and **32** exhibited antibacterial activity [84]. When tested against *E. coli*, *B. subtilis*, *S. aureus*, *Erwinia carotovora*, and *B. cereus*, **31** produced MIC values of 31.25 µg/mL, 15.5 µg/mL, 31.25, 15.5, and 31.25 µg/mL, respectively, while **32** produced MIC values of 31.25, 15.5, 15.5, 15.5 and 31.25 µg/mL, respectively. These values indicate a moderate level of antibacterial efficacy. Additional cytotoxicity experiments indicated **32** as a strong cytotoxic agent for human leukemia cells with IC_{50} values of 4.5 and 9.0 µg/mL, while **31** was not found to be cytotoxic (>50 µg/mL).

Compound **30** is not a component in *U. tomentosa* but has been mistakenly attributed to the plant in prior instances due to mistaken identity with close relative, *U. guianensis* [85]. In addition, there has been no isolation or structural characterization reported directly from *U. tomentosa*. Compounds **33** and **34** were incorrectly cited as being sourced from *U. tomentosa* in a review by Heitzman [12], which references a paper from Aimi and coworkers that isolate and characterize these compounds from *U. rhynchophylla* rather than *U. tomentosa* [51]. This correction is also directly related to the previously described error for compounds **7a**, **7b**, **8**, and **9**. We have not been able to find a source during our review that demonstrates the isolation or characterization of these compounds from a *U. tomentosa* plant source.

4.1.3. Flavan-3-ols

Like flavonols, flavan-3-ols of *U. tomentosa* contain a hydroxy group at C-3 of ring C. However, unlike the previous subclasses, flavon-3-ols contain a C ring that is saturated and therefore possesses stereochemistry. The stereochemistry of C-2 that links the B and C ring is in the *S* configuration for all flavan-3-ols identified from *U. tomentosa*, while the stereochemistry of the hydroxy group can alternate (Figure 5, **35**–**37**). Procyanidins formed from monomers of flavan-3-ols have been isolated in *U. tomentosa* [2,3,86]. The monomers identified in *U. tomentosa* are the compounds (−)–epicatechin (**35**) and (+)–catechin (**36**) (Figure 5). These compounds are stereoisomers. Several sources have indicated the presence of these monomers in *U. tomentosa* [2,3,82,86,87].

Procyanidin Type

Proanthocyanidins are polymeric structures composed of flavan-3-ol monomer subunits (Figure 6). The most prevalent types of proanthocyanidin structures present in *U. tomentosa* are procyanidins. Procyanidins are comprised of **35** and/or **36** flavan-3-ol monomers. These monomer units are described above and consist of a hydroxylated B ring, with the orientation of the C ring and hydroxy groups being in the *cis* or *trans* conformation. The prefix *epi* is used to indicate a *cis* configuration as indicated by (−)–epicatechin (**35**).

The number of monomers in a procyanidin structure can vary. Structures ranging from 2 to 10 monomers have been identified from polyphenolic assessment of *U. tomentosa* utilizing mass spectrometry [88]. The molecular weight of procyanidin structures has been indicated to affect bioactivity when consumed, with lower molecular weights (degree of polymerization (DP) < 3) leading to absorption into the gastrointestinal tract and higher molecular weights (DP >3) possessing a lower bioavailability [86].

The monomers that comprise procyanidins can be joined via two different types of interflavan linkages, known as A- and B-type linkages. A-type linkages have two linkages: one between C-4 of the C ring and C-6 or C-8 of the B ring and an ether linkage from a hydroxy group on ring A to C-2 of ring C. B-type linkages occur between C-4 of the C ring and C-6 or C-8 of the A ring. The types of interflavan linkages present in procyanidins of *U. tomentosa* include C-4→C-6 B-type and C-4→C-8 B-type linkages. The most common type of procyanidins found in nature consist of **35** with B-type linkages, which corresponds to those found in *U. tomentosa* [3,87–89].

Procyanidins from extractions of plant material are known to possess antibacterial activity. The procyanidin extraction of bark from the larch birch tree, *Larix gmelinii* (Rupr.) Rupr., was characterized via Fourier-transform infrared (FTIR) spectroscopy analysis to possess dimers comprised of **35** and **36** monomers joined via C-4→C-8 linkages. These dimer structures are similar to those identified in *U. tomentosa*, particularly procyanidins **38**–**41** (Figure 6). This extract exhibited a weak inhibitory effect on *S. aureus* with an MIC value of 1.75 mg/mL. There is supporting evidence that the extract's mode of action affects the integrity and permeability of the cell wall and membrane, protein synthesis, and binds to the grooves of DNA [90].

Procyanidin Dimers

The procyanidin dimer structures present in extracts of *U. tomentosa* have been identified extensively by Navarro and colleagues [2,3,86]. The dimer structures identified include procyanidin B1–B7 (Figure 6, **38**–**44**). These compounds can be more easily identified as reference material exists for these compounds unlike larger procyanidin structures. Some of the dimers have been indicated to possess antibacterial activity when isolated from other plant sources and tested for MIC. Evidence has been found to support the antibacterial activity of **38**–**40** when extracted from plants. Procyanidin **38** and **39** were isolated from *Antidesma bunius* L. and tested against a variety of bacteria. MIC values ranging from 0.12 to 125 μg/mL were reported against Gram-positive bacteria and less potent MIC values ranging from 7.25 to 125 μg/mL against Gram-negative bacteria [91]. This study also proposes that the mechanism of action can be attributed to an effect on the cellular membrane, referencing the stronger antibacterial effect on Gram-positive bacteria and previous investigations into the antimicrobial effect of other flavan-3-ols [92]. Additionally, **40** was isolated from *Quercus ilex* L. and demonstrated weak antibacterial activity ranging from 98.3 to 393.176 μg/mL [93].

Procyanidin Trimers

Three procyanidin trimers have also been identified by Navarro and colleagues. Two of the trimers were characterized using MS/MS alongside commercial standards. Procyanidin trimer T and C1 were identified, while the third trimer remained uncharacterized as reference material could not be obtained [2]. It should be noted that trace amounts of compound were obtained and reported, but not enough for full characterization. This compound was given the generic name procyanidin trimer B in the study.

Propelargonidin Type

Propelargonidins are polymers composed of flavan-3-ol monomers of the afzelechin type. Afzelechin (**37**, Figure 5) is similar in structure to **36** but with a single hydroxy substitution on the B ring. The polymeric structures have been identified in extractions of *U. tomentosa* [88,89]. The monomeric subunits of **37** have not been characterized independently in any reported instances. Propelargonidin dimers have been identified in extracts of *U. tomentosa* by ultra-performance liquid chromatography (UPLC) coupled with electrospray ionization (ESI) and triple quadrupole (TQD) tandem mass spectrometry (UPLC/TQD–ESI–MS). These structures have been identified as existing in dimers, trimers, and larger polymeric states, based on mass spectrometry results, but no information relating to linkage type or stereochemistry was provided due to a lack of reference material [89].

Proanthocyanidins Polymeric Structures (DP > 3)

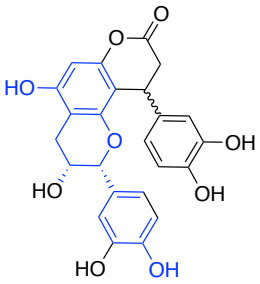
Polymeric structures comprised of both **35** and **37** monomers are also known to exist up to a DP of 11 in ethanol extracts of *U. tomentosa* [3,88]. These compounds are entirely formed with B-type linkages. The composition of these polymeric structures varies from being completely comprised of **35** to entirely made up of **37**, allowing the proanthocyanidins polymers to range from a procyanidin to propelargonidin polyphenol. The detection of the larger structures and their composition is attributed to the m/z charge through MS methods [3,88].

4.2. Miscellaneous Polyphenols

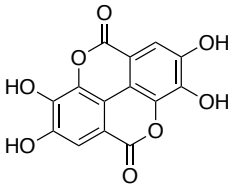
Two stereoisomeric cinchonain-type compounds **45a** and **45b** have been identified in *U. tomentosa* with their flavone core highlighted in blue in Figure 7. These compounds were identified in a constituent study investigating bioactive procyanidins of *U. tomentosa* [94]. The compound **45b** was later misrepresented in a 2005 review of the genus *Uncaria* [12], we have presented the original structure from the Wirth and Wagner study referenced herein. These compounds are flavonoids that possess the epicatechin monomer with a fused δ-valerolactone group replacing the hydroxy group of C-7 on ring A. The stereocenter of

these two compounds exists at the site where a catechol structure is linked to the beta carbon of the lactone structure, with **45a** in the *R* configuration and **45b** with the *S* configuration.

Ellagic acid (**46**) is a common phenolic constituent of flowering plants. This polyphenol is formed from the dimerization of two gallic acid molecules in a head to tail orientation, and subsequent oxidation, to form the two lactone groups present in the molecular structure [95]. The structure of **46** contains four-fused six member rings, two δ-valerolactone and two catechol rings. This molecule was isolated from *U. tomentosa* utilizing HPLC methods. The structure was characterized by comparing spectral analysis from 200–600 nm and comparisons of retention times with standard references [80]. This isolation and characterization were the only source that identified ellagic acid from an extraction of *U. tomentosa*. Compound **46** is known to possess antimicrobial activities and the mechanism for these activities include the hyper acidification of the plasma membrane, disruption of electron transport and ATP generation, as well as destabilization of the bacterial membrane [96].



Cinchonain 1a, **45a**: 10*R*
Cinchonain 1b, **45b**: 10*S*



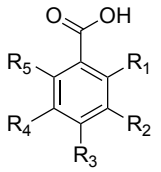
Ellagic Acid, **46**

Figure 7. Cinchonain structures and ellagic acid.

4.3. Phenolic Acids

Several phenolic acids have been identified and extracted from *U. tomentosa* [2,3,86,89]. The term phenolic acid is used to describe phenolic structures with a variety of hydroxy and methoxy substitutions around a single carboxylic acid substitution on a benzene ring. The two main types of phenolic acids identified from extractions of *U. tomentosa* are hydroxybenzoic and hydroxycinnamic acids (Tables 1 and 2, respectively). Ethanolic and aqueous extractions of *U. tomentosa* leaves gave a concentration of hydroxycinnamic acids from 33.6 to 188.3 µg/g and hydroxybenzoic acids from 113.2 to 983.0 µg/g. Extractions of bark from the same plants provided similar levels of hydroxycinnamic acids, but much higher concentrations of hydroxybenzoic acids ranging from 568.5 to 6206.3 µg/g [89].

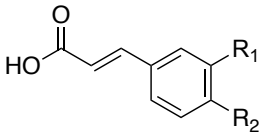
Table 1. Structures of hydroxybenzoic acid derivatives (**47**–**53**).



Hydroxybenzoic acids, **47-53**

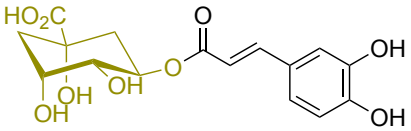
Compound	R_1	R_2	R_3	R_4	R_5
Benzoic, **47**	H	H	H	H	H
Salicylic acid, **48**	OH	H	H	H	H
4-Hydroxbenzoic, **49**	H	H	OH	H	H
Protocatechuic acid, **50**	H	OH	OH	H	H
Gallic acid, **51**	H	OH	OH	OH	H
Syringic, **52**	H	OMe	OH	OMe	H
Vanillic acid, **53**	H	OMe	OH	H	H

Table 2. Structures of hydroxycinnamic acid derivatives (**54**–**58**). Quinic acid is highlighted in olive.



Hydroxycinnamic acids, **54-57**

Compound	R_1	R_2
p-Coumaric acid, **54**	H	OH
Caffeic acid, **55**	OH	OH
Ferulic acid, **56**	OMe	OH
Isoferulic, **57**	OH	OMe



Chlorogenic acid, **58**

These phenolic acids are common natural products, found in a wide variety of plant life including fruits and vegetables [97]. These compounds are typically produced in plants through the shikimic pathway, a pathway used for the biosynthesis of aromatic compounds from precursors of simple carbohydrate molecules [98]. They are used by plants to perform a wide array of functions, some of which are not yet fully characterized or described [98]. Some of the functions are related to responses initiated by microbial contact. There is evidence to suggest that these compounds are utilized by plants in microbial interactions, for both symbiotic relationships and to combat infectious strains [99,100].

4.3.1. Hydroxybenzoic Acids

The hydroxybenzoic acids present in *U. tomentosa* are described in Table 1 (**47**–**53**). These compounds consist of a similar core structure to **47**, they then differ in amount and position of hydroxy or methoxy substitutions around the benzene ring. Compounds **48** and **49** are monohydroxylated in an *o*- and *p*-position with respect to the carboxylic acid. Compounds **50** and **53** have two substituents in addition to the carboxylic acid and is dihydroxylated in the *m*- and *p*-position for **50** or has a *m*-methoxy and a *p*-hydroxy substitution for **53**. Compounds **51** and **52** have three substituents in addition to the carboxylic acid, with **51** possessing three hydroxy groups, two in the *m*-positions and one in the *p*-position and **52** containing two *m*-groups and a one *p*-hydroxy group.

There are some structural trends that dictate antibacterial activity in these acids. It has been found that as the number of hydroxy and methoxy substitutions increases around the benzene ring, the antibacterial activity decreases [101–103]. The least substituted acid, benzoic acid (**47**), is commonly utilized as a food preservative due to its antibacterial activity as well as general safety at high dosages. In addition, it was noted in a comparative study that substitution of hydroxy groups with methoxy groups slightly increased the antibacterial activity with **52** performing better than **51** on *E. coli* and *B. subtilis* [101].

4.3.2. Hydroxycinnamic Acids

Hydroxycinnamic acids (**54**–**58**) are described in Table 2. It should be noted that chlorogenic acid (**58**) is structurally related to caffeic acid (**55**). Compounds **54**–**57** feature the cinnamic acid core, with substitutions *meta* and *para* to the short chain, unsaturated carboxylic acid. Compound **54** features a single *p*-hydroxy. Compounds **55**, **56**, and **57** have *m*- and *p*-substitutions with **55** containing two hydroxy groups, **56** a *m*-methoxy and *p*-hydroxy, and **57** a *m*-hydroxy and *p*-methoxy. Compound **58** differs in that a quinic acid is linked via esterification of caffeic acid. The double bond of the propene side chain can alternate between the *cis* and *trans* positions under increased energetic conditions; however, the *trans* configuration is more stable.

When compared to hydroxybenzoic acids these compounds generally have a stronger antimicrobial activity [101]. This has been attributed to the propene side chain leading to the carboxylic acid. It is assumed that the increased lipophilicity of this structure makes it more suitable for penetrating bacterial membranes [104]. The addition of hydroxy and methoxy groups also reduces the antibacterial activity of these compounds, but less than observed with hydroxybenzoic acids [101].

Transformation of cinnamic acid from *trans*- to *cis*-configuration raises a notable bactericidal and synergistic activity against multiple-drug resistant *Mycobacterium tuberculosis* [105]. The mechanism for antibacterial activity among these compounds is also well defined. Described as weak organic acids, these compounds' antimicrobial activity is strongly linked to their ability to diffuse across cell membranes, causing an acidification of the cytoplasm, which leads to cell death [103].

Several of the MICs for compounds **47**–**58** have been reported for common pathogenic bacteria. In general, these compounds do not possess strong antibacterial activity, with MIC values typically above 500 μg/mL [101,102]. Lower MIC values have been reported in some instances, such as **56** exhibiting an MIC value of 100 μg/mL for *E. coli* and *P. aeruginosa* [104]. In addition, **58** (3-0-caffeoylquinic acid or chlorogenic acid) produced MIC values of 100 μg/mL for *S. aureus* and *E. coli* and 200 μg/mL for *S. enterica* and *Vibrio parahaemolyticus* [106].

Additional sources also indicate a synergistic effect when used in combination with established antibacterial drugs. Compounds **54**–**56** and **58** all exhibit an enhancement of antibacterial activity when paired with commonly used antibiotics [107,108]. It was also suggested that this effect could be due to these compounds' ability to damage cell membranes and increase permeability of the antibiotics [108].

5. Terpenes

Terpenes or terpenoids are a large and diverse group of naturally occurring compounds found in a wide variety of plants. These secondary metabolites have a history of medicinal use, as their plant sources have been utilized as folk medicines for hundreds of years [109]. Terpenes continue to be used for medicinal applications to this day with various bioactivities reported due in part to the wide structural diversity of these natural compounds [110]. Antibacterial activity has been reported for this class, especially against Gram-positive bacteria [111]. The mechanism for the antibacterial efficacy is likely due to their lipophilic features which allows these compounds to penetrate microbial cell walls [112]. However, their lipophilic features make them relatively insoluble and difficult to work with respect to medicinal applications.

All terpenes are comprised of isoprene units, a 5-carbon structural unit. These units are assembled via condensation reactions of dimethylallyl diphosphate (DMAPP) with one or more iso-pentenyl diphosphates (IPP) to afford a 10 carbon intermediate geranyl diphosphate (GPP), 15 carbon farnesyl diphosphate (FPP), or 20 carbon geranylgeranyl diphosphate (GGPP) [113]. Larger carbon chains can then be formed from a condensation reaction of FPP and GGPP to form intermediates for terpenoids with up to 40 carbons [113]. The resulting terpenoid is typically classified as a mono-, sesqui-, di-, tri-, or tetra-terpenoid based on the number of isoprene units that comprise its carbon skeleton. Acyclic terpenoids formed from these reactions are then formed into cyclic structures via a cascade reaction catalyzed by plant enzymes [114]. The diversity of the structures created from the biosynthesis reactions is a current topic of research and investigation. More than 100 cyclical scaffolds of triterpenes have been identified, demonstrating the large structural diversity this class of compounds has to offer [115]. In this section, we will discuss the terpenoid structures identified from extracts of *U. tomentosa* as well as any indications of antibacterial activity.

The types of terpenoids identified and extracted from *U. tomentosa* to date include pentacyclic acid triterpenes of various skeletal structures including ursolic, oleanolic, quinovic, cincholic, saponins, phytosterols, and a single monoterpene. The references in which these compounds were isolated and characterized will be cited, as well as any instances of antibacterial activity noted for these compounds whether sourced from *U. tomentosa* or other plant sources.

5.1. Phytosterols

Phytosterols or plant sterols are a group of terpenoids that fall into the triterpene family. The core structure of phytosterols consists of a 29-carbon structure formed from the joining of six isoprene monomers (Figure 8). The core structure consists of four fused rings, three hexacyclic and one pentacyclic, all with *trans* ring junctions forming a planar structure, and an 8-carbon side chain emanating from C-17. There are three substitutions on the planar ring system, all with stereochemistry above the cyclic plane, a methyl group at C-18, a methyl group at C-19, and a hydroxy group at C-3 [116]. Variation in phytosterol structure can be found at C-4 which may or may not feature methyl or di-methyl substitution, the presence of a double bond at C-5, and/or C-7, methyl or ethyl substitution at C-24 with variable stereochemistry, and a double bond at C-22 with variable stereochemistry. The most abundant type of phytosterols found in nature feature no methyl substitution at C-4, a double bond between C-5, and a methyl or ethyl substitution at position C-24, similar to those found in *U. tomentosa* [117].

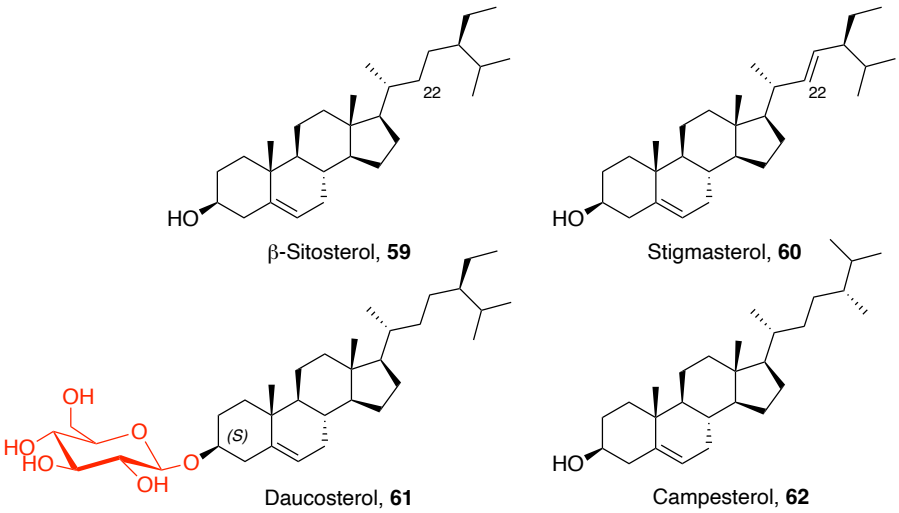


Figure 8. Structures of phytosterols (**59**–**62**). Sugar in red is *β*-D-glucose.

An important chemical attribute of sterols is their amphiphilicity due to the large planar non-polar regions interacting with hydrophobic membranes and the small, polar hydroxy substitution. Phytosterols play an important role in the regulation of plant cell membranes, affecting the fluidity and permeability [116]. In addition, phytosterols play roles in plant cell proliferation and development, as well as defense against biotic and abiotic stressors [118].

The types of phytosterols found in *U. tomentosa* consist of three of the most common phytosterols; *β*-sitosterol **59**, stigmasterol **60**, and campesterol **62** (Figure 8) [119]. These sterols are all 4-desmethyl sterols that feature a double bond at position C-5. Variation to the structure can be seen in substitutions to C-22 of the side chain. Compounds **59** and **60** feature an ethyl substitution, while compound **62** features a methyl substitution. These compounds also differ by the double bond at position C-22, with compound **60** possessing a double bond in the *trans* configuration and **59** and **62** being fully saturated at this position. The characterization of these compounds was determined via ^{1}H NMR spectroscopy and mass spectrometry [119].

Minor plant sterols found in *U. tomentosa* include a sterol glycoside. In this compound, the hydroxyl group at C-3 becomes a target for glycosylation. Compound **61**, or β-sitosterol-D-glucopyranoside, has a D-glucose moiety, which has been attached via the hydroxyl at C-3. The core structure of compound **59** is identical to β-stigmasterol. These compounds make up a small percentage of the steroidal fraction of *U. tomentosa* [120].

Phytosterols are bioactive compounds, with the most prominent activity related to their cholesterol lowering effect, due to the structural similarity between these compounds and cholesterol [118]. Phytosterols also exhibit antibacterial activity. Compound **59** exhibited antibacterial activity against *S. aureus* and *E. coli* producing zones of inhibition 17.83 $\pm$ 0.58 mm and 14.5 $\pm$ 1.84 mm [121], and 13 mm and 14 mm, respectively [122]. Compound **60** exhibited antibacterial activity against seven bacterial strains with MIC values between 12.5 and 25 µg/mL and minimum bactericidal concentration (MBC) values between 25 and 50 µg/mL [123]. Compound **61** indicated antibacterial activity against a variety of microbes with MIC and MBC values reported [124].

5.2. Pentacyclic Triterpene Acids

Pentacyclic triterpenes are a group of terpenoids identified in extracts of *U. tomentosa*. The core structure of pentacyclic triterpenes consists of five fused six-member rings. Common substitutions to the ring structure include a hydroxy group at C-3, methyl groups at C-10, C-8, C-27, C-19, and C-20, dimethyl groups at C-4 and C-20, carboxylic acids groups at C-17 and C-14, and a double bond at C-12. In general, these compounds are not very soluble in water giving them a low bioavailability and imparting challenges for biomedical applications. The plant biosynthesis of these compounds is thought to proceed through the intermediate β-amyrin [114]. It is known that these compounds accumulate in surface regions of stems and leaves, with evidence pointing toward a possible role in protection from dehydration or herbivores [114].

The plant *U. tomentosa* contains four varieties of pentacyclic triterpenes. The types of pentacyclic triterpenes include oleanolic, cincholic, ursolic, and quinovic acid (Figure 9). The pentacyclic triterpene families identified in *U. tomentosa* include a hydroxy group at C-3, a dimethyl substitution at C-4, methyl substitutions at C-10 and C-8, and a carboxylic acid at C-17. Variations to the core structure that distinguish each type of pentacyclic triterpene exist at C-14, C-19, and C-20. Compound **63** contains a methyl group at C-14, and a dimethyl group at C-20, whereas **64** contains a carboxylic acid at C-14 and dimethyl group at C-20. Compound **65** contains a methyl group at C-14, C-19, and C-20, whereas **66** contains a methyl group at C-19 and C-20 and a carboxylic acid at C-14.

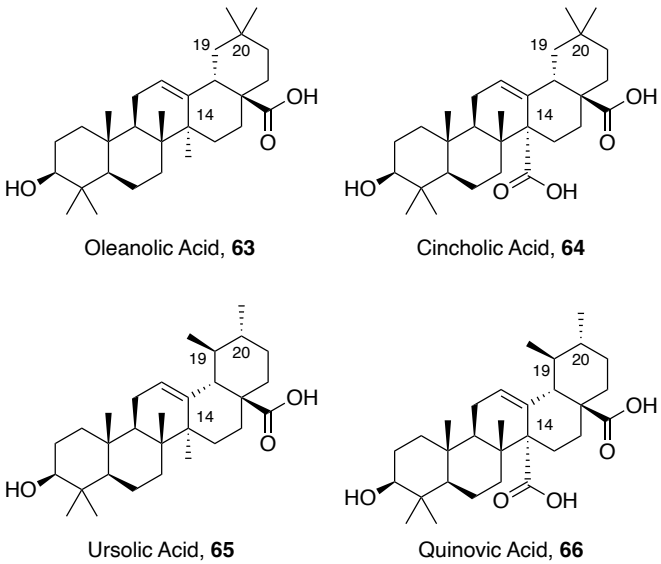


Figure 9. Triterpene acid structures (**63**–**66**).

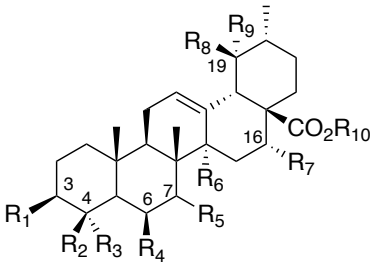
Several of the above pentacyclic triterpene acids above have been investigated for antibacterial activity. Compound **65** is the most extensively studied of the group as an antibacterial, with both reviews and individual studies available. Antibacterial evidence collected on **65** reveals a stronger inhibitory effect on Gram-positive bacteria than Gram-negative bacteria [125]. There has been specific interest in testing **65** and its derivatives to combat MRSA, as well as other drug resistant bacteria [126]. The mechanisms of antibacterial activity can be attributed to several factors including its ability to adhere to the cell membrane, reducing the bacteria's ability to adhere to epithelial cells, as well as its ability to disrupt and impair the bacterial cell membranes both inside and outside the cell [125]. In addition to targeting the bacterial membrane, **65** also exhibits antibiofilm activity [125], with some evidence supporting its ability to reduce expression of genes related to biofilm production [127,128]. Additional evidence supporting the synergistic effect of these compounds when used in combination with existing antibiotics also exists [126]. The issue surrounding the utilization of **65** is its low in vivo bioavailability, due to its poor solubility; however, these attributes can likely be improved by structural modifications, which has become a topic of several investigative studies [129–131].

The antibacterial activity of **63** has also been investigated. Like **65**, activity seems to increase in Gram-positive bacteria compared to Gram-negative bacteria. MIC values obtained from a microbroth dilution test were 64 μg/mL for *S. aureus* (ATCC 25923), 32 μg/mL for *S. aureus* (ATCC 29213), and 8 μg/mL for *E. faecalis* (ATCC 29212), while reported values of 256 μg/mL and above were found for *E. coli* (ATCC 25922) and *P. aeruginosa* (ATCC 27853) [132]. A review on the antibacterial activity of **63** against several bacterial strains can be found in reference [133]. A synergistic effect has also been noted when compound **63** and **65** were utilized with *β*-lactam-type antibiotics [134]. Antibacterial activity of compounds **64** and **66** was not found during the literature search.

5.2.1. Ursolic Acid Derivatives

Derivatives of **65** were also found in *U. tomentosa*, specifically compounds **67**–**77** in Table 3. These compounds contain various substitutions to the core structure of ursolic acid (**65**). The following section will discuss these substitutions.

Table 3. Ursolic Acid Derivatives (**67**–**77**).



Ursolic Acid Derivatives, **67-77**

Compound	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}
(3*β*)-3-Hydroxy-7-oxo-urs-12-ene-27,28-dioic acid, **67**	OH	Me	Me	H	=O	CO_2H	H	Me	H	H
(3*β*,16*α*)-16-Hydroxy-3-methoxy-ursa-12,19(29)-diene-27,28-dioic acid, **68**	MeO	Me	Me	H	H	CO_2H	OH	=		H
(3*β*,4*α*)-3,19-Dihydroxy-6,23-dioxo-urs-12-en-28-oic acid, **69**	OH	Me	CHO	=O	H	Me	H	Me	OH	H
(3*β*,4*α*)-3,19,23-trihydroxy-6-oxo-urs-12-en-28-oic acid, **70**	OH	Me	CH_2OH	=O	H	Me	H	Me	OH	H
(6*β*)-6,19-dihydroxy-3-oxo-urs-12-en-28-oic acid, **71**	=O	Me	Me	OH	H	Me	H	Me	OH	H
(3*β*,6*β*)-3,6,19-Trihydroxyurs-12-en-28-oic acid (uncaric acid), **72**	OH	Me	Me	OH	H	Me	H	Me	OH	H
(3*β*,4*α*,6*β*)-3,6,19-trihydroxy-23-oxo-norurs-12-en-28-oic acid, **73**	OH	=O		OH	H	Me	H	Me	OH	H
(3*β*,4*α*,6*β*)-3,6,19-trihydroxy-23-oxo-urs-12-en-28-oic acid, **74**	OH	Me	CHO	OH	H	Me	H	Me	OH	H
(3*β*,6*β*)-3,6,19-Trihydroxy-24-norursa-4(23),12-dien-28-oic acid (floridic acid), **75**	OH	=		OH	H	Me	H	Me	OH	H
(3*β*,4*α*,6*β*)-dimethyl ester-3,6,19-trihydroxy-urs-12-ene-23,28-dioic acid, **76**	OH	Me	CO_2Me	OH	H	Me	H	Me	OH	Me
(3*β*,4*α*,6*β*)-3,6,19,23-tetrahydroxy-urs-12-en-28-oic acid, **77**	OH	Me	CH_2OH	OH	H	Me	H	Me	OH	H

Compound **67** contains a ketone at R_5 and a carboxylic acid at R_6. Compound **68** contains a methoxy substitution at R_1, a carboxylic acid at R_6, hydroxy group at R_7, and an ethene at R_8. These compounds were identified in a methanol extract of dried root bark, separated using reverse phase HPLC (RP-HPLC), and characterized with ^{1}H and ^{13}C NMR spectroscopy [135]. Compounds **69** and **70** are similar in structure, both contain a ketone at R_4 and a hydroxy at R_9. However, at R_3, compound **69** possesses an aldehyde substituent while **70** possess a hydroxymethyl group. Compound **71** includes a ketone at R_1 and a hydroxy at R_4 and R_9. The characterization of compound **69**, **70**, and **71** was completed utilizing MS, ^{1}H, and ^{13}C NMR spectroscopy, on a methanol extraction of dried plant material, with **69** and **71** first characterized in the paper cited and **70** confirmed by comparison to previously reported data from another plant source [8]. Compound **72** possesses a hydroxy at R_4 and R_9. Antiviral activity for this compound against SARS-CoV-2 was investigated in silico [136]. The findings indicate the compound was a possible candidate of interest due to its binding affinity for an interface between the virus and human receptor cells and its druggability according to the Lipinski rules [136]. Compound **73** contains hydroxy groups at R_4 and R_9, as well as a ketone at R_2.

Compound **74** possesses an aldehyde at R_3 and hydroxy substituents at R_4 and R_9. Compound **75** possesses an ethene group at R_2 and hydroxy groups at R_4 and R_9. Compound **75** was also investigated in silico for potential antiviral activity against SARS-CoV-2 [136]. Compounds **72**, **74**, and **75** were all characterized using ^{1}H and ^{13}C NMR spectroscopy from a $CHCl_3$ extraction of plant materials [137]. Compound **75** was also identified in subsequent research by Kitajima and coworkers, and again characterized with ^{1}H and ^{13}C NMR spectroscopy [8]. Compound **76** contains a unique carbomethoxy group at R_3, as well as hydroxy groups at R_4 and R_9, and a methyl group at R_{10}. This compound was characterized from a $CHCl_3$-MeOH (9:1) extraction using ^{1}H and ^{13}C NMR [138]. Compound **77** contains a hydroxymethyl group at R_3, as well as hydroxy groups at R_4 and R_9. This compound was identified in *U. tomentosa* by Aquino and colleagues using an extraction of dried plant material in methanol and ^{1}H and ^{13}C NMR spectroscopy to structurally identify the compound [135]. The characterization was compared to established literature [139]. Compound **77** was also identified as possessing moderate antibacterial activity when tested against bacterial strains *B. subtilis* (ATCC6633), *S. aureus* (ATCC12600), *E. coli* (ATCC25922), *K. pneumoniae* (ATCC13883) and *P. stutzeri* (ATCC17588), with MIC values of 78 µg/mL for *S. aureus* (ATCC12600), 156 µg/mL for *P. stutzeri* (ATCC17588), and 312 µg/mL for all other bacterial strains reported [140].

5.2.2. Glycosylated Pentacyclic Triterpene Acids

The glycosylated versions of pentacyclic triterpenes are also commonly referred to as saponins. These compounds are comprised of a pentacyclic aglycone with various glycones attached at specific positions. These compounds have been identified as being much more soluble, due to their increased polarity, which increases the probability of bioactivity [114]. The glycosylation of the triterpenes is controlled by a family of enzymes known as carbohydrate-active-enzymes family 1 [141].

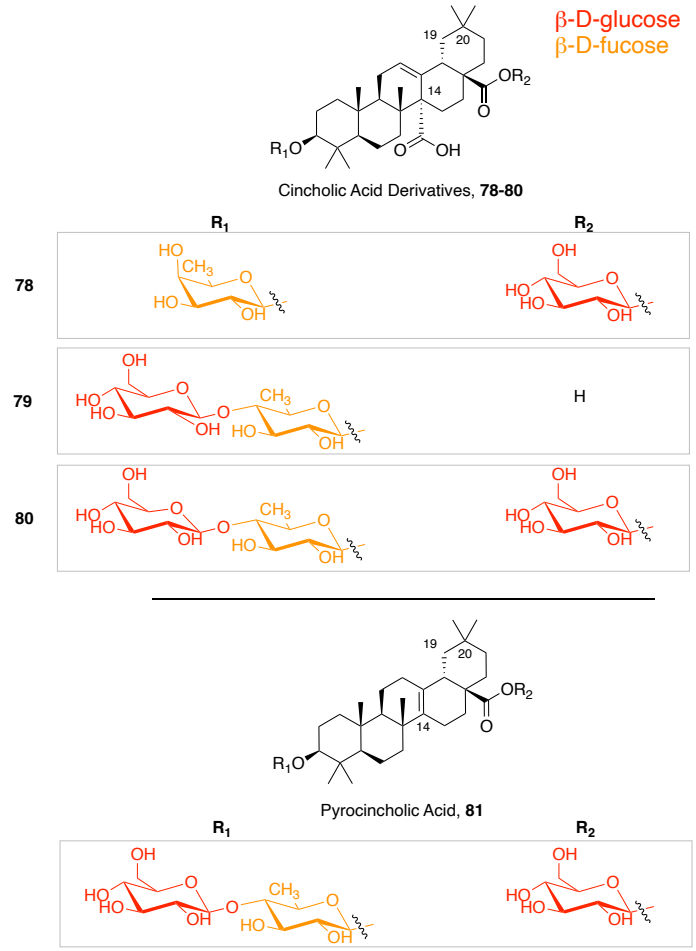
Several pentacyclic acid glycosides have been found in *U. tomentosa*, of which the aglycone has been identified as cincholic, pyrocincholic, quinovic, or pyroquinovic acid, and the glycones have been identified as the monosaccharides β-D-glucose, β-D-fucose, β-D-quinovose, β-D-galactose, α-L-rhamnose or the disaccharides of these sugars. It should be noted that in the literature, rhamnose, fucose, and quinovose can also be referred to as 6-deoxy-mannose, -galactose, and -glucose, respectively. The glycones are bound to the hydroxy group at C-3, as well as the hydroxy groups of the carboxylic acids at C-14 and C-17. All pentacyclic acid glycosides contain either one or two glycone additions.

Cincholic Acid Derivatives

Three cincholic acid derivatives have been isolated and characterized from an extract of *U. tomentosa*. The structure of compounds **78**–**80** were identified utilizing MS and ^{13}C

NMR spectroscopy [6] and are described in Table 4. These compounds only differ by the type of glycones attached to locations R_1 and R_2.

Table 4. Cincholic acid derivatives (**78**–**81**).



No.	Compound Name
78	Cincholic acid 27-O-*β*-D-fucopyranosyl-28-O-*β*-D-glucopyranoside
79	Cincholic acid 27-O-*β*-D-glucopyranosyl-(1→3)-*β*-D-fucopyranoside
80	Cincholic acid 27-O-*β*-D-glucopyranosyl-(1→3)-*β*-D-fucopyranosyl-28-O-*β*-D-glucopyranoside
81	Pyrocincholic acid 27-O-*β*-D-glucopyranosyl-(1→3)-*β*-D-fucopyranosyl-28-O-*β*-D-glucopyranoside (Tomentoside B)

Quinovic Acid Derivatives

Fourteen quinovic acid glycosides have been identified from *U. tomentosa* and make up most of the glycosides isolated to date [135,138,142,143]. Compounds **82**–**94** from Table 5 describe the structures of these compounds. Structural differences are reserved to the glycones attached to the hydroxyl group at C-3 and the hydroxyl group of the two carboxylic acid groups. Eight different glycones have been identified in the research to date, the monosaccharides that make up these glycones are listed in Table 5 and distinguished with individual colors. Improved methods for quantification and identification have been developed since the initial isolation and characterization [144]. Instances of antibacterial activity for **83** and **84** were reported. Compound **83** was investigated in silico for antibacterial activity utilizing a docking simulation with Staph GyraseB 24 and results indicated a comparable binding energy to novobiocin (a known antimicrobial used as the control for the study) [145]. Compound **84** demonstrated antibacterial activity against *Haemophilus influenzea* when isolated from *Nauclea latifolia* Smith with a MIC value of 12.5 µg/mL and a MBC value of 50.0 µg/mL [146].

Table 5. Quinovic Acid Glycosides (**82–95**).

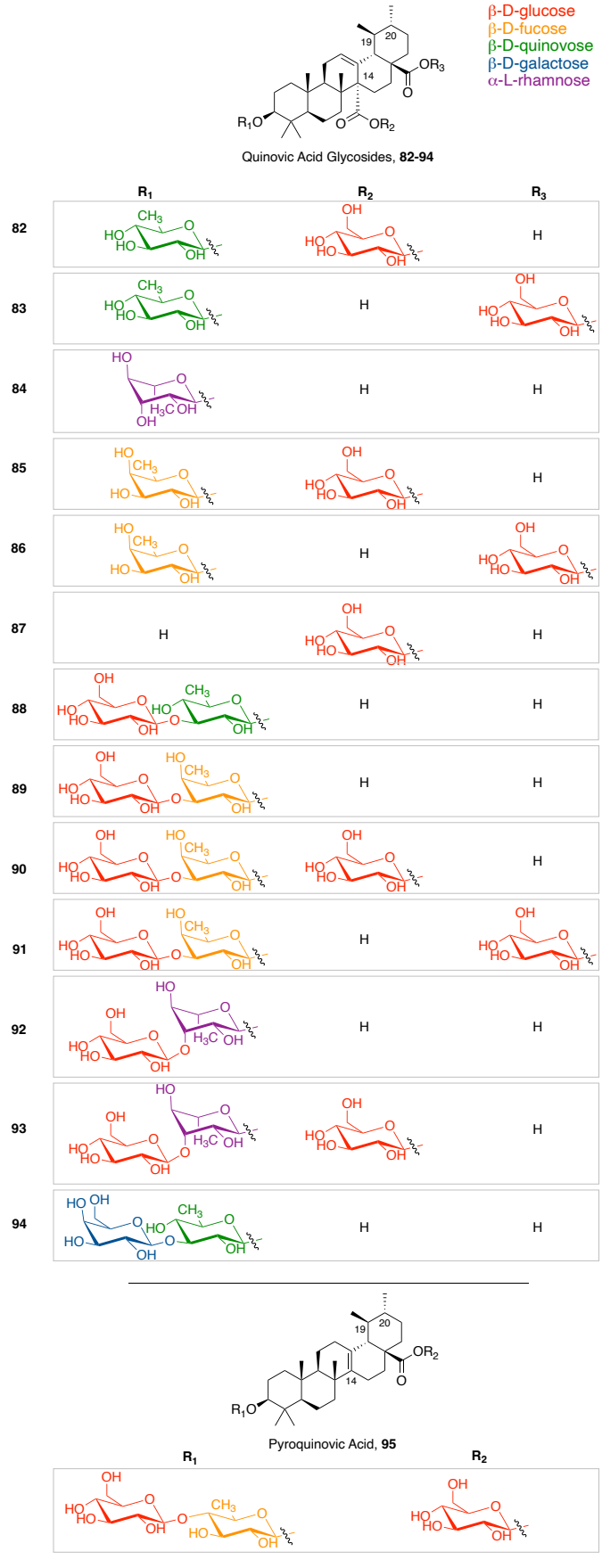


Table 5. *Cont.*

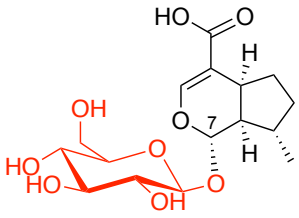
No.	Compound
82	Quinovic acid 3-O-*β*-D-quinovopyranosyl-27-O-*β*-D-glucopyranoside
83	Quinovic acid 3-O-*β*-D-quinovopyranosyl-28-O-*β*-D-glucopyranoside
84	Quinovic acid 3-O-*α*-L-rhamnoside
85	Quinovic acid 3-O-*β*-D-fucopyranosyl-27-O-*β*-D-glucopyranoside
86	Quinovic acid 3-O-*β*-D-fucopyranosyl-28-O-*β*-D-glucopyranoside
87	Quinovic acid 27-O-*β*-D-glucopyranoside
88	Quinovic acid 3-O-*β*-D-glucopyranosyl-(1→3)-*β*-D-quinovopyranoside
89	Quinovic acid 3-O-*β*-D-glucopyranosyl-(1→3)-*β*-D-fucopyranoside
90	Quinovic acid 3-O-*β*-D-glucopyranosyl-(1→3)-*β*-D-fucopyranosyl-27-O-*β*-D-glucopyranoside
91	Quinovic acid 3-O-*β*-D-glucopyranosyl-(1→3)-*β*-D-fucopyranosyl-28-O-*β*-D-glucopyranoside
92	Quinovic acid 3-O-*α*-L-rhamnopyranosyl-(3→1)-*β*-D-glucopyranoside
93	Quinovic acid 3-O-*α*-L-rhamnopyranosyl-(3→1)-*β*-D-glucopyranosyl-27-O-*β*-D-glucopyranoside
94	Quinovic acid 3-O-*β*-D-galactopyranosyl-(1→3)-*β*-D-quinovopyranoside
95	Pyroquinovic acid 3-O-*β*-D-glucopyranosyl-(1→3)-*β*-D-fucopyranosyl-28-O-*β*-D-glucopyranoside (Tomentoside A)

Pyroquinovic and Pyrocincholic Acid Derivatives

A pyroquinovic acid glycoside and a pyrocincholic acid glycoside were identified using ^{1}H and ^{13}C NMR spectroscopy [9]. These compounds interestingly, have only been identified in their glycosidic forms. The core structure of pyroquinovic and pyrocincholic acid have yet to be identified as independent structures in *U. tomentosa*. The pyroquinovic and pyrocincholic glycosides differ from quinovic and cincholic acid by the lack of a carboxylic acid group at C-14. Both compound **95** and **81** (Table 5), identified in *U. tomentosa* contain a disaccharide bound to the hydroxy group at C-3 and a monosaccharide bound to the carboxylic acid at C-17.

5.3. Miscellaneous Terpenoid

An additional terpenoid that does not fit into any of the classifications above has also been identified from extractions of *U. tomentosa*. The monoterpene glycoside, 7-deoxyloganic acid (**96**), has been identified using ^{1}H and ^{13}C NMR data (Figure 10) [120]. Compound **96** features a cyclopentapyran substituted with a carboxylic acid, the C-7 position with a *β*-D-glucose, and a methyl group. This compound is an intermediate of the secologanin and iridoid biosynthesis in other plant species; however, neither of these compound types have been identified directly in *U. tomentosa* in our research [147].



7-deoxyloganic acid, **96**

Figure 10. Miscellaneous terpenoid.

6. Conclusions

This review is unique in that it provides a substantiated, comprehensive collection of the known chemical constituents of *Uncaria tomentosa*, including their detailed structures. We have also provided corrections from the literature where compounds were accidentally attributed to *U. tomentosa*. This also demonstrates that extracts and several of the plant's isolated molecules have exhibited considerable potential as antibacterial agents, warranting further investigation. The significance of increasing bacterial resistance to the currently available array of antibiotics cannot be overstated. New antibiotic drugs are needed and medicinal plants such as cat's claw are a rich resource to provide new insights and inspiration.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/appliedchem2010001/s1.

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References

1. Newman, D.J.; Cragg, G.M. Natural Products as Sources of New Drugs over the Nearly Four Decades from 01/1981 to 09/2019. *J. Nat. Prod.* **2020**, *83*, 770–803. [CrossRef] [PubMed]
2. Navarro Hoyos, M.; Sánchez-Patán, F.; Murillo Masis, R.; Martín-Álvarez, P.; Zamora Ramirez, W.; Monagas, M.; Bartolomé, B. Phenolic Assesment of *Uncaria tomentosa* L. (Cat's Claw): Leaves, Stem, Bark and Wood Extracts. *Molecules* **2015**, *20*, 22703–22717. [CrossRef] [PubMed]
3. Navarro-Hoyos, M.; Lebrón-Aguilar, R.; Quintanilla-López, J.E.; Cueva, C.; Hevia, D.; Quesada, S.; Azofeifa, G.; Moreno-Arribas, M.; Monagas, M.; Bartolomé, B. Proanthocyanidin characterization and bioactivity of extracts from different parts of *Uncaria tomentosa* L. (cat's claw). *Antioxidants* **2017**, *6*, 12. [CrossRef] [PubMed]
4. Kitajima, M.; Yokoya, M.; Takayama, H.; Aimi, N. Co-occurrence of Harman and β-Carboline-type Monoterpenoid Glucoindole Alkaloids in Una de Gato (*Uncaria tomentosa*). *Nat. Med.* **2001**, *55*, 308–310.
5. Kitajima, M.; Hashimoto, K.-I.; Yokoya, M.; Takayama, H.; Aimi, N.; Sakai, S.-I. A New Gluco Indole Alkaloid, 3, 4-Dehydro-5-carboxystrictosidine, from Peruvian Una de Gato (*Uncaria tomentosa*). *Chem. Pharm. Bull.* **2000**, *48*, 1410–1412. [CrossRef] [PubMed]
6. Kitajima, M.; Hashimoto, K.-I.; Sandoval, M.; Aimi, N.; Takayama, H. New Oleanan-Type Triterpene and Cincholic Acid Glycosides from Peruvian "Uña de Gato" (*Uncaria tomentosa*). *Chem. Pharm. Bull.* **2004**, *52*, 1258–1261. [CrossRef]
7. Kitajima, M.; Yokoya, M.; Takayama, H.; Aimi, N. Synthesis and Absolute Configuration of a New 3,4-Dihydro-β-carboline-Type Alkaloid, 3,4-Dehydro-5(S)-5-carboxystrictosidine, Isolated from Peruvian Una de Gato (*Uncaria tomentosa*). *Chem. Pharm. Bull.* **2002**, *50*, 1376–1378. [CrossRef]
8. Kitajima, M.; Hashimoto, K.-i.; Yokoya, M.; Takayama, H.; Aimi, N. Two New 19-Hydroxyursolic Acid-type Triterpenes from Peruvian 'Uña de Gato' (*Uncaria tomentosa*). *Tetrahedron* **2000**, *56*, 547–552. [CrossRef]
9. Kitajima, M.; Hashimoto, K.-I.; Yokoya, M.; Takayama, H.; Sandoval, M.; Aimi, N. Two New Nor-triterpene Glycosides from Peruvian "Uña de Gato" (*Uncaria tomentosa*). *J. Nat. Prod.* **2003**, *66*, 320–323. [CrossRef]
10. Laus, G.; Brössner, D.; Keplinger, K. Alkaloids of peruvian *Uncaria tomentosa*. *Phytochemistry* **1997**, *45*, 855–860. [CrossRef]
11. Zhang, Q.; Zhao, J.J.; Xu, J.; Feng, F.; Qu, W. Medicinal uses, phytochemistry and pharmacology of the genus *Uncaria*. *J. Ethnopharmacol.* **2015**, *173*, 48–80. [CrossRef] [PubMed]
12. Heitzman, M.E.; Neto, C.C.; Winiarz, E.; Vaisberg, A.J.; Hammond, G.B. Ethnobotany, phytochemistry and pharmacology of *Uncaria* (Rubiaceae). *Phytochemistry* **2005**, *66*, 5–29. [CrossRef] [PubMed]

13. Batiha, G.E.-S.; Magdy Beshbishy, A.; Wasef, L.; Elewa, Y.H.; El-Hack, A.; Mohamed, E.; Taha, A.E.; Al-Sagheer, A.A.; Devkota, H.P.; Tufarelli, V. *Uncaria tomentosa* (Willd. ex Schult.) DC.: A Review on Chemical Constituents and Biological Activities. *Appl. Sci.* **2020**, *10*, 2668. [CrossRef]
14. Urdanibia, I.; Taylor, P. *Uncaria tomentosa* (Willd. ex Schult.) DC. and *Uncaria guianensis* (Aubl.) JF Gmell. In *Medicinal and Aromatic Plants of South America*; Springer: Berlin/Heidelberg, Germany, 2018; pp. 453–463.
15. Herrera, D.R.; Tay, L.Y.; Rezende, E.C.; Kozlowski, V.A., Jr.; dos Santos, E.B. In vitro antimicrobial activity of phytotherapic *Uncaria tomentosa* against endodontic pathogens. *J. Oral Sci.* **2010**, *52*, 473–476. [CrossRef]
16. Herrera, D.R.; Durand-Ramirez, J.E.; Falcao, A.; SILVA, E.J.L.N.d.; SANTOS, E.B.d.; GOMES, B.P.F.d.A. Antimicrobial activity and substantivity of *Uncaria tomentosa* in infected root canal dentin. *Braz. Oral Res.* **2016**, *30*, 1–5. [CrossRef]
17. Ccahuana-Vasquez, R.A.; Santos, S.S.F.d.; Koga-Ito, C.Y.; Jorge, A.O.C. Antimicrobial activity of *Uncaria tomentosa* against oral human pathogens. *Braz. Oral Res.* **2007**, *21*, 46–50. [CrossRef]
18. Silva, D.; Ribeiro, G.E.; Rufino, L.R.A.; Oliveira, N.M.S.; Fiorini, J.E. Atividade Antimicrobiana da *Uncaria tomentosa* (Willd) DC. *J. Basic Appl. Pharm. Sci.* **2014**, *35*, 53–57.
19. Kloucek, P.; Polesny, Z.; Svobodova, B.; Vlkova, E.; Kokoska, L. Antibacterial screening of some Peruvian medicinal plants used in Calleria District. *J. Ethnopharmacol.* **2005**, *99*, 309–312. [CrossRef]
20. Datar, A.N.; Kaur, N.; Patel, S.; Luecke, D.F.; Sapi, E. *In Vitro Effectiveness of Samento and Banderol Herbal Extracts on Different Morphological Forms of Borrelia Burgdorferi*; University of New Haven: West Haven, CT, USA, 2010.
21. Feng, J.; Leone, J.; Schweig, S.; Zhang, Y. Evaluation of Natural and Botanical Medicines for Activity against Growing and Non-growing Forms of *B. burgdorferi*. *Front. Med.* **2020**, *7*, 6. [CrossRef]
22. Sadilek, A.; Hswen, Y.; Bavadekar, S.; Shekel, T.; Brownstein, J.S.; Gabrilovich, E. Lymelight: Forecasting Lyme disease risk using web search data. *NPJ Digit. Med.* **2020**, *3*, 16. [CrossRef]
23. Kuehn, B.M. CDC estimates 300 000 US cases of Lyme disease annually. *JAMA* **2013**, *310*, 1110. [CrossRef] [PubMed]
24. Keplinger, K.; Laus, G.; Wurm, M.; Dierich, M.P.; Teppner, H. *Uncaria tomentosa* (Willd.) DC.—Ethnomedicinal use and new pharmacological, toxicological and botanical results. *J. Ethnopharmacol.* **1998**, *64*, 23–34. [CrossRef]
25. Reinhard, K.-H. *Uncaria tomentosa* (Willd.) D.C.: Cat's Claw, Uña de Gato, or Savéntaro. *J. Altern. Complement. Med.* **1999**, *5*, 143–151. [CrossRef] [PubMed]
26. Falkiewicz, B.; Lukasiak, J. Vilcacora (*Uncaria tomentosa* (Willd.) DC. and *Uncaria guianensis* (Aublet) Gmell.)—A review of published scientific literature. *Case Rep. Clin. Pract. Rev.* **2001**, *2*, 305–316.
27. Laus, G. Advances in chemistry and bioactivity of the genus *Uncaria*. *Phytother. Res.* **2004**, *18*, 259–274. [CrossRef]
28. Potawale, S.E.; Mehta, U.K.; Sadiq, M.W.M. Phytopharmacology of *Uncaria tomentosa*: A review. *Pharmacologyonline* **2008**, *2*, 197–214.
29. Andre, N.; Wang, X.; He, Y.; Pan, G.; Kojo, A.; Liu, Y. A review of the occurrence of non-alkaloid constituents in *Uncaria* species and their structure-activity relationships. *Am. J. Biomed. Life Sci.* **2013**, *1*, 79–98. [CrossRef]
30. Ravipati, A.S.; Reddy, N.; Koyyalamudi, S.R. Chapter 13—Biologically Active Compounds from the Genus *Uncaria* (Rubiaceae). In *Studies in Natural Products Chemistry*; Atta ur, R., Ed.; Elsevier: Amsterdam, The Netherlands, 2014; Volume 43, pp. 381–408.
31. Liang, J.-H.; Wang, C.; Huo, X.-K.; Tian, X.-G.; Zhao, W.-Y.; Wang, X.; Sun, C.-P.; Ma, X.-C. The genus *Uncaria*: A review on phytochemical metabolites and biological aspects. *Fitoterapia* **2020**, *147*, 104772. [CrossRef]
32. Rosales, P.F.; Bordin, G.S.; Gower, A.E.; Moura, S. Indole alkaloids: 2012 until now, highlighting the new chemical structures and biological activities. *Fitoterapia* **2020**, *143*, 104558. [CrossRef]
33. Cushnie, T.T.; Cushnie, B.; Lamb, A.J. Alkaloids: An overview of their antibacterial, antibiotic-enhancing and antivirulence activities. *Int. J. Antimicrob. Agents* **2014**, *44*, 377–386. [CrossRef]
34. Aniszewski, T. *Alkaloids: Chemistry, Biology, Ecology, and Applications*; Elsevier: Amsterdam, The Netherlands, 2015.
35. Hesse, M. *Alkaloids: Nature's Curse or Blessing?* John Wiley & Sons: Hoboken, NJ, USA, 2002.
36. O'Connor, S.E.; Maresh, J.J. Chemistry and biology of monoterpene indole alkaloid biosynthesis. *Nat. Prod. Rep.* **2006**, *23*, 532–547. [CrossRef] [PubMed]
37. Singh, T.P.; Singh, O.M. Recent progress in biological activities of indole and indole alkaloids. *Mini Rev. Med. Chem.* **2018**, *18*, 9–25. [CrossRef] [PubMed]
38. Mohammed, A.E.; Abdul-Hameed, Z.H.; Alotaibi, M.O.; Bawakid, N.O.; Sobahi, T.R.; Abdel-Lateff, A.; Alarif, W.M. Chemical Diversity and Bioactivities of Monoterpene Indole Alkaloids (MIAs) from Six Apocynaceae Genera. *Molecules* **2021**, *26*, 488. [CrossRef] [PubMed]
39. Phillipson, J.; Hemingway, S. Chromatographic and spectroscopic methods for the identification of alkaloids from herbarium samples of the genus *Uncaria*. *J. Chromatogr. A* **1975**, *105*, 163–178. [CrossRef]
40. Dembitsky, V.M.; Gloriozova, T.A.; Poroikov, V.V. Naturally occurring plant isoquinoline N-oxide alkaloids: Their pharmacological and SAR activities. *Phytomedicine* **2015**, *22*, 183–202. [CrossRef]
41. Phillipson, J.D.; Hemingway, S.R.; Ridsdale, C.E. *Alkaloids of Uncaria. V. Their Occurrence and Chemotaxonomy*; University of the Philippines: Quezon City, Philippines, 1978.

42. Mfuh, A.M.; Larionov, O.V. Heterocyclic N-Oxides—An Emerging Class of Therapeutic Agents. *Curr. Med. Chem.* **2015**, *22*, 2819–2857. [CrossRef]
43. Ihsan, A.; Wang, X.; Tu, H.G.; Zhang, W.; Dai, M.H.; Peng, D.P.; Wang, Y.L.; Huang, L.L.; Chen, D.M.; Mannan, S.; et al. Genotoxicity evaluation of Mequindox in different short-term tests. *Food Chem. Toxicol.* **2013**, *51*, 330–336. [CrossRef]
44. Keri, R.A.-O.; Pandule, S.S.; Budagumpi, S.; Nagaraja, B.M. Quinoxaline and quinoxaline-1,4-di-N-oxides: An emerging class of antimycobacterials. *Arch. Pharm.* **2018**, *351*, 1700325. [CrossRef]
45. Cheng, G.; Li, B.; Wang, C.; Zhang, H.; Liang, G.; Weng, Z.; Hao, H.; Wang, X.; Liu, Z.; Dai, M.; et al. Systematic and Molecular Basis of the Antibacterial Action of Quinoxaline 1,4-Di-N-Oxides against *Escherichia coli*. *PLoS ONE* **2015**, *10*, e0136450. [CrossRef]
46. Shamma, M.; Richey, J.M. The stereochemistry of the heteroyohimbine alkaloids. *J. Am. Chem. Soc.* **1963**, *85*, 2507–2512. [CrossRef]
47. Qin, N.; Lu, X.; Liu, Y.; Qiao, Y.; Qu, W.; Feng, F.; Sun, H. Recent research progress of *Uncaria* spp. based on alkaloids: Phytochemistry, pharmacology and structural chemistry. *Eur. J. Med. Chem.* **2021**, *210*, 112960. [CrossRef] [PubMed]
48. Huerta-Heredia, A.A.; Marín-López, R.; Ponce-Noyola, T.; Cerda-García-Rojas, C.M.; Trejo-Tapia, G.; Ramos-Valdivia, A.C. Oxidative stress induces alkaloid production in *Uncaria tomentosa* root and cell cultures in bioreactors. *Eng. Life Sci.* **2009**, *9*, 211–218. [CrossRef]
49. Vera-Reyes, I.; Huerta-Heredia, A.A.; Ponce-Noyola, T.; Flores-Sanchez, I.J.; Esparza-García, F.; Cerda-García-Rojas, C.M.; Trejo-Tapia, G.; Ramos-Valdivia, A.C. Strictosidine-related enzymes involved in the alkaloid biosynthesis of *Uncaria tomentosa* root cultures grown under oxidative stress. *Biotechnol. Prog.* **2013**, *29*, 621–630. [CrossRef] [PubMed]
50. Luna-Palencia, G.; Huerta-Heredia, A.; Cerda-García-Rojas, C.; Ramos-Valdivia, A. Differential alkaloid profile in *Uncaria tomentosa* micropropagated plantlets and root cultures. *Biotechnol. Lett.* **2013**, *35*, 791–797. [CrossRef] [PubMed]
51. Aimi, N.; Shito, T.; Fukushima, K.; Itai, Y.; Aoyama, C.; Kunisawa, K.; Sakai, S.; Haginiwa, J.; Yamasaki, K. Studies on Plants containing Indole Alkaloids. VIII Indole Alkaloid Glycosides and Other Constituents of the Leaves of *Uncaria rhynchophylla* MIQ. *Chem. Pharm. Bull.* **1982**, *30*, 4046–4051. [CrossRef]
52. Nenaah, G. Antibacterial and antifungal activities of (beta)-carboline alkaloids of *Peganum harmala* (L) seeds and their combination effects. *Fitoterapia* **2010**, *81*, 779–782. [CrossRef]
53. Dai, J.; Dan, W.; Ren, S.; Shang, C.; Wang, J. Design, synthesis and biological evaluations of quaternization harman analogues as potential antibacterial agents. *Eur. J. Med. Chem.* **2018**, *160*, 23–36. [CrossRef]
54. de Carvalho Junior, A.R.; Oliveira Ferreira, R.; de Souza Passos, M.; da Silva Boeno, S.I.; Glória das Virgens, L.D.L.; Ventura, T.L.B.; Calixto, S.D.; Lassounskaia, E.; de Carvalho, M.G.; Braz-Filho, R.; et al. Antimycobacterial and Nitric Oxide Production Inhibitory Activities of Triterpenes and Alkaloids from *Psychotria nuda* (Cham. & Schltdl.) Wawra. *Molecules* **2019**, *24*, 1026. [CrossRef]
55. Kaur, M.; Singh, M.; Chadha, N.; Silakari, O. Oxindole: A chemical prism carrying plethora of therapeutic benefits. *Eur. J. Med. Chem.* **2016**, *123*, 858–894. [CrossRef]
56. Ahmad, R.; Salim, F. Oxindole Alkaloids of *Uncaria* (Rubiaceae, Subfamily Cinchonoideae): A Review on Its Structure, Properties, and Bioactivities. In *Studies in Natural Products Chemistry*; Elsevier: Amsterdam, The Netherlands, 2015; Volume 45, pp. 485–525.
57. Lopes, A.A.; Chioca, B.; Musquiari, B.; Crevelin, E.J.; França, S.D.C.; Silva, M.F.D.G.F.D.; Pereira, A.M.S. Unnatural spirocyclic oxindole alkaloids biosynthesis in *Uncaria guianensis*. *Sci. Rep.* **2019**, *9*, 11349. [CrossRef]
58. Khetmalis, Y.M.; Shivani, M.; Murugesan, S.; Chandra Sekhar, K.V.G. Oxindole and its derivatives: A review on recent progress in biological activities. *Biomed. Pharmacother.* **2021**, *141*, 111842. [CrossRef] [PubMed]
59. Cerchiaro, G.; Ferreira, A.M.D.C. Oxindoles and copper complexes with oxindole-derivatives as potential pharmacological agents. *J. Braz. Chem. Soc.* **2006**, *17*, 1473–1485. [CrossRef]
60. Yurttaş, L.; Ertaş, M.; Cankılıç Yılmaz, M.; Demirayak, Ş. Synthesis and Antimycobacterial Activity Evaluation of Isatin-derived 3-[(4-aryl-2-thiazolyl])hydrazone]-1H-indol-2,3-diones. *Acta Pharm. Sci.* **2017**, *55*, 51–58. [CrossRef]
61. Bertol, G.; Franco, L.; Oliveira, B.H. HPLC Analysis of Oxindole Alkaloids in *Uncaria tomentosa*: Sample Preparation and Analysis Optimisation by Factorial Design. *Phytochem. Anal.* **2012**, *23*, 143–151. [CrossRef]
62. Luna-Palencia, G.; Cerda-Garcıa-Rojas, C.; Romo-Cruz, I.; Albarrán, J.; Ramos-Valdivia, A. Advances in the biosynthesis of oxindole alkaloids in *Uncaria tomentosa* cultures. In Proceedings of the Inter Symp Chem Pharmacol and Biosynthesis of Alkaloids, Belek, Antalya, Turkey, April 2006.
63. Luna-Palencia, G.R.; Cerda-García-Rojas, C.M.; Rodríguez-Monroy, M.; Ramos-Valdivia, A.C. Influence of Auxins and Sucrose in Monoterpenoid Oxindole Alkaloid Production by *Uncaria tomentosa* Cell Suspension Cultures. *Biotechnol. Prog.* **2005**, *21*, 198–204. [CrossRef]
64. Yuan, D.; Ma, B.; Wu, C.; Yang, J.; Zhang, L.; Liu, S.; Wu, L.; Kano, Y. Alkaloids from the Leaves of *Uncaria rhynchophylla* and Their Inhibitory Activity on NO Production in Lipopolysaccharide-Activated Microglia. *J. Nat. Prod.* **2008**, *71*, 1271–1274. [CrossRef]
65. Hemingway, S.R.; Phillipson, J.D. Alkaloids from S. American species of *Uncaria* (Rubiaceae). *J. Pharm. Pharmacol.* **2011**, *26*, 113P. [CrossRef]
66. Seki, H.; Takayama, H.; Aimi, N.; Sakai, S.-I.; Ponglux, D. A Nuclear Magnetic Resonance Study on the Eleven Stereoisomers of Heteroyohimbine-Type Oxindole Alkaloids. *Chem. Pharm. Bull.* **1993**, *41*, 2077–2086. [CrossRef]
67. Lounasmaa, M.; Kan, S.-K. A 400 mhz 1H NMR study of the eight basic heteroyohimbine alkaloids. *Tetrahedron* **1980**, *36*, 1607–1611. [CrossRef]

68. Paniagua-Pérez, R.; Madrigal-Bujaidar, E.; Molina-Jasso, D.; Reyes-Cadena, S.; Álvarez-González, I.; Sánchez-Chapul, L.; Pérez-Gallaga, J. Antigenotoxic, Antioxidant and Lymphocyte Induction Effects Produced by Pteropodine. *Basic Clin. Pharmacol. Toxicol.* **2009**, *104*, 222–227. [CrossRef]
69. Dreifuss, A.A.; Bastos-Pereira, A.L.; Fabossi, I.A.; Lívero, F.A.D.R.; Stolf, A.M.; de Souza, C.E.A.; Gomes, L.D.O.; Constantin, R.P.; Furman, A.E.F.; Strapasson, R.L.B.; et al. *Uncaria tomentosa* Exerts Extensive Anti-Neoplastic Effects against the Walker-256 Tumour by Modulating Oxidative Stress and Not by Alkaloid Activity. *PLoS ONE* **2013**, *8*, e54618. [CrossRef] [PubMed]
70. Azevedo, B.C.; Morel, L.J.F.; Carmona, F.; Cunha, T.M.; Contini, S.H.T.; Delprete, P.G.; Ramalho, F.S.; Crevelin, E.; Bertoni, B.W.; França, S.C. Aqueous extracts from *Uncaria tomentosa* (Willd. ex Schult.) DC. reduce bronchial hyperresponsiveness and inflammation in a murine model of asthma. *J. Ethnopharmacol.* **2018**, *218*, 76–89. [CrossRef]
71. Rojas-Duran, R.; González-Aspajo, G.; Ruiz-Martel, C.; Bourdy, G.; Doroteo-Ortega, V.H.; Alban-Castillo, J.; Robert, G.; Auberger, P.; Deharo, E. Anti-inflammatory activity of Mitraphylline isolated from *Uncaria tomentosa* bark. *J. Ethnopharmacol.* **2012**, *143*, 801–804. [CrossRef] [PubMed]
72. Kośmider, A.; Czepielewska, E.; Kuraś, M.; Gulewicz, K.; Pietrzak, W.; Nowak, R.; Nowicka, G. *Uncaria tomentosa* Leaves Decoction Modulates Differently ROS Production in Cancer and Normal Cells, and Effects Cisplatin Cytotoxicity. *Molecules* **2017**, *22*, 620. [CrossRef] [PubMed]
73. Erasto, P.; Marciale, C.; Omolo, J.J.; Hamilton, C.J. Potentiation of Isoniazid Efficacy against Isoniazid-resistant Mycobacteria Strains. *Res. J. Med. Plant* **2014**, *8*, 32–40. [CrossRef]
74. García, R.; Cayunao, C.; Bocic, R.; Backhouse, N.; Delporte, C.; Zaldivar, M.; Erazo, S. Antimicrobial activity of isopteropodine. *Z. Nat. C* **2005**, *60*, 385–388. [CrossRef]
75. Quideau, S.; Deffieux, D.; Douat-Casassus, C.; Pouységu, L. Plant polyphenols: Chemical properties, biological activities, and synthesis. *Angew. Chem. Int. Ed.* **2011**, *50*, 586–621. [CrossRef]
76. Ferrazzano, G.F.; Amato, I.; Ingenito, A.; Zarrelli, A.; Pinto, G.; Pollio, A. Plant polyphenols and their anti-cariogenic properties: A review. *Molecules* **2011**, *16*, 1486–1507. [CrossRef]
77. Luca, S.V.; Macovei, I.; Bujor, A.; Miron, A.; Skalicka-Woźniak, K.; Aprotosoaie, A.C.; Trifan, A. Bioactivity of dietary polyphenols: The role of metabolites. *Crit. Rev. Food Sci. Nutr.* **2020**, *60*, 626–659. [CrossRef]
78. Jovanović, A.; Petrović, P.; Đorđević, V.; Zdunić, G.; Šavikin, K.; Bugarski, B. Polyphenols extraction from plant sources. *Lek. Sirovine* **2017**, *37*, 45–49. [CrossRef]
79. Panche, A.; Diwan, A.; Chandra, S. Flavonoids: An overview. *J. Nutr. Sci.* **2016**, *5*, 1–15. [CrossRef] [PubMed]
80. Júnior, O.T.; Kuhn, F.; Padilha, P.J.M.; Vicente, L.R.M.; da Costa, S.W.; da Silva, B.C.; Schleder, D.D.; Nunes Nesi, C.; Magro, J.D.; de Lamo-Castellví, S. Survival of White Spot Syndrome Virus–Infected *Litopenaeus vannamei* Fed with Ethanol Extract of *Uncaria tomentosa*. *J. World Aquac. Soc.* **2018**, *49*, 165–174. [CrossRef]
81. White, G.; Bourbonnais-Spear, N.; Garner, F. Antibacterial constituents from *Uncaria tomentosa*. *Phytopharmacology* **2011**, *1*, 16–19.
82. Peñaloza, E.M.C.; Kaiser, S.; Resende, P.E.D.; Pittol, V.; Carvalho, Â.R.; Ortega, G.G. Chemical composition variability in the *Uncaria tomentosa* (cat s claw) wild population. *Química Nova* **2015**, *38*, 378–386.
83. Pavei, C.; Kaiser, S.; Borré, G.L.; Ortega, G.G. Validation of a LC method for polyphenols assay in cat's claw (*Uncaria tomentosa*). *J. Liq. Chromatogr. Relat. Technol.* **2010**, *33*, 1551–1561. [CrossRef]
84. Chen, J.; Chen, J.-J.; Gao, K. Chemical Constituents and Biological Activities of *Dicranopteris linearis*. *Chem. Nat. Compd.* **2014**, *49*, 1129–1131. [CrossRef]
85. Albuquerque, U.P.; Patil, U.; Máthé, Á. *Medicinal and Aromatic Plants of South America: Brazil*; Springer: Berlin/Heidelberg, Germany, 2018.
86. Yang, H.; Tuo, X.; Wang, L.; Tundis, R.; Portillo, M.P.; Simal-Gandara, J.; Yu, Y.; Zou, L.; Xiao, J.; Deng, J. Bioactive procyanidins from dietary sources: The relationship between bioactivity and polymerization degree. *Trends Food Sci. Technol.* **2021**, *111*, 114–127. [CrossRef]
87. Rue, E.A.; Rush, M.D.; van Breemen, R.B. Procyanidins: A comprehensive review encompassing structure elucidation via mass spectrometry. *Phytochem. Rev.* **2018**, *17*, 1–16. [CrossRef]
88. Monagas Juan, M.J.; Sánchez-Patán, F.; Quintanilla-López, J.E.; Lebrón-Aguilar, R.; Bartolomé, B.; Navarro Hoyos, M. Phenolic Extracts of *Uncaria tomentosa* L. (cats claw) Containing Procyanidins, Propelargonidins and Flavonolignans, Method for the Production Thereof, and Applicarions of Same. WO2014096488A1, 26 June 2014.
89. Navarro-Hoyos, M.; Alvarado-Corella, D.; Moreira-Gonzalez, I.; Arnaez-Serrano, E.; Monagas-Juan, M. Polyphenolic Composition and Antioxidant Activity of Aqueous and Ethanolic Extracts from *Uncaria tomentosa* Bark and Leaves. *Antioxidants* **2018**, *7*, 65. [CrossRef]
90. Li, X.; He, C.; Song, L.; Li, T.; Cui, S.; Zhang, L.; Jia, Y. Antimicrobial activity and mechanism of Larch bark procyanidins against *Staphylococcus aureus*. *Acta Biochim. Biophys. Sin.* **2017**, *49*, 1058–1066. [CrossRef]
91. Ibrahim, T.; Dib, R.; Al-Youssef, H.; Amina, M. Chemical composition and antimicrobial and cytotoxic activities of *Antidesm abunius* L. *Pak. J. Pharm. Sci.* **2019**, *32*, 153–163. [PubMed]
92. Ikigai, H.; Nakae, T.; Hara, Y.; Shimamura, T. Bactericidal catechins damage the lipid bilayer. *Biochim. Biophys. Acta (BBA) Biomembr.* **1993**, *1147*, 132–136. [CrossRef]

93. Karioti, A.; Sokovic, M.; Ciric, A.; Koukoulitsa, C.; Bilia, A.R.; Skaltsa, H. Antimicrobial Properties of *Quercus ilex* L. Proanthocyanidin Dimers and Simple Phenolics: Evaluation of Their Synergistic Activity with Conventional Antimicrobials and Prediction of Their Pharmacokinetic Profile. *J. Agric. Food Chem.* **2011**, *59*, 6412–6422. [CrossRef] [PubMed]
94. Wirth, C.; Wagner, H. Pharmacologically active procyanidines from the bark of *Uncaria tomentosa*. *Phytomedicine* **1997**, *4*, 265–266. [CrossRef]
95. Maas, J.L.; Galletta, G.J.; Stoner, G.D. Ellagic acid, an anticarcinogen in fruits, especially in strawberries: A review. *HortScience* **1991**, *26*, 10–14. [CrossRef]
96. Vattem, D.; Shetty, K. Biological functionality of ellagic acid: A review. *J. Food Biochem.* **2005**, *29*, 234–266. [CrossRef]
97. Robbins, R.J. Phenolic acids in foods: An overview of analytical methodology. *J. Agric. Food Chem.* **2003**, *51*, 2866–2887. [CrossRef]
98. Kumar, N.; Goel, N. Phenolic acids: Natural versatile molecules with promising therapeutic applications. *Biotechnol. Rep.* **2019**, *24*, e00370. [CrossRef]
99. Mandal, S.M.; Chakraborty, D.; Dey, S. Phenolic acids act as signaling molecules in plant-microbe symbioses. *Plant Signal. Behav.* **2010**, *5*, 359–368. [CrossRef]
100. Joshi, J.R.; Burdman, S.; Lipsky, A.; Yariv, S.; Yedidia, I. Plant phenolic acids affect the virulence of *Pectobacterium aroidearum* and *P. carotovorum* ssp. brasiliense via quorum sensing regulation. *Mol. Plant Pathol.* **2016**, *17*, 487–500. [CrossRef]
101. Sánchez-Maldonado, A.F.; Schieber, A.; Gänzle, M.G. Structure–function relationships of the antibacterial activity of phenolic acids and their metabolism by lactic acid bacteria. *J. Appl. Microbiol.* **2011**, *111*, 1176–1184. [CrossRef] [PubMed]
102. Cueva, C.; Moreno-Arribas, M.V.; Martín-Álvarez, P.J.; Bills, G.; Vicente, M.F.; Basilio, A.; Rivas, C.L.; Requena, T.; Rodríguez, J.M.; Bartolomé, B. Antimicrobial activity of phenolic acids against commensal, probiotic and pathogenic bacteria. *Res. Microbiol.* **2010**, *161*, 372–382. [CrossRef] [PubMed]
103. Godlewska-Żyłkiewicz, B.; Świsłocka, R.; Kalinowska, M.; Golonko, A.; Świderski, G.; Arciszewska, Ż.; Nalewajko-Sieliwoniuk, E.; Naumowicz, M.; Lewandowski, W. Biologically Active Compounds of Plants: Structure-Related Antioxidant, Microbiological and Cytotoxic Activity of Selected Carboxylic Acids. *Materials* **2020**, *13*, 4454. [CrossRef] [PubMed]
104. Borges, A.; Ferreira, C.; Saavedra, M.J.; Simões, M. Antibacterial activity and mode of action of ferulic and gallic acids against pathogenic bacteria. *Microb. Drug Resist.* **2013**, *19*, 256–265. [CrossRef]
105. Chen, Y.-L.; Huang, S.-T.; Sun, F.-M.; Chiang, Y.-L.; Chiang, C.-J.; Tsai, C.-M.; Weng, C.-J. Transformation of cinnamic acid from *trans*-to *cis*-form raises a notable bactericidal and synergistic activity against multiple-drug resistant *Mycobacterium tuberculosis*. *Eur. J. Pharm. Sci.* **2011**, *43*, 188–194. [CrossRef] [PubMed]
106. Xia, D.; Wu, X.; Shi, J.; Yang, Q.; Zhang, Y. Phenolic compounds from the edible seeds extract of Chinese Mei (*Prunus mume* Sieb. et Zucc) and their antimicrobial activity. *Food Sci. Technol.* **2011**, *44*, 347–349. [CrossRef]
107. Kępa, M.; Miklasińska-Majdanik, M.; Wojtyczka, R.D.; Idzik, D.; Korzeniowski, K.; Smoleń-Dzirba, J.; Wąsik, T.J. Antimicrobial potential of caffeic acid against *Staphylococcus aureus* clinical strains. *BioMed Res. Int.* **2018**, *2018*, 7413504. [CrossRef]
108. Hemaiswarya, S.; Doble, M. Synergistic interaction of phenylpropanoids with antibiotics against bacteria. *J. Med. Microbiol.* **2010**, *59*, 1469–1476. [CrossRef]
109. Cox-Georgian, D.; Ramadoss, N.; Dona, C.; Basu, C. Therapeutic and Medicinal Uses of Terpenes. In *Medicinal Plants*; Springer: Berlin/Heidelberg, Germany, 2019; pp. 333–359. [CrossRef]
110. Patočka, J. Biologically active pentacyclic triterpenes and their current medicine signification. *J. Appl. Biomed.* **2003**, *1*, 7–12. [CrossRef]
111. Vaou, N.; Stavropoulou, E.; Voidarou, C.; Tsigalou, C.; Bezirtzoglou, E. Towards advances in medicinal plant antimicrobial activity: A review study on challenges and future perspectives. *Microorganisms* **2021**, *9*, 2041. [CrossRef]
112. Copp, B.R. Antimycobacterial natural products. *Nat. Prod. Rep.* **2003**, *20*, 535–557. [CrossRef] [PubMed]
113. Oldfield, E.; Lin, F.Y. Terpene biosynthesis: Modularity rules. *Angew. Chem. Int. Ed.* **2012**, *51*, 1124–1137. [CrossRef] [PubMed]
114. Thimmappa, R.; Geisler, K.; Louveau, T.; O'Maille, P.; Osbourn, A. Triterpene biosynthesis in plants. *Annu. Rev. Plant Biol.* **2014**, *65*, 225–257. [CrossRef] [PubMed]
115. Cárdenas, P.D.; Almeida, A.; Bak, S. Evolution of Structural Diversity of Triterpenoids. *Front. Plant Sci.* **2019**, *10*, 1523. [CrossRef]
116. Piironen, V.; Lindsay, D.G.; Miettinen, T.A.; Toivo, J.; Lampi, A.M. Plant sterols: Biosynthesis, biological function and their importance to human nutrition. *J. Sci. Food Agric.* **2000**, *80*, 939–966. [CrossRef]
117. Benveniste, P. Biosynthesis and accumulation of sterols. *Annu. Rev. Plant Biol.* **2004**, *55*, 429–457. [CrossRef]
118. Miras-Moreno, B.; Sabater-Jara, A.B.; Pedreño, M.A.; Almagro, L. Bioactivity of Phytosterols and Their Production in Plant in Vitro Cultures. *J. Agric. Food Chem.* **2016**, *64*, 7049–7058. [CrossRef]
119. Senatore, A.; Cataldo, A.; Iaccarino, F.P.; Elberti, M.G. Phytochemical and biological study of *Uncaria tomentosa*. *Boll. della Soc. Ital. Biol. Sper.* **1989**, *65*, 517–520.
120. Muhammad, I.; Dunbar, D.C.; Khan, R.A.; Ganzera, M.; Khan, I.A. Investigation of Uña De Gato I. 7-Deoxyloganic acid and 15N NMR spectroscopic studies on pentacyclic oxindole alkaloids from *Uncaria tomentosa*. *Phytochemistry* **2001**, *57*, 781–785. [CrossRef]
121. Sen, A.; Dhavan, P.; Shukla, K.K.; Singh, S.; Tejovathi, G. Analysis of IR, NMR and antimicrobial activity of β-sitosterol isolated from *Momordica charantia*. *Sci. Secur. J. Biotechnol.* **2012**, *1*, 9–13.

122. Hoskeri, J.; Krishna, H.; Jignesh, V.; Roshan, S.; Vijay, S. In-silico drug designing using β-sitosterol isolated from *Flaveria trinervia* against peptide deformylase protein to hypothesize bactericidal effect. *Int. J. Pharm. Pharm. Sci.* **2012**, *4*, 192–196.
123. Mailafiya, M.M.; Yusuf, A.J.; Abdullahi, M.I.; Aleku, G.A.; Ibrahim, I.A.; Yahaya, M.; Abubakar, H.; Sanusi, A.; Adamu, H.W.; Alebiosu, C.O. Antimicrobial activity of stigmasterol from the stem bark of *Neocarya macrophylla*. *J. Med. Plants Econ. Dev.* **2018**, *2*, 1–5.
124. Kuete, V.; Eyong, K.; Folefoc, G.; Beng, V.; Hussain, H.; Krohn, K.; Nkengfack, A. Antimicrobial activity of the methanolic extract and of the chemical constituents isolated from *Newbouldia laevis*. *Pharmazie* **2007**, *62*, 552–556. [CrossRef] [PubMed]
125. Sycz, Z.; Tichaczek-Goska, D.; Wojnicz, D. Anti-Planktonic and Anti-Biofilm Properties of Pentacyclic Triterpenes—Asiatic Acid and Ursolic Acid as Promising Antibacterial Future Pharmaceuticals. *Biomolecules* **2022**, *12*, 98. [CrossRef] [PubMed]
126. Catteau, L.; Zhu, L.; Françoise Van, B.; Quetin-Leclercq, J. Natural and hemi-synthetic pentacyclic triterpenes as antimicrobials and resistance modifying agents against *Staphylococcus aureus*: A review. *Phytochem. Rev.* **2018**, *17*, 1129–1163. [CrossRef]
127. Ren, D.; Zuo, R.; Barrios, A.F.G.; Bedzyk, L.A.; Eldridge, G.R.; Pasmore, M.E.; Wood, T.K. Differential Gene Expression for Investigation of *Escherichia coli* Biofilm Inhibition by Plant Extract Ursolic Acid. *Appl. Environ. Microbiol.* **2005**, *71*, 4022–4034. [CrossRef] [PubMed]
128. Qin, N.; Tan, X.; Jiao, Y.; Liu, L.; Zhao, W.; Yang, S.; Jia, A. RNA-Seq-based transcriptome analysis of methicillin-resistant *Staphylococcus aureus* biofilm inhibition by ursolic acid and resveratrol. *Sci. Rep.* **2014**, *4*, 5467. [CrossRef]
129. Chen, H.; Gao, Y.; Wang, A.; Zhou, X.; Zheng, Y.; Zhou, J. Evolution in medicinal chemistry of ursolic acid derivatives as anticancer agents. *Eur. J. Med. Chem.* **2015**, *92*, 648–655. [CrossRef]
130. Shao, J.-W.; Dai, Y.-C.; Xue, J.-P.; Wang, J.-C.; Lin, F.-P.; Guo, Y.-H. In vitro and in vivo anticancer activity evaluation of ursolic acid derivatives. *Eur. J. Med. Chem.* **2011**, *46*, 2652–2661. [CrossRef]
131. Mlala, S.; Oyedeji, A.O.; Gondwe, M.; Oyedeji, O.O. Ursolic acid and its derivatives as bioactive agents. *Molecules* **2019**, *24*, 2751. [CrossRef]
132. Fontanay, S.; Grare, M.; Mayer, J.; Finance, C.; Duval, R.E. Ursolic, oleanolic and betulinic acids: Antibacterial spectra and selectivity indexes. *J. Ethnopharmacol.* **2008**, *120*, 272–276. [CrossRef] [PubMed]
133. Wolska, K.I.; Grudniak, A.M.; Fiecek, B.; Kraczkiewicz-Dowjat, A.; Kurek, A. Antibacterial activity of oleanolic and ursolic acids and their derivatives. *Cent. Eur. J. Biol.* **2010**, *5*, 543–553. [CrossRef]
134. Kurek, A.; Nadkowska, P.; Pliszka, S.; Wolska, K.I. Modulation of antibiotic resistance in bacterial pathogens by oleanolic acid and ursolic acid. *Phytomedicine* **2012**, *19*, 515–519. [CrossRef]
135. Aquino, R.; De Tommasi, N.; De Simone, F.; Pizza, C. Triterpenes and quinovic acid glycosides from *Uncaria tomentosa*. *Phytochemistry* **1997**, *45*, 1035–1040. [CrossRef]
136. Yepes-Pérez, A.F.; Herrera-Calderon, O.; Quintero-Saumeth, J. *Uncaria tomentosa* (cat's claw): A promising herbal medicine against SARS-CoV-2/ACE-2 junction and SARS-CoV-2 spike protein based on molecular modeling. *J. Biomol. Struct. Dyn.* **2020**, 1–17. [CrossRef]
137. Aquino, R.; De Simone, F.; Vincieri, F.F.; Pizza, C.; Gaćs-Baitz, E. New polyhydroxylated triterpenes from *Uncaria tomentosa*. *J. Nat. Prod.* **1990**, *53*, 559–564. [CrossRef]
138. Aquino, R.; De Feo, V.; De Simone, F.; Pizza, C.; Cirino, G. Plant metabolites. New compounds and anti-inflammatory activity of *Uncaria tomentosa*. *J. Nat. Prod.* **1991**, *54*, 453–459. [CrossRef]
139. Sakakibara, J.; Kaiya, T.; Fukuda, H. Triterpenoids from enkianthus campanulatus. *Phytochemistry* **1984**, *23*, 627–630. [CrossRef]
140. Amir, F.; Wong, K.C.; Eldeen, I.; Asmawi, M.Z.; Osman, H. Evaluation of biological activities of extracts and chemical constituents of *Mimusops elengi*. *Trop. J. Pharm. Res.* **2013**, *12*, 591–596. [CrossRef]
141. Cantarel, B.L.; Coutinho, P.M.; Rancurel, C.; Bernard, T.; Lombard, V.; Henrissat, B. The Carbohydrate-Active EnZymes database (CAZy): An expert resource for glycogenomics. *Nucleic Acids Res.* **2009**, *37*, D233–D238. [CrossRef]
142. Cerri, R.; Aquino, R.; de Simone, F.; Pizza, C. New Quinovic Acid Glycosides from *Uncaria tomentosa*. *J. Nat. Prod.* **1988**, *51*, 257–261. [CrossRef]
143. Aquino, R.; De Simone, F.; Pizza, C.; Conti, C.; Stein, M. Plant Metabolites. Structure and In Vitro Antiviral Activity of Quinovic Acid Glycosides from *Uncaria tomentosa* and *Guettarda platyipoda*. *J. Nat. Prod.* **1989**, *52*, 679–685. [CrossRef] [PubMed]
144. Pavei, C.; Kaiser, S.; Verza, S.G.; Borre, G.L.; Ortega, G.G. HPLC-PDA method for quinovic acid glycosides assay in Cat's claw (*Uncaria tomentosa*) associated with UPLC/Q-TOF–MS analysis. *J. Pharm. Biomed. Anal.* **2012**, *62*, 250–257. [CrossRef] [PubMed]
145. Mohammed, H.A.; Khan, R.A.; Abdel-Hafez, A.A.; Abdel-Aziz, M.; Ahmed, E.; Enany, S.; Mahgoub, S.; Al-Rugaie, O.; Alsharidah, M.; Aly, M.S.A.; et al. Phytochemical Profiling, In Vitro and In Silico Anti-Microbial and Anti-Cancer Activity Evaluations and Staph GyraseB and h-TOP-IIβ Receptor-Docking Studies of Major Constituents of *Zygophyllum coccineum* L. Aqueous-Ethanolic Extract and Its Subsequent Fractions: An Approach to Validate Traditional Phytomedicinal Knowledge. *Molecules* **2021**, *26*, 577. [CrossRef]

146. Kezetas Bankeu, J.J.; Kenou Kagho, D.U.; Fotsing Fongang, Y.S.p.; Kouipou Toghueo, R.M.; Mba'ning, B.M.r.; Tchouya Feuya, G.R.; Boyom Fekam, F.; Tchouankeu, J.C.; Ngouela, S.r.A.; Sewald, N.; et al. Constituents from *Nauclea latifolia* with Anti-Haemophilus influenzae Type b Inhibitory Activities. *J. Nat. Prod.* **2019**, *82*, 2580–2585. [CrossRef]
147. Asada, K.; Salim, V.; Masada-Atsumi, S.; Edmunds, E.; Nagatoshi, M.; Terasaka, K.; Mizukami, H.; De Luca, V. A 7-Deoxyloganetic Acid Glucosyltransferase Contributes a Key Step in Secologanin Biosynthesis in Madagascar Periwinkle. *Plant Cell* **2013**, *25*, 4123–4134. [CrossRef]