Review

Hunting Bioactive Molecules from the Agave Genus: An Update on Extraction and Biological Potential

Misaél Bermúdez-Bazán 1,*, Gustavo Adolfo Castillo-Herrera 1, Judith Esmeralda Urias-Silvas 1, Antonio Escobedo-Reyes 2, and Mirna Estarrón-Espinosa 1,‡

1 Centro de Investigación y Asistencia en Tecnología y Diseño del Estado de Jalisco, A.C., Unidad de Tecnología Alimentaria, Camino Arrenero 1227, El Bajio, Zapopan 45019, Mexico; mibermudez_al@ciatej.edu.mx (M.B.-B.); gcastillo@ciatej.mx (G.A.C.-H.); jurias@ciatej.mx (J.E.U.-S.)
2 Centro de Investigación y Asistencia en Tecnología y Diseño del Estado de Jalisco, A.C., Unidad de Servicios Analíticos y Metrologicos, Av. Normalistas No. 800, Guadalajara 44270, Mexico; aescobedo@ciatej.mx
* Correspondence: mestarron@ciatej.mx; Tel.: +33-334-552-00 (ext. 1940)

Abstract: Agaves are plants used in the production of alcoholic beverages and fibers. Ever since ancient times, pre-Hispanic cultures in Mexico have used them in traditional medicine to cure different ailments. Over the years, studies of the active principles responsible for the therapeutic benefits of agaves have increased. Leaves and fibers are the main agro-wastes generated in tequila and mezcal production, while fibers are the main waste product in the textile sector. Different investigations have referred to the agro-waste from agave processing as a source of bioactive molecules called secondary metabolites (SM). Among them, phenols, flavonoids, phytosterols, and saponins have been extracted, identified, and isolated from these plants. The role of these molecules in pest control and the prospect of metabolites with the biological potential to develop novel drugs for chronic and acute diseases represent new opportunities to add value to these agro-wastes. This review aims to update the biological activities and recent applications of the secondary metabolites of the genus Agave.

Keywords: secondary metabolites; bioactive compounds; agave agro-wastes; biological activity

1. Introduction

The agaves are perennial plants that use Crassulacean Acid Metabolism (CAM), which allows their adaptation to arid weather ecosystems [1]. The Agave genus is the largest of nine subgenera of the Asparagaceae family, with 210 species, of which 119 are endemic in Mexico; thus, it is considered the center of diversity of these plants [2,3]. Geographically, it is distributed within an area stretching from the southern United States to Ecuador [2]. The production of alcoholic beverages such as tequila, mezcal, and bacanora represents the most traditional use of these plants [4]. Nevertheless, the high demand for these products has led to the production of different agro-wastes that contaminate with the potential of being dangerous for the environment. Between 2015 and 2019, 1.434 billion liters of tequila were produced, which created an estimated 5,168,200 tons of agave leaves in waste. While the mezcal industry reportedly produced 27,663,459 liters, no official data regarding agro-waste generation of this beverage exist [5].

In the textile industry, obtaining fibers from Agave lechuguilla Torr. leaves is an important economic activity in this sector in Mexico. Within Mexico, the states of San Luis Potosi, Coahuila, Nuevo León, Zacatecas, Durango, and Tamaulipas are the main producers of this raw material, from which only 15% is product and 85% is an agro-waste called “guishe”. This industry generated 150 tons of guishe per year [6–8]. Agro-waste production in the form of leaves and fibers has become an environmental concern.
**Agave in Traditional Medicine**

In ancient times, pre-Hispanic cultures in Mexico such as the Mayans and the Aztecs used agaves for medicinal purposes because of their therapeutic properties [9,10]. For example, the Mayans obtained leaf juice from the *A. fourcroydes* Lem. to heal wounds via topical application. In contrast, the roots and leaves of *A. angustifolia* Haw. were used to treat cutaneous and excretory skin infections and treat snakebite [11].

The Aztecs squeezed the fresh leaves of *A. atrovirens*, *A. americana*, and *A. potatorum* Zucc. to obtain concentrated sap. Later, they mixed it with hot urine, salt, honey, and some other medicinal plants. Other preparations involved *Comelina pallida* as a hemostatic agent. Finally, the mixture was applied to deep wounds [12].

The Tarahumara indigenous culture from Chihuahua domesticated a few *Agave* species and used these plants in medicinal preparations that consisted of applying leaf juice to festering sores. The sap was used to treat ocular infections, while other preparations with whole leaves were used to cure headaches [13].

Worldwide, different indigenous cultures have used these plants for their therapeutic effects. They have employed some species in the treatment of insect-borne diseases [14], rheumatic inflammatory affections [15], and nervous system diseases such as meningitis and sciatica [16]. Other medicinal preparations were preserved over the years, for example, the remedies prepared from *A. angustifolia* Haw., described by García Mendoza et al. [17]. This and other medicinal uses of different *Agave* species are summarized in Table 1.

### Table 1. Medicinal uses of the *Agave* genus.

| Species/Tissue | Medicinal Use | References |
|---------------|--------------|------------|
| *A. potatorum* Zucc./leaf | Healing and cica[trization of wounds | [18] |
| | Infusions to heal respiratory infections | |
| *A. americana* L./leaf, roots | Healing and cica[trization of wounds from leaf gel | [19] |
| | Syphilis treatment, anesthetic, headache, rheumatic pain, and broken bones | [15] |
| | Treatment of gout disease, infections, and burns | [20] |
| *A. sisalana*/leaf | Treatment for tick-borne diseases | [14] |
| | Stomach detoxifier and constipation | [21] |
| | Antimicrobial against pathogen biota of the intestines and stomach | [22] |
| *A. sisalana*/roots | Antidiarrheic | [23] |
| *A. karattos* Linnaeous/leaf | Treatment against meningitis and sciatica | [16] |
| *A. angustifolia* Haw./leaf, roots, fibers, leaf juice and root | Skin eruptions, kidney disease, and hepatic affections. It has antiparasitic and anti-hemorrhagic qualities | [17] |

Until now, the medicinal applications of agave plant constituents were the prelude to many research studies conducted to discover the bioactive compounds responsible for their biological activity by applying different extraction technologies and analytical tools.

This review aims to describe various recent studies on secondary metabolites that have been extracted, isolated, and identified in different *Agave* species. It also describes those studies that have examined the bioactive properties of specific molecules and the biological activities of crude extracts with potential applications.

### 2. Extraction Methods Used to Recover Polyphenolic Compounds from *Agave* Agro-Waste

A previous review by Almaraz et al. [24] described the phenolic compounds of agaves. This section updates the information on the extraction and identification of different polyphenolic compounds and the factors that influence their extraction and occurrence in the *Agave* genus.

Phenolic compounds are polar molecules that possess an aromatic benzene ring, substituted with one or more hydroxyl (-OH) groups while flavonoids have more than one


phenyl ring. Their structure has a heterocyclic ring of benzo-γ-pyran, which is hydroxylated in distinct patterns [25]. Both types of metabolites can be methylated, glycosylated, and acylated. These structural modifications have been attributed to biochemical reactions of the vegetal metabolism and they impact the biological activity [26].

Because of the high polarity of glycosylated polyphenols, aqueous mixtures with a polar organic solvent have been employed to maximize their recovery. Barriada-Bernal et al. [27] used two extraction stages with 60% and 30% (v/v) ethanol, respectively, on A. durangensis Gentry flowers, and were able to identify through HPLC-UV-VIS, quercetin-3-O-[rhamnosyl-(1→6)-galactoside], kaempferol-3-O-[rhamnosyl-(1→6)-glycoside], kaempferol-3,7-O-diglycoside, and quercetin-3-O-glycoside as the most abundant molecules. Similarly, Almaraz-Abarca et al. [28] employed 60% (v/v) methanol on A. victoriae-reginae, A. striata Zucc., and A. lechuguilla Torr. leaves. They identified 25 glycosylated flavonoids and high levels of 3-O-glycosides of kaempferol were reported in these species. Besides, the presence of the glycosides of isorhamnetin, quercetin, and herbacetin were also reported.

Morreeuw, Escobedo-Fregoso, et al. [29] investigated the effect of binary aqueous mixtures solvents of A. lechuguilla Torr. leaves, and found that an ethanol–water mixture of 70:30 (v/v) enhanced the recovered yields of cyanidin and delphinidin. Conversely, an aqueous methanol mixture 60:40 (v/v) resulted in a more suitable extract for flavonoids due to its high polarity, and it obtained the highest yields of isorhamnetin and hesperidin. Later, Morreeuw, Castillo-Quiroz, et al. [30] confirmed with HPLC-MS/MS that the hydroalcoholic mixture 70:30 (v/v) of A. lechuguilla Torr. was plentiful in mono-, di- and tri-glycosylated derivatives of apigenin, isorhamnetin, quercetin, and anthocyanins. Additionally, it was observed that the presence of more than one glycoside moiety was influenced by regional factors. Therefore, those extracts that belonged to drought regions accumulated di or tri glycosylated flavonoids; these compounds can provide better tolerance to drought stress [30]. Other studies on other Agave species demonstrated that drought stress induced an increase in these compounds and other secondary metabolites [31,32].

Morán-Velázquez et al. [33] investigated the use of accelerated solvent extraction as applied to young leaf spines of A. fourcroydes Lem. The extracts were plentiful in proanthocyanidins; this was confirmed by UHPLC-MS/MS. The accumulation of these metabolites into the fiber of young spines was possibly due to the laccase enzyme activity implied in the proanthocyanidins biosynthesis pathway. The authors associated this finding with the high abundance of (+)-catechin, (−)-epicatechin, and their glycosylated derivatives, as well as flavonoids which are the precursors of these compounds. Iser et al. [34] found the presence of tannins, phenols, and flavonoids in ethanolic and aqueous extracts from stems of this species.

In general, the variation in the total phenolic and flavonoid contents and other secondary metabolites has been described in relation to the type of Agave species, plant age, geographical origin, and solvent [35–40]. Ben Hamissa et al. [41] showed that high temperatures and pressures also improved the yield of phenols and flavonoids. Furthermore, emerging extraction processes such as ultrasound-assisted extraction also enhanced the yield of these compounds and reduced extraction times [42].

Pretreatments prior to the process and extraction type also influence the nature of the recovery of polyphenols from agaves. Contreras-Hernández et al. [43] found through HPLC-MS/MS that the phenolic composition of acetone extracts (85% v/v) from leaves of A. durangensis Gentry pretreated at a temperature of 120 ºC and separately with an ultrasound had different phenolic profiles. Higher temperatures led to the partial degradation of lignin and the chemical conversion into new phenol molecules. Alternatively, the ultrasound-assisted extraction increased the content of specific flavonoids, such as quercetin, rutin, procyanidin B2, and others. Cavitation phenomena promote the rupture of the vacuoles, which leads to the release of aglycones from these compounds and consequently increases the yield of the recovered phenols [44].

A study reported by Avila-Gaxiola et al. [45] proved that a temperature of 100 ºC applied in the pretreatment stage did not degrade the recovered phenolic acids of an
aqueous extract of *A. tequilana* Weber. The thermal pretreatment promoted the generation of new phenolic compounds, such as 4-hydroxy-benzoic acid, pyrocatechol, acetovanillín, vanillín, and 2-furoic acid.

Because agave extracts are susceptible to undesirable degradation reactions by biologic contamination or high temperatures involved in their pre-processing, the stability and bioactivity of polyphenols and other secondary metabolites might be compromised. To overcome this, Santana-Jiménez et al. [46] found that the irradiation by UV-C light at doses of 10.93 mJ/cm² for 30 seconds inactivated the native microbiota from piña crude extracts of *A. tequilana* Weber and did not affect the antioxidant or extract color. In this way, the irradiation by UV-C light for short times may represent a suitable technology to preserve agave crude extracts.

Acid hydrolysis is another pretreatment used in the extraction of phenolic compounds. One study reported an increase in the yield of these compounds in hydrolyzed extracts of *A. lechuguilla* Torr. The extracts showed aglycones and dimeric flavonoids, such as quercetin-4β-afzelechin [47]. Contrary to these results, Mitchell et al. [48] reported trace amounts of phenolic acids in hydrolyzed leaf extracts of *A. americana*, *A. fourcroydes*, and *A. tequilana*, respectively.

### 3. Bioactivity of Identified Phytochemicals from the *Agave* Genus

This section focuses on the description of the biological activities of identified and isolated polar and non-polar compounds to show the potential of novel bioactive molecules that were found in the literature related to the *Agave* genus. This information is summarized in Table 2.

| Specie/Tissue | Compound(s) | Biological Activity | Dose | Study Model | References |
|---------------|-------------|---------------------|------|-------------|------------|
| *A. durangensis* Gentry Leaf | Flavonoid glycosides, aglycones, phenolic acids, proanthocyanins | Stimulant expression of enzymes | - | *N. crassa* ITD-G7, *A. niger* ITD-G1 | [43] |
| *A. lechuguilla* Torr. Leaf | Afzlequin-4-β-quercetin; dimeric flavonoids, quercetin, kaempferol | Anticancer | IC₅₀: 6.96 µg/mL | SK-LU-1 cells | [47] |
| *A. americana* L. Leaf | Flavonoid glycosides of kaempferol, quercetin, isorhamnetin, ellagic acid hexoside | Insecticide | 10.55 µg/insect, 0.055 µg/cm² | Tyrophillus oryzae | [49] |
| *A. lechuguilla* Leaf | 2,4,6-trinitrophnol, flavonoids, carboxylic acids, 2-aminomethil-propanol | Insecticide | LD₅₀: 1035 mg/mL | Bemisia tabaci | [50] |
| *A. pygmaea* Gentry *A. angustifolia* Haw. cv. *marginata* Leaf | Phenolic acids, flavonoid glycosides, homoisoflavonoids | Anti-inflammatory, Anti-ulcerogenic | 200 mg/kg, 20 mg/kg | Wistar rats: rat paw stomach | [51] |
| *A. americana* L. Leaf | Apigenin | Antifungal | IC₅₀: 72.15, 18.83 µM | *A. oryzae* α-amylase | [52] |
| *A. americana* L. Leaf | p-coumaric acid, puerarin | Antidiabetic | IC₅₀: 98.8 µM, 3.87 µM | Human α-amylase | [53] |
| *A. sisalana* Fiber | Acylated glycosyl flavonoids, flavonoid glycosides, phenolic acids | Stimulant and growth protection of microgreens | - | Microgreens | [54] |
Table 2. Cont.

| Specie/Tissue | Compound(s)                                             | Biological Activity | Dose          | Study Model | References |
|---------------|---------------------------------------------------------|---------------------|---------------|-------------|------------|
| **Saponins**  |                                                        |                     |               |             |            |
| *A. salmiana* Sap | Kammogenin-pentaglucoside and tetraglycoside, Gentrogenin pentaglucoside | Anticancer          | IC₅₀ 82.7, 108.4 µg/mL HT-29 cells | [55]        |
| *A. americana L. marginata Hort.* Leaf | Cantala-saponin-1                                         | Anti-neuroinflammatory | 5-10 mg/kg | Rat brain  | [56]        |
| *A. salmiana* Sap | Kammogenin-glycosides                                     | Anticancer          | 50 µg/mL Hep-G2, CaCo-2 cells | [57]        |
| *A. marmorata* Roezl. Leaf | Smilagenin-diglycoside                                    | Immunomodulatory    | IC₅₀: 50 mg/mL, 0.086 mg/mL RAW 264.7 cells | [58]        |
| *A. sisalana* Perrine Leaf juice | Glycosylated steroidal saponins Hecogenin-pentaglycoside | Cytotoxic           | IC₅₀: 125 µg/mL C6 cells | [59]        |
| *A. sisalana* Perrine Leaf juice | Steroidal saponins                                         | Antineoplastic      | 50 µg/mL Vero-cells Human lymphocytes, rats | [60]        |
| *A. angustifolia var. marginata* Leaf | Steroidal-hexaglycosylated saponin                        | Anti-ulcerogenic    | 100 mg/kg Rat stomach | [61]        |
| *A. seemanniana* Jacobi Leaf | Steroidal saponins                                         | Analgesic           | 100 mg/kg Rat stomach | [62]        |
| **Phytosterols** |                                                        |                     |               |             |            |
| *A. tequilana* Weber Piña | β-sitosterol-glycoside, stigmasta-3,5-dien-7-one Cicloartenone, cycloartenol | Immunomodulatory    | 50 µg/kg Urine, blood serum, kidney rat | [63]        |
| *A. angustifolia* Haw. Leaf | 3-O-[6′-O-palmitoyl]-β-D-glucopiranosyl-sitosterol         | Immunomodulatory    | 50 µg/kg Mice ear edema | [64]        |

RD: repellent dose, IC₅₀: Half maximal inhibitory concentration, LD₅₀: Median lethal dose.

3.1. Polar Compounds: Phenols and Flavonoids

The biological potential of polyphenols from different *Agave* species has been studied and assessed in vivo. The hydroalcoholic extract of *A. lechuguilla* showed insecticide activity against *Bemisia tabaci* at LD₅₀: 1057 mg/L after 72 h, no positive control was used [50]. Another study reported the insecticide activity of aqueous methanol extracts on *Sitophylus oryzae*, at LD₅₀: 10.55 µg/insect after 72 h vs. malathion at LD₅₀: 2.34 µg/insect after 24 h [49]. Interestingly, an *A. americana* L. extract exerted repellent activity at RC₅₀: 0.055 µg/cm² while malathion did not present this activity. Besides, the chemical profile of *A. americana* L. presented flavonoids such as quercetin, isorhamnetin, kaempferol, and their glycosylated derivates and an ellagic acid glycoside was also identified, with the repellent activity associated to these compounds [49].

The anti-inflammatory and immunomodulatory activity of leaf extracts from *A. desmettiana* Jacobi, *A. angustifolia* Haw. cv. *marginata*, *A. americana* L., *A. americana marginata* Trel, and *A. pygmaea* Gentry were studied by El-Hawary et al. [51]. In contrast, *A. pygmaea* Gentry and *A. angustifolia* Haw. cv. *marginata* exerted the highest immunomodulatory activity at a concentration of 200 mg/kg on in vivo inflammation models and decreased the concentration levels of pro-inflammatory cytokines, which were different and lower than indomethacin administration. Alternatively, the production of IL-10 cytokine increased, which promoted an anti-inflammatory effect. Overall, these species showed different phenolic acids, glycosylated flavonoids, and homoisoflavonoids in their metabolic profile, such as fukiic acid, sinapic acid, psicidic acid, methyl gallate, rutin, kaempferol, quercetin glucosides, euxomol, and dyhydroeuxomin, and its occurrence was associated with such effects.
Anticancer activity has also been seen against lung cancer cell-lines in ethanolic leaf extracts from *A. lechuguilla* Torr. The crude extracts showed 75.7% of cellular growth inhibition in SK-LU-1 cells at IC$_{50}$ 50 µg/mL vs. the anticancer drug Paclitaxel used as a positive control with 1.2% at 5 µg/mL. However, fractionated extracts presented this effect at a minor concentration (IC$_{50}$: 6.96 µg/mL) due to the elimination of residual sugars from extracts that are the substrates of these cell lines. These findings indicated that residual sugars in crude extracts attenuated the biological activity [47].

Both antifungal and antidiabetic properties were reportedly seen in *A. americana* L. leaf extracts. Two studies found that the bioactive potential is selective and depends on the nature of the isolated molecule. Puerarin and apigenin isolated from this species showed greater inhibitory effects against *A. oryzae* α-amylase, while p-coumaric acid proved a major inhibitor to human α-amylase at IC$_{50}$: 98.8 µM, with an inhibition rate 2.3 times higher than acarbose. Thus, isolated flavonoids may be used as therapeutic agents for postprandial glycemia [52,53].

Contreras-Hernández et al. [43] confirmed that the presence of phenolic compounds that were identified in *A. duragensis* Gentry leaves enabled the production of industrial enzymes during fermentation with *A. oryzae* and *N. crassa*. Another study of this species reported that fibers worked as a growth medium for microgreens because of the presence of phenolic acids and glycosylated flavonoids, which adopted a protector role during their development [54]. Some of these compounds include the glycosides and acyl glycosides of kaempferol and quercetin and novel phenolic acids (illustrated in Figures 1–3).

| Hydroxybenzoic acids | R$_1$ | R$_2$ | R$_3$ | R$_4$ | µg/L | Detection method |
|-----------------------|-----|-----|-----|-----|-----|-----------------|
| Chlorogenic acid       | OH  | OH  | H   | H   | QA  | HPLC-MS/MS [43] |
| Caffeic acid           | OH  | OH  | H   | H   | 48.79 ± 7.2 | UHPLC-MS/MS [44] |
| Caffeic hexoside       | O-glc | OH | H   | H   | 55.07 ± 8.1 | HPLC-MS/MS [43] |
| 4-Caffeoylquinic acid  | OH  | OH  | H   | H   | QA  | HPLC-MS/MS [43] |
| 3,4-Dicaffeoyl-quinic acid | OH | OH | H | H | QA | HPLC-MS/MS [43] |
| Ferulic acid           | H   | OH  | H   | H   | 20.12 ± 0.11 | HPLC-MS/MS [44] |
| Feruloyl-quinic acid   | H   | OH  | H   | QA  | 281.26 ± 54.2 | HPLC-MS/MS [44] |
| Feruloyl-glycoside     | H   | OH  | H   | O-glc | 84.61 ± 4.6 | HPLC-MS/MS [44] |
| p-Coumaric acid        | H   | OH  | H   | H   | -   | HPLC-MS/MS [43] |
| p-Coumaroyl-quinic acid | H | OH | H | H | QA | HPLC-MS/MS [43] |
| Rosmarinic acid        | OH  | OH  | H   | H   | DHLA | HPLC-MS/MS [16] |
| Sinapic acid           | H   | OCH$_3$ | OH | OCH$_3$ | - | HPLC-MS/MS [43] |
| Transcinnamic acid     | H   | H   | H   | H   | -   | HPLC-MS/MS [43] |

| Hydroxycinnamic acids  | R$_1$ | R$_2$ | R$_3$ | R$_4$ | µg/g DW | Detection method |
|------------------------|-----|-----|-----|-----|--------|-----------------|
| Cymarin                | OH  | OH  | H   | O   | 12.32 | HPLC-UV-MS [29] |
| Cymarin-3-O-glucoside  | OH  | H   | glc | OH  | -     | HPLC-MS/MS [29] |
| Cymarin-3-O-rutinoside | H   | OH  | O-rut | OH | - | HPLC-MS/MS [29] |
| Cymarin-3,5-Diglucoside| OH  | OH  | O-glc | O-glc | - | HPLC-UV-MS [29] |
| Delphinidin            | OH  | OH  | H   | OH  | 24.23 | HPLC-UV-MS [29] |
| Delphinidin-3-O-glucoside | OH | OH | glc | OH | - | HPLC-MS/MS [29] |
| Gentiodelphinine       | OH  | O-CA-glc | O-glc | O-CA-glc | - | HPLC-MS/MS [29] |

Figure 1. Cont.
Figure 1. Current phenolic acids and flavonoids identified and quantified in the *Agave* genus, CA = caffeic acid, GA = gallic acid, rut = rutinoside, glc = glucoside, QA: quinic acid, DHLA= 3,4-dihydroxyphenillactic acid [29,30,33,43,52–54].

Figure 2. Current phenolic acids identified in the *Agave* genus.
3.2. Non-Polar Compounds: Saponins

Saponins are a class of metabolites with both hydrophobic and hydrophilic properties. Their versatility as bioactive agents has been described through various bio-guided studies of the Agave species. From these plants, nearly 28 steroidal saponins and 86 glycosylated saponins have been isolated; however, these numbers are still increasing. These compounds have shown antifungal, anti-inflammatory, cytotoxic, anticancer, and hemolytic activities [65].

Santos-Zea et al. [55] investigated anticancer activity against pulmonary cancer cell lines by applying enriched fractions of tetra and penta-glycosylated steroidal saponin from A. salmiana sap. The author found that the fraction that showed agavoside C and gentro-genin pentaglycoside contributed to cell death by necrosis at IC$_{50}$: 108.4 ± 11.5 µg/mL, while the fraction that presented magueyosides B, C, and kammogenin tetraglycoside induced apoptosis at IC$_{50}$: 82.7 ± 3.6 µg/mL. Such effects were similar to the anticancer
drug cisplatin which exerted necrosis and apoptosis at 10 µg/mL. Therefore, the anticancer activity of saponins depended on the glycosylated saponin derivative.

Furthermore, different fermented fractions of *A. sisalana* sap have been reported to exert anticancer activity but selectively through their different metabolic profiles. A fermented fraction from *A. globiformis* inhibited the growth of Caco-2 cell lines, while a *Gordonia* sp. fraction reduced Hep-G2 viability. Moreover, magueyoside B, and kammogenin glycoside were the most abundant in this extract and were associated with this bioactivity [57]. Another study showed that steroidal saponin, isolated from *A. marmorata* Roezl inhibited the NF-κB activation which modulates the inflammatory pathway of different diseases at IC$_{50}$ of 0.01 µg/mL in RAW 264.7 macrophages [58].

The modulation of the neuroinflammatory response in rats was investigated by Herrera-Ruiz et al. [56] and it was reported that the leaf extracts of *A. tequilana* Weber and *A. americana* L. *marginata* Hort. at a dose of 125 mg/kg diminished TNF-α and IL-6 concentration levels compared to indomethacin at a dose of 5 mg/mL. In this research, cantala-saponin-1 was also isolated from an *A. americana* L. *marginata* Hort extract and it similarly decreased the concentration levels of these cytokines at 5 and 10 mg/kg of indomethacin. Alternatively, the administration of the extracts and the isolated saponin stimulated the production of the anti-inflammatory cytokine IL-10 [56].

Steroidal saponins have also showed gastroprotective activity. A recent study proved that isolated glycosylated steroidal saponin from *A. angustifolia marginata* did not exert mutagenic, cytotoxic, and neoplastic effects on Vero cells at a concentration of 50 mg/kg. At the same time, the positive control of cyclophosphamide showed clastogenic potential at the same dose [60]. Moreover, the hydrolysate extract reduced the levels of reactive oxygen species at 50 µg/mL. Interestingly, the author confirmed through HPLC-UV-vis a mixture of saponins with a variety of sugar moieties in hydrolysate extract [60]. Therefore, saponins could be safe and novel anti-neoplastic drugs compared to conventional chemotherapy agents.

Steroidal saponins have also showed gastroprotective activity. A recent study proved that isolated glycosylated steroidal saponin from *A. angustifolia marginata* did not produce hemolytic alterations in gastric tissue by the presence of different glycoside chain substitutions. This structural feature also reduced the affinity of cholesterol to the erythrocytes membrane and gave a cytoprotecting effect in these cells and non-cytotoxic to the damage [61]. Another study assessed the effect of a methanolic extract and a saponins-enriched fraction of *A. seemanniana* Jacobi leaves; both reduced ulcer severity in a similar way to ranitidine at 50 mg/kg. However, their effectiveness was at a concentration of 200 mg/kg [62]. The extracts also displayed anti-inflammatory and analgesic effects at a dose of 100 mg/kg. At this concentration, the therapeutic action was similar to aspirin (100 mg/kg) and indomethacin (20 mg/kg). In addition, the author confirmed through NMR the presence of glycosylated steroidal saponins in the active fractions [62].

The healing properties against ulcerative injuries in the rat colons were also investigated by applying extracts of *A. americana* Linn leaves. The effective dose of the extract was 200–400 mg/kg, and it reduced the catalytic activity of myeloperoxidase and lipoperoxidase, which are enzymatic markers involved in the inflammatory response of intestinal ulcerative colitis. After the application, the regeneration of the epithelial cells of the mucosa was observed. These healing effects were reached on the 11th day of application at a concentration of 400 mg/kg [66]. It is worth mentioning that at this concentration the extracts decreased the inflammation parameters such as colon length and weight more than acetic acid (4%) and indomethacin (7.5 mg/kg), which were used as positive controls in both studies. Besides, *A. americana* Linn leaves extracts had similar action to the standard drugs prednisolone and 1,3,3,3 tetra-ethoxy-propane used to treat this illness [66,67].

Steroidal glycosylated saponins were also identified in leaf extracts of *A. americana* var. *marginata*, *A. americana* L., *A. angustifolia* Haw cv. *marginata*, *A. desmettiana* Jacobi, and *A. pygmaea* Gentry, and the anti-inflammatory and ulceroprotective activities were attributed to these compounds, as well as fatty acid amides [31].

The study of the gastroprotective effect of isolated hecogenin of *A. sisalana* Perrine leaf was described on two ulcerative models, the ulcerative injuries were induced by ethanol
and indomethacin. Santos Cerqueira et al. [68] found that a dose of 90 mg/kg p.o. decreased the percentage of ulcerative injuries on the rats' stomachs, similar to commercial drugs such as ranitidine (100 mg/kg), N-acetylcysteine (300 mg/kg), and misoprostol in both ulcerative models. According to these findings, the author stated that hecogenin involved an antioxidant protector mechanism which consisted of the protection of thiol groups of non-protein molecules of gastric mucosa, antisecretory acid action, module inflammation, and through the regulated stimulation of prostaglandins biosynthesis. Additionally, the effective dose of hecogenin inhibited lipid peroxidation and myeloperoxidase release from neutrophils in the injury sites, which prevented the propagation of reactive oxygen species [68].

Overall, the obtention of natural products from agave agro-wastes might be advantageous in designing new therapies to treat gastrointestinal inflammatory diseases with novel antiulcerogenic agents.

Regarding the recovery of saponins, the assisted-ultrasound extraction was used on the bagasse of *A. salmiana*. The conditions that increased yields were 400-W, 24 kHz, and 60 °C. It is not recommended to use hydroalcoholic mixtures instead of water due to the low propagation of the ultrasound in those solvent systems [69]. Another technology employed on this agro-waste was supercritical fluid extraction assisted by an ultrasound. Increased antioxidant activity in the extracts was observed and the hexaglycosylated derivatives of hecogenin were identified among other steroidal saponins [70].

### 3.3. Phytosterols

Phytosterols are hydrophobic compounds, and their base structure is cholesterol. In plants, these metabolites do not occur in free form; rather, they can be presented as conjugates of esters, glycosides, and acyl groups [71].

A study using ultrasound-assisted extraction in the piña of *A. angustifolia* Haw. had high extraction yields of β-sitosterol-D-glycoside in short periods of the process compared to maceration extraction [72]. Hernández-Valle et al. [64] investigated the anti-inflammatory effect of acetone fractions of this species on a mice ear edema inflammation model induced by TPA. According to the authors, AaF16 was the most active fraction and decreased the levels of IL-1β, IL-6, and TNF-α at 0.8 mg/ear; this effect was greater than that of dexamethasone (0.1 mg/ear). Besides, the topical application of the fraction at this concentration showed minor mononuclear inflammatory cell infiltration than dexamethasone and TPA on skin and cartilage. The chemical profile obtained by NMR of the active fraction confirmed the presence of different phytosterols such as β-sitosteryl glycoside, stigmasterol, and a peracetylated derivative of 3-O-[6′-O-palmitoyl]-β-D-glucopyranosyl-sitosterol [64], which are depicted in Figure 4.

Gutiérrez Nava et al. [63] compared the effect of the acetone extract of *A. tequilana* Weber leaf on rats with systemic erythematous lupus (SLE) against methotrexate and prednisone, which are immunosuppressant and anti-inflammatory drugs used to treat this illness. The authors found that methotrexate (3 mg/kg) diminished the titer of DNA autoantibodies, but increased proteinuria levels; thus, it had a nephotoxic effect. Conversely, *A. tequilana* Weber extracts reduced proteinuria associated with SLE, and decreased the titer of DNA autoantibodies, but not significantly. On the other hand, both drugs dropped the levels of IL-1β, IL-6, TNF-α, and INF-γ which are similar to the acetone fraction of *A. tequilana* Weber (50 mg/kg) which also stimulated the production of the IL-10 cytokine, a key cytokine that regulates the autoimmune response [63]. Through GC-MS, phytosterols and terpenes such as β-sitosterol-glycoside (0.1995), stigmasta-3,5-dien-7-one (0.0285), cycloartenol (0.019), and a phytol (0.1615) mg/g extract, were identified and quantified which were associated with this activity [63].
Figure 4. Current phytosterols identified and isolated in the *Agave* genus.

Furthermore, in the piña extracts from *A. angustifolia* Haw., *A. cupreata* Trel. & A. Berger, *A. salmiana* ssp. *Crassispina*, *A. salmiana* var. *salmiana*, *A. karwinskii* Zucc., leaf extracts of *A. atrovirens*, *A. decipiens* Baker, and a lipophilic fraction of fiber of *A. sisalana*, 7-ketositosterol, stigmasta-3,5-dien-7-one, stigmasta-4-en-3-one, stigmasta-4-en-3,6-dione and stigmastane-3,6-dione were found. However, no information was reported in this research about their biological activity [73–76].

4. The Role of *Agave* Extracts as Biopesticides

The application of agave crude extracts from agro-wastes has been on a diversity of applications on livestock and agricultural sectors. Since they are useful for pest insect management, larvae and intermedial organisms are considered vectors of parasitic diseases and fungi crop infestations.

4.1. Insecticide Activity

Lopes et al. [77] appraised the use of no contaminant solvents and applied a hydroalcoholic extract from *A. sisalana* Perrine leaf against adult females of *Dactylopius opuntiae*. The median lethal dose (LD$_{50}$) was 43 mg/mL after 10 h of application. Alternatively, the combination between extract and synthetic insecticide in their LD$_{50}$ enhanced the mortality percentage because of the synergy between the insecticide compounds and extracts. This may be a strategy to introduce agave plants as biopesticides and diminish high concentrations of synthetic products in fields.

Guimarães de Oliveira et al. [78] observed that *A. sisalana* Perrine leaf juice had a cytotoxic effect on the hemocytes cells of *A. aegyptii* and increased at a dose of 6 mg/mL. As a result of the application of the extract, it incremented nitric oxide production, which stated a defense response against the secondary metabolites of the extract. On this agro-waste, saponins, triterpenoids, alkaloids, tannins, and flavonoids were detected by qualitative analysis and might be associated with this effect [79].

The leaf of *A. sisalana* Perrine has also been used for the biologic control of *Callosobruchus maculatus*. A concentration of 100 mg/mL reduced the oviposition, larvae survival and pupae stage, and their population on bean infested seeds [80].

The application of the leaf extract of *A. americana* var. *marginata* Trel. had a 70% mortality rate against *Brevicoryne brassicae* at a concentration of 0.75 mg/mL after 3 h of application [81]. Alternatively, this species activity showed 70.3% and 92% of mortality.
against Aphis gossypii at 25 mg/mL after 24 and 36 h of application, respectively. However, the extract was toxic for Artemisia salina, a non-target organism [82].

Cunha Pereira et al. [83] identified β-caryophyllene in the aqueous extract of A. americana L. leaves as the most abundant compound, which had no deleterious effects in two species of bees; even at a high extract concentration, it showed CL_{50} of 127.4 and 122.2 ng/µL for A. mellifera y P. helleri, respectively. In contrast, imidacloprid had CL_{50} of 0.09 and 0.11 ng/µL in both species; therefore, the application of this pesticide resulted in more noxious effects than the extract. Moreover, Marafeli et al. [84] sprayed an aqueous extract of this species on coffee leaves infested with Olygonychus ilicis and it presented a 100% mortality rate at 4% (v/v) after 72 h of application.

Other species, such as A. angustifolia Haw., A. tequilana Weber, A. sisalana Perrine, and A. attenuata showed insecticide activity against Bemicia tabaci, Tetranychus urticae, and Diuraphis noxia [85–87]. Particularly, the extract of A. attenuata presented methyl-jasmonate, 2,5-dimethyl-3,4-hexanediol, and n-hexadecanoic acid as the most abundant metabolites, which might effect insecticide activity [88].

4.2. Molluscicide Activity

The agave crude extracts have been used for the biological control of mollusk. These organisms are vectors of diseases that affect human health due to are host of dangerous parasites.

From the above, different research has found that some Agave species such as A. filifera, A. celsii, A. sisalana, A. decipiens Baker, and A. lophantha exerted molluscicide activity against Biomphalaria alexandrina [75,89–91], a snail vector of Schistosoma mansoni, which causes schistosomiasis. The effective lethal dose and extract type are summarized in Table 3.

| Species/Tissue | Extract | Targeted Organism | Affected Organism | Biological Activity | LD_{50} (mg/mL) | MI (%) | t | References |
|---------------|---------|-------------------|-------------------|---------------------|-----------------|-------|---|-----------|
| A. americana L. Leaf | M | Sitophilus oryzae (L.) | Triticum durum Desf. | Insecticide Repellent | 8.99 µg/cm² 0.055 µg/cm² | 50 24 h | | [49] |
| A. lechuguilla Torr. Leaf | HA | Bemisia tabaci | Phaseolus vulgaris | Insecticide | 1035 mg/L | - 72 h | | [50] |
| A. sisalana Perrine Leaf | HA | Dactylopius opuntiae | Opuntia ficus-indica | Insecticide | 17,46 | 51,97 10 Days | | [77] |
| A. sisalana Perrine Leaf juice | A | Aedes aegyptii | - | Ovicide Cytotoxic | 6 | 73.8 | 24 h | | [78] |
| A. sisalana Perrine Leaf Hxn | A | Callosobruchus maculatus | Phaseolus spp. | Insecticide Ovicide | 100 | 100 24–96 h | | [80] |
| A. americana var. Marginata Trel. Leaf | A | Brevicoryne brassicae | Brassica oleracea L. var. acephala | Insecticide | 0.750 | >70 3 h | | [81] |
| A. americana Leaf | A | Aphis gossypii | Gossypium hirsutum L. | Insecticide | 25,50 | 70.3, 92.5 24,36 h | | [82] |
| A. americana L. Leaf | A | Olygonichus ilicis | Coffea arabica L. Coffea canephora | Insecticide 4% (v/v) | 100 | 72 h | | [84] |
| A. angustifolia Haw. Leaf | A | Tetranychus urticae | Fragaria L. Fragaria | Insecticide 10% (v/v) | 88 | 5 Days | | [85] |
| A. tequilana Weber Leaf juice | A | Bemisia tabaci | Solanum lycopersicum | Insecticide | 20–40 | 90 | 24 h | | [86] |
| A. sisalana Perrine Leaf juice | A | Tetranychus urticae | Gossypium hirsutum L. | Insecticide | - | 100 35–65 Days | | [87] |
| A. attenuata Leaf | A | Dysaphis noxia | Triticum spp. | Insecticide | 0.838 | 98.75 | 24 h | | [88] |
| A. filifera Whole plant | A | Biophlalaria alcunadrina | Humans | Molluscicide Ovicide | 42.30 85.62 | 40.5 6 Weeks | | [89] |
| A. celsii Leaf | M | Biophlalaria alcunadrina | Humans | Molluscicide | 40,73 | - 24 h | | [90] |
| A. lophantha Leaf | B | Biophlalaria alcunadrina | Humans | Molluscicide | 17,100 | 100 | 48 h | | [91] |
Table 3. Cont.

| Species/Tissue | Extract | Targeted Organism | Affected Organism | Biological Activity | LD<sub>50</sub> (mg/mL) | MI (%) | t | References |
|----------------|---------|-------------------|-------------------|---------------------|--------------------------|--------|---|------------|
| A. attenuata Leaf | A | Bulinus africanus | Humans | Molluscicide | 65 | - | 24 h | [92] |
| A. legrelliana Jacobi, A. americana marginata L. Leaf juice | A | Praticolella grisola (Pfeiffer) | Animals/Crops | Molluscicide | 50% mL/L | 82.5 | 77.5 | 7 Days | [93] |
| A. americana var. expansa Leaf | A | Melanoides tuberculata (Thiaridae) | Native mollusks | Molluscicide | 1.01 mL/L | 65 | 24 h | [94] |
| A. americana Leaf | B | Indoplanorbis exutsus, Lymnaea luteola, Gyraulus convexiusculus | Humans/Animals | Molluscicide/Ovicide | 21.9, 18.5, 16, 16.4, 15.2, 15 | - | 24 h | [95] |
| A. sisalana Perrine Leaf A, B, E | | Pomacea canaliculata L. | Aegle marmelos | Molluscicide | 35.3 g/L, 93.3, 298.6 | - | 72 h | [96] |
| A. sisalana A. attenuata Leaf | E | Biophalaria alexandrina | Humans | Molluscicide | 82, 101 | - | 72 h | [97] |
| A. sisalana Perrine Leaf juice | A | A. aegypti | Humans | Larvicide | 4.5, 6.5 | 100 | 12, 24 h | [98] |
| A. sisalana Perrine Leaf A, M | A | A. aegypti, C. quinquefasciatus A. stephensi | Humans | Larvicide | 86, 76, 75, 82, 220, 36 | 100 | 24 h | [99] |
| A. sisalana Leaf | A | A. aegypti, C. quinquefasciatus | Humans | Larvicide | 100 | 100 | 3–4 Days | [100] |
| A. cantala (Haw.) Roxb. Ex Salm-Dyck Leaf Acr | | Plutella xylostella (L.) | Brassica oleracea | Larvicide | 60 | 35.77 | 12 h | [101] |
| A. sisalana Perrine Leaf juice | A | Radopholus similis | Masa x paradisiaca | Nematicide | 5, 25% (v/v) | 90.1, 99.2 | 24, 48 h | [102] |
| A. sisalana Perrine Leaf A | A | Meluidogene javanica | Solanum lycopersicum | Nematicide | 20% (v/v) | 100 | 48 h | [103] |
| A. sisalana Perrine Leaf juice | A | Scutellomena brahys | Dioscora esculenta | Nematicide | 20–40% (v/v) | 100 | - | [104] |
| A. angustifolia Haw. Leaf Acr | | Silocephal zonmais Motschulsky | Zea mays L. | Insecticide | 5% (v/v) | 34 | 72 h | [105] |
| A. angustifolia marginata Leaf | A | A. aegypti, C. quinquefasciatus A. stephensi | Humans | Larvicide | 28.27 µg/mL, 100 µg/mL | 100 | 12 h | [106] |

HA: Hydroalcoholic, A: Aqueous, Hxn: n-Hexane, M: Methanolic, E: Ethanolic, Acn: Acetone, B: Butanol, MI %: Mortality index, DL<sub>50</sub>: Median lethal dose, t: time.

Another study by Bakry and Salwa A.H [90] found that a dose of 22 mg/L of the methanolic leaf extract of A. celsii reduced the activity of the glycolytic enzymes of B. alexandrina and led the snails to an anoxia state. Alternatively, the extract administration caused the release of cellular content associated with the low enzyme activity of their energetic metabolism and diminished the oviposition rate, which prevented the propagation and infectivity of S. mansoni to B. alexandrina.

More studies have shown that the A. legrelliana Jacobi leaf juice extract exhibited molluscicidal activity against Praticolella grisola with an 82.5% mortality rate after seven days [93]. Besides, this agro-waste was able to diminish notably the cardiac frequency of Fossarium cubensis within a range of 0.105 to 7.718 mL/L after three days of application [107].

Molluscicidal activity of A. americana var. expansa was also assessed; the aqueous extract caused 65% of mortality against Melanoides tuberculata at LD<sub>50</sub> of 0.86 mL/L after 24 h of exposition [94]. However, another study employed a butanol extract, and it showed an ovicide effect against Indoplanorbis exutsus, Lymnaea luteola, and Gyraulus convexiusculus at LD<sub>50</sub> of 21.95, 18.56, and 16 mg/L, respectively [95].

The molluscicidal activity of aqueous, ethanolic, and butanol extracts of A. sisalana Perrine leaf against Pomacea canaliculata was appraised. Particularly, aqueous extracts showed the highest molluscicidal effect at LD<sub>50</sub> of 35.3 mg/L [96]. Besides, the effective
concentration decreased superoxide dismutase activity due to the oxidative stress produced by the phytochemicals of the extract. Similarly, Hamed et al. [97] observed a modification in the activity of the antioxidant enzymes within the effective molluscicide concentration range. Thus, it might have involved a defense response brought about by secondary metabolites.

The molluscicidal activity of saponins was also investigated. A study showed that isolated tigogenin diglycoside from *A. angustifolia* leaves killed 90% of the *B. alexandrina* population at a concentration of 61.4 mg/L after 24 h of exposition [108]. Furthermore, in other research, steroidal glycosylated saponins from *A. franzosinii* P. Sewell and *A. angustifolia* exhibited this effect at LD$_{50}$ similarly to niclosamide and praziquantel, which are synthetic molluscicides [109]. Moreover, neoruscogenin and neohecogenin isolated from *A. decipiens* Baker leaves had 90% mortality against this snail species at concentrations of 13 mg/mL and 6 mg/mL, respectively, after 24 h of application [75]. Considering this evidence, saponins might be an alternative to replace synthetic pesticides that might be noxious to the environment.

4.3. Larvicide Activity

Concerning larvicide activity, Kajla et al. [106] described that thermal stress on *A. angustifolia* var. *marginata* leaves swelled the concentrations of secondary metabolites in the extracts; this enhanced the mortality index against larvae *Aedes aegypti* at LD$_{50}$ of 28.26 µg/mL after 12 h of application. Alternatively, the reduction in LD$_{50}$ to 19.15 µg/mL was achieved, but during a longer exposition time (24 h). On the other hand, the extract also showed larvicide activity against *Culex quinquefasciatus* and *Anopheles stephensi*, but at 100 µg/mL.

Another study stated that the application of *A. sisalana* Perrine leaves juice killed *A. aegypti* larvae at LD$_{50}$ of 4.5 mg/mL; the author reported that the high concentration of this agro-waste exhibited hemocytes necrosis and reduced nitric oxide concentration, which is involved in the immune response of this organism, after 24 h of application [98].

Furthermore, leaf juice extracts from *A. sisalana* Perrine obtained with water and other organic solvents were appraised. The aqueous extract killed *C. quinquefasciatus*, *A. aegypti*, and *A. stephensi* larvae at LD$_{50}$ of 86, 76, and 75 mg/L, respectively. The highest mortality rate was on the III/IV growth stage of larvae. In contrast, the methanolic extract showed greater mortality at an LD$_{50}$ of 36 mg/mL [99]; however, applying an organic solvent in plant molluscicides might represent an environmental risk. Moreover, Pizarro et al. [100] assessed the larvicidal effect of aqueous extracts of this species against *C. quinquefasciatus*, and it showed a mortality of larvae at LD$_{50}$ of 322 mg/mL. In this research, the fractionation of crude extracts, was performed which enhanced the effect and reduced the LD$_{50}$ to 204 mg/L, due to the increase in the saponins content and the elimination of undesirable compounds.

The larvicidal activity of *A. cantala* (Haw.) Roxb. Ex Salm-Dyck against *Plutella Xylostella* (L.) was weak at a 60 mg/L concentration with 35.77% mortality. However, a 25 mg/mL concentration prolonged the growth periods of the pupae and larvae, decreasing the fecundity rate of adult females and the hatching of the egg by 94.5% [101]. Thus, the disruption of reproductive cycles represents a strategy for plague control of other organisms that affect industrial crops.

4.4. Nematicide Activity

The field of bionematicides development through agave plants has gradually broadened as different research has proved the efficacy of agro-waste against different phytone-matodes. Fábio et al. [102] observed that fresh leaf juice of *A. sisalana* Perrine exhibited 99.2% of mortality against *Radopholus similis* after 48 h, at 25% (v/v). In contrast, fermented juice at that concentration caused a phytotoxic effect on banana plants. Similarly, Damasceno et al. [103] found that the fresh juice of *A. sisalana* Perrine displayed 100% mortality on infested tomato crops with *Meloidogyne javanica* at 20% (v/v). In addition, the agro-waste
reduced nematode egg masses and the number of galls per plant. Conversely, fermented juice caused the inhibition of beneficial soil organisms. Likewise, Dos Santos Fernandes et al. [104] confirmed the nematicide activity of the liquid agro-waste of *A. sisalana* Perrine (20% v/v) against *Scutellomena bradyi* with a 100% mortality rate after 24 h.

Another approach on the bionematicides from agave is the management of gastrointestinal nematodes in the livestock sector. Different *Agave* species such as *A. angustifolia* Haw., *A. americana* L., *A. tequilana* Weber and *A. sisalana* Perrine exhibited nematicide activity against *Panagrellus redivivus*, *Meloidogyne incognita*, *Haemonchus* spp., *Oesophagostomum* and *Trichostrongylus*. Those studies used methanolic and aqueous extracts, which killed nematodes within 24 to 72 h of application [86,110–112]. Another study mentioned that during the administration of *A. sisalana* Perrine agro-waste on infested animals, no health issues were presented. Thus, its application was considered safe [113].

As it mentioned previously, leaf juice of *A. sisalana* has been the most studied agro-waste for its nematicide properties. Hecogenin, succinic acid, mannitol, homoisoflavonoids, and kaempferol were some of the metabolites identified in aqueous sisal liquid agro-waste in different research [114,115].

### 4.5. Antifungal Activity

The use of extracts from agave agro-wastes as bioweapons against phytopathogenic fungus is another potential approach in agricultural areas. In general, *Postia placenta*, *Alternaria brassicae*, *Fusarium oxysporum*, *P. aphanidermatum*, *Phytophthora cinnamomi*, *Penicillium digitatum*, *Sclerotium rolfsii*, *Pyricularia oryzae* are fungi agents that are causing different plant diseases that affect industrial crops. However, different *Agave* species were efficient in their biologic control.

Some *Agave* species such as *A. americana* L., *A. sisalana* Perrine, *A. scabra* Salm-Dyck, *A. marginata*, *A. ferox* K. Koch, *A. lechuguilla* Torr., *A. montana* Villareal and *A. sisalana* Perrine inhibited mycelial hyphal growth or showed antisporulant effects against the previous fungi [116–121]. The effective concentration, extract type, type of inhibition, and affected crop were summarized in Table 4.

| Species/Tissue | Extract | Target Organism | Affected Crop | Biological Activity | LD₅₀/MIC | IG (%) | t | References |
|---------------|---------|----------------|--------------|---------------------|---------|--------|---|-----------|
| *A. montana* Villareal | AM      | *Postia placenta* | -            | Antifungal          | -       | 69.31ᵇ | 7 days | [116]     |
| *A. marginata* | A       | *Alternaria brassicae* | *Brassica juncea* | Antifungal          | 40 µg/mL| -      | 4 days | [117]     |
| *A. americana* L. Leaf | A       | *Pyricularia oryzae* | *Oryza sativa* L. | Antifungal          | 3% (v/v) | 100ᵃ   | 10 days | [118]     |
| *A. lechuguilla* Torr. Leaf | A       | *Fusarium oxysporum* | *Pythium aphanidermatum* | Antifungal          | 28.87 mg/mL | 60ᵃ | - | [119]     |
| *A. americana* L. Leaf | A       | *Zingiber officinale* | *Rosc.* | Antifungal          | -       | 67.98ᵇ | 96 h | [120]     |
| *A. scabra*, Salm Dyck Leaf | HA      | *Botrytis cinerea* | -            | Antifungal          | -       | 90ᶜ  | 86.6ᵇ | 7 days | [121]     |
| *A. americana* L. Leaf | M       | *Penicillium digitatum* | *Sclerotium rolfsii* | Antifungal          | 11.86 µg/well | 87.73ᵃ | 80.81ᵃ | 9 days | [122]     |
| *A. americana* L. Leaf | M       | *Sclerospora graminicola* | *Cenchrus americanus* | Antisporulant | -       | -     | 12–14 h | [123]     |
| *A. lechuguilla* Torr. Leaf | L       | *Rhizoctonia solani* | -            | Antifungal          | 1.70 × 10⁴ᵃ | 6.72 × 10³ᵃ | mg/L | 14.1ᶜ | - [124] |
| *A. americana* L. Leaf | A       | *Aspergillus parasiticus* | Cereal crops | Reduce aflatoxin production | -       | - | 7 days | [125]     |
Table 4. Cont.

| Species/Tissue | Extract | Target Organism | Affected Crop | Biological Activity | LD₅₀/MIC | IG (%) | t | References |
|----------------|---------|-----------------|---------------|---------------------|---------|-------|---|------------|
| Leaf           | E       | Penicillium sp.  | Phaseolus lunatus L. | Antifungal         | -       | 85 c  | 92.5 c  | 100 c  | 7 days [126] |
| A. americana L. | A       | Physopothora megakarya | Theobroma cacao L. | Antifungal         | 60 mg/mL| 54.33 a |           |           | 7 days [127] |
| A. sisalana Perrine Leaf juice | A | Lasiodiplodia theobromae | - | Antifungal         | 75.60 a |           |           |           | 3 days [128] |
| A. americana L. Leaf | - | Leveillula taurica (Lev.) Arn | Capsicum annum L. | Weak antifungal | - | - | 10 days | [129] |
| A. cantala (Haw.) Roxb. Ex Salm-Dyck Leaf | A | Peronospora farinosa | Vinis vinifera L. | Fungal protection | - | - | 10 days | [130] |
| A. marginata A. americana L. | AM | Macrophomina phaseolina | - | Antifungal         | -       | 64.75 b  | 61.69 b  | 59.39 b  | 7 days [131] |
| A. cantala (Haw.) Roxb. Ex Salm-Dyck Leaf | A | Plasmodura viticola | Vinis vinifera L. | Fungal protection | - | - | 10 days | [132] |
| A. americana L. Leaf | A | Sclerospora graminicola | Cenchrus americanus | Antisporulant | - | - | 12-14 h | [133] |

LD₅₀: Median lethal dose, % IG: Inhibition growth percentage, MIC: Minimal inhibitory concentration, E: Ethanolic, M: Methanol, A: Aqueous, L: Lanolin, HA: Hydroalcoholic, AM: Aqueous methanol, C: Cocoa butter, a: Mycelial growth inhibition, b: Hyphal growth inhibition, c: Growth inhibition.

Maazoun, Hamdane, et al. [122] confirmed the antifungal effect of A. americana L. leaf extract against P. digitatum. Besides, the protease activity of this microorganism was inhibited at an IC₅₀ concentration of 108.03 µg/mL. Another finding was that long exposition times of the extract to P. digitatum brought about the release of cell constituents which were correlated with the presence of saponins. On the other hand, the A. americana L. crude extract showed an antisporulant effect against S. graminicola. This effect was held after the extracts were diluted 10-fold. However, high diluted rates led to a lost antifungal effect [133].

The use of organic solvents such as methanol, n-hexane, and chloroform showed high antifungal activity [38,122]. Although, their application might be limited due to environmental issues. Castillo et al. [124] employed lanolin and cocoa butter instead of organic solvents on A. lechuguilla Torr. leaves with high tannin content. Additionally, these emulsions inhibited the mycelium growth of R. solani at concentrations of 1.70 × 10⁴ and 6.72 × 10³ mg/L, respectively. Similarly, Francisco et al. [119] confirmed the antifungal activity of lanolin extract of this species against P. cinnamomi at IC₅₀ of 23.07 mg/mL. In contrast, lanolin extract exhibited an antifungal concentration lower than ethanolic extract but similarly to aqueous extract (28.87 mg/mL), which suggested that lanolin emulsions can also be efficient solvents to recover bioactive compounds.

The regulation of fungal disease of downy mildew on vitis vinifera L through A. cantala (Haw.) Roxb. Ex Salm-Dyck leaf extracts was investigated by Vishal Naik et al. [132]. It found that ten days of after the extract was sprayed, it stimulated the enzymatic activity of polyphenol oxidase and catalase. Such enzymes are involved in the production of reactive oxygen species and quinones, which act as a defense response against phytopathogenic fungi. On the same topic, another study reported that the leaf extract of A. cantala (Haw.) Roxb. Ex Salm-Dyck contained high polyphenolic content with radical scavenger capacity [134]. Thus, by the previous study, the content of phenolic compounds might play a key role in the regulation of fungi diseases.

The chemical nature of the secondary metabolites was a factor that influenced antifungal activity. Yang et al. [135] isolated different saponin glycosides from A. americana leaves and found that tigogenin tetracyglosides with one xylose unit enhanced this effect while...
two or more xylose units decreased it. Therefore, the sugar chains impacted the antifungal potential of glycosylated steroidal saponins.

The agave crude extracts have also been referred to as excellent fungal toxin suppressors. Rosas-Taraco et al. [125] found that the aqueous extract of A. americana L. leaves decreased norsolorinic acid production by 75% at a concentration of 10 mg/mL. Norsolorinic acid is a precursor to the aflatoxin biosynthetic pathway. As a result of this, it reduced the aflatoxin concentration on A. parasiticus. Another study confirmed that aqueous extracts of A. asperrima Jacobi and A. striata Gentry inhibited 99% of the production of cyclopiazonic acid, a toxin biosynthesized by A. flavus on infested corn during storage [136]. Thus, agave extracts could have a useful application on cereal crop protection.

4.6. Antiparasitic Activity

There is little information about the potential of agave agro-waste extracts against parasites that are harmful to human health. At least two studies informed the antiparasitic activity against Leishmania donovani, the causal agent of visceral leishmaniasis.

According to the research of Singh et al. [137], the A. americana L. leaf extracts at 0.05 mg/L killed amastigotes and promastigotes of L. donovani, but this effect was preferentially observed on amastigotes with 100% of mortality. Besides, the author compared the toxicity of extracts to amphotericin B, which resulted similarly to this commercial drug that is often used to treat visceral leishmaniasis. High costs, however, are a limitation in their treatment.

A second study reported that fractionated ethyl-acetate extracts from A. americana L. leaves obtained 100% mortality at 50 µg/mL against promastigotes and intracellular amastigotes of L. donovani at IC_{50} of 25 µg/mL. The application at effective doses increased nitric oxide levels in macrophages infested with amastigotes, which was suggested as a possible action mechanism of the extracts. However, after 48 h of dosing, a cytotoxic and hemolytic effect on macrophages was observed [138].

A third study reported by Quintanilla-Licea et al. [139] informed the antiparasitic activity of A. lechuguilla Torr. against Entamoeba hystolytica, the causal agent of amoebiasis, with a 69.66% growth inhibition; nevertheless, no median lethal dose was referred. More studies are required in this area, which offers a line of research to discover the antiparasitic effect of new molecules.

5. Conclusions

The hunting of novel bioactive molecules of the genus Agave and their biological activities shows that these plants are a valuable source of therapeutic agents, which can help generate new therapies for autoimmune, inflammatory, and chronic degenerative diseases. On the other hand, its use to obtain natural products might be a strategy to revalorize the agave agro-wastes, which could benefit the livestock and agricultural sectors due to the presence of secondary metabolites that play a protective role in biowarfare and pest control. Overall, natural extracts from agave agro-wastes might be an alternative for agricultural purposes because of their safety and low toxicity to the non-target organism compared to synthetic pesticides, which are harmful to the environment and human health. Being a material rich in different compounds of agro-industrial interest, future research focused on the isolation, purification, and protection of the secondary metabolites of the agave using environmentally friendly processes, as well as the latest sensitive and reliable technology instrumentation for their identification remain topics of interest for the use of agave agro-waste. On the other hand, delving into the development of products based on the use of these pure metabolites or its extracts, the evaluation of its stability and bioactivity, as well as its application in different areas of science will allow us to contribute to the circular economy of the production chain of the Agave.
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