Abstract: The Cactaceae family is an important source of triterpenes and sterols. The wide uses
of those plants include food, gathering, medicinal, and live fences. Several studies have led to
the isolation and characterization of many bioactive compounds. This review is focused on the
chemistry and biological properties of sterols and triterpenes isolated mainly from some species with
columnar and arborescent growth forms of Mexican Cactaceae. Regarding the biological properties
of those compounds, apart from a few cases, their molecular mechanisms displayed are not still
fully understand. To contribute to the above, computational chemistry tools have given a boost to
traditional methods used in natural products research, allowing a more comprehensive exploration
of chemistry and biological activities of isolated compounds and extracts. From this information an
in silico bioprospection was carried out. The results suggest that sterols and triterpenoids present in
Cactaceae have interesting substitution patterns that allow them to interact with some bio targets
related to inflammation, metabolic diseases, and neurodegenerative processes. Thus, they should
be considered as attractive leads for the development of drugs for the management of chronic
degenerative diseases.

Keywords: Cactaceae; bioprospection; sterol; triterpene; bioactivity; in silico screening; inflammation; diabetes

1. Introduction

The word Cactaceae derived from the Greek, "kaktos", used in antiquity to name a species of
thorny thistle, possibly the cardo Cynara cardunculus (Asteraceae), being used as a generic name by
Carlos Linneo in 1753, for several plants of diverse sorts of the Cactaceae family [1]. This family,
originally from America, groups about 1500 species. It is estimated that about 700 species grouped in
68 genera are present in Mexico, although there is considerable variability in these data [2–4].

The most apparent characteristic of cacti is the presence of the areola, considered as buds
homologous to the axillary buds of the other dicotyledons. One main characteristic of buds or areolas
is its capacity to form reduced leaves, flowers, new stems, thorns, glands, bristles, and hairs, even
sometimes adventitious roots [2]. The ethnobotanical importance of cacti has been described extensively
in the literature, including their use as food, medicine, among others. Some species of the family
Cactaceae have been used as natural remedies for many centuries in Mexican traditional medicine.
For example, peyote (Lophophora williamsii) has been used not only as a means of communication of
man to the spiritual world but also as an analgesic and antiinflammatory. On the other hand, Ariocarpus
kotschoubeyanus has been used as an analgesic for bruises, the stems of Pachycereus pecten-aboriginum have been used to cure gastric ulcers, and as dressings to calm rheumatic pains and inflammatory processes, the latex of Mammillaria heyderi has been used by the Tarahumara’s community for earache and deafness. Parts of Stenocereus thurberi have been used to relieve pain in general [5].

Despite the widespread use of these species, in general, the literature concerning the chemistry, biological activities, or toxicity of these plant resources is scarce. This situation evidences the lack of studies, except for the so-called “nopales” and their fruits called tunas (Opuntia spp.), among other plants with minor importance. For example, some species of the genus Opuntia have been used as the food of high nutritional importance [6–10]. Anticancer, antioxidant, anti-inflammatory, antiviral, antidiabetic, among other bioactivities, have been reported, from both stem and fruit extracts of these species, which demonstrated good effectiveness in different in vitro and in vivo models (reviewed in [11]).

Of the Mexican cacti, columnar species have also occupied an essential place in ethnobotany, and some of them have been used for various purposes, including medicinal, among others [2,3,12]. Compounds have been isolated from some cacti species that were active in models of inflammation induced by chemical agents such as 12-O-tetradecanoylphorbol 13-acetate (TPA), as well as inhibitors of the proliferation of tumor cells in cultures in vitro [13], concisely reviewed by Harlev et al. in 2013 [14]. Although the biological effects of compounds isolated from Cactaceae have been reported, their mechanisms and molecular targets are not always discussed. Many of the molecules, like sterols or triterpenes, display a wide range of biological activities, but it is necessary to explore how they act in biological systems. Our group has decided to explore the molecular mechanisms of natural product bioactivities through an in silico bioprospection approach.

Computational chemistry tools have boosted traditional natural product research. Among the strategies that have been used, Docking-Based Virtual Screening (DBVS) [15,16] has given relevant results. Though it has some critical limitations, DBVS has demonstrated to be a useful strategy to suggest the action mechanism or for proposing new biological activities of known products or extracts [17–25]. The selection of the bio targets to be analyzed is not always an easy feature as could be biased by the research group. Then, it is essential to carry out a profound review of the chemistry and experimentally demonstrated bioactivities of extracts and isolated compounds, and from this information, choose the most relevant bio targets for the in silico study.

Our group has dedicated for the last fifteen years, to perform systematic studies about the chemistry and biological activities of cacti [26–33]. Thus, this work presents a review of the chemistry and bioactivities of sterols and triterpenes found in Mexican Columnar Cactaceae, and in the last section, from the collected information about the chemistry and biological activities displayed from those, we selected some bioactivities and their molecular targets to be explored in the DBVS, intending to perform the in silico bioprospection of compounds found in Mexican Columnar cacti.

2. Chemistry of Cactaceae

The chemistry of the Cactaceae Family has been described intensively over the years. The first report about the biological effects and chemistry of a cactus was made early in the second part of the eighteenth century [34], which describes the use of Cereus grandiflorus (Linnaeus) Mill (nowadays the species is classified as Selenicereus grandiflorus (Linnaeus) Britton & Rose, [3,35,36]), for the treatment of certain heart diseases. The above report was described in one of the first reviews of Cactaceae chemistry [37]. Although the alkaloids and polyphenols have already been described in several species, their biological activities have been studied extensively, and a recent report has been published [12]. However, the systematic revision of the chemistry of sterols and triterpenes from cacti and their biological activities is pending. Due to the length of the topic, this review covers only aspects related to the chemistry and biological activities of sterols and triterpenes that have been isolated from Mexican species of the subfamily Cactoideae, tribe Phyllocacteae, mainly from the subtribe Pachycereeeae [3,4], also named Echinocereinae [38], which is recognized as a largely North and Central
American taxon. Some exceptions are made for sterols and triterpenes isolated from species belonging to other tribes or subfamilies, the unique characteristics of which are worth mentioning. The chemistry and biological activities of other chemical groups like alkaloids or betalain-pigments are not reviewed in this opportunity.

2.1. Sterols from Mexican Columnar Cactaceae

There is not enough data to generalize the type of the preferred sterol skeleton, the substitution pattern, and the quantities of sterols present in the different species, genera, clade or subfamily of Cactaceae. With an exception of some Sonoran Desert species (Carnegiea gigantea, Pachycereus pringlei, Machaerocereus gummosus, Lemaireocereus thurberi, among others) whose chemistry has been described exhaustively because of its ecological implications in the Cactus-Microorganism-Drosophila Model System of the Sonoran Desert [39–41]. The structures of sterols isolated from Mexican Cactaceae are presented in Table 1.

Cactaceae is a rich source of sterols, many of them with some special features (e.g., the presence of extra methyl groups at C4 or C14, or the positions of double bonds in cholesterol skeleton). The isolation of the sterols from Cactaceae began early with lophenol, schottenol, 24-methylene-lophenol, lathosterol, 5α-campe-7-en-3β-ol, spinasterol, together with locereol, and 5α-cholesta-8, 14-dien-3β-ol, which were isolated from aerial parts of Lophocereus schotii [42,43]. In a subsequent study, isolation of viperidinone and viperidone was reported, and deoxiviperidone from Wilcoxia viperina [44,45], species now called Peniocereus viperinus [46].

In other studies, from roots of Peniocereus fosterianus and P. macdougallii were isolated two 3β, 6α-dihydroxysterol: peniocerol and macdougallin respectively, together with small amounts of lophenol and campesterol [45,47,48]. Special mention is made for macdougallin, which is a very particular 14α-methylcholesterol that will be discussed later.

Besides, from the root of P. greggii was performed an investigation to find other 14α-methylcholesterols similar to macdougallin, but the authors were not successful [49]. However, from this species, they isolated deoxiviperidone, peniocerol, viperidone, viperidinone, together with a new molecule in the form of its acetylated derivative, which presented the unusual cis-fusion between rings A and B of the cholesterol skeleton, which they called 5β-desoxyviperidone.

On the other hand, small amounts of cholesterol were isolated from Stenocereus thurberi, some common sterols like campesterol and β-sitosterol [50], together with peniocerol, madougallin, and three new 3β, 6α-dihydroxysterols, named cyclostenol, stenocereol, and thurberol, the last two with the characteristic double bond in C-8 like peniocerol [51].

In another study, Jiang et al. isolated a new sterol from the aerial parts of Opuntia dillenii, which they called opuntisterol. Although the genera Opuntia does not belong to columnar Cactaceae, opuntisterol and other compounds present in Opuntia spp. were included in the present review because of the special feature of the configuration 5β in a sterol configuration, an infrequent feature in cacti sterols [52], but common in ecysterooids and related phytocdysteroids [53,54].

Finally, from the pollen of Carnegiea gigantea, was found 24-methylene-cholesterol, while 24-dehydropollinastanol, fucosterol, among other sterols, were found in O. phaeacantha and O. versicolor.

With these data together with that previously reported [55], it can be inferred that the sterols found most frequently in the Cactaceae family are the typical C29 and C28 compounds, with the common Δ5 unsaturations such as β-sitosterol, campesterol or stigmasterol. However, a distinctive feature of some species is the presence of C27 sterols, with Δ8 unsaturations, with an extra 6α-hydroxyl group as peniocerol. Another one distinctive feature of some species is the presence of compounds considered intermediaries in the “normal” biosynthetic pathways as lophenol or macdougallin, which strongly suggests that these plants possess modified metabolic pathways [43,45,56]. On the other hand, the presence of some sterols with unusual cis fusion in the joint of rings A/B like 5β-desoxyviperidone and opuntisterol, which presents the same configuration like ec dysone (the molting hormone in
arthropods) could be relevant to the chemical defensive mechanisms in Cactaceae, as was previously hypothesized [27]. The species and the isolated sterols, together with the bioactivities of those compounds, are showed in Tables 2 and 3, respectively.

Table 1. Chemical structures of sterols isolated from Cactaceae.

| Sterol Name          | R_1 | R_2 | R_3 | R_4 | R_5 | R_6 | R_7 | R_8 | Σ^1 |
|----------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Cholesterol          | β-OH| H   | -   | -   | H   | H   | H   | H   | 5   |
| Lophenol             | β-OH| CH_3| H   | H   | H   | -   | H   | H   | 7   |
| Schottenol           | β-OH| H   | H   | H   | H   | -   | H   | H   | β-CH_2CH_3| 7  |
| 24-methylenelophenol | β-OH| CH_3| H   | H   | -   | H   | H   | =CH_2 | 7   |
| Lathosterol          | β-OH| H   | H   | H   | H   | -   | H   | H   | 7   |
| 5α-campest-7-en-3β-ol| β-OH| H   | H   | H   | -   | H   | H   | β-CH_3 | 7   |
| Spinasterol          | β-OH| H   | H   | H   | -   | H   | H   | β-CH_2CH_3| 7  |
| Locereol             | β-OH| CH_3| H   | H   | H   | -   | -   | -   | 8, 14|
| 5α-cholesta-6,14-dien-3β-ol| β-OH| H   | H   | H   | -   | -   | -   | H   | 8, 14|
| Viperidinone         | β-OH| H   | H   | H   | =O  | -   | α-OH| OH  | H   | 7   |
| Viperidone           | β-OH| H   | H   | H   | =O  | -   | α-OH| H   | H   | 7   |
| Deoxiviperidone      | β-OH| H   | H   | H   | =O  | -   | H   | H   | H   | 7   |
| Peniocerol           | β-OH| H   | H   | H   | α-OH| -   | -   | H   | H   | 8   |
| Macdougallin         | β-OH| H   | H   | α-OH| -   | -   | CH_3| H   | 8   |
| 5β-deoxiviperidone   | β-OH| H   | β-H  | =O  | -   | H   | H   | H   | 7   |
| Cyclostenol **       | β-OH| H   | H   | α-OH| H   | -   | CH_3| H   | -   |
| Stenocerol           | β-OH| H   | H   | α-OH| -   | -   | CH_3| H   | 8,24(25)|
| Thocerol             | β-OH| H   | H   | α-OH| -   | -   | -   | H   | 8, 14|
| Opuntisterol ***     | H   | H   | β-H  | β-OH| H   | -   | H   | β-CH_2CH_3| 9  |
| 24-methylenecholesterol| β-OH| H   | -   | -   | H   | H   | =CH_2| 5,24(28)|
| 24-dehydropollinasterol**| β-OH| H   | H   | H   | H   | -   | CH_3| H   | 24(25)|
| Fucosterol           | β-OH| H   | -   | -   | H   | H   | =CH-CH_3| 5,24(28)|
| β-Sitosterol         | β-OH| H   | -   | -   | H   | H   | β-CH_2CH_3| 5   |
* Both sterols, 5β-deoxiviperidone and opuntisterol present the cis configuration in rings A–B fusion. ** Cyclostenol and 24-dehydropollinasterol presents a β-cyclopropane moiety at C19–C9. *** Opuntisterol special feature is the presence of a 12α-OH. ^1 The specific position of the double bond of each compound is defined by the absence of the respective atom or atoms in carbon positions, and the position of the double bond designed in the column with the symbol Δ.
Table 2. List of species and the isolated sterols.

| Genus          | Specie                                                     | Compound                        | Isolated from | Reference |
|----------------|------------------------------------------------------------|---------------------------------|---------------|-----------|
| Lophocereus    | *L. schotti* (Engelm.) Britton & Rose                     | Lophenol                        | AP            | [42,43]   |
|                |                                                             | Schottenol                      |               |           |
|                |                                                             | 24-methylenecholophenol         |               |           |
|                |                                                             | Lathosterol                     |               |           |
|                |                                                             | 5α-campesten-7-ene-3β-ol        |               |           |
|                |                                                             | Spinasterol                     |               |           |
|                |                                                             | Locereol                        |               |           |
|                |                                                             | 5α-cholesta-7,14-dien-3β-ol    |               |           |
| Leptocereus    | *L. quadricostatus* (Bello) Britton & Rose                 | Viperidone                      | AP            | [57]      |
| Peniocereus    | *P. v. (F.A.C. Weber) Buxb.                                 | Viperidinone                    | R             | [44]      |
|                |                                                             | Viperidone                      |               |           |
|                |                                                             | Deoxiviperidone                 |               |           |
|                | *P. fosterianus* (Cutak) Lode                              | Peniocerol                      | R             | [47]      |
|                | *P. macdugalli* Cutak                                       | Lophenol                        | R             | [45]      |
|                |                                                             | Peniocerol                      |               |           |
|                |                                                             | Macdougallin                    |               |           |
|                |                                                             | 5β-desoxyviperidone             |               |           |
| Myrtillocactus | *M. geometrizans* (Mart. ex Pleif.) Console                | Peniocerol                      | R             | [26,33]   |
| Stenocereus    | *S. thurberi* (Engelm.) Buxb.                               | Cyclosterol                     | AP            | [51]      |
|                |                                                             | Stenocereol                     |               |           |
|                |                                                             | Thurberol                       |               |           |
| Opuntia *      | *O. dilleni* (Ker Gawl.) Haw.                              | Opuntisterol                    | AP            | [52]      |
|                |                                                             |                                |               |           |
|                | *O. phaeacantha* Engelm.                                    | 24-methylcholesterol            | P             | [58]      |
|                |                                                             |                                |               |           |
|                |                                                             | Pollinastanol                   | P             | [58]      |
|                |                                                             | 24-methylenecholesterol         |               |           |
|                |                                                             | Fucosterol                      |               |           |
| Carnegia       | *C. gigantea* (Engelm.) Britton & Rose                     | 24-methylcholesterol            | P             | [59,60]   |
| Pachycereus    | *P. pringlei* (Watson) Britton & Rose                      | 24-methylcholesterol            | P             | [58]      |

* Although *Opuntia* is not in the Pachycereae tribe (Opuntiaceae, Opuntioideae, Cactaceae), because of the diversity and special conformation in one of their sterols, we decide to include it in this review. ** O. versicolor is a synonymus of *Cylindropuntia versicolor* (Engelm. ex J.M.Coulter) F.M.Knuth. 1 AP: aerial parts; R: roots; P: pollen.

Table 3. Bioactivities of selected Cactaceae sterols.

| Compound     | Activity | Description                                                                 | Reference |
|--------------|----------|-----------------------------------------------------------------------------|-----------|
| Lophenol     | AD, CT   | AD = Agonist of PPARα and PPARγ, changing the expression of genes involved in fatty acid transport, binding and oxidation in mouse liver. | [61–63]   |
|              |          | CT = Moderate cytotoxic effect against the L5178Y-R cell line.                |           |
| Schottenol   | MM       | LXR agonists modulating gene expression of LXRα and LXRβ live nuclear receptors. | [64]      |
| Lathosterol  | AM and CT | AM = Anti-mutagenic activity against MNNG and NQO. CT = Moderate cytotoxic effect was shown by the compound against MES-SA, MCF-7, and HK-2 cell lines. | [65,66]   |
| Spinasterol  | AI, AN, CR, CT and MM | AI = Inhibitory activity against COX-1 and COX-2 enzymes and antagonistic effect on the TRPV1 receptor. AN = Inhibitory activity against Helicobacter pylori CR = Antidepressant-like effect due to the regulation of the TRPV1 receptor. CT = Moderate cytotoxic effect against HeLa, MCF-7, MDA-MB-231, and SKOV-3 cell lines by inducing G0/G1 arrest stimulating the expression of p53 and Bax genes and lower expression of cyclind1/6 genes. MM = LXR agonists modulating gene expression of LXRα and LXRβ live nuclear receptors. | [64,67–73] |
2.2. Triterpenes from Mexican Columnar Cactaceae

One of the best-studied chemical groups of cacti is the triterpenes since they constitute, in many cases, the most abundant compounds found in Cactaceae. The triterpenes display a wide diversity of structural features, with characteristic oxidation patterns, and a particular distribution in the species, reasons why they are used for chemotaxonomic studies [94]. In addition to the above, many of the triterpenes isolated from these plants present biological activities ranging from their ecological effects [40], as well as effects on models of inflammation and anti-nociception [13,26,95], which makes their research attractive. Information of structures with an emphasis on the origin of the skeleton of each compound isolated from Cactaceae is presented in Tables 4–6. In Table 4, pentacyclic triterpenes cycloartenol, 24-methylenecycloartenol and 25(27)-dehydrolanost-8-enol are described, while lupane- and oleanane-type triterpenes are described in Tables 5 and 6 respectively.
Table 4. Cycloartane terpenes isolated from Cactaceae.

| Triterpene Name | R_1 | R_2 | R_3 | R_4 | R_5 | R_6 | R_7 | R_8 | Δ |
|-----------------|-----|-----|-----|-----|-----|-----|-----|-----|---|
| Cycloartenol    | H   | H   | CH_3|     |     |     |     |     | 24(25) |
| 24-methylene cycloartenol | H | =CH_2 | CH_3 |     |     |     |     |     | 24(31) |
| 25(27)-dehydrolanos-8-enol * | - | H | =CH_2 | 8(9), 25(27) |

* The cyclopropane moiety is absent instead of a C-19 β-methyl group, and the presence of a double bond between 8(9).

Table 5. Lupane-type triterpenes from Mexican Columnar Cactaceae.

| Triterpene Name | R_1 | R_2 | R_3 | R_4 | R_5 | R_6 | R_7 | R_8 | Δ |
|-----------------|-----|-----|-----|-----|-----|-----|-----|-----|---|
| Lupeol          | β-OH| H   | H   | H   | H   | =CH_2|    | CH_3| 20(30) |
| Betulin         | β-OH| H   | H   | H   | H   | =CH_2|    | CH_2OH| 20(30) |
| Betulinic acid  | β-OH| H   | H   | H   | H   | =CH_2|    | COOH| 20(30) |
| Stellatogenin * | β-OH| H   | H   | H   | H   | β-O-| CH_3| OH  | CO- | - |
| Lupenone        | =O  | H   | H   | H   | H   | =CH_2|    | CH_3| 20(30) |
| Thurberogenin * | β-OH| H   | H   | H   | H   | β-O-| =CH_2|    | CO- | 20(30) |
| 21-ketobetulinic acid | β-OH| H   | H   | H   | =O  | CH_2 |    | COOH| 20(30) |
| 16β-hydroxybetulinic acid | β-OH| H   | OH  | H   | H   | =CH_2|    | COOH| 20(30) |
| 22β-hydroxystellatogenin * | β-OH| H   | OH  | OH  | β-O-| CH_3| OH  | CO- | - |
| 16β-hydroxystellatogenin * | β-OH| H   | OH  | H   | H   | β-O-| CH_3| OH  | CO- | - |
| Calenduladiol   | β-OH| OH  | H   | H   | H   | =CH_2|    | CH_3| 20(30) |
| Betulinic aldehyde | β-OH| H   | H   | H   | H   | =CH_2|    | COH | 20(30) |

* Stellatogenin, Thurberogenin, 22β-hydroxystellatogenin, and 16β-hydroxystellatogenin display a β-γ-lactone between C-28 and C-21.
Table 6. Oleanane-type triterpenes isolated from Mexican columnar Cactaceae.

| Triterpene Name           | R₁ | R₂ | R₃ | R₄ | R₅   | R₆   | R₇   |
|---------------------------|----|----|----|----|------|------|------|
| β-amyrin                  | H  | H  | H  | H  | CH₃  | CH₃  | CH₃  |
| Oleanolic acid            | H  | H  | H  | H  | -    | CH₃  | CH₃  |
| Oleanolic aldehyde        | H  | H  | H  | H  | COH  | CH₃  | CH₃  |
| Erythrodiol               | H  | H  | H  | H  | CH₂OH| CH₃  | CH₃  |
| Maniladiol                | H  | OH | H  | H  | -    | CH₃  | CH₃  |
| Longispinogenin           | H  | OH | H  | H  | CH₂OH| CH₃  | CH₃  |
| Dumortierigenin *         | -  | H  | H  | OH | CO-  | CH₃  | CH₃  |
| Cochalic acid             | H  | OH | H  | H  | COOH | CH₃  | CH₃  |
| Myrtillogenic acid        | H  | OH | H  | H  | CH₂OH| COOH | CH₃  |
| Chichipegenin             | H  | OH | H  | H  | CH₂OH| CH₃  | CH₃  |
| Olean-12-ene-3β,16β,22α-triol | H  | OH | H  | OH | -    | CH₃  | CH₃  |
| Alamosogenin              | H  | OH | H  | H  | -    | COH  | CH₃  | CH₂OH|
| Gummosogenin              | H  | OH | H  | H  | COH  | CH₃  | CH₃  |
| Machaerogenin *           | H  | H  | β-O-| H  | CO-  | CH₃  | CH₂OH|
| Machaeric acid            | H  | H  | =O | H  | COOH | CH₃  | CH₃  |
| Queretaroic acid          | H  | H  | H  | H  | COOH | CH₃  | CH₂OH|
| Treleasegenic acid        | H  | H  | β-OH| H  | COOH | CH₃  | CH₂OH|
| Machaerinic acid          | H  | H  | β-OH| H  | COOH | CH₃  | CH₃  |

* Dumortierigenin and machaerogenin possess a lactone moiety at C-15, C-28, and C-21, C-28, respectively.

Although only Mexican columnar cacti were considered to the construction of the present review, a special mention is necessary to describe the triterpene content of *Trichocereus pachanoi*, a cactus plant from South America, which is an important source of some compounds named pachanols A-D (Table 7). These compounds possess a particular type of triterpene skeleton, called pachanane, characterized by the presence of five six-membered rings, and the position of the 27α-CH₃ attached to C-15 [96,97]. Additionally, for the construction of the present review, only the aglycones of triterpenes were considered. In the first reports regarding the isolation and elucidation of those compounds, the routine procedure began with the hydrolysis of the organic extracts, isolating only the aglycones. The pattern of glycosylation of the natural compounds, and the number and relative positions of sugar moieties should be discussed in another review. Specific information about the content of triterpenes by species, as well as their biological activities, are described in Tables 8 and 9, respectively.
Molecules by species, as well as their biological activities, are described in Tables 8 and 9, respectively. In the first reports regarding the isolation and elucidation of those compounds, the pattern of glycosylation of the natural compounds, and the number and relative positions of sugar residues were considered. Additionally, for the construction of the present review, only the aglycones of triterpenes were reviewed, a special mention is necessary to describe the triterpene content of some species.

Table 7. Structures of some additional triterpenes isolated from Cactaceae.

| Triterpene Name | R 1 R 2 R 3 R 4 R 5 R 6 R 7 |
|-----------------|---------------------|---------------------|
| Oleanolic acid  | H H H H COOH CH 3 CH 3 |
| Betulinic acid  | β-OH H COOH CH 3 CH 2OH |
| -O- H CO- CH 3 CH 2OH |

Table 8. Triterpene content by species in Mexican columnar cacti.

| Genus             | Specie                                | Compound                                         | Isolated from | Reference |
|-------------------|---------------------------------------|--------------------------------------------------|---------------|-----------|
| Carnegia          | C. gigante (Engelm.) Britton & Rose   | Cycloartenol, 24-methyleneacycloartenol 25(27)-dehydrolanost-8-enol Lupeol | P             | [60]      |
| Escontria         | E. chiotilla (Weber) Rose             | Betulin, Betulinic acid, Maniladiol, Erythrodiol Longispinogenin | AP            | [98]      |
| Escontria         | I. dumortieri (Scheidweiler) Backerberg | Dumortierigenin Pachanol D                       | AP            | [99–101]  |
| Lophocereus       | L. schotti (Engelm.) Britton & Rose   | Lupeol                                           | AP            | [42,43]   |
| Myrtillocactus     | M. cochal (Ocutt) Britton & Rose      | Longispinogenin, Cochalic acid, Myrtilligenic acid Chichipegenin | AP            |           |
| Myrtillocactus     | M. geometriczis (Mart. ex Pfeiff.)    | Lonispinogenin, Cochalic acid, Myrtilligenic acid Chichipegenin | AP            | [102–106] |
| Myrtillocactus     | M. echinacidus Britton & Rose         | Oleanic acid, Maniladiol, Cochalic acid, Myrtilligenic acid Chichipegenin | AP            |           |
| Pachycereus       | P. pringlei (Watson) Britton & Rose   | Lupeol                                           | P             | [58]      |
| Pachycereus       | P. weveri (Coulter) Britton & Rose    | Cochalic acid                                    | AP            | [95]      |
| Genus          | Specie                        | Compound                                  | Isolated from | Reference |
|---------------|-------------------------------|-------------------------------------------|---------------|-----------|
| *Peniocereus* | *P. fosterianus* (Cutak) Lodé | Chichipegenin                              | R             | [47]      |
|               | *P. madougallii* Cutak         | β-amyrin                                  | R             | [45]      |
| *Polaskia*    | *P. chende* Gibson & Horak     | Oleaneolic acid                           | AP            | [107]     |
|               |                               | Erythrodiol                               |               |           |
|               |                               | Oleaneolic aldehyde                       |               |           |
| *P. chichipe* (Gosselin) Backeberg |                   | Oleaneolic acid                           | AP            | [103,108] |
|               |                               | Longispinogenin                           |               |           |
|               |                               | Chichipegenin                             |               |           |
|               |                               | Olean-12-ene-3β,16β,22α-triol             |               |           |
| *Stenocereus* | *S. alamosensis* (Coulter) Gibson & Horak (Rathbunia alamosensis) | Alamosogenin                               | AP            | [109,110] |
|               | *S. aragonii* (Weber) Buxbaum  | β-amyrin                                  | AP            | [111]     |
|               | *S. benekei* (Ehrenberg) Buxbaum | Lupeol                                    | AP            | [112–114] |
|               |                               | Oleaneolic acid                           |               |           |
|               |                               | β-amyrin                                  |               |           |
|               |                               | Lupeone                                   |               |           |
|               |                               | Queeretaronic acid                        |               |           |
|               | *S. echilamii* (Britton & Rose) Buxbaum | Oleaneolic acid                           | AP            | [115]     |
|               |                               | Erythrodiol                               |               |           |
|               |                               | Longispinogenin                           |               |           |
|               | *S. euruca* (Brandegee) Gibson & Horak | Oleaneolic acid                           | AP            | [111,116–118] |
|               |                               | Betulinic acid                            |               |           |
|               |                               | Stellatogenin                             |               |           |
|               |                               | Turboegenin                               |               |           |
|               |                               | Machaerogenin                             |               |           |
|               |                               | Machaeric acid                            |               |           |
|               |                               | 21-ketobetulinic acid                     |               |           |
|               |                               | 16β-hydroxybetulinic acid                 |               |           |
|               |                               | 22β-hydroxistellatogenin                 |               |           |
|               |                               | Morolic acid                              |               |           |
|               |                               | Queeretaronic acid                        |               |           |
|               |                               | 27-desoxyfillirigenin                     |               |           |
|               |                               | Trelesagenic acid                         |               |           |
|               | *S. fimbriatus* (Lamark) Lourteig | Oleaneolic acid                           | AP            | [119]     |
|               |                               | Betulinic acid                            |               |           |
|               |                               | Erythrodiol                               |               |           |
|               | *S. griseus* (Haworth) Buxbaum | Oleaneolic acid                           | AP            | [98]      |
|               |                               | Betulinic acid                            |               |           |
|               |                               | Erythrodiol                               |               |           |
|               | *S. gummosus* (Brandegee) Gibson & Horak | Gummosogenin                               | AP            | [109,111,120] |
|               |                               | Machaeronic acid                          |               |           |
|               |                               | Machenteric acid                          |               |           |
|               | *S. pruinosa* (Otto) Buxbaum   | Oleaneolic acid                           | AP            | [32,95,111] |
|               |                               | Erythrodiol                               |               |           |
|               |                               | Longispinogenin                           |               |           |
|               |                               | 3β-hydrox-11α,12α-epoxyolean-28,13β-olide |               |           |
|               | *S. queretarocensis* (Weber) Buxbaum | Oleaneolic acid                           | AP            | [114]     |
|               |                               | Queretaronic acid                         |               |           |
|               | *S. quvedonis* (Ortega) Buxbaum | Oleaneolic acid                           | AP            | [98]      |
|               |                               | Betulinic acid                            |               |           |
|               |                               | Longispinogenin                           |               |           |
Table 8. Cont.

| Genus                        | Specie                          | Compound                          | Isolated from | Reference         |
|------------------------------|---------------------------------|-----------------------------------|---------------|------------------|
| S. stellatus (Pfeiffer) Riccobono |                                | Oleanolic acid                   | AP            | [98,116,121]     |
|                              |                                 | Betulinic acid                   |               |                  |
|                              |                                 | Stellatogenin                    |               |                  |
|                              |                                 | Turberogenin                     |               |                  |
|                              |                                 | Machaerogenin                    |               |                  |
|                              |                                 | Queretarolic acid                |               |                  |
|                              |                                 | 16β-hydroxistellatogenin         |               |                  |
| S. thurberi (Engelmann) Buxbaum |                                | Lupeol                            | AP            | [50,111,113,114, 122–125] |
|                              |                                 | Oleanolic acid                   |               |                  |
|                              |                                 | Betulin                          |               |                  |
|                              |                                 | Maniladiol                       |               |                  |
|                              |                                 | Erithrodiol                      |               |                  |
|                              |                                 | Longispinogeninβ-amyrin          |               |                  |
|                              |                                 | Oleanolic aldehyde               |               |                  |
|                              |                                 | Betulinic aldehyde               |               |                  |
|                              |                                 | Turberogenin                     |               |                  |
|                              |                                 | Queretarolic acid                |               |                  |
|                              |                                 | Calenduladiol                    |               |                  |
| S. treleasei (Britton & Rose) Backeberg |                    | Oleanolic acid                   | AP            | [111,126]        |
|                              |                                 | Longispinogenin Treleasegenic acid |             |                  |

1 AP: aerial parts; R: roots; P: pollen.

It should be noted that of the following genera listed in Mexico: Acanthocereus, Bergerocactus, Cephalocereus, Echinocereus, and Neobuxbaumia, have not been revised for their sterol nor triterpenoid content, so the chemistry of those species will have to be explored, to generate knowledge about the kind of natural products presents in each genus and their bioactivities.

From this review, it is evident that sterols and triterpenes from Cactaceae exhibit a myriad of bioactivities, mainly anti-inflammatory, metabolic regulatory, and CNS protective activities standing out. The lack of information about the molecular mechanism displayed of sterols and terpenoids prompt us to perform an in silico bioprospection in some molecular targets. Among the targets that have been commonly assayed against each biological process, only COX-1, COX-2, PTP1B, PPAR-α, PPAR-γ, acetylcholinesterase (AChE), LXR-α and LXR-β were selected for the in silico study to explore the theoretical molecular affinity of sterols and triterpenoids against each target. Then, the information presented in the results section, do not represent a validation of the molecular mechanism in the case of good molecular coupling between the ligands and the targets, nor do they represent the verification of the null activity of the ligands in the molecular targets. The data from molecular docking only represents a guide to future research designed to discover the specific molecular mechanisms that each molecule presents in biological models.
Table 9. Most representative biological activities of triterpenes isolated from Mexican columnar Cactaceae.

| Compound      | Activity | Description                                                                                     | Reference               |
|---------------|----------|-------------------------------------------------------------------------------------------------|-------------------------|
| Lupeol        | AD, AO, AN, AI, CT, RN, HP | AD = moderate inhibition of α-Glucosidase and α-Amylase and selective allosteric inhibition of PTP1B.  
AO = decreases ROS and LPO generation.  
AN = growth inhibitory activity against several bacteria as *M. smegmatis*, *M. aurum*, and *E. faecalis*, the parasites *P. falciparum* and *L. donovani*, and the virus HSV-1 and the reverse transcriptase of HIV-1.  
AI = inhibition of IL-1β and NF-κB produced an inhibitory effect on the carrageenan-induced edema assay.  
CT = inhibits cell growth by several mechanisms: inhibition of the phosphorylation of ECFR, Topoisomerase and WNT/β-catenin regulation, induction of cell cycle arrest and mitochondria-mediated apoptosis.  
IN = moderate larvicidal activity against *A. aegypti*.  
RN = strong protective effect of cisplatin-induced nephrotoxicity by upregulating the phosphorylation of MAPKs.  
HP = alleviate liver injury by GalN/LPS through suppression of the IRAK-mediated TLR4 signal pathway. | [13,87,127–144] |
| Oleanolic acid| AD, AN, AI, CR, CT, IM, HP | AD = strong regulation of PPARγ and miR-98-5p/PGC-1β axis causing a hypolipidemic effect.  
AN = growth inhibitory activity against several bacteria as *S. aureus*, *M. smegmatis*, *E. faecalis*, *L. monocytogenes*, *B. cereus*, and *P. berghei* and the parasite *Leishmania* spp. and inhibitory activity against the reverse transcriptase of HIV-1.  
AI = inhibition of Lipoxygenase and phospholipase A2 activity.  
CR = modulation of the BDNF-ERK1/2-CREB pathway through TrkB activation.  
CT = inhibition of cervical (HeLa), ovary (SK-OV-3), breast (MCF-7), colon (DLD-1) cancer cell lines proliferation.  
IM = reduce the synthesis of pro-inflammatory mediators, auto-antibody production, suppression of endogenous leptin production, and inhibits migration of leukocytes in the CNS.  
OT = increase bone mineral density. Its effect is associated with effects on Ca and vitamin D metabolism.  
HP = showed moderate activity towards in vitro immunological liver injury and low hepatotoxicity. | [13,136,145–155] |
| Compound      | Activity | Description                                                                 | Reference                                      |
|---------------|----------|-----------------------------------------------------------------------------|-----------------------------------------------|
| Betulin       | AD, AN, CR, AI, CT | \(AD =\) selective allosteric inhibition of PTP1B, noncompetitive inhibitor of \(\alpha\)-amylase and inhibition of \(\alpha\)-glucosidase. \(AN =\) growth inhibitory activity against several bacteria as M. smegmatis and M. aurum, the parasite P. falciparum, and the virus HSV-1 and the reverse transcriptase of HIV-1. \(CR =\) protective effect on cognition inhibiting the NF-\(\kappa\)B pathway, by regulation of the GABA\(\alpha\) receptor, and by moderate cholinesterase inhibition. It also reduced 6-hydroxydopamine-induced dopaminergic neuron degeneration. \(AI =\) decreases NO production, iNOS expression in vitro, and NF-\(\kappa\)B activity. It also decreases the levels of MPO, IL-1\(\beta\), and TNF-\(\alpha\) in liver tissue. \(CT =\) strong inhibitory effect on the proliferation of several cell lines triggering apoptosis by mitochondrial pathway and NOXA induction. | [87,127,133,137–139,143,156–166] |
| Betulinic acid| AD, AN, IN, AI, CT, RN, HP | \(AD =\) selective allosteric inhibition of PTP1B, noncompetitive inhibitor of \(\alpha\)-amylase and inhibition of \(\alpha\)-glucosidase. It also stimulates insulin secretion by the mediation of potassium and chloride channels. \(AN =\) growth inhibitory activity against several bacteria as M. smegmatis, M. aurum, S. aureus, B subtilis, E. faecalis, and B. cereus, the parasites P. falciparum and T. cruzi, and the virus HSV-1 and the reverse transcriptase inhibitor of HIV-1. \(IN =\) inhibitor of tyrosinase and could be used as an insecticidal agent. \(CR =\) neuroprotective effect on cognition by moderate cholinesterase inhibition. It also improves cAMP, cGMP and BDNF levels. \(AI =\) decreases NO production and iNOS and IL-6 expression in vitro. \(CT =\) inhibition of cervical (HeLa), ovary (SK-OV-3), breast (MCF-7), colon (DLD-1) cancer cell lines proliferation. It has also shown to induce apoptosis by DNA damage, G2/M cell cycle arrest, and Bcl-2/Bax signaling regulation. \(RN =\) strong protective effect of cisplatin-induced nephrotoxicity by upregulating the phosphorylation of MAPKs. \(HP =\) inhibition of liver oxidative stress in the iron/ascorbate system and showed hepatoprotective effects against D-GalN/TNF-\(\alpha\)-induced cell dead. | [13,19,87,127,133,135–138,143,147,160,161,163,167–171] |
| Maniladiol    | AN, AI   | \(AN =\) growth inhibitory activity against M. tuberculosis and the reverse transcriptase inhibition of HIV-1. \(AI =\) decreases the production of pro-inflammatory cytokines such as TNF-\(\alpha\), IL-1, and IL-6 and inhibits NO production. | [164,172,173] |
### Table 9. Cont.

| Compound       | Activity | Description                                                                                           | Reference                  |
|----------------|----------|-------------------------------------------------------------------------------------------------------|----------------------------|
| Erythrodiol    | AN, CT, HT, IM, HP | AN = growth inhibitory activity against several bacteria as B. subtilis, E. coli, and C. albicans and the reverse transcriptase inhibitor of HIV-1. Inhibitor of tyrosinase and could be used as an insecticidal agent AI = edema inhibition in the TPA-induced inflammation assay. CT = potent anti-proliferative effect inducing apoptosis, cell cycle arrest, and ROS generation. HT = reduce cardiac remodeling by inhibiting angiotensin II-induced proliferation via PPAR-γ. IM = reduce the synthesis of pro-inflammatory mediators, auto-antibody production, suppression of endogenous leptin production, and inhibits migration of leukocytes in the CNS. HP = high protection of human hepatoma cells against CCl4-induced injury with ALT level decreased. | [13,153,164,167,174–179] |
| Longispinogenin| AN, AI, CT | AN = growth inhibitory activity against M. tuberculosis. AI = edema inhibition in the TPA-induced inflammation assay. CT = inhibition of cervical (HeLa) cancer cell line proliferation. | [173,180,181] |
| Pachanol D     | AC       | AC = strong inhibitory effect on the acetic acid-induced writhing test.                                 | [95]                       |
| Cochalic acid  | CT       | CT = potent inhibition of cervical (HeLa) cancer cell line proliferation.                               | [180]                      |
| Chichipegenin  | AI, CT   | AI = edema inhibition in the TPA-induced inflammation assay. CT = inhibition of breast and colon carcinoma MCF-7 and HCT-15 cell lines proliferation. | [26]                       |
| Stellatogenin  | AC       | AC = strong inhibitory effect on the acetic acid-induced writhing test.                                 | [95]                       |
| β-amyrin       | AD, AN, AI, CR, CT, HP | AD = moderate inhibition of α-Glucosidase and α-Amylase. AN = growth inhibitory activity against several bacteria as B. subtilis, S. aureus, and C. albicans, the parasite T. cruzi, and antiviral inhibitory activity against the reverse transcriptase of HIV-1 and IAV. AI = decreases the production of pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6 and inhibits NO production CR = interaction with the GABAA receptor and produce sedative and hypnotic, increasing noradrenergic activity. It also showed neuroprotective activity reducing α-synuclein aggregation upregulating LGG-1 expression. CT = inhibition of proliferation in the cervical (HeLa), ovary (SK-OV-3), breast (MCF-7), colon (DLD-1), and other cancer cell lines. HP = hepatoprotective effect against acetaminophen-induced hepatotoxicity. | [143,147,164,171,172,182–186] |
Table 9. Cont.

| Compound               | Activity | Description                                                                                                                                                                                                                                                                                                                                 | Reference                          |
|------------------------|----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|
| Oleanolic aldehyde     | AD, AN   | AD = dose-dependent enhancement of insulin secretion by INS-1 cells. AN = growth inhibitory activity against S. mutans and P. gingivalis.                                                                                                                                                                                                         | [187,188]                          |
| Gummosogenin           | AC, CT   | AC = strong inhibitory effect on the acetic acid-induced writhing test. CT = inhibition of cervical (HeLa) cancer cell line proliferation.                                                                                                                                                                                                 | [95,180]                           |
| Lupeone                | AN, AD, AI, RN | AN = reverse transcriptase inhibitor of HIV-1. AD = moderate inhibition of α-Glucosidase and selective allosteric inhibition of PTP1B. AI = decreases the production of pro-inflammatory cytokines such as IL-12 and IL-6. RN = strong protective effect of cisplatin-induced nephrotoxicity. | [128,133,135,164,183,189]          |
| Turberogenin           | AC, CT   | AC = strong inhibitory effect on the acetic acid-induced writhing test. CT = low inhibition of cervical (HeLa) cancer cell line proliferation.                                                                                                                                                                                                   | [95,180]                           |
| Morolic acid           | AD, AI   | AD = induced a significant reduction of blood glucose levels by inhibition of 11β-HSD1. AI = inhibition of the leukocyte dermal infiltration and inhibition of key inflammatory enzymes as PLA2 and 5-LOX.                                                                                                                                               | [190,191]                          |
| Queretaroic acid       | CT       | CT = inhibition of cervical (HeLa) cancer cell line proliferation.                                                                                                                                                                                                                                                                           | [180]                              |
| Calenduladiol          | CR, CT   | CR = inhibition of acetylcholinesterase and butyrylcholinesterase in vitro. CT = inhibition of leukemia (NB4 and K562) cancer cell lines proliferation.                                                                                                                                                                                            | [192,193]                          |
| Cycloartenol           | AD, AN, and CT | AD = Decrease glucose intestinal absorption that could be associated with SGLT1 regulation as well as α-glucosidase inhibition. Downregulation of fatty acid synthesis and interferes with the absorption of cholesterol. AN = Inhibitory effect against bacteria E. coli and P. aeruginosa and low inhibition of the parasite P. falciparum. CT = Weak cytotoxic activity against HL60 cell line and p38MAPK-mediated apoptosis in the U87 cell line. | [91,194–200]                      |
| Betulinic aldehyde     | AN, CT   | AN = growth inhibitory activity against bacteria P. smartii, E. faecalis, S. aureus, and E. coli and antiviral activity against Influenza virus (KBNP-0028) and the reverse transcriptase of HIV-1. CT = inhibition of cervical (HeLa), ovary (SK-OV-3), breast (MCF-7), colon (HCT-116) and melanoma (SK-MEL-5) cancer cell lines proliferation. | [88,135,164,201]                  |

AD = Antidiabetic, AM = Antimitogenic, AO = Antioxidant, AN = Anti-infective, CR = CNS Regulation, AI = Anti-inflammatory, CT = Citotoxic, MM = Modulation of Cholesterol metabolism, HT = Hypertension, IN = insecticidal, IM = Immune modulation, RN = renoprotective, AC = Anti nociceptive, HP = Hepatoprotective.
3. In Silico Bioprospection of Bioactive Compounds

All sterols and triterpenes described in this review were constructed as ligands using Chem Sketch from Advanced Chemistry Development [202] and exported to Spartan '10 as mol files. The geometry of all molecules was optimized using MMFF/HF 6-31 G*, and final structures were included in an SDF file. The docking studies were carried out using Molegro Virtual Docker v.6.0.1 [203] based on the crystal structures of some bio targets that have been proposed for the biological activities of Cactaceae extracts or purified compounds derived from them: (a) anti-inflammatory activity—cyclooxygenase-1 (COX-1, PDB code: 1Q4G [204]) and cyclooxygenase-2 (COX-2, PDB code: 3NT1 [205]); (b) metabolic activity—PPAR-α (PDB code: 2ZNN [206]), PPAR-γ (PDB code: 5Y2T [82]) and PTP1B (PDB code: 1C83 [207]); (c) neuroprotective activity—LXR-α (PDB code: 3IPU [208]) LXR-β (PDB code: 1P8D [209]) and acetylcholinesterase (PDB code: 4EY6 [210]). All 3D protein structures were retrieved from the Protein Data Bank [211]. Docking studies were carried out using a previously reported methodology [17,18]. Briefly, all the solvent molecules and cocrystallized ligands were removed from the downloaded structures. The active sites of each enzyme or the ligand-binding domain (LBD) were chosen as the searching sites centered on the cocrystallized ligand, except for PTP1B where the docking area was centered on allosteric site B as previously described [212], and delimited with a 15 Å radius sphere. Standard software procedure was used using the MolOptimizer algorithm. The assignments of charges on each protein were based on standard templates; no other charges were necessary to be set. The Root Mean Square Deviation (RMSD) threshold for multiple cluster poses was set to <2.00 Å. The docking algorithm was set to 5000 maximum iterations with a simplex evolution population size of 50 and 25 runs for each ligand. After docking, MolDock Score was calculated as the theoretical binding affinity, lower values of the score are related to better binding. For each ligand, the pose with the lowest score was selected for further analysis. Cocrystralized ligands were also docked to their respective receptors to verify the efficacy of this procedure, the top-ranking score was recorded, and the RMSD of that pose from the PDB original structure was computed. In all the cases, the RMSD values were lower than 2.5 Å.

3.1. Antiinflammatory Molecular Targets

Tables 10 and 11 show the results obtained for the docking study carried on COX-1 and COX-2. In both tables, the top-10 compounds with higher affinity are displayed, but a complete table of all the results is included as part of Supplementary information. Table 10 shows the data from sterol derivatives, and Table 11 shows the data from triterpene derivatives that had lower MolDock scores.

| Ligand                      | COX-1 | COX-2 |
|-----------------------------|-------|-------|
| Thurberol                   | −132.1| −144.1|
| Locereol                    | −133.1| −141.1|
| Fucosterol                  | −130.6| −141.7|
| 5α-cholesta-8,14-dien-3 β-ol| −130.4| −141.5|
| Spinasterol                 | −130.6| −138.5|
| 24-methylenecholesterol     | −127.3| −139.9|
| β-sitosterol                | −124.3| −136.9|
| Peniocerol                  | −124.3| −134.1|
| 24-Methyleneolphenol        | −127.3| −130.7|
| Lophenol                    | −123.7| −131.2|
Table 11. Top-10 ranked triterpene compounds in the COX-1 and COX-2 docking study.

| Ligand               | COX-1  | COX-2  |
|----------------------|--------|--------|
| Lupeone              | −104.0 | −97.1  |
| Thurberogenin        | −92.3  | −93.6  |
| Lupeol               | −97.7  | −87.3  |
| Betulinic aldehyde   | −94.9  | −88.6  |
| 16β-hydroxybetulinic acid | −82.9 | −95.1  |
| Calenduladiol        | −92.8  | −85.1  |
| 16β-hydroxystellatogenin | −93.8 | −83.0  |
| 22β-hydroxystellatogenin | −94.0 | −79.3  |
| 21-ketobetulinic acid | −81.6  | −87.1  |
| Machaerogenin        | −87.0  | −79.4  |

The analysis of the binding mode of the sterols with higher affinity reveals some structural features that improve ligand binding. In the first instance, among sterols, the oxidation pattern at C3, C6, and C7 appears to be relevant for the interaction with residues Leu 384, Tyr 385, Trp 387 and Met 522 in both COX enzymes. Notably, a hydrogen bond interaction to Met 522 is constant in all 6-OH substituted derivatives like peniocerol. Interestingly, a small hydrophobic pocket is located between these residues (in yellow in Figure 1a) and is occupied by the methyl group in position 4 of locereol, slightly increasing theoretical affinity. Other critical structural factors for enzyme binding are the unsaturations in rings B and D. The unsaturation in ring B seems to be necessary for optimal interaction of substituents in position 6 and potentially 7 with Met 522. Whereas, unsaturation in ring D is needed for accommodation of the aliphatic chain in a hydrophobic pocket formed by Val 116, Val 349, and Tyr 355 (for example, thurberol has better theoretical affinity than peniocerol). Additional substituents in the aliphatic chain improve enzyme binding, as compounds with additional methylene or ethylene groups have slightly more affinity than their analogs than do not bear these groups. (i.e., 24-methylenelophenol has more affinity than lophenol).

Figure 1. Docking poses of (a) peniocerol, a sterol, and (b) 22-hydroxystellatogenine, a triterpene with COX-1.

On the other hand, the analysis of the interaction of triterpenes shows that they could similarly bind to COX-1 and COX-2 as sterols. Interestingly, the first 9 compounds with better theoretical affinities belong to the lupane skeleton. In general, the ring A of all compounds interacts with Leu 384, Tyr 385, Trp 387, and Met 522 in the same fashion as sterols (in yellow in Figure 1a,b). The 4,4-dimethyl group in ring A occupies the small hydrophobic group ubicated between these residues. However, it seems to be too large to fit on this site, leading to a lower theoretical affinity. The most oxidized rings (usually rings D and E) in 22β-hydroxystellatogenin interact with the same residues that the side chain of sterol does. The interaction is through hydrogen bonding to residues Ser 353, Tyr 349, and Try 355 of COX-1 or Tyr 348 and Try 385 in COX-2 (in green in Figure 1b). Although hydroxylation in rings D and
E improves theoretical affinity, the number of hydroxy or keto groups is not correlated with theoretical affinity, suggesting that hydrophobic interaction is more critical of ligand binding.

COX-2 is one of the preferred molecular targets of NSAIDs [17]. The literature is full of research papers about the design, synthesis or isolation together with in silico, in vivo and ex vivo studies to the development of new anti-inflammatory drugs. Although the clinical importance of selectivity against COX-2 vs COX-1 was earlier discussed [213], many groups focus their research programs to discover selective COX-2 drugs. The top ten sterols and triterpenes with the highest MolDock scores cannot be considered selective against any COX enzyme if we consider the MolDock Score as a measure of the theoretical affinity of the compound. From the top 10 ligands with better MolDock score, fucosterol, spinasterol, 24-methylenecholesterol, β-sitosterol, and peniocerol in the sterols group and lupeone and lupeol of triterpene group are well known anti-inflammatory molecules, with mechanisms including COX-2 inhibitory activities. It is possible to focus the next survey to isolate and determine the anti-inflammatory activities and their molecular mechanisms of compounds like thurberol, locereol or lophenol, together with thurberogenine, betulinic aldehyde, 16β- and 22β-hydroxystellatogenin or machaerogenine which anti-inflammatory activities or their inhibitory activities against COX enzymes are still unknown.

3.2. Antidiabetic and Metabolic Activities

Several studies have positioned both sterols and triterpenes as hits for the development of drugs for the treatment of metabolic diseases, including diabetes mellitus type 2 [214,215]. Table 12 shows the top 10 sterol ligands, which exhibited the highest theoretical affinity for PTP1B, PPAR-α, and PPAR-γ. Ligands showed in Table 12 exhibited the highest affinity for all the three bio targets and could be considered as potential multitarget molecules for the management of complex metabolic diseases like metabolic syndrome. However, other sterols not shown in this Table exhibited a good affinity for two of the targets like lophenol, locereol, and 5a-cholesta-8,14-dien-3β-ol, which had good theoretical affinity against PPAR-α and PPAR-γ, some synthetic ligands have been developed as PPARα/γ dual agonists to achieve a broad spectrum of metabolic effects with actions against dyslipidemia and hyperglycemia. Deoxyviperidone, 5β-deoxyviperidone, and lathosterol had good scores against PTP1B and PPAR-γ, which could be a good combination of bio targets for the treatment of diabetes mellitus type 2. Well known antidiabetic sterols like fucosterol, lophenol and β-sitosterol have demonstrated in several studies their potential to regulate at different levels both PTP1B and/or PPAR proteins [61,216,217]. Although lophenol does not belong to the top 10 molecules with higher theoretical affinity, the Moldock score values for both PPAR-α and PPAR-γ proteins were -130.9 and -129.7, suggesting that the methodology used correctly predicts the biological activity. Special attention should be taken with sterols like schottenol, spinasterol, thurberol, cyclostenol, 24-methylenecholesterol, peniocerol, among other sterols that were considered as good candidates to future antidiabetic research.

Table 12. Top-10 ranked sterol derivatives in the PTP1B, PPAR-α and PPAR-γ docking study.

| LIGAND              | PTP1B | PPAR-α | PPAR-γ |
|---------------------|-------|--------|--------|
| Fucosterol          | -141.7| -135.7 | -138.9 |
| β-sitosterol        | -131.6| -141.0 | -142.4 |
| Schottenol          | -132.9| -139.0 | -138.9 |
| Spinasterol         | -133.1| -140.8 | -131.2 |
| Thurberol           | -135.4| -129.3 | -140.4 |
| Cyclostenol         | -140.4| -137.3 | -126.4 |
| 24-Methylenecholesterol | -132.7| -133.5 | -136.0 |
| Peniocerol          | -132.4| -127.9 | -140.5 |
| Opuntisterol        | -126.0| -141.5 | -132.7 |
| Steneocerol         | -133.0| -136.2 | -126.2 |
In the case of triterpenes (Table 13), the results strongly suggest that the hydroxylation pattern in rings D and E seems important for enzyme binding. Notably, it is remarkable that many of the triterpene derivatives bear a 17-carboxylic group.

Table 13. Top-10 ranked triterpene derivatives in the PTP1B, PPAR-α and PPAR-γ docking study.

| LIGAND                        | PTP1B  | PPAR-α  | PPAR-γ  |
|-------------------------------|--------|---------|---------|
| 16β-hydroxystellatogenin      | −98.5  | −128.7  | −119.5  |
| Thurberogenin                 | −104.8 | −123.4  | −114.8  |
| Stellatogenin                 | −99.4  | −124.8  | −116.9  |
| Myrtillogenic acid            | −95.4  | −123.8  | −119.3  |
| Alamosogenin                  | −98.1  | −120.5  | −118.2  |
| 22β-hydroxystellatogenin      | −93.4  | −130.0  | −112.6  |
| Oleanolic acid                | −101.6 | −118.9  | −114.2  |
| Machaeric acid                | −105.2 | −112.3  | −115.6  |
| Oleanolic aldehyde            | −100.4 | −116.8  | −115.6  |
| Machaerinic acid              | −103.8 | −114.0  | −114.8  |

Analysis of the predicted complexes show that despite the searching area was centered on the close allosteric site B, which is comprised by residues Arg24, Arg254, Glu262, Tyr46, Asp48, Val49, Ile219, and Met258 [218], both sterols and triterpenes can interact with this site but also with the catalytic site, particularly with two of the most critical residues Cys215 and Arg221. This finding could explain the non-competitive and mixed-inhibition properties of some compounds, which has been experimentally demonstrated [212,219]. For example, fucosterol and β-sitosterol mainly occupy allosteric site B, while 6-hydroxy substituted sterols bind to both the catalytic site (via the 3β-OH group, the 6α-OH interacts through a hydrogen bond to Tyr46 and Lys120) and the allosteric site (Figure 2a). In the case of triterpenes, some of the derivatives with better affinity have hydroxy or carboxylic groups in rings D and E which can interact with amino acids located in site B like Arg47 (for 17-COOH substituted derivatives) and Asp48 (for lactone derivatives as shown in Figure 2b).

Figure 2. Docking poses of (a) peniocerol, a sterol, and (b) 22-hydroxystellatogenin, a triterpene with PTP1B. In yellow, the active catalytic site, in green the allosteric site B.

Analysis of the predicted poses of the testes compounds to PPAR-α revealed three potential binding modes (Figure 3): (a) sterols with no hydroxyl groups in ring B interact in a cavity distinct to the one occupied by known synthetic partial agonists; (b) 6-hydroxy substituted sterols (like thurberol and peniocerol) and lactone bearing triterpenes (like stellatogenin) bind to the same site of synthetic agonists; and (c) acidic triterpenes occupy the same site as known partial agonists, with the carboxyl group approximating to the same residues that interact with the carboxyl group present in the majority of PPAR partial agonists. This mode of interaction could explain the demonstrated activity of oleanolic acid as a PPAR-α activator [220]. For the PPAR-γ docking study, two different modes of binding were found. The first one was common for most triterpenes, these compounds bounded in a different site
than that of known synthetic agonists, away from the thiazolidinedione (TZD) binding site formed by residues Ser 289, His 323, His 449 and Tyr 473. The second one was common for sterols; the tetracyclic skeleton occupied an alternative pocket, and the lateral chain could locate either inside or outside of the TZD binding site (Figure 3b). It would be expected that these alternative modes of binding in both nuclear receptors lead to none or different levels of activation. Thus, additional studies should be carried out.

Some triterpenes from Cactaceae like β-amyrin, oleanolic aid, oleanolic aldehyde, lupeol, betulin, betulinic acid, lupeone and cycloartenol which are well known to regulate some molecular targets of diabetes pathology, with a good prediction in this review. We need to explore the antidiabetic activities, particularly the activity against molecular targets involved in metabolic diseases, of some triterpenes like 16β-hydroxystellatogenin, thurberogenin, stellatogenin, myrtillogenic acid, alamosogenin, 22β-hydroxystellatogenin, machaeric acid, and machaerinic acid, all of them characteristic items of the Cactaceae chemistry, which display some specific oxidation patterns as was discussed above.

3.3. Neuroprotective Activity

As life expectancy has increased, neurodegenerative diseases have become a growing concern, and the need for efficient treatments has become an urgency. Acetylcholinesterase inhibitors have been used for the management of Alzheimer’s disease, and some have suggested their neuroprotective potential. Also, agonists of LXR-α and LXR-β have been studied for their potential use as neuroprotectors. Then, the development of agonists of these receptors that could also act as AChE inhibitors could lead to interesting treatments. Tables 14 and 15, respectively, show the sterols and triterpenes ligands with a higher affinity to the previously mentioned targets.
Table 14. Top-10 ranked sterol derivatives in the LXR-α, LXR-β and acetylcholinesterase (AChE) docking study.

| LIGAND             | LXR-α  | LXR-β  | AChE  |
|--------------------|--------|--------|-------|
| Fucosterol         | -167.1 | -167.7 | -152.9|
| β-sitosterol       | -165.2 | -164.3 | -151.7|
| Methyleneolesterol | -163.1 | -157.8 | -148.6|
| Thurberol          | -161.9 | -158.7 | -147.5|
| Spinasterol        | -157.0 | -158.2 | -152.6|
| Opuntisterol       | -155.9 | -157.9 | -152.1|
| Cyclostenol        | -155.4 | -158.2 | -147.7|
| Peniocerol         | -158.6 | -155.8 | -143.4|
| Schottenol         | -155.9 | -153.6 | -147.4|
| 24-Methylenelophenol | -155.7 | -154.6 | -146.3|

Table 15. Top-10 ranked triterpene derivatives in the LXR-α, LXR-β and AChE docking study.

| LIGAND                  | LXR-α    | LXR-β    | AChE    |
|-------------------------|----------|----------|---------|
| Thurberogenin           | -153.915 | -155.492 | -143.2  |
| 16β-hydroxystellatogenin | -149.154 | -152.308 | -134.8  |
| Betulinic acid          | -141.254 | -155.181 | -137.3  |
| Stellatogenin           | -142.879 | -150.498 | -139.4  |
| 16β-hydroxybetulinic acid | -145.372 | -156.064 | -127.6  |
| Calenduladiol           | -147.818 | -152.858 | -127.8  |
| Betulin                 | -141.428 | -153.007 | -133.0  |
| Lupenone                | -145.652 | -146.987 | -134.2  |
| Lupeol                  | -146.667 | -148.674 | -129.8  |
| Alamosogenin            | -141.635 | -144.049 | -138.3  |

For LXR-α, it was found that both sterols and triterpenes bind to the same site (Figure 4a) but with different interaction patterns. Sterols bind through hydrogen bonding via the 3β-OH group to Glu 267 and Asn 225 while the side alkyl chain interacts with residues Phe 257, Leu 260, Thr 302, and Phe 315. In general, oxidation of ring B improves ligand binding, and slight differences in docking score can be attributed to the nature of the alkyl chain; theoretical affinity increased with the incorporation of additional methylene groups, probably through new hydrophobic interactions. Triterpene derivatives interact with residues Thr 302 and Arg 305 via hydrogen bonding to the lactone or the 17-COOH group of rings D and E. The absence of hydroxy groups in these rings slightly diminishes the theoretical affinity.
Figure 4. Predicted poses for selected sterol (thurberol) and triterpene (thurberogenin) to some bio targets related to neuroprotection. (a) Thurberol—LXR-α; (b) thurberogenine—LXR-α; (c) thurberol—LXR-β; (d) thurberogenine—LXR-β; (e) thurberol—AChE; (f) thurberogenine—AChE. Residues relevant for interactions through hydrogen bonding are labeled.

According to the results, for the interaction of triterpenes with the enzyme acetylcholinesterase, the substitution pattern in ring A is essential, since that ring A is the one that can approximate the catalytic site. On the other hand, in the B ring, the presence of a hydroxyl group in the C6 helps due to the interaction of the oxygen in the hydroxyl moiety with the Trp 86 located in the protein gorge.

In the same set of interactions shown by these compounds, the side chain of cholesterol is stuck with the outer part (mouth) of the enzyme. In triterpenes, the E ring is the one that interacts with the catalytic site through interactions of C17-COOH or lactone moieties, with some residues in the active site. The absence of these features diminishes slightly the affinity. On the other hand, the H atom of 3β-OH of the triterpenes interacts with Tyr 341. In this review is evident the potential that some sterols and triterpenoids from Cactaceae, to the development of new neuroprotectors, via the inhibition of acetylcholinesterase and LXR-α and LXR-β.

4. Conclusions

The docking score calculated for the predicted complexes of the analyzed sterols and triterpenes is close to the score for the known LXR-β ligand 24(S),25-epoxycholesterol (MolDock score = 151.3). The interaction of the 3β-OH group to Asn 239, Glu 281, and Arg 319 are constant in all derivatives (Figure 4c). As it was the case of LXR-α docking study, oxidation in position 6 improves theoretical affinity through interaction to Phe 243, and Phe 329 and additional differences in docking score among sterols can be accredited to the nature of the alkyl chain side. Whereas triterpenes interact through hydrogen bonding to residue Thr 316 via oxygen atoms of lactone ring or 17-COOH, this interaction pattern was common in most of the derivatives analyzed. Interestingly, ring A lays close to residues His 435 and Trp 457, which interact with the epoxy group of 24(S),25-epoxycholesterol, and could interact with hydroxyl groups of 22-hydroxycholesterol and 24-hydroxycholesterol, known endogenous ligands of LXRs. It has been reported that oxidation at both C-22 and C-24 increases LXR activation [221].

According to the results, for the interaction of triterpenes with the enzyme acetylcholinesterase, the substitution pattern in ring A is essential, since that ring A is the one that can approximate the catalytic site. On the other hand, in the B ring, the presence of a hydroxyl group in the C6 helps due
to the interaction of the oxygen in the hydroxyl moiety with the Trp 86 located in the protein gorge. In the same set of interactions shown by these compounds, the side chain of cholesterol is stuck with the outer part (mouth) of the enzyme. In triterpenes, the E ring is the one that interacts with the catalytic site through interactions of C17-COOH or lactone moieties, with some residues in the active site. The absence of these features diminishes slightly the affinity. On the other hand, the H atom of 3β-OH of the triterpenes interacts with Tyr 341. In this review is evident the potential that some sterols and triterpenoids from Cactaceae, to the development of new neuroprotectors, via the inhibition of acetylcholinesterase and LXR-α and LXR-β.

4. Conclusions

The oxidation pattern in sterols and triterpenes from Cactaceae is an extraordinary feature. The oxidation at C6 to form a 6α-hydroxyl group in cholesterol moiety in sterols like peniocerol, macdougallin, cyclostenol, stenocereol, and thurberol, as well as the C6 ketone in viperidinone, vipersidone, deoxyvipersidone, and 5β-deoxyvipersidone, appears to be essential to explaining the possible molecular mechanisms behind the biological activities of those kinds of compounds, as suggested by the available experimental bioactivities and the results of the present in silico study. On the other hand, the oxidation pattern in E ring in oleanane and lupane triterpenes appears as a pivotal factor in controlling the affinity of compounds. At least in the in vitro assays, the presence of hydroxyl, ketone, carboxylic acid, or lactone groups (thurberogenin and 16β-hydroxystelltogenin) in ring E appears to be important in the selectivity of the sterols and triterpenes with their preferred target.

The chemistry of sterols and triterpenoids of some species, from the subfamily Cactoideae, tribe Phyllocacteae, mainly from the subtribe Echinocereinae, was reviewed, together with their biological activities. The information generated about the sterols reveals the presence of the typical Δ5 sterols like sitosterol, among others, but interestingly the presence of a very unusual family of Δ8 sterols with a pattern of oxidation in a sterol moiety of 27 carbons. Two sterols are of biosynthetic importance because it appears as unusual intermediaries in a truncated demethylation process. On the other hand, triterpenes appear as common compounds with unique features, including the oxidation pattern in rings C/D. The compounds found in Cactaceae have been extensively studied because of their biological properties. In this paper, we focused only on three biological activities. At least at an in silico level, it is possible to correlate the biological activities with the theoretical affinities showed between the compounds and some of the specific receptors involved as molecular targets of chronic diseases like inflammation, type 2 diabetes or neurodegenerative disorders. Regarding the in silico bioprospection, this study reveals that the oxidation pattern in ring B of sterol skeleton and rings D and E of triterpenes, together with the presence of lactones, contribute to the biological activities of Cactaceae triterpenes. The above prompt us to continue with this methodological approach to find highly bioactive hits from the sterols and triterpene of Cactaceae, useful for the development of semisynthetic drugs for the management of chronic degenerative diseases with a multitarget approach.

Supplementary Materials: The following are available online, Table S1: Complete docking results from the in silico bioprospection on compounds isolated from Mexican Columnar Cactaceae.

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