Nature is an important source for the discovery of new bioactive compounds. Natural compounds constitute a strategic starting point for the development of novel drugs, since they exhibit a wide range of pharmacophores and a large number of chiral centers that allow the interaction with proteins and biological targets.

Terpenes are natural isoprene-derived compounds and are classified according to the number of carbon atoms in monoterpenes (C10), sesquiterpenes (C15), diterpenes (C20), triterpenes (C30), tetraterpenes (C40) and polyterpenes (C > 40). Many of these compounds are considered secondary metabolites in plants. They showed a variety of biological activities, such as anticancer, anti-inflammatory, antimicrobial, antiparasitic, antiviral, etc. They constitute the largest group of natural compounds with more than 50,000 molecules of diverse chemical structures. They are of great interest, both in the cosmetic and the food market as well as in the pharmaceutical industry [1].

Among terpenoids, sesquiterpene lactones and diterpenes stand out due to their role in human health and as a source of new drugs. The medicinal potential of plant terpenoids has been reviewed by Bergman et al. [2]. In this review, the sesquiterpene lactone artemisinin, isolated from the medicinal Chinese plant *Artemisia annua* (Asteraceae) is described. This compound and its semisynthetic derivatives are used nowadays for the treatment of malaria. Its mechanism of action is related to the heme metabolism of *Plasmodium* spp. Another sesquiterpene lactone mentioned by the authors is thapsigargin, a guaianolide-type sesquiterpene lactone produced by *Thapsia garganica* (Apiaceae), which has been proved to interact with pathways regulating Ca\(^{2+}\) homeostasis in mammalian cells. The effect of the derivative mispsagargin is being evaluated in clinical trials for hepatocellular carcinoma. As regards diterpenoids, the antineoplastic agent paclitaxel isolated from *Taxus brevifolia* (Taxaceae) has been described. This compound acts as a microtubule stabilizer and a mitosis inhibitor. Paclitaxel is used for refractory ovarian cancer and metastatic breast cancer. It is currently obtained by semisynthesis from baccatins and from which docetaxel and analogs have been developed. Ingenol mebutate and prostratin are also diterpenoids with anti-tumor and anti-HIV activities.

Other examples of bioactive terpenoids are forskolin, a labdan diterpene from *Coleus forskohlii* (Lamiaceae) and the sesquiterpene lactone arglabin, isolated from *Artemisia myrianthia* (Asteraceae), as well as its derivative dimethylamino-arglabin, which have been demonstrated to be potential antitumor agents. Other sesquiterpene lactones with promising activity and which are under study are parthenolide and its analog dimethylamino-parthenolide, which are active against breast cancer cells, leukemia and pancreatic carcinoma cells; artemisinin, which has been studied for the treatment of different types of cancers such as breast and colorectal cancer [3,4]; and dehydrocostus lactone and costunolide for breast cancer and leukemia [5]. Other sesquiterpene lactones such as psilostachyin, psilostachyin C, helenalin, mexicanin, cumanin, deoxymikanolide, lychnopholide and goy-
Molecules 2021, 26, 1251

azensolide were found to be active against tumor cell lines and against Trypanosoma cruzi, the causative agent of Chagas disease [6–9].

Over the last years, several updates have been published in Molecules regarding the potential of sesquiterpene lactones and diterpenes for the development of novel drugs. In this sense, Remy and Litaudon (2019) reviewed the properties of macrocyclic diterpenoids of plants of the Euphorbiaceae family and their capacity to inhibit chikungunya virus replication [10]. Jin et al. (2019), published a review on daphnane-type diterpenoids [11]. These authors highlighted the activities demonstrated for this type of compounds: anti-HIV, anticancer, antileukemic, neurotrophic, pesticidal and cytotoxic. Ullah et al. (2019) reviewed the pharmacological potential of steviol and isosteviol and derivatives as cytotoxic, antiviral, antibacterial, antihypertensive, anti-inflammatory and antihyperglycemic agents, among others [12]. Li et al. (2018) published a review describing ent-kaurane diterpenoids, specifically spirolactone-type diterpenoids, which exhibit attractive activities, especially antiproliferative activity [13]. Herrera Acevedo et al. [14] focused on the importance of in silico studies using sesquiterpene lactones for the detection of potential compounds for the treatment of leishmaniasis, schistosomiasis, Chagas disease and sleeping sickness.

Apart from the reviews mentioned, research articles describing bioactive sesquiterpene lactones and diterpenoids have also been published in Molecules. A brief summary of selected articles published in 2019–2020 is also presented.

The synthesis, crystallography and antileukemic activity of amino adducts of dehydroleucodine have been reported by Ordoñez et al. [15]. The cytotoxic activity of the sesquiterpene lactones was evaluated against acute myeloid leukemia cell lines. The proline adduct showed the highest antileukemic activity and was about 270 times more water soluble than the natural compound.

The isolation of the sesquiterpene lactones 4,15-iso-atriplicolide tiglate, methacrylate and isobutyrate from Helianthus tuberosus (Asteraceae) has been reported by Galkina et al. [16]. These compounds were evaluated against Trypanosoma brucei rhodesiense, Trypanosoma cruzi, Leishmania donovani and Plasmodium falciparum. The 4,15-iso-atriplicolide tiglate showed a promising activity and selectivity against T. b. rhodesiense, the etiologic agent of African human trypanosomiasis (IC$_{50}$ = 0.015 ± 0.003 µM). Lenz et al. demonstrated that this sesquiterpene lactone inhibited trypanothione reductase (TR). This enzyme is responsible for the maintenance of the cellular redox state of the parasite [17]. Other analogs belonging to the furanoheliangolide-type sesquiterpene lactones were also found to inhibit TR.

The sesquiterpene lactones α-santonin, argablin, schkuhrin II, vernolepin and eucannabinolide were loaded into polyactic acid (PLA) nanoparticles and evaluated against T. b. rhodesiense. Argablin, vernolepin and eucannabinolide showed trypanocidal activity with IC$_{50}$ values of 3.67, 1.11 and 3.32 µM, respectively. None of the nanoparticle formulations were cytotoxic to mammalian cells [18].

The synthesis of oxygenated and oxy-nitrogenated derivatives of the sesquiterpene lactones cumanin, helenalin and hymenin was reported by Beer et al. [19]. The natural compounds and analogs were evaluated against human cancer cell lines. The silylated derivatives of helenalin were the most active (GI$_{50}$ = 0.15–0.59 µM). The ditriazolyl cumanin was more active and selective than cumanin on the cell lines employed. This analog showed a GI$_{50}$ of 2.3 µM and an SI of 227.9 on WiDr human colon tumor cell lines.

Andrographolide is a labdene diterpene lactone studied by Li et al. (2020) [20]. The activity of three 14-aryloxy analogs of this diterpenoid was evaluated against Zika virus (ZIKV) and dengue virus (DENV). One of the derivatives (ZAD-1) showed higher activity against both ZIKV and DENV than the natural compound. The EC$_{50}$ values against ZIKV and DENV-2 were 27.9 ± 1.7 µM and 22.6 ± 1.8 µM, respectively.

The natural ent-kaurane diterpenoid adenanthin, isolated from Isodon adenantha, has shown activity against leukemic and hepatocellular carcinoma cells. This diterpene has been tested as a potential agent for the prevention of obesity [21]. Adenanthin inhibited
adipogenesis in 3T3-L1 and mouse embryonic fibroblasts and reduced the growing body weight and adipose tissue mass during high-fat diet-induced obesity of mice.

Estafietin is a guaianolide-type sesquiterpene lactone isolated from Stevia alpina (Asteraceae). This natural compound and four semisynthetic derivatives were evaluated against Trypanosoma cruzi and Leishmania braziliensis. Epoxyestafietin was the most active compound against trypomastigotes and amastigotes, with IC50 values of 18.7 and 2.0 µg/mL, respectively. Regarding leishmanial activity, estafietin and 11βH,13-dihydroestafietin were the most active and selective compounds on L. braziliensis (IC50 values of 1.0 and 1.3 µg/mL, respectively) [19].

The in vitro and in vivo trypanocidal activity of eupatoriopicrin has been reported by Elso et al. (2020) [22]. This compound was active and selective against Trypanosoma cruzi amastigotes and triatomastigotes (IC50 = 2.3 µg/mL and 7.2 µg/mL, respectively). Eupatoriopicrin was also active in an in vivo model of Chagas disease, producing a significant reduction in the parasitemia levels in comparison with non-treated animals. Skeletal muscular tissues from eupatoriopicrin-treated mice displayed only focal and interstitial lymphocyte inflammatory infiltrates and small areas of necrosis. In contrast, infected mice treated with the vehicle showed severe lymphocyte inflammatory infiltrates with necrosis of the adjacent myocytes.

The results detailed herein show the potential of sesquiterpene lactones and diterpenoids for drug discovery and development. The wide variety of skeletal types as well as the differences in oxidation and substitution patterns determine a wide range of biological activities, being the anticancer, antiparasitic, antiviral and the anti-inflammatory activities some of the most mentioned for these classes of phytochemicals.

Funding: This research was funded by Universidad de Buenos Aires, grant number 20020170100316BA, Consejo Nacional de Investigaciones Científicas y Técnicas, grant number 11220150100158CO and Agencia Nacional de Promoción Científica y Tecnológica, grant number PICT 2015-3531.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Conflicts of Interest: The author declares no conflict of interest.

References
1. Yang, W.; Chen, X.; Li, Y.; Guo, S.; Wang, Z.; Yu, X. Advances in Pharmacological Activities of Terpenoids. Nat. Prod. Commun. 2020, 15, 1–13. [CrossRef]
2. Bergman, M.E.; Davis, B.; Phillips, M.A. Medically Useful Plant Terpenoids: Biosynthesis, Occurrence, and Mechanism of Action. Molecules 2019, 24, 3961. [CrossRef] [PubMed]
3. Sapió, L.; Gallo, M.; Illiano, M.; Chiosi, E.; Naviglio, D.; Spina, A.; Naviglio, S. The Natural cAMP Elevating Compound Forskolin in Cancer Therapy: Is It Time? J. Cell. Physiol. 2017, 232, 922–927. [CrossRef] [PubMed]
4. Sülsen, V.; Martino, V. Overview. In Sesquiterpene Lactones. Advances in their Chemistry and Biological Aspects; Sülsen, V., Martino, V., Eds.; Springer: Cham, Switzerland, 2018; pp. 303–324.
5. Li, Q.; Wang, Z.; Xie, Y.; Hu, H. Antitumor activity and mechanism of costunolide and dehydrocostus lactone: Two natural sesquiterpene lactones from the Asteraceae family. Biomed. Pharmacother. 2020, 125, 109955. [CrossRef] [PubMed]
6. Sanchez Alberti, A.; Cerny, N.; Bivona, A.; Cazorla, S. Antitrypanosomal and Antileishmanial Activities. In Sesquiterpene Lactones. Advances in their Chemistry and Biological Aspects; Sülsen, V., Martino, V., Eds.; Springer: Cham, Switzerland, 2018; pp. 175–192.
7. Anesini, C.; Alonso, M.R.; Martino, R. Antiproliferative and Cytotoxic Activities. In Sesquiterpene Lactones. Advances in their Chemistry and Biological Aspects; Sülsen, V., Martino, V., Eds.; Springer: Cham, Switzerland, 2018; pp. 303–324.
8. Branquinho, R.T.; Campos de Mello, C.G.; Tavares Oliveira, M.; Soares Reis, L.E.; De Abreu Vieira, P.M.; Saúde-Guimarães, D.A.; Furtado Mosqueira, V.C.; de Lana, M. Lycnopholide in poly(D,L-lactide)-block-polyethylene glicol nanocapsules cures infection with a drug-resistant Trypanosoma cruzi strain at acute and chronic phases. Antimicrob. Agents Chemother. 2020, 64, e01937-19. [CrossRef] [PubMed]
9. Milagre, M.M.; Branquinho, R.T.; Gonçalves, M.F.; de Assis, G.; de Oliveira, M.T.; Reis, L.; Saúde-Guimarães, D.A.; de Lana, M. Activity of the sesquiterpene lactone goyazensolide against Trypanosoma cruzi in vitro and in vivo. Parasitology 2020, 147, 108–119. [CrossRef] [PubMed]
10. Remy, S.; Litaudon, M. Macroyclic Diterpenoids from Euphorbiaceae as A Source of Potent and Selective Inhibitors of Chikungunya Virus Replication. Molecules 2019, 24, 2336. [CrossRef] [PubMed]
11. Jin, Y.X.; Shi, L.L.; Zhang, D.P.; Wei, H.Y.; Si, Y.; Ma, G.X.; Zhang, J. A Review on Daphnane-Type Diterpenoids and Their Bioactive Studies. *Molecules* 2019, 24, 1842. [CrossRef] [PubMed]

12. Ullah, A.; Munir, S.; Mabkhot, Y.; Badshah, S.L. Bioactivity Profile of the Diterpene Isosteviol and its Derivatives. *Molecules* 2019, 24, 678. [CrossRef] [PubMed]

13. Li, H.; Jiao, R.; Mu, J.; Xu, S.; Li, X.; Wang, X.; Li, Z.; Xu, J.; Hua, H.; Li, D. Bioactive Natural Spiro lactone-Type 6,7-sec-o-ent-Kaurane Diterpenoids and Synthetic Derivatives. *Molecules* 2018, 23, 2914. [CrossRef] [PubMed]

14. Herrera Acevedo, C.; Scotti, L.; Feitosa Alves, M.; Formiga Melo Diniz, M.F.; Scotti, M.T. Computer-Aided Drug Design Using Sesquiterpene Lactones as Sources of New Structures with Potential Activity against Infectious Neglected Diseases. *Molecules* 2017, 22, 79. [CrossRef]

15. Ordoñez, P.E.; Mery, D.E.; Sharma, K.K.; Nemu, S.; Reynolds, W.F.; Enriquez, R.G.; Burns, D.C.; Malagón, O.; Jones, D.E.; Guzman, M.L.; et al. Synthesis, Crystallography, and Anti-Leukemic Activity of the Amino Adducts of Dehydroleucodine. *Molecules* 2020, 25, 4825. [CrossRef] [PubMed]

16. Galkina, A.; Krause, N.; Lenz, M.; Daniliuc, C.G.; Kaiser, M.; Schmidt, T.J. Antitrypanosomal Activity of Sesquiterpene Lactones from *Helianthus tuberosus* L. Including a New Furanoheliangolide with an Unusual Structure. *Molecules* 2019, 24, 1068. [CrossRef] [PubMed]

17. Lenz, M.; Krauth-Siegel, R.L.; Schmidt, T.J. Natural Sesquiterpene Lactones of the 4,15-iso-Atriplicolide Type are Inhibitors of Trypanothione Reductase. *Molecules* 2019, 24, 3737. [CrossRef] [PubMed]

18. Kimani, N.M.; Backhaus, S.; Matasyoh, J.C.; Kaiser, M.; Herrmann, F.C.; Schmidt, T.J.; Langer, K. Preparation of Sesquiterpene Lactone-Loaded PLA Nanoparticles and Evaluation of Their Antitrypanosomal Activity. *Molecules* 2019, 24, 2110. [CrossRef] [PubMed]

19. Beer, M.F.; Bivona, A.E.; Sánchez Alberti, A.; Cerny, N.; Reta, G.F.; Martín, V.S.; Padrón, J.M.; Malchiodi, E.L.; Sülse, V.P.; Donadel, O.J. Preparation of Sesquiterpene Lactone Derivatives: Cytotoxic Activity and Selectivity of Action. *Molecules* 2019, 24, 1113. [CrossRef] [PubMed]

20. Li, F.; Khanom, W.; Sun, X.; Paemanee, A.; Roytrakul, S.; Wang, D.; Smith, D.R.; Zhou, G.C. Andrographolide and Its 14-Aryloxy Analogues Inhibit Zika and Dengue Virus Infection. *Molecules* 2020, 25, 5037. [CrossRef] [PubMed]

21. Hu, J.; Li, X.; Tian, W.; Lu, Y.; Xu, Y.; Wang, F.; Qin, W.; Ma, X.; Puno, F.T.; Xiong, W. Adenanthin, a Natural ent-Kaurane Diterpenoid Isolated from the Herb *Isodon adenantha* Inhibits Adipogenesis and the Development of Obesity by Regulation of ROS. *Molecules* 2019, 24, 158. [CrossRef] [PubMed]

22. Elso, O.G.; Bivona, A.E.; Sanchez Alberti, A.; Cerny, N.; Fabian, L.; Morales, C.; Catalán, C.A.N.; Malchiodi, E.L.; Cazorla, S.I.; Sülse, V.P. Trypanocidal Activity of Four Sesquiterpene Lactones Isolated from Asteraceae Species. *Molecules* 2020, 25, 2014. [CrossRef] [PubMed]