

Review

Potential Applications of Guayulins to Improve Feasibility of Guayule Cultivation

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Abstract: Guayule (*Parthenium argentatum* Gray) is an interesting alternative and renewable source of rubber/latex which has been used in the past. Guayule rubber and latex products are not available in the market largely because the raw material cost is higher than the current sources produced in South-East Asia and other tropical countries (*Hevea brasiliensis*). Guayule contains many other compounds whose joint exploitation could make guayule cultivation profitable, especially in semi-desert areas where cultivation of other crops is difficult or impossible. Guayulins A–D, sesquiterpene esters, appear to have some commercial promise. Despite being accumulated in relatively high concentrations (its majority representative, guayulin A, can account for up to 13.7% of the resin content of this plant, which itself ranges from 6%–12%), guayulins have received little direct attention from scientists. This review presents the current knowledge about the activity of these compounds and, based on known activities of similar compounds from other species, potential uses as fungicides, miticides and insecticides are suggested.

Keywords: guayule; resin; guayulins; sesquiterpene ester; sesquiterpene lactone

1. Guayule: More than Rubber

Guayule (*Parthenium argentatum* Gray) is a silver-gray-green perennial shrub used as a renewable source of natural rubber or latex. Native to the semi-arid areas of Northern Mexico and Texas, specifically the Chihuahuan desert, it was commercially exploited during periods of rubber shortage caused by petroleum embargos or lack of supplies linked to the two world wars, mainly to manufacture tyres. Guayule is arguably the leading alternative rubber source to the rubber tree (*Hevea brasiliensis*) [1].

However, the expansion of guayule commercialization faces many barriers, including the low cost of commodity Hevea rubber, lack of developed market demand for guayule rubber in high-value niches, low rubber yields or growth rates, and limited information on potential uses of guayule resins and bagasse as value-added coproducts to enhance guayule's economic competitiveness [2].

This is now a propitious time to develop guayule into a commercially viable crop. The consumption of natural rubber is expected to increase to 15.30 million tons by 2030 [3], while the world production of natural rubber from Hevea was 13.74 million tons in 2018 [3]. The interplay of synthetic and natural rubber production with rapidly expanding economies creates unacceptable price volatility (Price in US cent/pound of natural rubber: Dec 2008 56.7; Apr 2010 179.0; Feb 2011 280.8; Dec 2015 55.3; [4]). Consequently, natural rubber is now listed as a critical raw material (MRC) of the European Union [5], which consumes 9% of the world's production [6].

Natural rubber cannot be replaced by synthetic alternatives in many significant applications due to its unique properties: resilience, elasticity, resistance to abrasion and impact, efficient heat dispersion, malleability at cold temperatures, and ability to crystallize and strengthen under strain [7]. Furthermore, alternatives to Hevea natural rubber are needed to avoid the latex protein allergens responsible for prevalent moderate to severe allergic reactions [8] that still affect between 1% and 6% of the general population [9]. These proteins are not present in guayule latex, which could be used to manufacture allergy-safe materials [10]. However, measures to further support guayule sustainability have to be taken including valorization of co-products. Only then can a secure guayule rubber supply be established at a production level that could consistently meet rubber demands [2]. Utilization of guayule bagasse (>80% of total dry biomass) and resin (up to 10% of total dry biomass), may offset a substantial amount of the growing and processing costs and increase sustainability [11]. However, the potential use of many specific terpenoid compounds within the resin fraction are greatly under-valorized [12,13]. As new varieties were developed since WW II with an improved rubber yield per hectare, their resin content increased significantly. Before the breeding procedure, the resin content used to be about 40% of the rubber content, while after such a process, it increased up to 150% [14]. Sesqui- and tri-terpenes account for 37% and 52% of the resin produced by resin vessels [12] with the sesquiterpene, guayulin A, alone, accumulating to 1%–13.7% [15–17] depending on the variety and harvest date. Three other guayulins (B, C and D) occur in smaller amounts. This review suggests potential industrial applications of the guayulins and some advances in their characterization that could help their commercial exploitation.

2. Guayulins

The resinous material from guayule is composed of readily recognizable fatty acid triglycerides and complex mixtures of terpene and sesquiterpenoid compounds [13]. The compounds identified include organic acids (cinnamic, p-anisic, palmitic, stearic, oleic, linoleic, and linolenic acid), sesquiterpene esters (guayulin A, B, C, and D), triterpenoid esters (argentatin A–H) [18] and polyphenols (tannins and flavonoids) [16].

2.1. Guayulin Structure

Guayulins are both isoprenoids and aromatic acid esters [19]. Guayulins A and B are the trans-cinnamic and p-anisic acid esters of partheniol, a sesquiterpene alcohol, whereas guayulin C and D are likely formed by the oxidation of guayulin A and B, respectively [12,20] (Figure 1). This is because guayulins C and D are often absent from freshly prepared acetone extracts [19] of guayule tissues. However, fresh extracts of leaves contained as much C and D as A and B, suggested that they were actively synthesized in the leaves, and not generated by oxidation post-extraction [21].

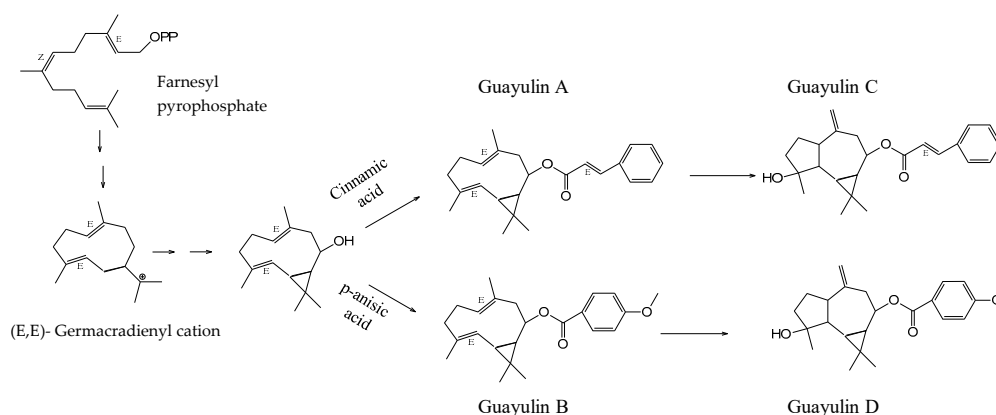


Figure 1. Structure of guayulins (sesquiterpene esters) present in guayule resin. Proposed biosynthetic pathway for guayulins and their interconversion (elaborated from references [19,22]).

2.2. Similar or Related Sesquiterpenes

Sesquiterpenes are C-15 terpenoids which occur as hydrocarbons or in oxygenated forms such as alcohols, ketones, aldehydes, acids or lactones in nature. All sesquiterpenes share in common a C15 backbone derived from the linear precursor FPP (farnesyl pyrophosphate), which is typically cyclized by class I terpene synthases known as sesquiterpene synthases [23–25]. Structural relationships among other members of the same biosynthetic route are shown in Figure 2, where we have gathered knowledge from pyrethrum [26] and maize [27], among many others, and related their relationships to the guayulins.

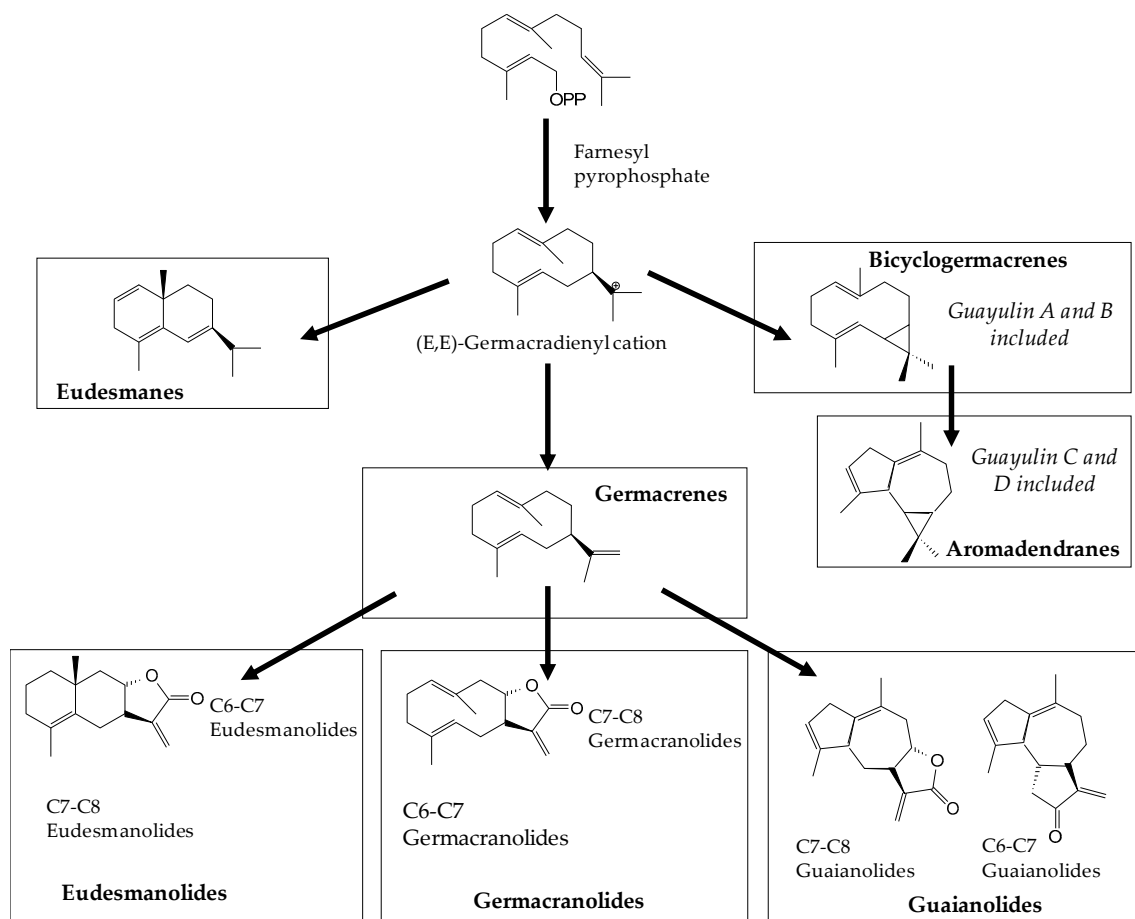
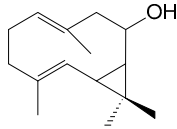
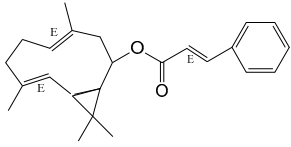
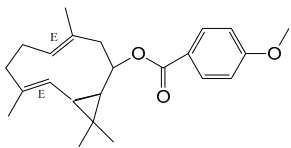
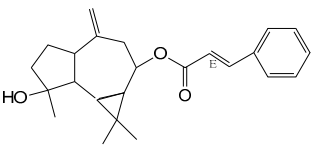
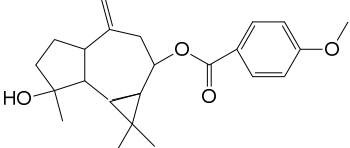
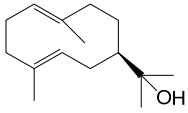
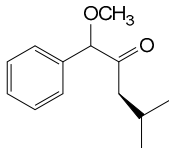


Figure 2. Simplified structural relationships among sesquiterpenes (elaborated from references [22,26,27]).

Guayulins A and B are thought to act as cinnamate and p-anisate reservoirs in guayule shrub, with metabolic turnover occurring at times when release of the free acids into the cellular environment is required [28]. They belong to the family of bicyclgermacrenes, while guayulins C and D would belong to the family of aromadendranes. Other sesquiterpenes found in guayule, apart from guayulins, that have shown biological activity are eudesmol (eudesmane), partheniol (bicyclgermacrene), and guayulone (their structures are shown in Table 1).

Table 1. Activity reported in the bibliography for guayulins and structurally related compounds extracted from guayule.

Bicyclogermacrenes	
	Partheniol (C1) Fungistatic against <i>Aspergillus niger</i> [28] Toxic vs termites [29]
	Guayulin A (C2) Effective against 7 wood fungi and 3 termites [30]
	Guayulin B (C3) Termites antifeedant [29]
Aromadendranes	
	Guayulin C (C4) Effective against 7 wood fungi and 3 termites [30]
	Guayulin D (C5) Effective against 7 wood fungi and 3 termites [30]
Eudesmanes	
	Eudesmol (C6) Fungistatic against <i>Aspergillus fumigatus</i> , <i>A. niger</i> [31,32]
Guayulone	
	Guayulone (C7) Compound extracted from the interspecific hybrid AZ-101 (<i>P. argentatum</i> x <i>P. tomentosa</i>) Moderate fungistatic activity against <i>A. niger</i> [29]

3. Reported Guayule Resins or Its Components Activity

Although large quantities of guayulins can be found [19,21] and have potential applications as sesquiterpenes, there are few guayulin-specific reports in the scientific literature. Only 17 records were found in searchable databases (Web of Science, Scopus and PubMed) when the term “guayulin” is searched as relevant in title or abstract or keyword. Most corresponding to their isolation (1), structural elucidation (4), quantification under different culture conditions (7), and analysis of its allergenic potential (2). An additional report considers the role of guayulins as promoters of seed germination.

Guayule resins are well known to have activity against fungi and insects suggesting their potential use as wood protectants [13,30,33,34]. The first authors working on the valuation of resins coproducts

as both antifungal and antifeeding concluded that specifically, the resin imparted protection against damage by *Teredinidae* and *Limnoria* sp., and particularly, wood exposed to the very destructive *Coptotermes* termite species [30].

It is difficult to assign antifungal and insecticidal activities specifically to the guayulins because only crude resin was tested initially. Later research (summarized in Table 2) connected partheniol (C1) with the inhibition of 75% *Aspergillus niger* culture growth and absolute inhibition of sporulation, as well as guayulone (C7) with 40% of growth inhibition. Six eudesmane sesquiterpenoids were isolated and identified (C6) from AZ-101, an interspecific hybrid of *P. argentatum* and *P. tomentosa*, several of which displayed in vitro fungicidal activity against *A. niger* (UA-172-1) and *A. fumigatus* (ATCC-13073) (Maatooq et al. 1996). Partheniol (C1) and guayulin B (C3), isolated after saponification of a neutral fraction of guayule extract [12], were proved to have moderate to weak antifeedant and toxic effects against the termite *Reticulitermes flavipes* [30]. However, guayulin B (3), the ester of partheniol (C1) with a p-anisoyl group, was not toxic to *R. flavipes* so the free hydroxyl group in partheniol (C1) may be relevant to its bioactivity. Guayulins A (C2) and B (C3) did not inhibit larval growth of the Lepidopterous species, *Heliothis zea* and *Spodoptera exigua* [35].

Besides the potential of guayule resins as wood protectants against rot and termites [13,30,33], other studies have reported potential applications as paints, adhesives [13] or soil amendments [13,36].

Guayulin A and B also have been postulated to play a role in the chemical defense system of guayule and may also possess significant antibacterial and anticancer activity [37], in close analogy to sesquiterpene lactones in other species [38]. Indeed, guayulins A and B act as biological triggers in the synthesis of lychnostatine and paclitaxel, which are antineoplastic agents used in breast cancer treatment [37] and whose markets have developed rapidly. The paclitaxel market has an average growth rate of 12.3%, and 2600 kg commanded a global revenue of 80 M USD in 2017 [39]. Guayulins, once transformed into partheniol, can also be the substrate for the fermentation of different species of fungi to obtain compounds with different bioactivity [40,41].

4. New Potential Applications

Resins and their components are valuable coproducts and their use may improve the overall economic and environmental sustainability of the guayule shrub and offset a substantial amount of the growing and processing costs [11]. New applications may be informed by examination and potential extrapolation of known bioactivities for closely related compounds produced by other plant species (Table 2). For instance, 6 β -cinnamoyloxy-4 β ,9 β , 15 trihydroxyeudesmane (C12) and 6 β -cinnamoyloxy-1 β , 15-dihydroxyeudesm-4-en-3-one (C13), esterified with *trans*-cinnamic acids such as guayulin A and C, have antifungal capability; spathulenol (C17) and spathulenol isomer (C18), which are related to guayulin C and D, show repellent and anti-feedant activity. In general, similar bioactivity patterns are apparent by members of the eudesmanolides, eudesmanes and guaianolides against fungi (compounds C8, C9, C12, C13, C19, C21 in Table 2), members of the eudesmanolides and aromadendranes against insects (C11, C17, C18) and members of the eudesmanes and germacrene against mites (C14, C15). Apparently, and as argued by Durán-Peña [22], the presence of the gem-dimethylcyclopropyl group in the bicyclogermacrene (A and B) and aromadendranes (guayulins C and D) (Figure 2) imposes a conformational rigidity that may be responsible for biological activity of all these kinds of compounds.

Table 2. Known biological activity of sesquiterpenes from different vegetal sources structurally related to guayulins.

Eudesmanolides		Germacrenes	
	8α-O-(4,5-diacetoxyangeloyl) sonchucarpolide (C8) <i>Centaurea zuccariniana</i> Antifungal [42]		Germacrene D (C15) <i>Hyptis suaveolens</i> , <i>Ligustrum japonicum</i> Acaricidal 4 species [43]
	Zuccarinin (C9) <i>Centaurea zuccariniana</i> Antifungal against 8 fungi [42]	Germacranolides	
			Parthenolide (C16) <i>Tarconanthus camphoratus</i> Antibacterial against <i>S. aureus</i> & <i>B. subtilis</i> [44]
	Alantolactone (C10) <i>Inula helenium</i> Antifungal vs <i>M. cookei</i> , <i>T. mentagrophytes</i> and <i>Trichothecium roseum</i> [45]	Aromadendranes	
			Spathulenol (C17) <i>Melampodium divaricatum</i> Repellent leafcutter ant <i>Atta cephalotes</i> [46]
	Isoalantolactone (C11) <i>Inula helenium</i> Larvicidal activity against <i>Aedes aegypti</i> mosquito [47]		Spathulenol isomer (C18) <i>Dipterocarpus grandifloras</i> Antitermitic effect [48]
Eudesmanes		Guaianolides	
6β-cinnamoyloxy-4β,9β,15-trihydroxyeudesmane (C12) <i>Verbesina lanata</i> Fungistatic against <i>Plasmopara viticola</i> [49]	6β-cinnamoyloxy-1β,15-dihydroxyeudesm-4-en-3-one (C13) <i>Verbesina lanata</i> Fungistatic against <i>Plasmopara viticola</i> . [49]		Dehydrozalanin (C19) Several Asteraceae Fungicidal against 3 <i>Colletotrichum</i> species [50]
			Dehydroleucodine (C20) <i>Artemisia douglasiana</i> Bactericidal <i>Helicobacter pylori</i> [51]
	Costic Acid (C14) <i>Dittrichia viscosa</i> Acaricidal against <i>Varroa destructor</i> [52]		(-)-dehydrocostuslactone (C21) <i>Saussurea lappa</i> Antifungal vs <i>C. echinulate</i> [53]

Thus, these compounds are potential bioactive substances for the manufacture of bio-pesticides (fungicides, insecticides or miticides). Bio-pesticides are in high demand in the agricultural, food and livestock industries, for which the development of safer agrochemicals with reduced environmental and mammalian toxicity is a major concern.

In agriculture, the use of plant protection products (PPPs), including fungicides and insecticides, is increasing. While the development of new conventional (synthetic) PPPs or novel active chemicals has decreased during the last decades, the number of available natural PPPs or bio-pesticides increases each year. Recently, 67% of 484 active substances previously approved by the EU, have been banned from the market because of safety concerns, mostly around toxic organophosphate and carbamate

groups [54]. More than 17,000 pesticide products are currently on the U.S. market, with many of them approved through “conditional registration”, a regulatory loophole that allows products to be marketed quickly without thorough review [55]. The availability of less toxic substances could lead to more PPPs and slow the development of resistance to existing PPPs, because rotation among active ingredients with different modes of action is a common approach to this slowing resistance [54]. Guayulins could play an important role as healthier PPPs-active substances than the existing ones. New compounds that follow the recommendations of the Human Rights Council of the United Nations [56] to promote agroecology by evolving technology in pesticide manufacture. All based on supposedly less toxicity to humans. The Indians from Mexico used to chew guayule, spitting out the rubber and vegetable matter separately, to produce natural rubber to make balls to play with [57]. In this process, part of the guayulins, at least of the most soluble parts, the C and D, would surely be ingested.

Guayulins may also have efficacy in reduction of food spoilage and loss, which remain critical issues in spite of technological advances. It is estimated that up to one-third of all food is spoiled or squandered before consumption (about 1.3 billion tons per year) due to problems in the supply chain [58], and that 5%–10% of the world’s food production is lost due to fungal spoilage. Natural solutions are now demanded to ensure both food safety and long food shelf-life [59]. Guayulins could be offered, for example, as natural antimicrobial compounds for dairy products, which are mainly spoiled by yeasts such as *Yarrowia lipolytica* or *Candida* spp., or moulds such as *Aspergillus*, *Cladosporium*, *Penicillium*, and *Phoma* genera. Guayulins could be also useful against mites or insects in stored-grains (e.g., *Coleoptera* order, *Angoumois* moths, *Sitophilus oryzae*, *S. Zeamais*, *Sitotroga cerealella*, *Tyrophagus putrescentiae*), which cause losses of 20%–58% in developing countries [60].

The livestock industry may also be served by guayulin-based bioactives to eliminate pesticide residues accumulated in animals via contaminated feed, or direct application onto animals to control external parasites. Such pesticides are absorbed dermally and also, through licking, although symptomatic poisoning of animals is commonly associated with human error [61]. Novel antimicrobial plant-derived compounds in new chemical classes will lack cross-resistance to chemicals currently used. Guayulin-based miticides could be useful against ticks and tick-borne diseases, which affect 80% of the world’s cattle population and are widely distributed throughout the continents, particularly in the tropics and subtropics, costing between US\$ 13.9 billion and US\$ 18.7 billion every year [62].

5. Guayulin Extraction Processes

Several procedures have been developed to extract the rubber and resin from guayule [63]. Relatively large bench-scale isolation of guayulin A (9 g) from defoliated guayule (30 kg), which also allowed the isolation of guayulin B albeit in relatively low yield, has been demonstrated [64]. The method consisted of double extraction of ground guayule branches in acetone at 50 °C for an hour, which were combined and evaporated to generate a viscous turbid green syrup. The resins were then extracted by dissolving the syrup in ethyl acetate followed by washing with brine and partitioning the organic layer from the aqueous layer and semi-solid rubber. Guayulin A purified from the rubber-free resin was achieved in a two-stage process of (i) gravity chromatography to separate nonpolar components enriched in guayulins A and B from other more polar fractions; and (ii) flash chromatography to isolate guayulin A in greater than 98% purity. A patented method for the separation of the isoprenic constituents of guayule (including guayulins A and B) is ambiguous and underdeveloped since neither the type of plant nor the isolated compound, the solvents employed nor even the process conditions are sufficiently defined [65].

All parts of guayule need to be developed for market opportunities if they can be identified. Performance advantages in latex thin films and allergy safety are being exploited [66]. Sustainable guayule commercialization requires sufficient crop acreage to provide a secure and economically feasible supply of several products, guayulins included.

6. Economic Considerations

Currently the guayule industry is on the brink of development in industrialized regions with access to technological innovation and efficient practices, where employee safety and environmental protection is incorporated in company management strategies [2]. Sustainable processing practices, including coproducts production processes, are needed since they have potential to positively change environmental impacts of guayule rubber production.

Research on co-products and their potential applications should continue. In spite of various potential uses of guayule coproducts, which could contribute to reduce the environmental and economic costs of rubber production [2,13,67], commercial applications for guayule coproducts have been minimal at best. It is predicted that when the quantity of guayule bagasse starts to increase as rubber production increases, the economics of coproducts will improve [13].

An economic feasibility analysis of a potential commercial facility in Europe [68], to produce latex, crude rubber, resin and bagasse as final products, showed that the breakeven price for guayule could change from 8.16 € kg⁻¹ of dry rubber (far above the market price and not currently feasible) to 2.46 € kg⁻¹ (approximately US\$ 2.76 kg⁻¹) when additional sources of revenue are included (rubber at 2.15 € kg⁻¹, resin at 2.10 € and bagasse at 0.10 €). This is a profitability calculated from a production of 810 kg ha⁻¹ year⁻¹ of natural rubber (90 ton total dry biomass in 10 year cultivation cycle, containing 9% of natural rubber) [68], while the expected production of the crop in the USA is 1400 kg ha⁻¹ year⁻¹ [66]. Valorized guayulin production could help off-set processing costs. Guayulin market price would likely fall closer to parthenolide price (US\$ 30,000 kg⁻¹, Globalquimia S.L., Barcelona, Spain), a sesquiterpene lactone with a similar structure to the guayulins (compound 16, Table 2), rather than other vegetable monoterpenes price (US\$ 10.07–60.40 kg⁻¹, Globalquimia S.L., Barcelona, Spain). Probably at the top of the range established for the price of sesquiterpenes (100–1000 € kg⁻¹) [69]. This could significantly increase the net profit estimated at 211€ t⁻¹ [68]. They could be introduced in the market as active substances for manufacturing pesticides (fungicides, insecticides and miticides) for agriculture, food and livestock industries, mature and relevant markets worldwide, with one billion pounds of pesticides annually applied to U.S. farms or among 350,000 and 400,000 ton of PPPs sale in the EU per year.

7. Conclusions

Guayulin production at an industrial level could be achieved by extracting guayule bagasse once a significant guayule crop is in production. Because of their structural similarity to other sesquiterpenes with demonstrated biological activity, they should be tested to combat fungi, mites and other pests in various applications in different industries. Their use as starting material for semi-synthesis of other compounds may also be of interest to chemical and pharmaceutical companies.

Extraction and isolation methods should be updated and scaled up from optimized laboratory-scale methods. Efficient and cost-effective methods are key to serving a viable guayulin market.

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