RESEARCH ARTICLE

Medically related products obtainable from *Eucalyptus* trees

Donald L. Rockwood[1*] and Randall L. Bowman[2]

Affiliations:

1 *School of Forest Resources and Conservation, University of Florida, Gainesville, FL, USA, 32611-0410. E-Mail: dlrock@ufl.edu*

2 *Sustainable Earth Partners, 3532 Esteva Place, Gainesville, GA, USA 30506 E-Mail: rbio.sep@gmail.com*

*** Corresponding author:** Donald L. Rockwood, E-Mail: dlrock@ufl.edu

Abstract: *Eucalyptus* is grown worldwide for a variety of products. We previously described their general importance for energy products and now update their various applications and potential as short-term and likely long-term medically related products. Many products currently derived from petrochemicals can be produced from *Eucalyptus* biomass. Eucalyptus bioproducts, which may be classified as naturally occurring, generated by biochemical processes, or as the result of thermochemical processes, have a broad and exciting range of applications.

Keywords: *Eucalyptus*; biofuels, biochemicals, carbon fiber, nanoparticles.

Conflict of interest and financial support: None

1. Introduction

Over 700 *Eucalyptus* species, commonly called eucalypts, are native to Australia and nearby islands. Eucalypts, the most widely planted hardwoods (18 million ha in 90 countries [1]), are grown extensively in tropical, subtropical, and temperate regions of Africa, South America, Asia, Australia, Europe, and North America. Almost 12 million ha of eucalypt plantations in 2005 [2] were established in 12 countries, and eucalypt planting has since intensified, especially in tropical countries. Four species and their hybrids from the subgenus *Symphyomyrtus*, *E. grandis* (*EG*), *E. urophylla* (*EU*), *E. camaldulensis*, and *E. globulus*, account for about 80% of eucalypt plantations worldwide. For pulp production and increasingly for solid wood, *EG*, *EU*, and *EGxEU* hybrids are favored in tropical and subtropical regions. Rotations can be as short as 3 years with yields as high as 70 m^3/ha/yr.

Elite cultivars with superior wood quality, rapid growth, and disease resistance [e.g., 3] are commonly grown for products including paper [4], lumber, plywood, veneer, solid and engineered flooring, fiberboard [5,6], wood cement composites [7,8], mine props, poles, firewood, charcoal, essential oils [9-12], honey, tannin, landscape mulch [13], shade, windbreaks, and phytoremediation [14-17]. Because demand for renewable, carbon neutral, and sulfur-free biofuels, biochemicals, and biomaterials is increasing [18] along with the knowledge that many products currently derived from petrochemicals can be produced from woody biomass [19], the general objective of this representative review is to update a review completed in 2008 [20] with specific relevance to medically related products.

2. Products

Sustainable, abundant ligno-cellulosic feedstocks are critical to the development of 2nd-generation technologies for the commercialization of biofuels [21] and other bioproducts. Bioproducts derived from eucalypts may be classified as naturally occurring, generated by biochemical processes, or the result of thermochemical processes.

2.1. Naturally Occurring

Eucalyptus compounds have several natural roles [9], including defense against insects, herbivores, UV radiation, and cold stress. Terpenoids give *Eucalyptus* foliage its characteristic smell. *Eucalyptus* also produces phenolics such as tannins. While some phenolics have supported past industries, newly identified formylated phloroglucinol compounds (FPCs) have many biological actions and are powerful antifeedants. FPCs are most concentrated in subgenus *Symphyomyrtus* [22]. Recent efforts have identified opportunities to use these compounds as insecticidal, repellant, antimicrobial, antifungal, and anticancer agents.

The larvicidal activity of leaf essential oils from *E. camaldulensis* and *E. urophylla*, and their chemical constituents, against *Aedes aegypti* and *A. albopictus* was investigated [23]. The essential oil from *E. camaldulensis* was highly inhibitory against both. Of the 12 pure constituents extracted from the two essential oils, among the six effective constituents, a-terpinene exhibited the best larvicidal effect against both *A. aegypti* and *A. albopictus* larvae. Leaf essential oil of *E. camaldulensis* and its effective constituents may be suitable for the production of natural mosquito larvicides.

To repel insects and arthropods, natural products with good efficacy and environmental attributes are alternatives to synthetic chemicals that raise environmental and human health concerns [24]. Among plant essential oils (volatile mixtures of hydrocarbons with a diversity of functional groups whose repellent activity is due to monoterpenes and sesquiterpenes) and extracts that have been extensively tested to assess their repellent properties, those of *Eucalyptus* are well documented, e.g., leaves of *E. maculata* and *E. globulus* and dried fruit of *E. camaldulensis*. These have high repellency against *Ixodes ricinus, A. albopictus*, *Mansonia* and *P. humanus capitis*. Repellents from eucalyptus oils have been formulated and evaluated against biting midges. Individual compounds with high repellent activity include a-pinene, limonene, citronellol, citronellal, camphor, and thymol.

E. citriodora, a species known for its wood and medicinal usages, was examined for endophytic and epiphytic fungi on healthy leaves [25]. Nine of 33 fungal species were common in leaf tissues and surfaces, and of 478 fungal isolates, 279 were epiphytic and 199 were endophytic. *Cladosporium cladosporioides* was dominant on leaves while *Botrytis cinerea* dominated in leaves. Eight of 16 endophytic isolates were antagonistic against a variety of fungal pathogens of both humans and plants.

An environmentally friendly, economical, and quick method for producing antibacterial agents and biofilm inhibitors from *E. globulus* (ELE) has been identified [26], specifically, a microwave assisted method for producing silver nanoparticles (AgNPs) using aqueous leaf extract. The antimicrobial activity of ELE-AgNPs against *Pseudo-*

monas aeruginosa, *Escherichia coli* and methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-sensitive *S. aureus* (MSSA) indicated that *S. aureus* was more sensitive than *E. coli* and *P. aeruginosa*, MRSA was more sensitive than MSSA, and *P. aeruginosa* was more sensitive than *E. coli*. Significant biofilm inhibition was observed for *S. aureus* and *P. aeruginosa.*

Inhibition of the growth of bacteria and fungi indicated that *E. camaldulensis* might be used to develop and formulate antibacterial and antifungal drugs [27]. The chemical composition and antibacterial, antifungal, and antioxidant activities of methanolic extracts from leaves of *E. camaldulensis* and *E. gomphocephala* was documented. *E. camaldulensis* extracts had the highest phenolic content, antioxidant, and antimicrobial activities.

Eucalypt extracts may have anticancer properties [28]. *E. microcorys* phytochemicals might have efficacy against pancreatic cancer cells. Extracts of *E. microcorys* leaves and fruit inhibited the growth of glioblastoma, neuroblastoma, lung and pancreatic cancer cells. *E. microcorys* and *E. saligna* extracts were less effective than an *E. robusta* extract in MIA PaCa-2 cells.

While *Eucalyptus* species contain many useful phytochemicals [29], their cost effective capture is critical to commercial use. An integrated system producing large volumes of high-cineole eucalyptus oil from mallee eucalypts [11] illustrates one possible approach that involves harvesting trees on a 3-4 year cycle to provide pharmaceutical oils, activated carbon, heat and power, tradeable renewable energy certificates, and even carbon credits.

2.2. Biochemicals

Significant advances have recently been made in lignocellulosic-based biofuels technology. One is in the production of ethanol from pretreated phosphoric acid-impregnated, steam-exploded biomass [30]. Using *E. benthamii*, a conversion process (Figure 1) involving pretreatment, enzymatic hydrolysis of the whole slurry, and fermentation of both C5 and C6-sugars, including a presaccharification step, yielded 275 and 304 L/tonne DW, among the highest reported for *Eucalyptus* chips.

Numerous other bioproducts may be obtained from a phosphoric lignocellulosic biorefinery (Figure 1). From lactate, biochemical derivatives for parenteral and dialysis applications include calcium gluconate for delivering minerals and electrolytes, minerals salts, and sodium lactate for IV solutions used in dialysis [31]. From succinate may come acrylic acid, lactic, acid, muconic acid, and fumaric acid [32]. Alanine can be used as a nutritional supplement and seasoning, as well as a chiral source for broad spectrum antibiotics.

Other bioproducts have considerable potential. Cross-linking nanofibrillated cellulose with matrix polymer forms hydrogels with enhanced absorbency [34]. Cellulose nanocrystals (CNCs) and cellulose nanofibrils (CNFs) are nanoscale cellulose fibers that differ in shape, size and composition [35]. Because at the same nanocellulose concentration, CNFs have higher strength and modulus, systematic comparisons can develop criteria for selecting the proper nanocellulose for a biobased nano-reinforcement material in polymer nanocomposites.

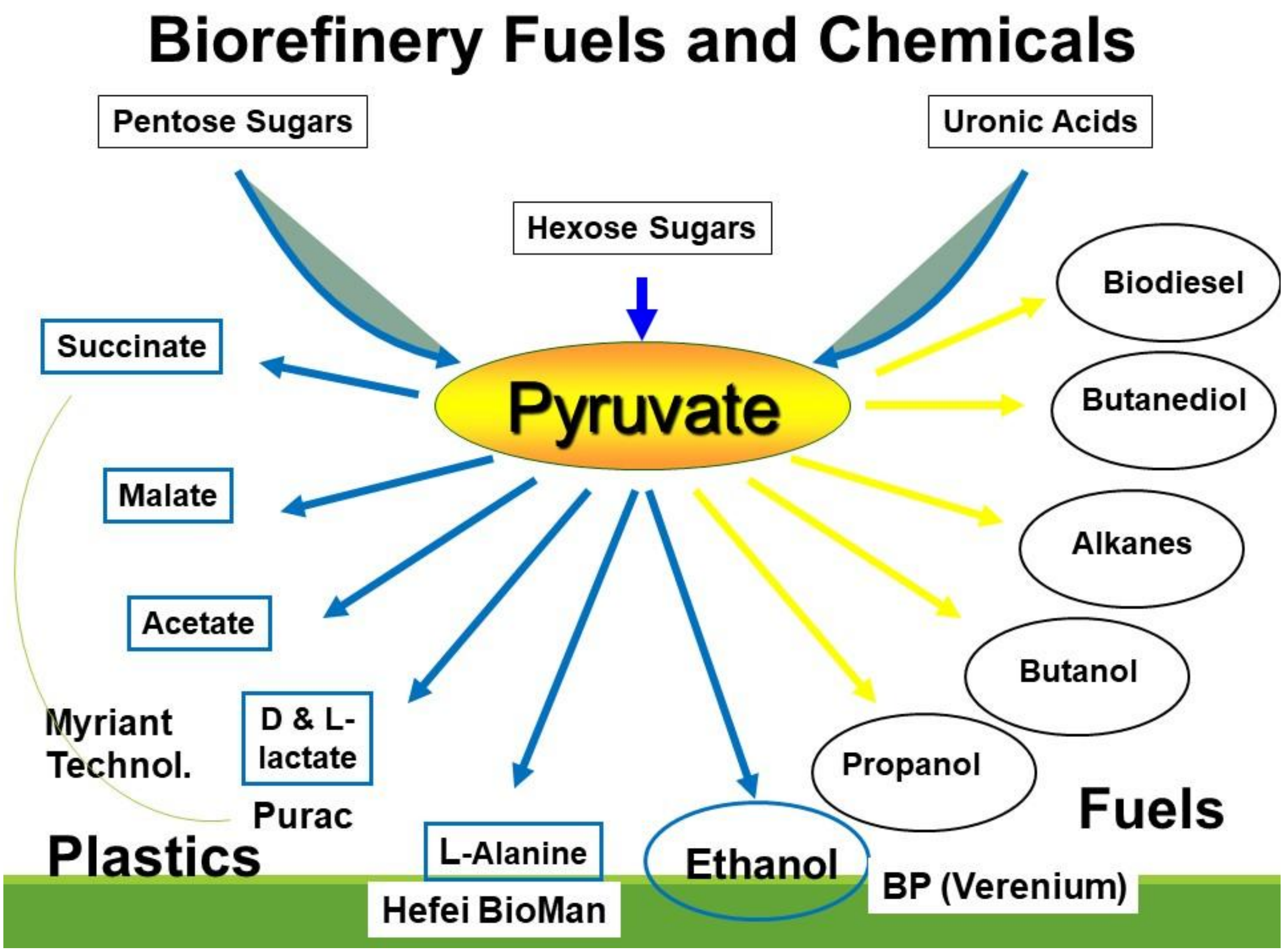

Figure 1. Diagram of a phosphoric lignocellulosic biorefinery steps and products with licensing partners [33].

2.3. Thermochemical

Since the early 2000s, a great deal of attention and funding has been applied to creating bio-oils via pyrolysis. The resulting bio-oils are a soup of nearly 800 organic compounds, many highly oxygenated. Adding energy content to the oils via fast pyrolysis and upgrading mostly utilizing hydrotreating and hydrocracking to convert the amorphic bio-oils into transportation fuels has been largely abandoned. The art remains very convoluted, energy intensive, elusive, and unwieldy.

Several technology developers have attempted to scale up biomass gasification creating a synthesis gas conversion pathway, but it is difficult to remove the tars and produce a consistent syngas suitable for cleanup and catalytic conversion via Fischer-Tropsch (FT catalytics). While there are reports of success with gas clean-up and the utilization of micro channel FT methods, inconsistent syngas streams, poisoning of the catalyst, and the sheer size required of the projects in terms of CAPEX have largely thwarted efforts to broadly commercialize various technologies. The industry continues to report projects being developed, though announcements appear to be premature, and published development time horizons are continually exceeded. In addition to the liquid fuels, the processes yield a substantial fraction of valuable paraffin and olefin co-products, which drive the hoped for profitability. Confidence remains high for these developers.

Recent breakthroughs in hybrid high temperature (>1000°C) pyrolysis/gasification systems have resulted in the commercial production of hydrogen, electric power, and/or "drop in" synthetic/green diesel fuel (Figures 2 and 3). The "drop in" diesel is produced via a low temperature and pressure process without costly catalyst, a technology breakthrough that places synthetic diesel and hydrogen production in a competitive position with fossil fuel derived hydrogen and diesel and creates a new low carbon footprint for diesel fuel (97% reduced) while creating a new Renewable Identification Number (RIN) path contributing to overall financial viability. The co-products are a highly porous char and water, both of which should find commercial markets. Profitability when purchasing biomass at market prices remains a challenge until bankable markets for the co-products can be developed. Early adopters include project owners already dealing with a biomass waste disposal issue. The process also yields market opportunities for biomass derived from forest management activities associated with thinning, slash, and other wood waste streams. Process yields are guaranteed at 90 gallons of low sulfur "drop in" diesel per bone dry metric ton.

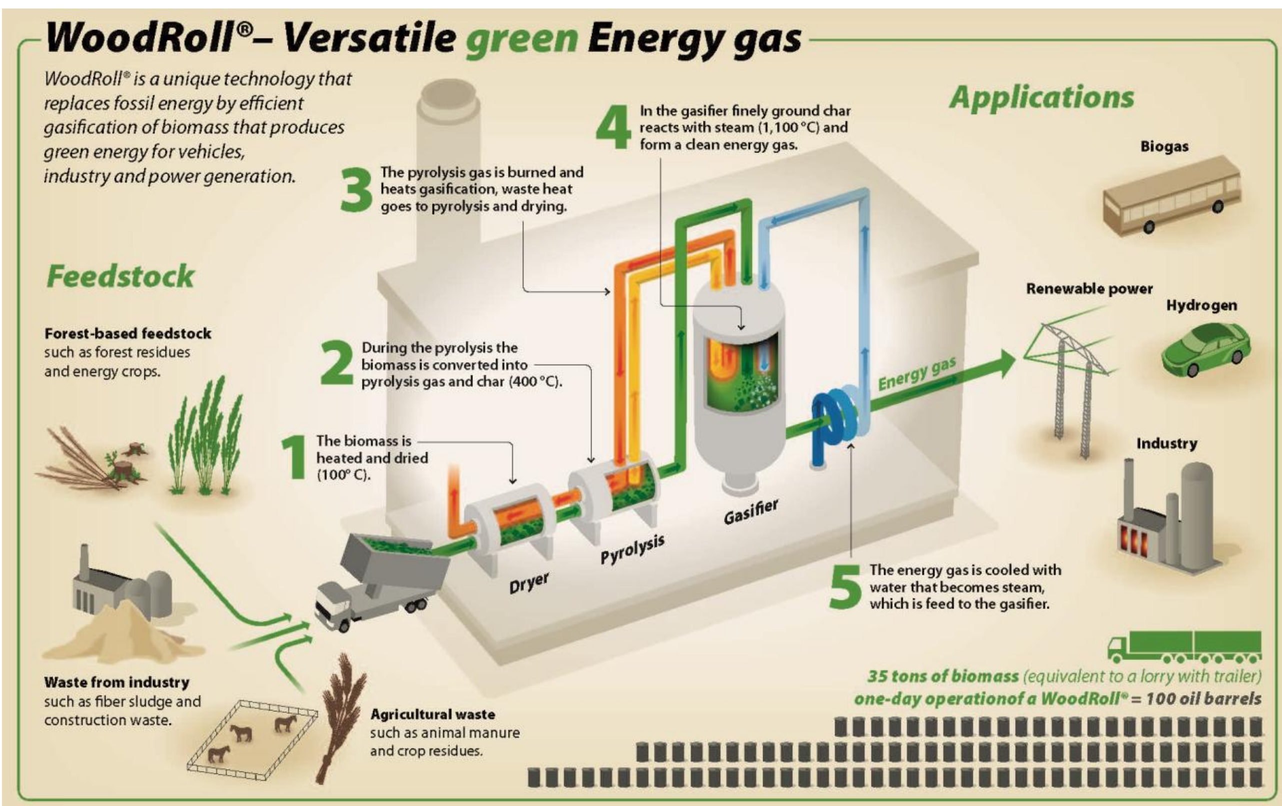

Figure 2. Flow diagram for WoodRoll biomass gasification system [36].

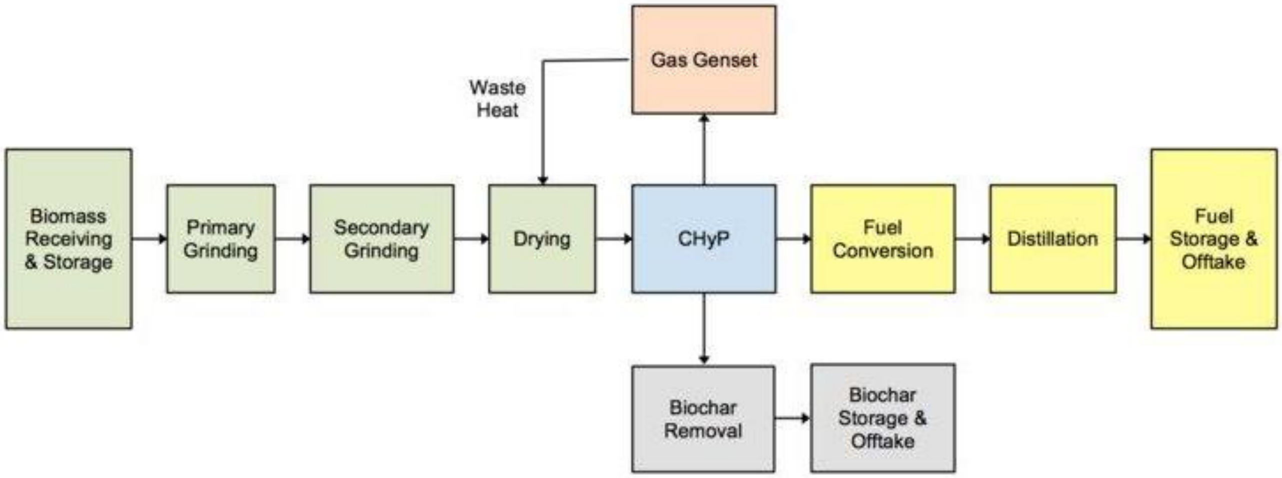

Figure 3. Flow diagram for Proton Power ChyP system and fuel conversion system [37].

Products resulting from high temperature pyrolysis/gasification, such as carbon fiber (CF) and graphene, have an extraordinary range of applications. CF consists of a multitude of unique physical, chemical and biological characteristics that can be utilized and exploited for a number of diverse applications [38]. CF has recently expanded to surgical implants. In orthopedics, CF has provided innovative internal fixation to a wide variety of indications, fractures, joint arthrodesis and neoplastic lesion treatments. CF's physical properties of superior tensile strength, fatigue strength, and strength to weight ratio challenge conventional materials. Its elastic modulus has lessened stress shielding, allowing better callous formation and stronger union. Its radiolucency puts it at the forefront of successful spine procedures. Radiolucency is also particularly advantageous in orthopedic oncology. CF implants cause no allergic reaction and in orthopedics will continue to improve procedures and confer advantages as it is employed in new applications. CF may also be used for dry fabrics, filters, prosthetics, orthotics, artificial legs and arms, implants, wheel chairs, care beds, portable slope, surgical instruments, reinforced plastics, imaging tables supporting limbs being X-rayed or treated with radiation, nails, and inserts.

Graphene's structure and exceptional physical and chemical properties lead to many potential medical applications [39] - e.g., drug delivery, cancer therapy and biological imaging. Current research on delivery of drugs and genes will likely extend to proteins, growth factors, and other biomolecules, either in single or combined use, for cancer and other disease therapies.

Graphene could play a crucial role in artificial implants [40]. Graphene's biocompatibility, coupled with its mechanical strength, is beneficial for various composite bio-materials, and its electrical conductivity can be used for organs that require such attributes. Graphene is showing exceptional performance in detecting food toxins, environmental pollution, specific germs and bacteria, etc. Graphene-oxide (GO), an oxygenated form of graphene, binds to the protein-like structure of specific toxins to produce an enhanced signal that enables hyper-sensitive sensors that detect toxins at very low levels. An example is a sensor that predicts heart attacks, using GO's ability to detect specific microparticles released in the blood prior to heart attacks. GO could also be used for drug delivery.

Graphene may detect and treat cancer using a single-cell sensor based on graphene field-effect transistors. GO, acting as an anti-cancer agent that selectively targets cancer stem cells, combined with existing treatments could lead to tumor shrinkage and preventing cancer spread. Graphene may also assist in cancer drug delivery. Graphene may also be an anti-cancer agent by creating heat to eliminate proteins and DNA inside cancer cells. Nanopore sequencing using graphene-enabled DNA would allow DNA analyzing one nucleotide at a time. Additional concepts involve graphene-based DNA sensors, and other alternative ways of making DNA sequencing faster and more efficient.

Because carbon nanotubes (CNTs) are extremely light, very strong, and conduct heat and electricity far better than other materials, they offer promise for making lightweight, high-capacity batteries [41]. CNTs increase electrical connectivity and mechanical integrity, thus enhancing rate capability and cycle life (42).

Given the prominence of current and future *Eucalyptus* plantations in areas with large energy needs and biomass production potential, *Eucalyptus* can be a significant contributor for a range of energy and medically related products. Key drivers for worldwide biomass expansion are: 1) meeting increasing demands where indigenous fossil fuel sources are non-existent or in decline, 2) meeting greenhouse gas emission targets, 3) supporting domestic and industrial waste management projects, 4) utilizing forest, crop and livestock residues, 5) rising fossil fuel prices.

3. Conclusions

Eucalypts are widely planted and produce abundant biomass. Many conversion technologies are well understood, and several are being developed. While these technologies have seemingly unlimited potential, eucalypt biomass characteristics, difficulty in securing adequate and cost effective supplies, and planning remain constraints to *Eucalyptus* bioproducts reaching their full potential. However, increased biomass productivity and quality, carbon trading, research, and government incentives should foster *Eucalyptus* biomass use for a range of bioproducts.

References

1. FAO. Global forest resources assessment 2005 - main report. FAO Forestry Paper, 2005; available online: ftp://ftp.fao.org/docrep/fao/008/A0400E/A0400E00.pdf.

2. FAO. Global planted forests thematic study: results and analysis. Planted forests and trees. FAO Working Paper FP38E, 2006; available online: http://www.fao.org/forestry/webview/media?mediaId=12139&langId=1.

3. Rockwood DL. History and status of Eucalyptus improvement in Florida. *International Journal of Forest Research* Volume 2012 (2012), Article ID 607879, 10 pages. http://www.hindawi.com/journals/ijfr/2012/607879/

4. Tournier, V.; Grat, S.; Marque, C.; El Kayal, W.; Penchel, R.; de Andrade, G.; Boudet, A.M.; Teulieres, C. An efficient procedure to stably introduce genes into an economically important pulp tree (*Eucalyptus grandis* x *Eucalyptus urophylla*). *Transgenic Research* **2003**, *12*(4), 403411.

5. Gorrini B, Poblete H, Hernandez G, Dunn F. Particleboard and MDF using *Eucalyptus nitens*: Industrial scale

experiments. *Bosque* **2004**, *25*(3), 89-97.

6. Krzysik AM, Muehl JH, Youngquist JA, Franca FS. Medium density fiberboard made from Eucalyptus saligna. *Forest Products Journal* **2001**, *51*(10), 47-50.

7. Eusebio D, Cabangon R, Soriano F, Evans PD. Manufacture of low-cost wood-cement composites in the Philippines using plantation grown Australian species I. Eucalypts. In Proceedings 5th Pacific Rim Biobased Composites Symposium, Canberra, Australia, 10-13 December, 2000, pp. 9.

8. Coutts RSP. A review of Australian research into natural fibre cement composites. *Cement and Concrete Composites* **2005**, *27*(5), 518-526.

9. Foley W, Lassak E. The potential of bioactive constituents of *Eucalyptus* foliage as non-wood products from plantations. *Rural Industries Research and Development Corporation. Publication*, **2004**, *154*, 4; available online: http://www.rirdc.gov.au/reports/AFT/04-154.pdf.

10. Nishimura H, Noma Y, Mizutani J. Eucalyptus as biomass. Novel compounds from microbial conversion of 1, 8-Cineole. *Agricultural and Biological Chemistry* **1982**, *46*(10), 2601-2604.

11. Barton A. Industrial uses of eucalyptus oil. White Paper, 2007; available online: http://www.oilmallee.com.au/docs/BARTON.doc.

12. Ogunwande IA, Olawore NO, Schmidt JM, Setzer WN, Walker TM, Silifat JT, Olaleye ON, Aboaba SA. *In vitro* cytotoxicity activities of essential oils of *Eucalyptus torreliana* F. v. Muell (leaves and fruits). *Journal of Essential Oil-Bearing Plants* **2005**, *8*(2), 110-119.

13. Scotts Florida, https://www.scotts.com/en-us/products/mulch-soil-garden/scotts-florida-selecttm-eucalyptus-mulch (accessed 2017).

14. Langholtz M, Carter D, Alavalapati J, Rockwood D. The economic feasibility of reclaiming phosphate mined lands with short-rotation woody crops in Florida. *J. For. Econ.* **2007**, *12*(4), 237-249.

15. Rockwood DL, Naidu CV, Carter DR, Rahmani M, Spriggs T, Lin C, Alker GA, Isebrands JG, Segrest SA. Short-rotation woody crops and phytoremediation: Opportunities for agroforestry? In *New Vistas in Agroforestry*, A Compendium for the 1st World Congress of Agroforestry, Nair PKR, Rao MR, Buck LE, Eds.; Kluwer Academic Publishers, Dordrecht, The Netherlands, 2004

16. Langholtz M, Carter DR, Rockwood DL, Alavalapati JRR, Green AES. Effect of dendroremediation incentives on the profitability of short-rotation woody cropping of Eucalyptus grandis. *Forest Policy and Economics* **2005**, *7*(5), 806-817.

17. Tancredi NC, Cordero T, Rodriguez-Mirasol J, Rodriguez JJ. Activated carbons from Uruguayan eucalyptus wood. *Fuel* **1996**, *75*(15), 1701-1706.

18. Rocha JD, Coutinho AR, Luengo CA. Biopitch produced from eucalyptus wood pyrolysis liquids as a renewable binder for carbon electrode manufacture. Braz. *J. Chem. Eng.* **2002**, *19*, 127-132.

19. Sims REH, Hastings A, Schlamadinger B, Taylor G, Smith P. Energy crops: current status and future prospects. *Global Change Biology* **2006**, *12* (11), 2054-2076.

20. Rockwood DL, Rudie AW, Ralph SA, Zhu J, Winandy JE. Energy product options for Eucalyptus species grown as short rotation woody crops. *Int. J. Mol. Sci.* 9:1361-1378. http://www.mdpi.org/ ijms/papers/i9081361.pdf.

21. Sims REH, Mabee W, Saddler JN, Taylor M. An overview of second generation biofuel technologies. *Bioresource Technology* 2010:1570-1580.

22. Eschler BM, Pass DM, Willis M, Foley WJ. Distribution of foliar formylated phloroglucinol derivatives amongst *Eucalyptus* species. *Biochem. Syst. Ecol.* **2000**, *28*(90), 813-824.

23. Cheng SS, Huang CG, Chen YJ, Yu JJ, Chen WJ, Chang ST. Chemical compositions and larvicidal activities of leaf essential oils from two eucalyptus species. *Bioresource Technology* 100 (2009): 452–456.

24. Nerio LS, Olivero-Verbel J, Stashenko E. Repellent activity of essential oils: A review. *Bioresource Technology* 101 (2010) 372–378.

25. Kharwar RN, Gond SK, Kumar A, Mishra A. A comparative study of endophytic and epiphytic fungal association with leaf of Eucalyptus citriodora Hook., and their antimicrobial activity. *World J Microbiol Biotechnol* (2010) 26:1941–1948. DOI 10.1007/s11274-010-0374-y

26. Ali K, Ahmed B, Dwivedi S, Saquib Q, Al-Khedhairy AA, Musarrat J. Microwave Accelerated Green Synthesis of Stable Silver Nanoparticles with *Eucalyptus globulus* Leaf extract and their antibacterial and antibiofilm activity on clinical isolates. *PLOS One*. https://doi.org/10.1371/journal.pone.0131178.

27. Elansary HO, Salem MZM, Ashmawy NA, Yessoufou K, El-Settawy AAA: In vitro antibacterial, antifungal and antioxidant activities of Eucalyptus spp. leaf extracts related to phenolic composition. *Nat Prod Res*; 2017 Mar 16:1-4

28. Bhuyan DJ, Sakoff J, Bond DR, Predebon M, Vuong QV, Chalmers AC, van Altena IA, Bowyer MC, Scarlett CJ. In vitro anticancer properties of selected Eucalyptus species. *In Vitro Cell Dev Biol Anim*; 2017 Aug;53(7):604-615

29. Batish DR, Singh HP, Kohli RK, Kaur S. Eucalyptus essential oil as a natural pesticide. *For. Ecol. Man.* 256(2008):2166-2174.

30. Castro E, Nieves IU, Mullinnix MT, Sagues WJ, Hoffman RW, Fernández-Sandoval MT, Tian Z, Rockwood DL, Tamang B, Ingram LO. Optimization of dilute-phosphoric-acid steam pretreatment of *Eucalyptus benthamii* for biofuel production. *Applied Energy* 125(2014): 76-83.

31. Corbion. www.corbion.com/biochemicals/pharma/brands/purac. (accessed 2017)

32. Myriant. www.myriant.com/products/index.cfm. (accessed 2017)

33. http://fcrc.ifas.ufl.edu/wp-content/uploads/2014/04/2013SAFNCEucalyptusUses1.pdf. (accessed 2017)

34. Nair SS, Zhu JY, Deng Y, Ragauskas AJ. Hydrogels prepared from cross-linked nanofibrillated cellulose. *ACS Sustainable Chem. Eng.* 2014 (2): 772−780

35. Xu X, Liu F, Jiang L, Zhu JY, Haagenson D, Wiesenborn DP. Cellulose nanocrystals vs. cellulose nanofibrils: A comparative study on their microstructures and effects as polymer reinforcing agents. *ACS Appl. Mater. Interfaces***,** 2013, *5* (8): 2999–3009. DOI:10.1021/am302624t

36. Cortus. http://www.cortus.se/technology.html. (accessed 2017)

37. Proton Power. http://www.protonpower.com/synfuels. (accessed 2017)

38. Hillock R, Howard S. Utility of carbon fiber implants in orthopedic surgery: Literature review. *Reconstructive Review* 4(1), March 2014.

39. Shen H, Zhang L, Liu M, Zhang Z. Biomedical applications of graphene. *Theranostics* 2012; 2(3):283-294. doi: 10.7150/thno.3642

40. Peleg R. Graphene: The next medical revolution. https://www.medgadget.com/2015/05/graphene-next-medical-revolution.html. (accessed 2017)

41. Martinez A. In search of a better battery. http://www.floridatrend.com/article/22903/in-search-of-a-better-battery. (accessed 2017)

42. De Volder MFL, Tawfick SH, Baughman RH, Hart AJ. Carbon nanotubes: Present and future commercial applications. *Science* 339(2013), 535-539. DOI:10.1126/science.1222453.

