

Trends in the chemical and pharmacological research on the tropical trees *Calophyllum brasiliense* and *Calophyllum inophyllum*, a global context

J. Gómez-Verjan¹ · I. Gonzalez-Sanchez¹ · E. Estrella-Parra¹ · R. Reyes-Chilpa¹

Received: 11 August 2015 / Published online: 2 September 2015
© Akadémiai Kiadó, Budapest, Hungary 2015

Abstract Tropical trees of *Calophyllum* genus (Calophyllaceae) have chemical and biological importance as potential source of secondary active metabolites which can lead to the development of new drugs. Research on this species has been rising since 1992 due to the discovering of anti-HIV properties of Calanolide A found in *Calophyllum inophyllum* leaves. This compound is the most important natural product for potential development of new anti-HIV drugs and phytomedicines. The scientometric analysis (1953–2014) here performed revealed that the most studied species of *Calophyllum* genus are: *C. inophyllum* and *C. brasiliense*, distributed in the Asian, and American continents, respectively. Current research on these species is carried out mainly in India and Brazil, respectively, where these species grow. Research on *C. brasiliense* is focused mainly on ecological, antiparasitic, cytotoxic properties, and isolation of new compounds. Chemical studies and biodiesel development are the main topics in the case of *C. inophyllum*. Text mining analysis revealed that coumarins, and xanthenes are the main secondary active metabolites responsible for most of the reported pharmacological properties, and are potential compounds for the treatment of leukemia and against intracellular parasites causing American Trypanosomiasis and Leshmaniasis. On the other hand, *C. inophyllum* represents an important source for the development of 2nd generation biodiesel. Medicinal and industrial applications of these species may impulse sustainable forest plantations. To our knowledge this is the first scientometric and text mining analysis of chemical and biomedical research on *Calophyllum* genus, *C. brasiliense* and *C. inophyllum*.

Keywords *C. brasiliense* · *C. inophyllum* · Text mining · Natural products · *Calophyllum* spp.

✉ R. Reyes-Chilpa
chilpa@unam.mx

¹ Departamento de Productos Naturales, Instituto de Química, Universidad Nacional Autónoma de México, 04510 Mexico City, Distrito Federal, Mexico

Mathematics Subject Classification 92-08 (Biology and other natural sciences—computational methods)

Abbreviations

RT	Reverse transcriptase
HIV-1	Human immunodeficiency virus type 1
XAO	Xanthine oxidase
ACE	Angiotensin converting enzyme
PAF	Platelet-activating factor
SULT1A1	Sulfotransferase 1A1
SULT1A2	Sulfotransferase 1A2

Introduction

Pharmaceutical industry is facing a productivity crisis, as there is a stagnant in the number of new drug approvals, and an increasing expenditure in the research and development processes (Rafols et al. 2014). Natural products have been proposed to develop new drugs that could be effectively introduced into the pharmaceutical market (Butler et al. 2014), or as phytomedicines (plant extracts chemically and pharmacologically standardized). In this context, *Calophyllum* genus, a large group (180–200 species) of tropical trees belonging to the Calophyllaceae family, and mainly distributed in tropical regions of Asia, Africa, the Americas, Australasia, and the Pacific Islands (Stevens 1980), represent an important source of natural products, mainly coumarins, xanthenes, flavonoids, biflavonoids, chromanones, and triterpenes, with significant biological activities such as cytotoxic, antiviral, chemopreventive, antisecretory, cytoprotective, analgesic, and antimicrobial properties (Saklani and Kutty 2008; César et al. 2011). Some species of this genus are used in folk medicine to treat peptic ulcers, malaria, tumors, infections, venereal disease, blood pressure, diuretic, pain, and inflammation (Filho et al. 2009). Among *Calophyllum* spp. the two most important species are: *Calophyllum brasiliense* which is widely distributed in the American continent, from Brazil to Mexico, and *Calophyllum inophyllum* located in Asia, Africa, Pacific region, and Australia.

Calophyllum brasiliense

It is a large tree of the Tropical Rain Forests, and distributed mainly in Central, and South America and the Caribbean region; it can reach 40 m height and 1–3 m diameter. In Brazil is commonly known as “Guanandi”, and is used in traditional medicine to treat rheumatism, varicose hemorrhoids, ulcers, inflammation, and pain (Filho et al. 2009). In Mexico, its most common name is “Bari”, and the infusion of the cortex is consumed in the Sierra de Atoyac, Guerrero by women over 9 days for “cleaning” the womb after child-birth, while the seeds provide an oil used for lighting and for healing skin afflictions (Reyes-Chilpa et al. 2008; Do Carmo Souza et al. 2009). In Colombia, the peasants call this tree “árbol de aceite” (oil tree), and the yellow latex exuded from the cortex is applied topically for healing the navels of newborn children (García-Barriga, 1992). There are several studies about biological activities of this species: antimicrobial, cytotoxic, anti-neoplastic, antispasmodic, antinociceptive, anti-HIV, and antiulcer properties (Reyes-

Chilpa et al. 2004, 2008; Huerta-Reyes et al. 2004; Brenzan et al. 2007, 2008, 2012). Briefly, brasiliensic acid and isobrasiliensic acids have been isolated from stem resin, 1,5-dihydroxyxanthone, friedelin, and betulinic acid from the roots; gallic and protocatechuic acid from the fruits (Da Silva et al. 2001). Protocatechuic acid and epicatechin were isolated from the flowers (Isaias et al. 2004). From the trunk bark different xanthenes were isolated: brasixanthone A, B, C, D, E, F, G, and toxiloxixanthone A, 6-desoxijacareubin, 3,8-dyhydroxy-1,2-dimethoxyxanthone, 8-desoxygartanin, cudraxanthone F, 4-hydroxyxanthone, 1,2-dimethoxyxanthone, piranojacareubine, garcinin B, and latisxanthone C (Filho et al. 2009). Moreover, polyphenols have been isolated from AcOEt fractions of leaves: quercetin, amentoflavone, hyperoside, gallic and proatechuic acid (Da Silva et al. 2001). Finally, different types of coumarins have been isolated from different polar and non polar extracts of leaves: dipyrancoumarins, such as calanolides A, B, C, D, and E and soulatrolide, and on the other hand 5,7-dyoxy coumarinic coumarins of the mammea type such as mammea type A/BA, A/BB, B/BA, B/BB, C/AO, C/OB, B/BA, B/BA F cycle, and B/BB F cycle among others. It has been proposed the existence of two different chemotypes (chemical phenotypes) of *C. brasiliense* based on the kind of main compounds that are biosynthesized (Zavaleta-Mancera et al. 2011).

Calophyllum inophyllum

It is a large tree native from the Tropical Rain Forests of Australasia, and East Africa, and commonly known as *Alexandrian laurel*. It can reach 22 m of height; the flowers are used in some countries for ornamental purposes. It has many traditional uses in different countries. The fruit oil is indicated to treat rheumatism, gonorrhoea and itching; the bark is used to treat hemorrhage, ulcer, and as an expectorant, antiseptic, diuretic and purgative (Potti and Kurup 1970). This species has been widely studied from a phytochemical perspective. Briefly, from roots it have been isolated: caloxanthone A and B, 1,5-dihydroxyxanthone-6-desoxijacareubin, epicatechin, amentoflavone, inophyllum, isoinophyllum, inophyllin A, friedelin and stigmaterol (Jantan et al. 2001). In addition, 4-phenylcoumarins inophyllum A, C, D and E, three tricyclic coumarins such as calocoumarin A, B, and C, calofoloid, apetatolide, and phenolic cinnamic acid have also been isolated from the roots. Several xanthenes such as inoxanthone, caloxanthone A and B, macluraxanthone, 1,5-dihydroxyxanthone, calophynic acid, brasiliensic acid, inophylloic acid, calaustralin, calophyllolide, and inophyllum C and E have been isolated the leaves, as well as, friedelin-type triterpenoids, such ascanophyllol, canophyllic acid, friedelin, friedelan-3-one, 3,4-secofriedelane-3,28-dioic acid, 27-(acetyloxy) canophyllic acid, and 27-(acetyloxy)-3-oxofriedelan-28-oic acid (Ito et al. 2006; Laure et al. 2005).

Nowadays there is an increase in biomedical research providing a rich source of knowledge for pharmaceutical research, most of this knowledge can get lost among the great number of papers produced each year, for example, searching on Scopus Database the word “Cancer” retrieved more than 132,736 results only for 2014; clearly it is impossible for one person to read all these publications. Nevertheless, the development of new powerful analytical tools for scientometric analysis, and text mining are now facilitating research by helping to find new knowledge for the development of chemical and biomedical research. For drug and pharmaceutical development (Zhu et al. 2013) in natural products databases could help to reduce hit multiplicity and improve the process of *hit to lead* identification, or biotechnological approach. In this paper, we perform a scientometric and text mining analysis of chemical and biomedical research on *Calophyllum* genus focusing mainly on *C. brasiliense* and *C. inophyllum*.

Results and discussion

Scientometric analysis

During the period 1953–2014 we found 626 published papers indexed in Scopus database referent to *Calophyllum* spp. most of them (554) are original papers, while the others are *errata*, notes to editor, conference papers, among others. The main Journals which have published the original contributions are Phytochemistry, Journal of Natural Products, Forest Ecology and Management, Tetrahedron Letters, and Planta Medica. Concerning to species, 139 papers are on *C. brasiliense*, and 222 papers on *C. inophyllum* (Fig. 1). This states that most of the research performed on *Calophyllum* genus has focused on phytochemical studies, biological properties of such compounds, and ecology research.

As depicted in Fig. 1, there is an increase in the number of publication in the 90s, rising up in 1994, this probably due to the fact that calanolides (a novel class of benzotripyranones) were reported in 1992 to be highly active against HIV-1, since it is a potent inhibitor of the viral enzyme reverse transcriptase (Kashman et al. 1992). Even so, calanolides A and B were reported to be highly active against HIV-1 replication (Patil et al. 1993), leading calanolide A to reach the clinical phase II with infected patients (Butler 2005) since it was found in the previous stage to be well tolerated by healthy volunteers showing mild side effects (Creagh et al. 2001). Until 2005 Calanolide A was considered as a promising candidate to be approved by the FDA as a new drug for HIV-AIDS treatment (Butler 2005); however, the development of Calanolide A and related compounds is currently on hold, and its fate will be decided by the Sarawak government who owns the pharmaceutical company (Saklani and Kutty 2008). It is interesting to note that the first patents that protect the pharmaceutical applications, and synthesis of this group of compounds are about to expire, since the first patents were conferred since 1997.

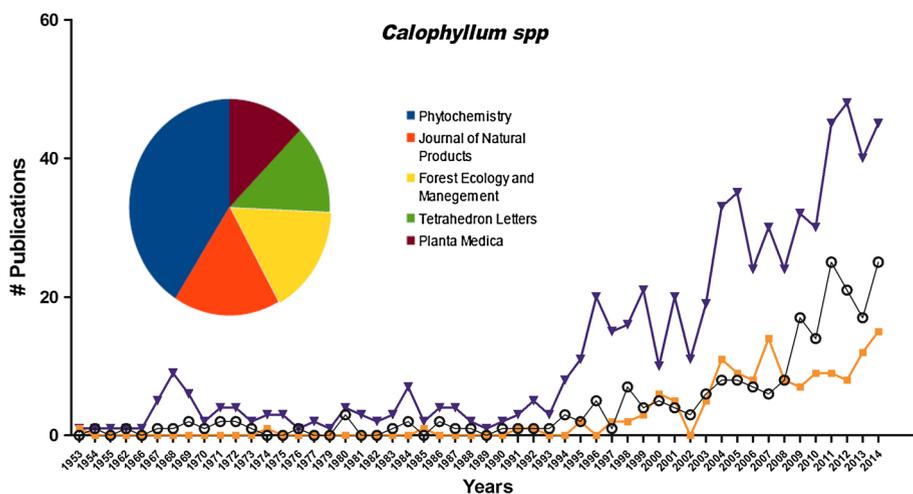


Fig. 1 Publications and main journals publishing research on inverted filled triangle: *Calophyllum* spp.; circle: *Calophyllum inophyllum*; and filled square: *Calophyllum brasiliense*

Another peak in research publications occurs in 2004, this might probably be due to the isolation of new tricyclic coumarins, and the discovering of new pharmacological activities (antimicrobial, antiparasite, antimalarial, and against coronavirus, among others) of the coumarins, chromanones, and xanthenes isolated from this genus (Su et al. 2008). Additionally interest in this genus, arises from the possible development of 2nd generation biodiesel from seeds of *C. inophyllum*, as it might represent an important source of non-edible oil (Atabani and César 2014).

As seen in Table 1, the main bibliometric indicators for the genus are a low PNC and *h* value, as well as P, indicating an increasing in the interest of research on this genus; nevertheless, there are more P, CPP and PR on *C. inophyllum* compared to *C. brasiliense*. This probably due to the fact that research on its biotechnological applications as a non edible oil source for 2nd generation biodiesel production have shown to be quite remarkable and productive, as the most quoted article on *C. inophyllum* is on this topic (Sanjid et al. 2013). On the other hand, for *C. brasiliense* the most cited articles have been for ecological applications, such as reforestation (Cusack and Montagnini 2004) (Fig. 1), nevertheless the CPP and PR on this species has been very low compared to *C. inophyllum*.

Table 2 indicates that the main countries that perform research on *Calophyllum* spp. are India, Brazil, USA, Malaysia and Japan, this is not surprising as most of these countries posses interesting research programs in natural products; moreover, the USA-NIH program for bioprospecting in collaboration with Malaysia government involved the development of calanolide A as a potential compound against HIV-1 that resulted in the creation of Sarawak Medichem Inc. Species of *Calophyllum* can also be found in the forest of several of the research leader countries, such as India, Brazil, and Malaysia. Brazil is the leader country on *C. brasiliense* research, and India is the main country for *C. inophyllum*.

The leader institutions in research on *Calophyllum* genus, *C. brasiliense* and *C. inophyllum* are University of Putra, Malaysia, Universidade Estadual de Maringá, and University of Malaysia, respectively. This is not surprising as the University of Putra Malaysia possess an interesting program for developing new products (PutraInnotech) among them natural products. University of Malaysia is located at Sarawak.

Table 2 and Fig. 2 show the main authors and co-authorship (more than five publications) leaders on research on *Calophyllum* spp. Richomme P. (Universite d’Angers) is the main author and co-author head in research of this genus, since he has the highest number of publications, specially on *C. caledonicum* and *C. dispar*. On the other side, Montagnini F.

Table 1 Scientometric indicators for research into *Calophyllum* spp.; *Calophyllum brasiliense*; and *Calophyllum inophyllum*, in the last 5 years 2009–2015

Indicator	<i>Calophyllum</i> spp.	<i>C. brasiliense</i>	<i>C. inophyllum</i>
<i>P</i>	240	60	119
<i>C</i>	1507	231	1132
CPP	6.2	3.8	9.5
PNC	33.8	35	36.1
PR	8.3	1.5	6.7
<i>h</i>	17	9	15

The indicators are: number of publications (*P*), number of citations (© mean number of citations per publication (CPP), percentage of publications not cited (PNC), percentage of reviews (PR) and Hirsch index (*h*)

Table 2 Top main countries, authors and institutions involved into *Calophyllum* spp. research, according to Scopus database

<i>Calophyllum</i> spp.	<i>P</i>	<i>h</i>	<i>C. brasiliense</i>	<i>P</i>	<i>h</i>	<i>C. inophyllum</i>	<i>P</i>	<i>h</i>
<i>Top 5 main countries</i>								
India	112	18	Brazil	80	18	India	80	16
Brazil	94	21	USA	26	10	Malaysia	26	10
USA	85	29	Mexico	18	16	Japan	18	11
Malaysia	55	14	Japan	10	8	China	18	5
Japan	46	21	Costa Rica	9	9	France	14	7
<i>Top 5 main authors</i>								
Richomme P.	15	11	Montagnini F.	10	10	Masjuki H.	12	8
Goh S.	14	8	Brenzan M.	9	6	Hathurusingha S.	7	3
Masjuki H.	12	4	Cortez D.	9	6	Ashtwa N.	7	2
Ee G.	11	8	Nakamura C.	9	5	Kalam M.	6	4
Sim K.	11	6	Reyes-Chilpa R.	9	10	Pawar K.	6	5
<i>Top 5 main institutions</i>								
U. Putra Malaysia	14	5	U. de Estadual de Maringa	17	6	U. of Malaya	13	9
U. of Malaya	10	10	Yale	17	10	U. of Ibadan	9	4
National U. of Singapore	9	9	U. do Vale do Itajai	16	7	National Chemical Laboratory India	9	4
Institut de Chimie des Substances Naturelles	9	6	U. Nacional Autonoma de México	13	6	Central Queensland	9	3
University of Peradeniya	8	10	U. Federal de Mato Grosso	13	5	U. Putra Malaysia	7	4

The indicators used are: number of publications (*P*); and Hirsch index (*h*)

(Yale University) is the leader on research on *C. brasiliense*, she posses several studies on ecological applications for this species; nevertheless, does not possess to many co-authorship relations (Fig. 2). Finally, Masjuki H.H (U. of Malaya) is the leader on *C. inophyllum* publications (Table 2) and one of the main coauthors in this topic (Fig. 2), he has focused mainly on biodiesel applications of this species.

As seen in Fig. 3 the main biological research over the last years in *C. brasiliense* have been focused on its enviromental and ecological applications; for instance, it has been proposed the development of a phytomedicine (a extract from the leaves containing anti-HIV coumarins) as a strategy to impulse sustainable plantations, contributing to stop deforestation (César et al. 2011; Tapia-Tapia and Reyes-Chilpa 2008). Even so, there is an important amount of papers for anti-parasitic activities, mostly related to mammea type coumarins, antileishmania (Brenzan et al. 2007); and trypanocidal (Reyes-Chilpa et al. 2008), as well as for cytotoxic properties specially against leukemia cell lines such as K562 and HL-60 (Ito et al. 2006; Gomez-Verjan et al. 2014; Kimura et al. 2005), and antimicrobial properties mostly related to inhibition of *Mycobacterium tuberculosis* (Pires et al. 2014) and *Helicobacter pylori* (Su et al. 2008). This highlight *C. brasiliense* as a potential source of natural products, particulary mammea type coumarins with potential for the development of new drugs with antiparasite properties, and against leukemia.

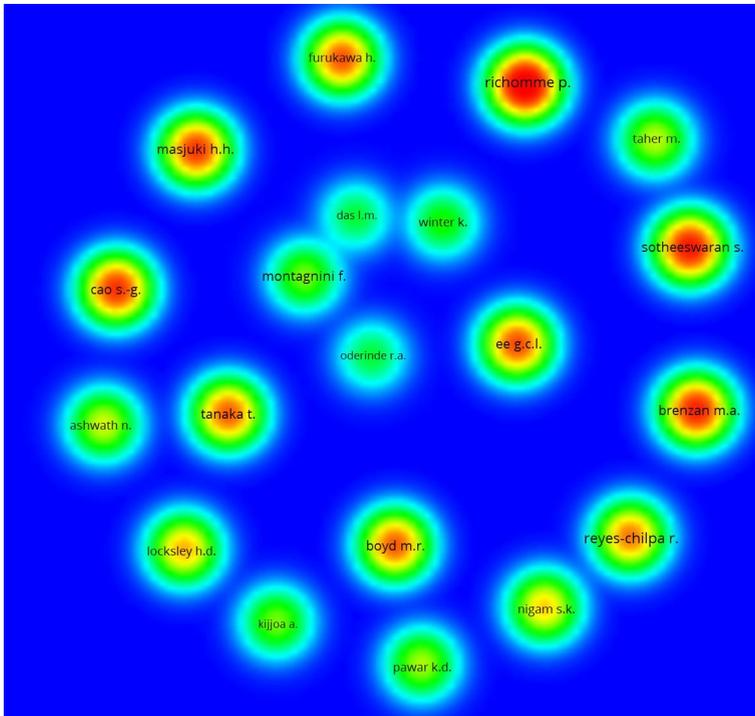


Fig. 2 Main authors with more than 5 co-authorship research publications on *Calophyllum* genus, the density (size and red color) accordingly to co-authorship importance (number of coauthorships). (Color figure online)

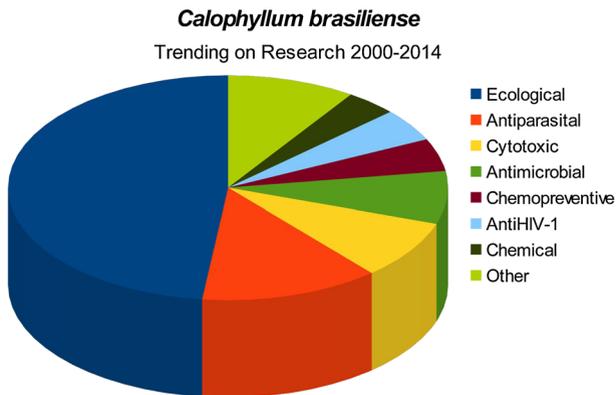


Fig. 3 Biological and pharmacological activities tested on *C. brasiliense*. Other: analgesic, relaxant, moluscicidal, immunomodulatory, antiulceral, inhibitors of SULT1A1, SULT1A2, ACE, H+K+ ATPase

Calophyllum inophyllum has a higher number of publications (147) and different categories of research as compared to *C. brasiliense* (Fig. 4). The biotechnological applications have been the most studied topic on this species compared to its pharmacological

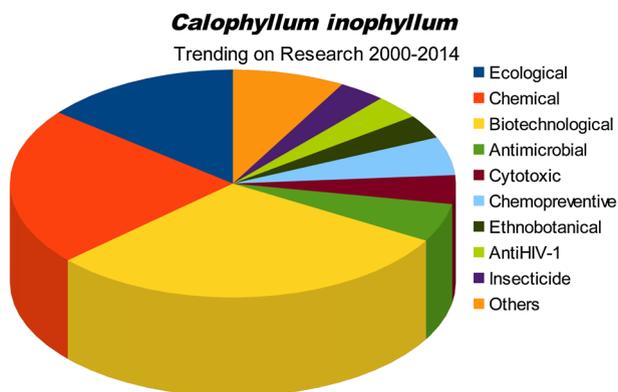


Fig. 4 Pharmacological and Biological activities of *C. inophyllum*. Others: clinical use report, ocular burn healing, analgesic, anti-platelet, anti-hypertension, anti-inflammatory, anxiolytic, inhibitor (PAF, XAO)

activities, since there are more than 40 papers on the non-edible oil from its seeds. “Honne oil” is a 2nd generation source of biodiesel. The annual yield of a mature tree is about 100 kg of seeds, which produce approximately 18 kg of oil (Rizwanul Fattah et al. 2014); once, it has been de-gummed and neutralized its capacities as a biofuel are improved (Ong et al. 2014). It has been proved that *C. inophyllum* biodiesel blends can be used effectively in a diesel engine without modification (Rizwanul Fattah et al. 2014). There are also an important amount of papers dedicated uniquely to the isolation of new and majoritarian compounds, such as coumarins (tetracyclic, tricyclic, and mammea type) and xanthenes, some of them restricted to this species. Interestingly, *C. inophyllum* coumarins possess interesting activities as chemopreventive agent against Eipstein Barr Virus; while some xanthenes have antimicrobial properties.

The text mining analysis performed with Arrowsmith software (that uses the MEDLINE database) showed a higher correlation (0.99–0.98) between the topics *Calophyllum* spp. AND Research with the terms RT-HIV-1, biodiesel production, biohydrogen, biosorption, *Rhodobacter sphaeroide*, *Enterobacter aerogenes*, antibacterial, antifungal, antileishmanial, coumarins, and xanthenes. The terms: antimicrobial activity, antibacterial activity, antileishmanial, K562, antiproliferative, and *Mycobacterium tuberculosis* correlated (0.99–0.96) with *C. brasiliense* and Research. The terms HIV-1 reverse transcriptase inhibitor, biodiesel, biohydrogen correlated (0.99–0.96) with *C. inophyllum* and Research, since one of the trending topics over the last years on this species is the obtention of non-edible oil from the seeds for the production of 2nd generation biodiesel. Correlation with *R. sphaeroide* and *E. aerogenes* is related to the fact that a two-step biodiesel production method has been proposed with these bacteria (Venkanna and Reddy 2009; Arumugam et al. 2014).

The text mining analysis indicated that the most interesting secondary metabolites isolated from *C. brasiliense* are coumarins and xanthenes, responsible for its activity against RT-HIV-1, antimicrobial and antiparasital properties. For example, calanolide A, and soulatrolide, have been proposed as a dual agents against *M. tuberculosis* and HIV-1, the former is an opportunistic microorganism associated with AIDS (Pires et al. 2014; Xu et al. 2004; Huerta-Reyes et al. 2004). The relationship between *Calophyllum* spp. and the term Cancer showed correlation (0.99–0.96) with the terms HL-60, selective COX-2 inhibitor, coumarins, apoptosis inductor, raw 264 cells, K562 cells. Moreover, there is a

strong relationship between leukemia cell lines and mammae type coumarins, since these have shown the induction of cell death by apoptosis tested against several types of leukemia cell lines such as K562 and HL-60 (Ito et al. 2006; Gomez-Verjan et al. 2014).

Conclusions

Pharmacological and biological research on *Calophyllum* spp. has been increasing over the last years (1994 to date), due to its potential as an important source of pharmacologically active compounds against HIV-1, intracellular parasites, cancer cell lines, especially leukemia, among others. In addition, *C. inophyllum* has shown potential as source of oil for 2nd generation biodiesel. Further studies should focus on toxicological research in order to validate if active secondary metabolites (xanthenes and coumarins) have real opportunities for the development of new active drugs or that extracts could be developed as phyto-medicines. Medicinal and industrial applications of the main species *C. brasiliense*, and *C. inophyllum* could also impulse sustainable forest plantations.

Experimental section

We use Scopus database which covers an expanded spectrum of journals and a faster citation analysis (Falagas et al. 2008). Searches for publications on *Calophyllum*, *C. brasiliense* and *C. inophyllum* were performed for the period 1900–2014 using the search statement:

“Topic” = (*Calophyllum*) AND [EXCLUDE(DOCTYPE, “er” OR EXCLUDE (DOCTYPE, “no”) (*C. brasiliense*)] AND [EXCLUDE(DOCTYPE, “er” OR EXCLUDE (DOCTYPE, “no”), *C. inophyllum*)] AND [EXCLUDE(DOCTYPE, “er” OR EXCLUDE (DOCTYPE, “no”)], respectively. “Topic” refers to *ALL FIELD*.

Scientometric indicators

We used bibliometric indicators described in the literature for bibliometric studies (Li and Willett 2010); number of publications (*P*), number of citations (© mean number of citations per publication (CPP), percentage of publications not cited (PNC), percentage of reviews (PR) and Hirsch index (*h*).

Scientometric cluster analysis (more than 5 co-authorship publications), density (number of co-authorship publications) and network (authors related in the co-authorship clusters) were built with freely available software VOSviewer version 1.6.0 (Van Eck and Waltman 2010).

For trending topics on *Calophyllum* research we performed text mining analysis with free on line software Arrowsmith (Smalheiser et al. 2009), which identify meaningful links between two sets of Medline articles, a UIC-based site for searching links between two literatures within Medline, we search for the intersection (B-list) of *Calophyllum* AND research (Job ID: 196081), *C. brasiliense* AND research (Job ID: 19981), *C. inophyllum* AND research (Job ID:20010), *Calophyllum* AND Cancer (Job ID:20039), *Calophyllum* AND biodiesel (Job ID:20184). All other graphs were made by GraphPad Prism 5 statistical software.

Acknowledgments Juan Carlos Gomez Verjan is grateful with Posgrado en Ciencias Biomédicas-UNAM and CONACyT for providing a scholarship number 220346. This work was submitted in fulfillment of the requirements to obtain PhD degree at Doctorado en Ciencias Biomédicas and Universidad Nacional Autónoma de México. This research was supported by Grant IG200513 from DGAPA-UNAM. I. Gonzalez-Sanchez was supported by a post-doctoral Grant (DGAPA-UNAM).

References

- Arumugam, A., Sandhya, M., & Ponnusami, V. (2014). Biohydrogen and polyhydroxyalkanoate co-production by *Enterobacter aerogenes* and *Rhodobacter sphaeroides* from *Calophyllum inophyllum* oil cake. *Bioresource Technology*, *164*, 170–176.
- Atabani, A. E., & César, A. D. S. (2014). *Calophyllum inophyllum* L.—A prospective non-edible biodiesel feedstock: study of biodiesel production, properties, fatty acid composition, blending and engine performance. *Renewable and Sustainable Energy Reviews*, *37*, 644–655.
- Brenzan, M. A., Nakamura, C. V., Dias Filho, B. P., Ueda-Nakamura, T., Young, M. C. M., Córrea, A. G., et al. (2008). Structure–activity relationship of (–) mamea A/BB derivatives against *Leishmania amazonensis*. *Biomedicine & Pharmacotherapy*, *62*, 651–658.
- Brenzan, M. A., Nakamura, C. V., Dias Filho, B. P., Ueda-Nakamura, T., Young, M., & Cortez, D. A. G. (2007). Antileishmanial activity of crude extract and coumarin from *Calophyllum brasiliense* leaves against *Leishmania amazonensis*. *Parasitology Research*, *101*, 715–722.
- Brenzan, M. A., Santos, A. O., Nakamura, C. V., Filho, B. P. D., Ueda-Nakamura, T., Young, M. C. M., et al. (2012). Effects of (–) mamea A/BB Isolated from *Calophyllum brasiliense* leaves and derivatives on mitochondrial membrane of *Leishmania amazonensis*. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology*, *19*, 223–230.
- Butler, M. S. (2005). Natural products to drugs: natural product derived compounds in clinical trials. *Natural Products Reports*, *22*, 162–195.
- Butler, M. S., Robertson, A. A. B., & Cooper, M. A. (2014). Natural product and natural product derived drugs in clinical trials. *Natural Products Reports*, *31*, 1612–1661.
- César, G. Z. J., Alfonso, M. G. G., Marius, M. M., Elizabeth, E.-M., Ángel, C. B. M., Maira, H.-R., et al. (2011). Inhibition of HIV-1 reverse transcriptase, toxicological and chemical profile of *Calophyllum brasiliense* extracts from Chiapas, Mexico. *Fitoterapia*, *82*, 1027–1034.
- Creagh, T., Ruckle, J. L., Tolbert, D. T., Giltner, J., Eiznhamer, D. A., Dutta, B., et al. (2001). Safety and Pharmacokinetics of Single Doses of (+)-Calanolide A, a novel, naturally occurring nonnucleoside reverse transcriptase inhibitor, in healthy, human immunodeficiency virus-negative human subjects. *Antimicrobial Agents and Chemotherapy*, *45*, 1379–1386.
- Cusack, D., & Montagnini, F. (2004). The role of native species plantations in recovery of understory woody diversity in degraded pasturelands of Costa Rica. *Forest Ecology and Management*, *188*, 1–15.
- Da Silva, K. L., dos Santos, A. R., Mattos, P. E., Yunes, R. A., Delle-Monache, F., & Cechinel-Filho, V. (2001). Chemical composition and analgesic activity of *Calophyllum brasiliense* leaves. *Therapie*, *56*, 431–434.
- Do Carmo Souza, M., Beserra, A. M. S., Martins, D. C., Real, V. V., dos Santos, R. A. N., Rao, V. S., et al. (2009). In vitro and in vivo anti-helicobacter pylori activity of *Calophyllum brasiliense* Camb. *Journal of Ethnopharmacology*, *123*, 452–458.
- Falagas, M. E., Pitsouni, E. I., Malietzis, G. A., & Pappas, G. (2008). Comparison of PubMed, Scopus, Web of Science, and Google Scholar: Strengths and weaknesses. *FASEB Journal*, *22*, 338–342.
- Filho, V., Meyre-Silva, C., & Niero, R. (2009). Chemical and pharmacological aspects of the genus *Calophyllum*. *Chemistry & Biodiversity*, *6*, 313–327.
- García-Barriga, H. (1992). *Flora Medicinal de Colombia*. *Botanica Medica* (Vol. 2). Bogota: Tercer Mundo Editores.
- Gomez-Verjan, J. C., Estrella-Parra, E. A., González-Sánchez, I., Vázquez-Martínez, E. R., Vergara-Castañeda, E., Cerbón, M. A., & Reyes-Chilpa, R. (2014). Molecular mechanisms involved in the cytotoxicity induced by coumarins from *Calophyllum brasiliense* in K562 leukaemia cells. *Journal of Pharmacy and Pharmacology*, *66*, 1189–1195.
- Huerta-Reyes, M., Basualdo, M. D. C., Abe, F., Jimenez-Estrada, M., Soler, C., & Reyes-Chilpa, R. (2004). HIV-1 inhibitory compounds from *Calophyllum brasiliense* leaves. *Biological and Pharmaceutical Bulletin*, *27*, 1471–1475.

- Isaias, D. E., Niero, R., Noldin, V. F., de Campos-Buzzi, F., Yunes, R. A., Delle-Monache, F., & Cechinel-Filho, V. (2004). Pharmacological and phytochemical investigations of different parts of *Calophyllum brasiliense* (Clusiaceae). *Pharmazie*, 59, 879–881.
- Ito, C., Murata, T., Itoigawa, M., Nakao, K., Kaneda, N., & Furukawa, H. (2006). Apoptosis inducing activity of 4-substituted coumarins from *Calophyllum brasiliense* in human leukaemia HL-60 cells. *Journal of Pharmacy and Pharmacology*, 58, 975–980.
- Jantan, I., Juriyati, J., & Warif, N. A. (2001). Inhibitory effects of xanthenes on platelet activating factor receptor binding in vitro. *Journal of Ethnopharmacology*, 75, 287–290.
- Kashman, Y., Gustafson, K. R., Fuller, R. W., Cardellina, J. H., McMahon, J. B., Currens, M. J., et al. (1992). The calanolides, a novel HIV-inhibitory class of coumarin derivatives from the tropical rainforest tree, *Calophyllum Lanigerum*. *Journal of Medicinal Chemistry*, 35, 2735–2743.
- Kimura, S., Ito, C., Jyoko, N., Segawa, H., Kuroda, J., Okada, M., et al. (2005). Inhibition of Leukemic cell growth by a novel anti-cancer drug (GUT-70) from *Calophyllum brasiliense* that acts by induction of apoptosis. *International Journal of Cancer*, 113, 158–165.
- Laure, F., Herbette, G., Faure, R., Bianchini, J. P., Raharivelomanana, P., & Fogliani, B. (2005). Structures of new secofriedelane and friedelane acids from *Calophyllum inophyllum* of French Polynesia. *Magnetic Resonance in Chemistry*, 43, 65–68.
- Li, J., & Willett, P. (2010). Bibliometric analysis of chinese research on cyclization, MALDI-TOF and antibiotics. *Journal of Chemical Information and Modeling*, 50, 22–29.
- Ong, H. C., Masjuki, H. H., Mahlia, T. M. I., Silitonga, A. S., Chong, W. T., & Leong, K. Y. (2014). Optimization of biodiesel production and engine performance from high free fatty acid *Calophyllum inophyllum* oil in CI diesel engine. *Energy Conversion and Management*, 81, 30–40.
- Patil, A. D., Freyer, A. J., Eggleston, D. S., Haltiwanger, R. C., Bean, M. F., Taylor, P. B., et al. (1993). The inophyllums, novel inhibitors of HIV-1 reverse transcriptase isolated from the Malaysian tree, *Calophyllum inophyllum* Linn. *Journal of Medicinal Chemistry*, 36, 4131–4138.
- Pires, C. T. A. T., Brenzan, M. A., Scodro, R. B. D. L., Cortez, D. A. G., Lopes, L. D. G., Siqueira, V. L. D., & Cardoso, R. F. F. (2014). Anti-mycobacterium tuberculosis activity and cytotoxicity of *Calophyllum brasiliense* Cambess (Clusiaceae). *Memórias do Instituto Oswaldo Cruz*, 109, 324–329.
- Potti, G. R., & Kurup, P. A. (1970). Antibacterial principle of the root bark of *Calophyllum inophyllum*: Isolation and antibacterial activity. *Indian Journal of Experimental Biology*, 8, 39–40.
- Rafols, I., Hopkins, M. M., Hoekman, J., Siepel, J., O'Hare, A., Perianes-Rodríguez, A., & Nightingale, P. (2014). Big pharma, little science? *Technological Forecasting and Social Change*, 81, 22–38.
- Reyes-Chilpa, R., Estrada-Muñiz, E., Apan, T. R. R., Amekraz, B., Aumelas, A., Jankowski, C. K., & Vázquez-Torres, M. (2004). Cytotoxic effects of mammea type coumarins from *Calophyllum brasiliense*. *Life Sciences*, 75, 1635–1647.
- Reyes-Chilpa, R., Estrada-Muñiz, E., Vega-Avila, E., Abe, F., Kinjo, J., & Hernández-Ortega, S. (2008). Trypanocidal constituents in plants: 7. Mammea-type coumarins. *Memórias do Instituto Oswaldo Cruz*, 103(5), 431–436.
- Rizwanul Fattah, I. M., Masjuki, H. H., Kalam, M. A., Wakil, M. A., Ashraf, A. M., & Shahir, S. A. (2014). Experimental investigation of performance and regulated emissions of a diesel engine with *Calophyllum inophyllum* biodiesel blends accompanied by oxidation inhibitors. *Energy Conversion and Management*, 83, 232–240.
- Saklani, A., & Kutty, S. K. (2008). Plant-derived compounds in clinical trials. *Drug Discovery Today*, 13, 161–171.
- Sanjid, A., Masjuki, H. H., Kalam, M. A., Rahman, S. M. A., Abedin, M. J., & Palash, S. M. (2013). Impact of palm, mustard, waste cooking oil and *Calophyllum inophyllum* biofuels on performance and emission of CI engine. *Renewable and Sustainable Energy Reviews*, 27, 664–682.
- Smalheiser, N. R., Torvik, V. I., & Zhou, W. (2009). Arrowsmith two-node search interface: A tutorial on finding meaningful links between two disparate sets of articles in MEDLINE. *Computer Methods and Programs in Biomedicine*, 94, 190–197.
- Stevens, P. F. (1980). A revision of the old world species of *Calophyllum* (Guttiferae). *Journal of Arnold Arboretum*, 61, 117–699.
- Su, X.-H. H., Zhang, M.-L. L., Li, L.-G. G., Huo, C.-H. H., Gu, Y.-C. C., & Shi, Q.-W. W. (2008). Chemical constituents of the plants of the genus *Calophyllum*. *Chemistry & Biodiversity*, 5, 2579–2608.
- Tapia Tapia, E. C., & Reyes Chilpa, R. (2008). Productos Forestales No Maderables En México : Aspectos Económicos Para El Desarrollo Sustentable Mexican non-wood forest products: Economic aspects for sustainable development. *Maderas y Bosques*, 14, 95–112.
- Van Eck, N. J., & Waltman, L. (2010). Software survey: VOSviewer, a computer program for bibliometric mapping. *Scientometrics*, 84, 523–538.

- Venkanna, B. K., & Reddy, C. V. (2009). Biodiesel production and optimization from *Calophyllum inophyllum* linn oil (honne oil)—A three stage method. *Bioresource Technology*, *100*, 5122–5125.
- Xu, Z.-Q., Barrow, W. W., Suling, W. J., Westbrook, L., Barrow, E., Lin, Y.-M., & Flavin, M. T. (2004). Anti-HIV natural product (+)-calanolide A is active against both drug-susceptible and drug-resistant strains of mycobacterium tuberculosis. *Bioorganic & Medicinal Chemistry*, *12*, 1199–1207.
- Zavaleta-Mancera, H., Reyes-Chilpa, R., & García-Zebadua, J. (2011). Leaf structure of two chemotypes of *Calophyllum brasiliense* from Mexico. *Microscopy and Microanalysis*, *17*, 340–341.
- Zhu, X.-F., Hao, J.-F., & Xin, L. (2013). Scientific publications in obstetrics and gynecology journals from China, 2000–2009. *International Journal of Gynaecology and Obstetrics*, *123*, 96–100.