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

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Abstract

As a possible source of secondary active compounds that could result in the creation of novel medications, tropical plants belonging to the Calophyllum genus (Calophyllaceae) are significant both chemically and biologically. Since 1992, research on this species has increased as a result of the discovery that Calanolide A, which is present in the leaves of Calophyllum inophyllum, has anti-HIV potential. The most significant natural product for the possible creation of novel anti-HIV medications and phytomedicines is this molecule. The most researched species of the Calophyllum genus are C. inophyllum and C. brasiliense, which are found in the Asian and American continents, respectively, according to the scientometric study conducted here between 1953 and 2014. The majority of the current research on these species is conducted in Brazil and India, respectively, where they are found. The primary areas of study for C. brasiliense are its ecological, antiparasitic, cytotoxic, and novel chemical isolation characteristics. The primary subjects in the case of C. inophyllum are chemical investigations and the production of biodiesel. According to text mining analysis, coumarins and xanthones are the primary secondary active metabolites that account for the majority of the reported pharmacological properties. These compounds have the potential to treat leukemia and fight intracellular parasites that cause leshmaniasis and American trypanosomiasis. Conversely, C. inophyllum is a significant source for the production of second-generation biodiesel. These plants' industrial and medicinal uses could encourage the development of sustainable forest plantations. To the best of our knowledge, this is the first text mining and scientometric study of chemical and biological studies on the Calophyllum genus, namely C. brasiliense and C. inophyllum.

Keywords: text mining, natural products, C. brasiliense, C. inophyllum, Calophyllum spp.

Introduction

The pharmaceutical sector is experiencing a productivity crisis due to rising research and development costs and a stagnation in the number of new medicine approvals (Rafols et al. 2014). Natural products have been suggested as phytomedicines (chemically and pharmacologically standardized plant extracts) or as new medications that may be successfully launched into the pharmaceutical market (Butler et al. 2014). In this regard, the Calophyllum genus, which comprises 180–200 species of tropical trees that are primarily found in tropical regions of Asia, Africa, the Americas, Australasia, and the Pacific Islands (Stevens 1980), is a significant source of natural products, primarily coumarins, xanthones, flavonoids, biflavonoids, chromanones, and triterpenes. These compounds have important biological activities, including cytotoxic, antiviral, chemopreventive, antisecretory, analgesic, and antimicrobial qualities (Saklani and Kutty 2008; Cesar et al. 2011). Peptic ulcers, malaria, tumors, infections, venereal illness, blood pressure, diuretics, pain, and inflammation are among the conditions that some species of this genus are used to treat in traditional medicine (Filho et al. 2009). The two most significant species of Calophyllum spp. are Calophyllum brasiliense, which is found throughout the American continent from Brazil to Mexico, and Calophyllum inophyllum, which is found in Asia, Africa, the Pacific area, and Australia.

Calophyllum Brasiliense

It is a huge tree that grows to a height of 40 meters and a diameter of 1 to 3 meters. It is primarily found in Central and South America as well as the Caribbean. Known as "Guanandi" in Brazil, it is used in traditional medicine to treat pain, inflammation, ulcers, rheumatism, and varicose hemorroids (Filho et al. 2009). Its most popular name in Mexico is "Bari." In the Sierra de Atoyac, Guerrero, women over nine days old drink the cortex infusion to "clean" their wombs after giving birth, and the seeds yield an oil that is used for lighting and to treat skin conditions (Reyes-Chilpa et al. 2008; Do Carmo Souza et al. 2009). The yellow latex that emerges from the cortex of this tree, which the peasants in Colombia refer to as "oil tree," is applied topically to treat newborns' navels (Garcia-Barriga, 1992). Numerous studies have examined this species' biological activities, including its antibacterial, cytotoxic, anti-neoplastic, antispasmodic, antinociceptive, anti-HIV, and antiulcer qualities (Reyes-Huerta-Reyes et al. 2004; Brenzan et al. 2007, 2008, 2012; Chilpa et al. 2004, 2008). Stem resin, 1,5-dihydroxyxanthone, friedelin, and betulinic acid from the roots, as well as gallic and protocatechuic acid from the fruits, have all been shown to include brasiliensic and isobrasiliensic acids (Da Silva et al. 2001). The blooms were shown to contain epicatechin and protocatechuic acid (Isaias et al. 2004). Several xanthones were extracted from the trunk bark, including 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). Additionally, quercetin, amentoflavone, hyperoside, gallic acid, and proatechuic acid have been identified as polyphenols from AcOEt fractions of leaves (Da Silva et al. 2001). Lastly, a variety of coumarins, including dipyranocoumarins like calanolides A, B, C, D, and E and soulatrolide, as well as 5,7-dyoxycoumarinic coumarins of the mammea type, including 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. Two distinct chemo-types (chemical phenotypes) of C have been suggested to exist. brasiliense according to the primary substances that are produced through biosynthesis (Zavaleta-Mancera et al. 2011).

Calophyllum inophyllum

This big tree, often called Alexandrian laurel, is native to the tropical rain forests of East Africa and Australasia. It may grow up to 22 meters tall, and the blossoms are utilized as decorations in several nations. It has numerous customary applications across various nations. The bark is used as an expectorant, antimicrobial, diuretic, and purgative; the fruit oil is used to cure rheumatism, gonorrhea, and itching; and the bark is used to treat ulcers and bleeding (Potti and Kurup 1970). This plant has been the subject of much phytochemical research. In summary, caloxanthone A and B, 1,5-dihydroxyxanthone-6-desoxijacarubin, epicatechin, amentoflavone, inophyllum, isoinophyllum, inophyllin A, friedelin, and stigmasterol have all been extracted from roots (Jantan et al. 2001). Furthermore, three tricyclic coumarins, including calofoloid, apetatolide, phenolic cinnamic acid, and 4-phenylcoumarins inophyllum A, C, D, and E, have been identified from the roots. In addition to friedelin-type triterpenoids like canophyllol, canophyllic acid, friedelin, friedelan-3-one, 3,4-secofriedelane-3,28-dioic acid, 27-(acetyloxy) canophyllic acid, and 27-(acetyloxy)-3-oxofriedelan-28-oicacid(Itoetal.2006;Laureetal.2005). These days, there is a surge in biomedical research, which is a rich source of information for pharmaceutical research. However, most of this information may be lost in the enormous volume of papers produced annually. For instance, searching for "cancer" on the Scopus database yielded over 132,736 results for 2014 alone; it is obviously impossible for one person to read all of these publications. However, the creation of new, potent analytical tools for text mining and scientometric analysis is currently facilitating research by assisting in the discovery of new information for the advancement of chemical and biological research. Natural product databases could aid in lowering hit multiplicity and enhancing the hit-to-lead identification process, or biotechnological technique, for medication and pharmaceutical development (Zhu et al. 2013). In this work, we conduct a text mining and scientometric analysis of chemical and biological studies on the Calophyllum genus, primarily concentrating on C. brasiliense and C. inophyllum.

Results and discussion

Scientometric evaluation

We discovered 626 published papers related to Calophyllum spp. that were indexed in the Scopus database between 1953 and 2014. The majority of them (554) are original papers; the remainder include conference papers, errata, and notes to editors, among other things. Phytochemistry, Journal of Natural Products, Forest Ecology and Management, Tetrahedron Letters, and Planta Medica are the primary journals that published the original contributions. In terms of species, there are 222 papers on C. inophyllum and 139 papers on C. brasiliense (Fig. 1). According to this, the majority of studies conducted on the Calophyllum genus have concentrated on phytochemical analyses, the biological characteristics of these substances, and ecology.As shown in Fig. 1, the number of publications increased during the 1990s, peaking in 1994. This is likely because calanolides, a novel class of benzo-tripyranones, were reported to be highly active against HIV-1 in 1992 due to

their potent inhibition of the viral enzyme reverse transcriptase (Kashman et al. 1992). Despite this, calanolides A and B were found to be very effective against HIV-1 replication (Patil et al. 1993). As a result, calanolide A was found to be well tolerated by healthy volunteers with mild side effects (Creagh et al. 2001), which allowed it to advance to clinical phase II with infected patients (Butler 2005). The development of Calanolide A and related compounds is currently on hold, and the Sarawak government, which owns the pharmaceutical company, will decide its fate (Saklani and Kutty 2008). Prior to 2005, Calanolide A was thought to be a promising candidate to be approved by the FDA as a new drug for HIV-AIDS treatment (Butler 2005). Interestingly, given the first patents covering the production and pharmacological uses of this class of chemicals were granted in 1997, they are about to expire.

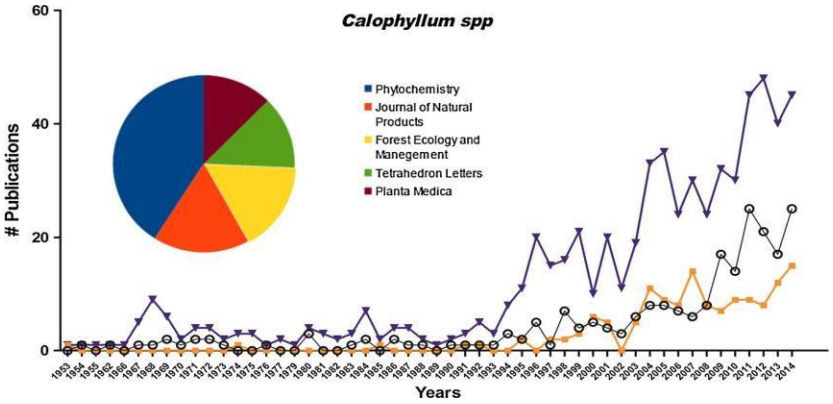

Fig. 1 Publications and main journals publishing research on inverted filled triangle: *Calophyllum* spp.; circle: *Calophyllum inophyllum*; and filled square: *Calophyllum brasiliense*

The isolation of novel tricyclyc coumarins and the identification of novel pharmacological activities (antimicrobial, antiparasite, antimalarial, and against coronavirus, among others) of the coumarins, chromanones, and xanthones isolated from this genus may have contributed to another peak in research publications in 2004 (Su et al. 2008). The potential production of second-generation biodiesel from C. inophyllum seeds, which might be a significant supply of non-edible oil, is another reason for attention in this genus (Atabani and Cesar 2014). Although there are more P, CPP, and PR on C. inophyllum than C. brasiliense, Table 1 shows that the primary bibliometric indicators for the species are a low PNC and h value as well as P, indicating a rising interest in research on this genus. This is likely because research on its biotechnological uses as a non-edible oil source for the creation of second-generation biodiesel has shown to be quite impressive and fruitful, as evidenced by the most cited article on C. inophyllum (Sanjid et al. 2013). However, compared to C. inophyllum, the CPP and PR on C. brasiliense have been extremely low. The most cited publications for this plant have been for ecological uses, such as reforestation (Cusack and Montagnini 2004) (Fig. 1). In addition, the USA-NIH program for bioprospecting in partnership with the Malaysian government involved the development of calanolide A as a potential compound against HIV-1, which led to the establishment of Sarawak Medichem Inc. Table 2 shows that India, Brazil, the USA, Malaysia, and Japan are the main countries that conduct research on Calophyllum spp. Additionally, the forests of several of the top research nations, including Brazil, Malaysia, and India, contain species of Calophyllum. India is the primary country for C. inophyllum research, whereas Brazil is the leader in C. brasiliense research. The University of Putra, Malaysia, Universidade Estadual de Maringa, and University of Malaysia are the leading institutes in research on the Calophyllum genus, specifically C. brasiliense and C. ino-phyllum. This is not shocking because the University of Putra Malaysia has an intriguing program for creating new products, including natural products, called PutraInnotech. Sarawak is home to the University of Malaysia. The primary authors and co-authorship leaders (more than five publications) on research on Calophyllum spp. are displayed in Table 2 and Fig. 2. With the most publications, particularly on C. caledonicum and C. dispar, Richomme P. (Universite d'Angers) is the primary author and co-author head in this genus's study. Conversely, Montagini F.

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

Indicator	*Calophyllum* spp.	*C. brasiliense*	*C. inophyllum*
P	240	60	119

C	1507	231	1132
CPP	6.2	3.8	9.5
PNC	33.8	35	36.1
PR	8.3	1.5	6.7
h	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

Calophyllum spp.	*P*	*h*	*C. brasiliense*	*P*	*h*	*C. inophyllum*	*P*	*h*
Top 5 main countries								
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
Top 5 main authors								
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
Top 5 main institutions								
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 Me´xico	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 foremost authority on C. brasiliense research and has a number of papers on ecological uses for this species; nevertheless, she does not have many co-authorship relationships (Fig. 2). Lastly, Masjuki H.H. (U. of Malaya) is one of the primary coauthors on this issue (Fig. 2) and the leader in C. inophyllum publications (Table 2). He has mostly concentrated on the use of this species in biodiesel.
The development of a phytomedicine (an extract from the leaves containing anti-HIV coumarins) has been suggested as a strategy to stimulate sustainable plantations and stop deforestation (Cesar et al. 2011; Tapia-Tapia and Reyes-Chilpa 2008). As shown in Fig. 3, the majority of biological research in C. brasiliense over the past few years has been focused on its environmental and ecological applications. Nevertheless, a significant number of studies have reported anti-parasitic activities, primarily associated with mammea type coumarins, antileishmania (Brenzan et al. 2007), trypanocidal (Reyes-Chilpa et al. 2008), and cytotoxic properties, particularly against leukemia cell lines like K562 and HL-60 (Ito et al. 2006; Gomez-Verjan et al. 2014; Kimura et al. 2005). This highlights C. brasiliense as a possible source of natural compounds, especially coumarins of the Mammea type, which may be used to create novel medications with antiparasite and anti-leukemia effects.

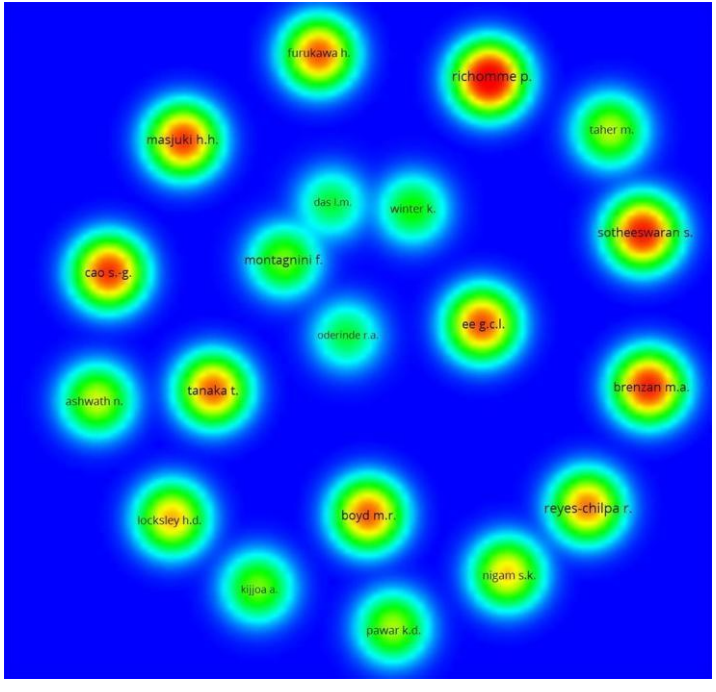

Fig. 2 Main authors with more than 5 co-authorship research publications on *Calophyllum* genus, the density (size and *red color*) accordingly to co-authorship importance (number of coauthorships). (Color figure online)

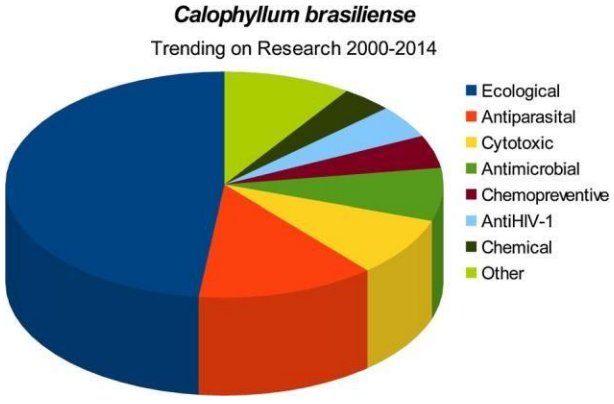

Fig. 3 Biological and pharmacological activities tested on *C. brasiliense.* Other: analgesic, relaxant, molusicidal, immunomodulatory, antiulceral, inhibitors of SULT1A1, SULT1A2, ACE, H+K+ ATPase

Compared to C. brasiliense, Calophyllum inophyllum has more publications (147) and a variety of study categories (Fig. 4). Compared to its pharmaceutical uses, this species' biotechnological applications have been the most researched.

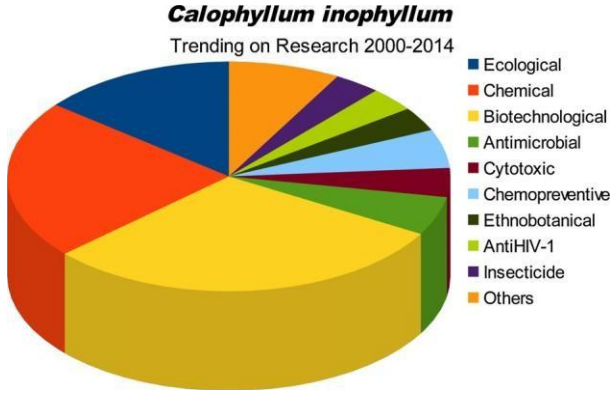

Fig. 4 Pharmacological and Biological activities of *C. inophyllum.* Others: clinical use report, ocular burn healing, analgesic, anti-platelet, anti-hypertension, anti-inflammatory, anxiolytic, inhibitor (PAF, XAO)

activity, since over 40 studies have examined the non-edible oil from its seeds. "Honne oil" is a source of second-generation biodiesel. According to Rizwanul Fattah et al. (2014), a mature tree produces roughly 100 kg of seeds per year, which provides about 18 kg of oil; when it has been de-gummed and neutralized, its potential as a biofuel is increased (Ong et al. 2014). It has been demonstrated that C. inophyllum biodiesel blends function efficiently in diesel engines without modification (Rizwanul Fattah et al. 2014). The isolation of novel and majoritarian compounds, such as xanthones and coumarins (tetracyclic, tricyclic, and mammea type), some of which are exclusive to this species, is also the focus of a large number of papers. C. inophyllum coumarins have interesting chemopreventive efficacy against Eipstein Barr Virus, whereas several xanthones have antibacterial properties. In the text mining analysis using Arrowsmith software (which uses the MEDLINE database), 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 xanthones showed a higher correlation (0.99–0.98). The terms "antimicrobial activity," "antibacterial activity," "antileishmanial," "K562,"

"antiproliferative," and "Mycobacterium tuberculosis" demonstrated a link (0.99–0.96) with C. brasiliense and research. Because getting non-edible oil from the seeds for the production of second-generation biodiesel has been a prominent topic on this species in recent years, the terms HIV-1 reverse transcriptase inhibitor, biodiesel, and biohydrogen are associated (0.99–0.96) with C. inophyllum and study. The suggestion of a two-step biodiesel production process utilizing R. sphaeroide and E. aerogenes is linked to the correlation (Venkanna and Reddy 2009;Arumugam et al. 2014).The text mining study revealed that coumarins and xanthones, which are responsible for the antibacterial, antiparasital, and RT-HIV-1 activities of C. brasiliense, are the most interesting secondary metabolites recovered from the plant. For example, soulatrolide and calanolide A have been proposed as dual medicines against M. tuberculosis and HIV-1, an opportunistic bacterium associated with AIDS (Pires et al. 2014; Xu et al. 2004; Huerta-Reyes et al. 2004). The relationships between species of Calophyllum. Additionally, there was a link (0.99–0.96) between the terms HL-60, selective COX-2 inhibitor, coumarins, apoptosis inductor, raw 264 cells, and K562 cells with the term "cancer." Furthermore, there is a Mammea type coumarins have been shown to induce cell death by apoptosis when tested against a variety of leukemia cell lines, such as K562 and HL-60, indicating a strong association between them and leukemia cell lines (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 leu- kemia, 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 (xanthones and coumarins) have real opportunities for the development of new active drugs or that extracts could be developed as phy- tomedicines. Medicinal and industrial applications of the main species *C. brasiliense*, and *C. inophyllum* could also impulse sustainable forest plantations.

Experimental section

We employ the Scopus database, which offers a quicker citation analysis and a wider range of journals (Falagas et al. 2008). The following search statement was used to look for papers on Calophyllum, C. brasiliense, and C. inophyllum from 1900 to 2014:

‘‘Top´ıc’’ = (*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 markers

The 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) were the bibliometric indicators we used, as described in the literature for bibliometric studies (Li and Willett 2010).Using the open-source program VOSviewer version 1.6.0, scientometric cluster analysis (more than five co-authorship publications), density (number of co-authorship publications), and network (authors associated in the co-authorship clusters) were constructed (Van Eck and Waltman 2010). We searched 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), and Calophyllum AND biodiesel (Job ID: 20184) using the free online program Arrowsmith (Smalheiser et al. 2009). GraphPad Prism 5 statistical software was used to create all other graphics.

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