

NEOFLAVONOIDS AND ITS IMPLICATIONS WITH RELATION TO TREATMENT OF NEGLECTED DISEASES: A TECHNOLOGICAL FORECASTING

NEOFLAVONOIDES E SUAS IMPLICAÇÕES COM RELAÇÃO AO TRATAMENTO DE DOENÇAS NEGLIGENCIADAS: UMA PROSPECÇÃO TECNOLÓGICA

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Abstract

The present work aimed to make a technological forecasting about the neoflavonoids and its implications in treatment of neglected diseases (NDs). Thus, this research was carried out through a comprehensive and systematic bibliographic search in articles and patents. The articles were searched in the database of the Periodical of CAPES, Science Direct, Scopus, Pub Med, Web of Science and ACS Publications. The patent research was performed in bases of the INPI, EPO, WIPO, USPTO and SIPO. According to the results obtained, it was possible to observe that the neoflavonoids may be a new source of medications for the treatment of NDs, since were found studies that attributed activity for the treatment of malaria, trypanosomiasis and leishmaniasis. Large part of published documents was in the form of scientific articles and a small part in the form of deposit of record of patent applications. In this way, this work can serve as an incentive of technological innovation for the development of new research involving neoflavonoids, seen that the record number of deposits of patent applications is still relatively insufficient to meet the current demand for technological and scientific innovation with relation to NDs.

Key words: *Neglected diseases, neoflavonoids, technological forecasting.*

Resumo

O presente trabalho teve como objetivo realizar uma prospecção tecnológica sobre os neoflavonoides e suas implicações sobre o tratamento das doenças negligenciadas (DNs). Sendo assim, esta prospecção foi realizada através de uma pesquisa bibliográfica abrangente e sistemática em artigos e patentes. Os artigos foram pesquisados no banco de dados do Periódico da CAPES, Science Direct, Scopus, Pub Med, Web of Science e ACS Publications. A pesquisa de patentes foi realizada nas bases do INPI, EPO, WIPO, USPTO e SIPO. De acordo com os resultados obtidos, foi

possível observar que os neoflavonoides podem ser uma nova fonte de medicamentos para o tratamento das DN, visto que foram encontrados estudos que atribuíram atividade para o tratamento da malária, tripanossomose e leishmaniose. Grande parte dos documentos publicados foi na forma de artigos científicos e uma pequena parte na forma de depósito de registro de pedidos de patentes. Dessa forma, esse trabalho pode servir como um incentivo de inovação tecnológica para o desenvolvimento de novas pesquisas envolvendo neoflavonoides, visto que o número de registro de depósitos de pedidos de patente ainda é relativamente insuficiente para atender a atual demanda por inovação tecnológica e científica com relação as DTNs.

Palavras-chave: Doenças negligenciadas, neoflavonoides, prospecção tecnológica.

1. Introduction

Neglected diseases (NDs) affect more than 1 billion people worldwide and are responsible by deaths of more than one million people annually (MACKEY; LIANG, 2012; ROSALES-MENDOZA et al., 2012). The NDs have several characteristics in common, being main the poverty, lack of sanitation and health services. Among the NDs (Figure 1) more prevalent, can quote the lymphatic filariasis, hookworm, malaria, onchocerciasis, trachoma, leishmaniasis, chagas disease and schistosomiasis, in which are needed new drugs of low-cost, safe and effective (YAJIMA et al., 2012).

Figure 1 - Neglected diseases and the number of people infected.



Source: (FENWICK, 2012).

The treatment of many NDs imposes financial charges and therefore there is little incentive on the private market to develop new treatments, being exactly one fundamental problem as induce pharmaceutical companies to invest resources for the development of medicines that treat DN. The problem arises because the majority of NDs mainly affects the poorest part of the world population and even with potential demand for new medicines, the pharmaceutical industries resist in make investments, since the market value of the medicines is low and because the affected can not afford by medications (DIMITRI, 2012; JANSEN et al., 2012; RIDLEY; SÁNCHEZ, 2010).

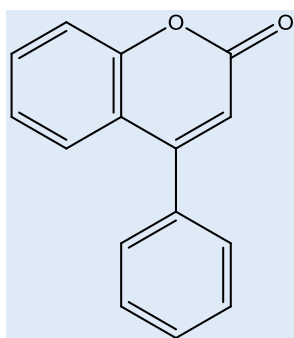
Therefore, there is an increasing need for developing new medicines and nature by means of plants has provided countless numbers of new bioactive chemicals that can be used to treat of many diseases, among them, the DN. Natural compounds and derivatives as phenolics, coumarins, quinones, alkaloids, saponins and terpenoid have been reported in the scientific literature as

promising drugs for the treatment of various NDs (SCHMIDT et al., 2012b; SEN; CHATTERJEE, 2011).

Besides of the natural compounds discussed in the previous paragraph, can be cited the substances belonging to the group of phenolic compounds such as neoflavonoids. The neoflavonoids possess several pharmacological and biochemical properties and are present in a wide variety of higher plant of families Clusiaceae, Fabaceae, Rubiaceae, Thelypteridaceae, Passifloraceae, Asteraceae and Rutaceae, being that up to the present moment, more than 1000 structurally distinct neoflavonoids has been described (GARAZD; GARAZD; KHILYA, 2003).

Even with few chemical structures identified until the present moment, there are already scientific studies confirming that these compounds and their derivatives can be highlighted as promising medications for the treatment of NDs (SCHMIDT et al., 2012a; VEROTTA et al., 2004). The neoflavonoides represent a group of natural compounds that possessing as basic structure characteristic the 4-phenylcoumarin, in which is represented by Figure 2.

Figure 2 - Basic chemical structure of neoflavonoids.



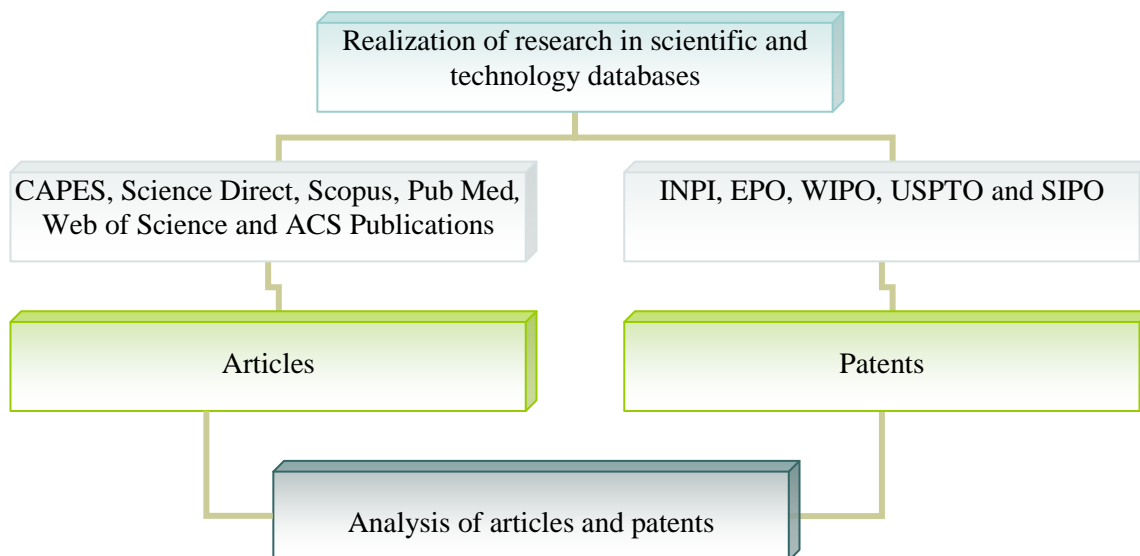
The objective of this work was perform a technological forecasting on the neoflavonoids and its implications with relation to treatment of NDs, being that for this, will be used information available in scientific and technology databases national and international. Therefore, the present may facilitate and guide future research with respect to the use of neoflavonoids for the treatment of NDs.

2. Methodology

This work was accomplished through of a comprehensive and systematic bibliographic search in articles and patents. The articles were searched in databases of periodical of CAPES, Science Direct, Scopus, Pub Med, Web of Science and ACS Publications. Then the patent search was performed in the database of the National Institute of Industrial Property of Brazil (INPI), European Patent Office (EPO), World Intellectual Property Organization (WIPO), United States

Patent and Trademark Office (USPTO) and State Intellectual Property Office of the People's Republic of China (SIPO). The periodicity of this research was performed in September 2013. A flowchart showing the steps of realization of this research is shown in Figure 3.

Figure 3 - Flowchart of steps of realization of this research.



The focus of this research was the use of neoflavonoids with implications in the treatment of NDs, and per this, the key words used were the terms neoflavonoids and 4-phenylcoumarin. The combinations of terms, “neoflavonoids and neglected diseases” and “4-phenylcoumarin and neglected diseases”, were also used for the development of this work. The references found during the realization of this research were studied in detail.

The term 4-phenylcoumarin was used as key word per be the basic structure of neoflavonoids and by that many scientific papers using the name 4-phenylcoumarin instead of neoflavonoides in the title of scientific work. The terms in english were used for international databases, while the terms in portuguese were used to search of documents in national basis, being considered valid documents that presented these terms in the title and/or abstract.

3. Results and Discussion

3.1. Results of prospecting of documents found in portal of the periodicals of CAPES, Science Direct, Scopus, Pub Med, Web of Science and ACS Publications.

Using the keyword neoflavonoids and 4-phenylcoumarin in field "search subject" on Portal of journals of Capes, were found respectively 178 and 188 documents. Of 178 documents found

regarding neoflavonoids, 162 are articles and of 188 documents relating to the 4-phenylcoumarin, 177 are articles. With regard to research by the combination of terms at Portal of the CAPES, 3 documents were found for “Neoflavonoids and neglected diseases” and only 1 document for “4-phenylcoumarin and neglected diseases”. At portal of periodical Science Direct, Scopus, *Pub Med*, Web of Science and ACS Publications, were found respectively 141, 57, 14, 53 e 31 documents for the term neoflavonoids. When it was used the term 4-phenylcoumarin, there was an increase in the total number of documents found, being 262 in Science Direct, 118 in Scopus, 43 in Pub Med, 73 in Web of Science and 59 in ACS Publications. As well as at Portal of the CAPES, few documents concerning the combination of terms “Neoflavonoids and neglected diseases” and “4-phenylcoumarin and neglected diseases” were found at site Science Direct, Pub Med, Web of Science e ACS Publications. The results of search for documents are shown in Table 1.

Table 1 - Results of prospecting carried out in articles.

keywords	CAPES	Science Direct	Scopus	Pub Med	Web of Science	ACS Publications
Neoflavonoids	178	141	57	14	53	31
4-phenylcoumarin	188	262	118	43	73	59
Neoflavonoids and neglected diseases	3	1	0	1	0	0
4-phenylcoumarin and neglected diseases	1	1	0	0	0	1

Source: Authorship Own (2013).

Using the combinations of terms “neoflavonoids and neglected diseases” and “4-phenylcoumarin and neglected diseases”, were found a total of 7 documents and only 1 document addresses the use of neoflavonoides in treatment of neglected diseases. Analyzing the documents found regarding the keyword neoflavonoids, was observed that out of the total of 474 documents, 5 shows possible implications of neoflavonoids in treatment of neglected diseases. Using the keyword 4-phenylcoumarin, were found 743 documents, being that of this total, 8 attributed pharmacological properties of neoflavonoids in treatment of neglected diseases. In Table 2 are summarized some scientific studies that indicates the use of these natural compounds as promising drugs for the treatment of several neglected diseases.

Table 2 - Neoflavonoids with implications for the treatment of neglected diseases.

Title of Article	Reference
Antimalarial 4-Phenylcoumarins from the Stem Bark of <i>Hintonia latiflora</i>	Argotte-Ramos and collaborators (2006)
Leishmanicidal Activity of crude extract and coumarin from leaves of <i>Calophyllum brasiliense</i> against <i>Leishmania amazonensis</i>	Brenzan and collaborators (2007)
Structure–activity relationship of (–) mammea A/BB derivatives against <i>Leishmania amazonensis</i>	Brenzan and collaborators (2008)
Effects of (–) mammea A/BB isolated from <i>Calophyllum brasiliense</i> leaves and derivatives on mitochondrial membrane of <i>Leishmania amazonensis</i>	Brenzan and collaborators (2012)
Synthesis and antiprotozoaria activity of 4-aryl coumarins	Pierson and collaborators (2010)
4-Alkyl- and 4-phenylcoumarins from <i>Mesua ferrea</i> as promising multidrug resistant antibacterials	Verotta and collaborators (2004)
Trypanocidal constituents in plants: 7. Mammea-type coumarins	Reyes-Chilpa e colaboradores (2008)
<i>In vitro</i> Antiprotozoal and Cytotoxic Activities of Some Alkaloids, Quinones, Flavonoids, and Coumarins	Del Rayo Camacho and collaborators (2004)
<i>In vitro</i> Antiplasmodial Activity of 4-Phenylcoumarins from <i>Exostema mexicanum</i>	Köhler and collaborators (2001)
The potential of Secondary Metabolites of Plants as drugs or Leads against Protozoan neglected diseases - Part I	Schmidt and collaborators (2012)
The potential of Secondary Metabolites of Plants as drugs or Leads against Protozoan neglected diseases - Part II	Schmidt and collaborators (2012)
Natural Products from Plants as Drug Candidates and Lead Compounds Against Leishmaniasis and Trypanosomiasis	Salem; Werbovetz (2006)

Source: Authorship Own (2013).

The NDs are a serious public health problem in tropical countries in development, being the NDs responsible for 11.4% of the global burden of disease (MACKEY; LIANG, 2012). Therefore, the limitation of the availability and accessibility of new medicaments signify that the majority of the world's population depends on new medicaments. Thus, the natural products have been the main

sources in conduction of the discovery of new medicaments and even considering that the studies related to neoflavonoids for the treatment of diseases considered overlooked are few, observing Table 2, these compounds and their derivatives are likely to provide a valuable source of new medicinal agents for the treatment of NDs.

3.2. Results of prospecting of patents found in INPI, EPO, USPTO, WIPO e SIPO.

Many technological information can be found in publications of patents, which are regarded as an essential source of scientific knowledge and technology that has information about the publication number, registration number, title of the invention, the name of the inventor, international classification of patents (ICP), summary and a detailed description of the invention and claims (MONTECCHI; RUSSO; LIU, 2013).

During the realization of this research, it was found only 1 request for deposit of patent at basis of the INPI, 3 deposits of patents at basis of the EPO, 3 at base of the WIPO and 2 at base of the SIPO, totalizing 9 requests of deposits of patents for the keyword neoflavonoids (Table 3). With respect to the term 4-phenylcoumarin, we found no patent application in databases of the INPI, EPO, WIPO, USPTO and SIPO. The data set in Table 2 demonstrate that there is a greater quantity of documents for the keyword 4-phenylcoumarin than for the word neoflavonoids. However, unlike the data set out in Table 2, no deposit of patent application in databases of the INPI, EPO, USPTO, WIPO and SIPO was found for the term 4-phenylcoumarin (Table 3), indicating that the dissemination of scientific knowledge with respect to the term 4-phenylcoumarin occurs mainly through the publication of scientific articles.

Table 3 - Total deposits of patents in bases of INPI, EPO, USPTO, WIPO and SIPO.

Keywords	INPI	EPO	USPTO	WIPO	SIPO
Neoflavonoids	1	3	0	3	2
4-phenylcoumarin	0	0	0	0	0
Neoflavonoids and neglected diseases	0	0	0	0	0
4-phenylcoumarin and neglected diseases	0	0	0	0	0

Source: Authorship Own (2013).

It is observed in Table 3 no deposit of patent application in databases of the INPI, EPO, USPTO, WIPO and SIPO, when it is using the combinations of terms “neoflavonoids and neglected diseases” and “4-phenylcoumarin and neglected diseases”.

A more specific analysis of patents found in base of the INPI, EPO, WIPO and SIPO is described in Table 4 with the number, year, title and abstract of the patent. It was observed that the

deposits of patent applications found at the base of WIPO are the same documents deposited at the base of the EPO.

Table 4 - Description of patents found in base of the INPI, EPO, WIPO and SIPO.

Number of Patent/Year	Inventor /Depository	Title	Summary
INPI			
PI9802163-0 A2/1998	Marçal de Queiroz Paulo/ Ind. e Com. de Prod. Farmaceuticos Quim. e Nat. Ltda-me. (BR/PB)	Pharmaceutical Compositions for the Treatment of Viral Infections Comprising Substances Neoflavonoids (4- arilculmarinas)	The present invention relates to the use of substances neoflavonoids for preparation of pharmaceutical compositions, prophylaxis and treatment of infections caused by Herpes virus and Herpes zoster.
EPO			
US2012136161 3420120914/20 11	Backes Michael; Voessing Tobias; Ley Jakob Peter and Paetz Susanne.	The use of certain neoflavonoids to intensify and/or produce a sensory impression of sweetness.	The present invention relates primarily to the use of one or a plurality of neoflavonoids and/or a plurality of physiologically acceptable salts to produce a sensory impression of sweetness in an oral preparation of consumption or to intensify the impression of sweetness of a sensorial preparation consumable.
US2012136160 3720120914/20 11/	Backes Michael; Voessing Tobias; Ley Jakob Peter; Paetz Susanne	Use of neoflavonoides for modifying the flavor.	The present invention concerns the use of neoflavonoides for modifying flavor, or changing an impression of taste bitter, astringent and/or metal of a substance of bitter taste.
EP19990104597 19990308/ 1998	Dr. Sensch Karl Heinz; Dr. Zoukas Thomas.	Manufacturing Process of an extract from the stem bark of Copalchi and use of neoflavonoids for the treatment of diabetes.	The present invention concerns the use of neoflavonoids bark of Copalchi for the treatment of diabetes.
WIPO			
20130084252/ 2013	Backes Michael; Voessing Tobias; Ley Jakob Peter and Paetz Susanne.	The use of certain neoflavonoids to intensify and/or produce a sensory impression of sweetness.	The present invention relates primarily to the use of one or a plurality of neoflavonoids and/or a plurality of physiologically acceptable salts to produce a sensory impression of sweetness in an oral preparation of consumption or to intensify the impression of sweetness of a sensorial preparation consumable.
20130078192/ 2013	Backes Michael; Voessing Tobias; Ley Jakob Peter; Paetz Susanne	Use of neoflavonoids for modification of the flavor.	The present invention concerns the use of neoflavonoids for modifying flavor, or changing an impression of taste bitter, astringent and/or metal of a substance of bitter taste.
0950411/1999	Dr. Sensch Karl Heinz; Dr. Zoukas Thomas.	Manufacturing Process of an extract from the stem bark of Copalchi and use of neoflavonoids for the treatment of diabetes.	The present invention concerns the use of neoflavonoids bark of Copalchi for the treatment of diabetes.
SIPO			
200810123645/ 2008	Li Baolin; Zhang Xiquan; Yang Zhanjun; Jiang	Composed neoflavonoide of the root of <i>Girald pteroxygonum</i>	The present invention concerns a method for preparing neoflavonoids and use of neoflavonoids for treatment of

	Linling; Hongmei	Gu		diseases associated with free radicals.
200910095870/ 2009	Xu Runsheng; Yuan Ke	Compounds separated and purified from <i>Tridax procumbens</i> and method of preparing of the same.	neoflavonoides and method	The invention concerns the separation and purification of various neoflavonoides from <i>Tridax procumbens</i> , and a method of preparing of the same.

Source: Authorship Own (2013).

4. Conclusion

Through this exploration, it was possible to analyze the studies published on websites of the CAPES, Science Direct, Scopus, Pub Med, ACS Publications, INPI, EPO, WIPO, USPTO and SIPO regarding neoflavonoids and its implications for the treatment of NDs. Thus, it is observed that the majority of documents is published in the form of scientific articles, and a small fraction in the form of filing patent applications.

Despite being few studied when compared with other classes of compounds, as observed in the present study, the neoflavonoids can be of great interest to the pharmaceutical industries. The neoflavonoids presented therapeutic implications for malaria, leishmaniasis and American trypanosomiasis (Chagas Disease), thus providing new opportunities for the development of new bioactive compounds that may in future be used to treat NDs.

Moreover, this prospecting can serve as an incentive for technological innovation for the development of new research involving neoflavonoids, since the number of deposits of patent applications is relatively low.

References

ARGOTTE-RAMOS, R.; RAMÍREZ-AVILA, G.; RODRÍGUEZ-GUTIÉRREZ, M.D.C.; OVILLA-MUÑOZ, M.; LANZ-MENDOZA, H.; RODRÍGUEZ, M.H.; GONZÁLEZ-CORTAZAR, M.; ALVAREZ, L. Antimalarial 4-Phenylcoumarins from the Stem Bark of *Hintonia latiflora*. **Journal of Natural Products**, v. 69, n. 10, p. 1442-1444, 2006..

BREZZAN, M.; NAKAMURA, C.; PRADO DIAS FILHO, B.; UEDA-NAKAMURA, T.; YOUNG, M.; APARÍCIO GARCIA CORTEZ, D. Antileishmanial activity of crude extract and coumarin from *Calophyllum brasiliense* leaves against *Leishmania amazonensis*. **Parasitology Research**, v. 101, n. 3, p. 715-722, 2007.

BREZZAN, M.A.; NAKAMURA, C.V.; DIAS FILHO, B.P.; UEDA-NAKAMURA, T.; YOUNG, M.C.M.; CÔRREA, A.G.; JÚNIOR, J.A.; DOS SANTOS, A.O.; CORTEZ, D.A.G. Structure-activity relationship of (-) mammea A/BB derivatives against *Leishmania amazonensis*. **Biomedicine & Pharmacotherapy**, v. 62, n. 9, p. 651-658, 2008.

BRENZAN, M.A.; SANTOS, A.O.; NAKAMURA, C.V.; FILHO, B.P.D.; UEDA-NAKAMURA, T.; YOUNG, M.C.M.; CÔRREA, A.G.; JÚNIOR, J.A.; MORGADO-DÍAZ, J.A.; CORTEZ, D.A.G. Effects of (-) mammea A/BB isolated from *Calophyllum brasiliense* leaves and derivatives on mitochondrial membrane of *Leishmania amazonensis*. **Phytochemistry**, v. 19, n. 3–4, p. 223-230, 2012.

DEL RAYO CAMACHO, M.; PHILLIPSON, J.D.; CROFT, S.L.; YARDLEY, V.; SOLIS, P.N. In vitro Antiprotozoal and Cytotoxic Activities of Some Alkaloids, Quinones, Flavonoids, and Coumarins. **Planta Med**, v. 70, n. 01, p. 70-72, 2004.

DIMITRI, N. R&D investments for neglected diseases can be sensitive to the economic goal of pharmaceutical companies. **Drug Discovery Today**, v. 17, n. 15–16, p. 818-823, 2012.

FENWICK, A. The global burden of neglected tropical diseases. **Public Health**, v. 126, n. 3, p. 233-236, 2012.

GARAZD, M. M.; GARAZD, Y. L.; KHILYA, V. P. Neoflavones. 1. Natural Distribution and Spectral and Biological Properties. **Chemistry of Natural Compounds**, v. 39, n. 1, p. 54-121, 2003.

SCHMIDT, T.; A. KHALID, S.; J. ROMANHA, A.; MA. ALVES.; BIAVATTI, M.; BRUN, R.; DA COSTA, F.; DE CASTRO, S.; F. FERREIRA, V.; V.G. DE LACERDA, M.; H.G. LAGO, J.; L. LEON, L.; P. LOPES, N.; C. DAS NEVES AMORIM, R.; NIEHUES, M.; V. OGUNGBE, I.; M. POHLIT, A.; T. SCOTTI, M.; N. SETZER, W.; N.C. SOEIRO, M.; STEINDEL, M.; G. TEMPONE, A. The Potential of Secondary Metabolites from Plants as Drugs or Leads Against Protozoan Neglected Diseases - Part II. **Current Medicinal Chemistry**, v. 19, n. 14, p. 2176-2228, 2012a.

SCHMIDT, T.; A. KHALID, S.; J. ROMANHA, A.; MA. ALVES.; BIAVATTI, M.; BRUN, R.; DA COSTA, F.; DE CASTRO, S.; F. FERREIRA, V.; V.G. DE LACERDA, M.; H.G. LAGO, J.; L. LEON, L.; P. LOPES, N.; C. DAS NEVES AMORIM, R.; NIEHUES, M.; V. OGUNGBE, I.; M. POHLIT, A.; T. SCOTTI, M.; N. SETZER, W.; N.C. SOEIRO, M.; STEINDEL, M.; G. TEMPONE, A. The Potential of Secondary Metabolites from Plants as Drugs or Leads Against Protozoan Neglected Diseases; Part I. **Current Medicinal Chemistry**, v. 19, n. 14, p. 2128-2175, 2012b.

JANSEN, J.M.; CORNELL, W.; TSENG, Y.J.; AMARO, R.E.; Teach–Discover–Treat (TDT): Collaborative computational drug discovery for neglected diseases. **Journal of Molecular Graphics and Modelling**, v. 38, p. 360-362, 2012.

KÖHLER, I.; JENETT-SIEMS, K.; MOCKENHAUPT, F.P.; SIEMS, K.; JAKUPOVIC, J.; GONZÁLEZ, J.C.; HERNÁNDEZ, R.; IBARRA, W.A.; BERENDSOHN, U.G.; BIENZLE, E.; EICH. In vitro Antiplasmodial Activity of 4-Phenylcoumarins from *Exostema mexicanum*. **Planta Med**, v. 67, n. 01, p. 89-91, 2001.

MACKEY, T. K.; LIANG, B. A. Threats from emerging and re-emerging neglected tropical diseases (NTDs). **Infection Ecology & Epidemiology**, v. 1, n. 2, p. 1-7, 2012.

MONTECCHI, T.; RUSSO, D.; LIU, Y. Searching in Cooperative Patent Classification: Comparison between keyword and concept-based search. **Advanced Engineering Informatics**, v. 27, n. 3, p. 335-345, 2013.

REYES-CHILPA, R.; ESTRADA-MUÑIZ, E.; VEGA-AVILA, E.; ABE, F.; KINJO, J.; HERNÁNDEZ-ORTEGA, S. Trypanocidal constituents in plants: 7. Mammea-type coumarins. **Memórias do Instituto Oswaldo Cruz**, v. 103, p. 431-436, 2008.

RIDLEY, D. B.; SÁNCHEZ, A. C. Introduction of European priority review vouchers to encourage development of new medicines for neglected diseases. **The Lancet**, v. 376, n. 9744, p. 922-927, 2010.

ROSALES-MENDOZA, S.; GOVEA-ALONSO, D.O.; MONREAL-ESCALANTE, E.; FRAGOSO, G.; SCIUTTO, E. Developing plant-based vaccines against neglected tropical diseases: Where are we? **Vaccine**, v. 31, n. 1, p. 40-48, 2012.

SALEM, M. M.; WERBOVETZ, K. A. Natural Products from Plants as Drug Candidates and Lead Compounds Against Leishmaniasis and Trypanosomiasis. **Current Medicinal Chemistry**, v. 13, n. 21, p. 2571-2598, 2006.

SEN, R.; CHATTERJEE, M. Plant derived therapeutics for the treatment of Leishmaniasis. **Phytomedicine**, v. 18, n. 12, p. 1056-1069, 2011.

VEROTTA, L.; LOVAGLIO, E.; VIDARI, G.; FINZI, P.V.; NERI, M.G.; RAIMONDI, A.; PARAPINI, S.; TARAMELLI, D.; RIVA, A.; BOMBARDELLI, E. 4-Alkyl- and 4-phenylcoumarins from *Mesua ferrea* as promising multidrug resistant antibacterials. **Phytochemistry**, v. 65, n. 21, p. 2867-2879, 2004.

YAJIMA, A.; MIKHAILOV, A.; MBABAZI, P.S.; GABRIELLI, A.F.; MINCHIOTTI, S.; MONTRESOR, A.; ENGELS, D. Preventive Chemotherapy and Transmission Control (PCT) databank: a tool for planning, implementation and monitoring of integrated preventive chemotherapy for control of neglected tropical diseases. **Transactions of the Royal Society of Tropical Medicine and Hygiene**, v. 106, n. 4, p. 215-222, 2012.

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