

Applications of Monoterpenic Essential Oils in Neglected Diseases: Nerol in a Prospection

REVIEW

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Abstract

Monoterpenes are the naturally occurred essential oils in various plant species having a wide range of biological activities. Attentions on the natural compounds, especially those are plant-derived is growing day by day. Nerol, a monoterpene having some important biological activities along with its other applications, may be a hopeful tool in this context. By considering the above circumstances, this study aimed to perform a scientific and technological prospective study on this charming monoterpene with an emphasis on the treatment of neglected diseases along with other monoterpenes. We conducted a comprehensive and systematic search for published articles, periodicals, magazines in the *CAPES*, *ScienceDirect* and *Pubmed*, while for patents we have gone through search in *National Institute of Industrial Property of Brazil (INPI)*, *European Patent Office (EPO)*, *World Intellectual Property Organization (WIPO)* and *United States Patent and Trademark Office (USPTO)*. Results suggesting monoterpenes have therapeutic potentials against malaria, dengue, schistosomiasis, tuberculosis, leprosy, leishmaniasis and chagas diseases. Nerol has anti-tuberculosis potential. In conclusion, more researches are recommended with nerol in a context of treatment of neglected diseases.

Introduction

Nowadays, natural products are in a great attention to the peoples for the treatment of various ailments [1]. Having less adverse effects and promising therapeutic making them to consider as health promoting tools. Essential oils are one of them. Monoterpenes, a class of terpe-

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nes under the EOs are now evident to have a good number of biological activities [2, 3].

Nerol (*cis*-2,6-dimethyl-2,6-octadien-8-ol), a monoterpene has potential biological activities in various *in vitro* and *in vivo* test systems [1]. Studies regarding its action on the central nervous system (CNS) with antidepressant, anxiolytic, antinociceptive and anticonvulsant, along with the antioxidant, anti-inflammatory, antimicrobial and anthelmintic activities [4-7]. To be mentioned that nerol is found in various medicinal plants, those are reported to have significant antioxidant, antimicrobial and neuroprotective activities [8-10]. Furthermore, nerol is used as a fragrance in cosmetics and toiletries [11].

However, naturally occurring substances reveals therapeutic alternatives for the neglected diseases (ND), which are a group of illnesses representing mortality in a race-independent manner of people worldwide [12]. People from the remote rural areas, urban slums or conflict zones are the most susceptible in this context. RDs are not only directly affect health, but also represent a vicious cycle of socio-economic events that reinforce the feedback on the other [13]. It is noteworthy that the existing therapies for the RDs are largely based on drugs having toxicity and prone to serious side effects, which leading to search new agents with more effectively and safety [12].

Therefore, this study aimed to carry out a systematic revision in a scientific and technological viewpoint on monoterpenes with the applications to NDs underlying a special attention to nerol.

Materials and methods

For articles we searched in the following databases of CAPES Periodicals (<http://www.periodicos.capes.gov.br>), ScienceDirect (<http://www.sciencedirect.com>) and PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) while National Institute of Industrial Pro-

perty of Brazil (INPI), European Patent Office (EPO), World Intellectual Property Organization (WIPO) and United States Patent and Trademark Office (USPTO) databases were considered for patents. Evidences having same information were replaced by the newer.

Search (until November, 2015) has been made with the listed keywords as 'monoterpenes', 'nerol' and were them paired with 'neglected diseases', 'malaria', 'leprosy', 'leishmaniasis', 'dengue', 'chagas disease', 'tuberculosis' and 'schistosomiasis'. No language restrictions were imposed.

Findings

Scientific and technological

In the search for articles, periodicals and magazines, monoterpenes constitute 57 periodicals, and 98 articles in CAPES, PM and SD in which SD occupied 61.29% while CAPES and PM by 36.77% and 1.94%, respectively. Among the 213 evidences, 66.19% articles belong to the database, SD leaving 27.23% periodicals, and 6.57% articles behind the CAPES and PM, respectively. However, patents searched in the databases, demonstrating that WIPO constitutes 47.06% then followed by 41.18% and 11.76% in EPO and INPI, respectively for monoterpenes. No patents were found in the USPTO. Otherwise, nerol constitutes 76 patents, among which 98.68% belongs to USPTO leaving behind 1.32% of WIPP database. No patents were funded in INPI and EPO databases (**Table 1**).

Table 2 suggests that evidences (periodicals, magazines and articles) on malaria (41.11%) are prominent for nerol then followed by tuberculosis (25.89%), dengue (8.12%) = leprosy (8.12%), schistosomiasis (6.59%) and leishmaniasis (5.08%) = chagas disease (5.08%), respectively. More evidence was found in SD, which was then followed an order of CAPES>PM. Patent search compromised with an order of malaria (30.00%)> leishmaniasis (22.50%)>

Table 1. Databasic evidences of monoterpenes and nerol in neglected diseases (after sorting).

Substances	Articles, periodicals and magazines			Patents			
	CAPEs	PM	SD	INPI	EPO	USPTO	WIPO
Monoterpenes	57	3	95	2	7	0	8
Nerol	58	14	141	0	0	75	1

PM: PubMed; SD: ScienceDirect; INPI: National Institute of Industrial Property of Brazil; EPO: European Patent Office; WIPO: World Intellectual Property Organization; USPTO: United States Patent and Trademark Office.

Table 2. Neglected diseases-wise databasic evidences of nerol.

Neglected diseases (NDs)	Articles, periodicals and magazines			Patents			
	CAPEs	PM	SD	INPI	EPO	USPTO	WIPO
Malaria	38	2	45	0	0	23	1
Dengue	7	2	7	0	0	12	0
Schistosomiasis	0	3	10	0	0	4	0
Tuberculosis	3	2	48	0	0	16	0
Leprosy	0	0	16	0	0	6	0
Leishmaniasis	0	1	9	0	0	18	0
Chagas disease	0	4	6	0	0	0	0

PM: PubMed; SD: ScienceDirect; INPI: National Institute of Industrial Property of Brazil; EPO: European Patent Office; WIPO: World Intellectual Property Organization; USPTO: United States Patent and Trademark Office.

tuberculosis (20.00%)> dengue (15.00%)> leprosy (7.50%)> schistosomiasis (5.00%)> chagas disease (0.00%). USPTO constitutes 98.75% patents, while WIPO by 1.25%. no patents were observed in INPI and EPO databases.

Figure 1 telling that IL is the owner of 31.06% patents on NDs, which was then followed an order of AW> US> CA> MA=NL=PA> AT=IN=LU> BS=FG=GA=IT=JP=ML=NO=UY, respectively.

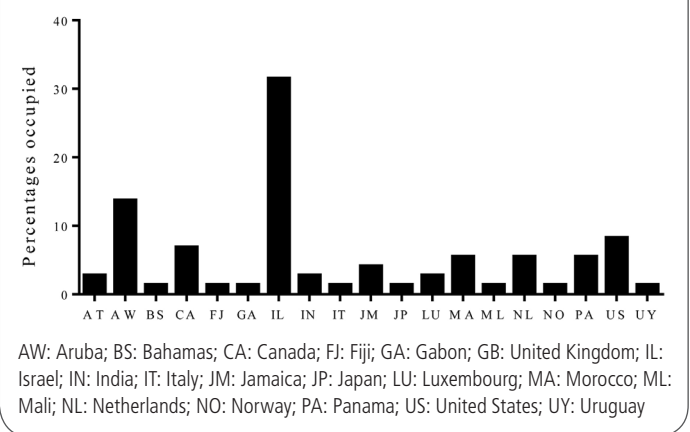
Patents were found from 1992 to 2014 suggest in 2004, 2009 and 2013 constitute 8 of each then followed by the order of 2010 (7)> 2007 (6)> 2003 (5) = 2006 (5)> 2000 (4) = 2001 (4) = 2012 (4)> 1997 (3) = 2002 (3) = 2014 (3)> 1992 (1) = 1994 (1) = 1995 (1) = 1999 (1) = 2011 (1), respectively.

Findings on neglected diseases (NDs)

Antimalarial activity

Terpenes are the potential sources of antimalarial activity [14]. Chloroform extract of *Couroupita*

Figure 1: Patients on neglected diseases belonging to the owners with percentage occupied.



guianensis fruit was found to act against a number of pathogenic microbes including mycobacteria. It also significantly inhibited the formation of biofilm of the pathogens [15]. EOs in the leaf extract of *Plinia cerrocampianensis* was found to produce significant antimalarial activity [16]. Kpo-

viessi et al. founded EOs from the genus *Cymbopogon* having a potential anti-*Trypanosoma brucei* and anti-*Plasmodium falciparum* activity [17]. EOs from *Lippia multiflora* is also evident to act against *P. falciparum* [18]. The ethanol extract of *Ocimum sanctum* is also evident to have antimalarial capacity [19]. An *in vivo* antimalarial activity was demonstrated with the allylic alcohol, geraniol by [20]. Parshikov et al. also introduced few new terpenes with anti-malaria activity [14]. A number of EOs derived from plants, including monoterpenes were introduced having mosquito repellent potential by Pohlit et al. [21]. Nanocapsules prepared with onopordopicrin, a sesquiterpene was suggested to have a significant antimalaria activity [22].

Activity against dengue

Conti et al. reported that the *Aede albopictus* larvae are susceptible to the EOs of *Achillea millefolium*, *Lavandula angustifolia*, *Helichrysum italicum*, *Foeniculum vulgare*, *Myrtus communis*, and *Rosmarinus officinalis* [23]. EOs of the leaves of *Salvia dorisiana*, *S. longifolia*, and *S. sclarea* under the family, Lamiaceae exhibited potent anti-*A. albopictus* activity [24]. Additionally, EOs from *Citrus sinensis*, *C. limon* and *C. paraiso* shells and its components were found to exhibit larvicidal potential against a number of mosquito [25]. Pohlit et al. did a revision demonstrating EOs to have promising mosquito repellent capacity [21].

A research conducted by Pandey et al. of eugenyl acetate, linalyl acetate, terpinyl acetate, menthyl acetate, geranyl acetate along with the monoterpenes eugenol, linalool, terpineol, L-menthol and geraniol suggesting significant anti-*A. aegypti* activity with an LC₅₀ value range between 50.2 to 415 ppm [26]. A research done by Nyasembe et al. suggests that volatile phytochemicals may be good options for to repeal mosquito [27].

Anti-schistosomiasis activity

Mors et al. suggested all-trans (-)-14,15-epoxygeranyl-geraniol to have a potential anti-schistosomiasis activity [28]. Thymol, β -citronellol, carvacrol and geraniol strongly inhibited snail-vector of *Schistosoma mansoni* [29]. EOs isolated from *Cymbopogon winterianus* exhibited significant anti-schistosomiasis activity between the LC₅₀ value of 22.0 and 181.0 mg/L [30].

Anti-tuberculosis potential

EOs from *C. guianensis* fruit was found to act *Mycobacterium tuberculosis* [15]. Kumar et al. observed that the *Plumeria bicolor* extract significantly inhibited the growth of *M. tuberculosis* and multi-drug resistant *M. tuberculosis*. Along with nerol, plumericin and isoplumericin were claimed as a potential candidate for antituberculosis activity. The antituberculosis activity of EOs was also observed by Kumar et al. with *Plumeria bicolor* extract [31]. The meso-dihydroguaiaietic also exhibited a potential anti-*M. tuberculosis* [32]. According to Chinsemu EOs may be one of the potential sources of antituberculosis activity [33].

Anti-leprosis activity

Ross suggested that thymol (a natural monoterpene phenol derivative of cymene) has an anti-leprosis activity [34]. In 1955 Floch and Gelard also demonstrated similarly [35].

Anti-leishmaniasis and anti-chagas disease potentials

Monoterpenes with this type of activity is still to be investigated, despite of a number of medicinal plants have been introduced having anti-leishmaniasis potential [36-44]. Saponins from *Calliandra pulcherrima* and *Quillaja saponaria* were found to exhibit significant anti-leishmaniasis activity against *Leishmania donovani* and *L. chagasi*. [45]. Two monoterpenes, minutin A and B from purified from *Micromelum minutum* leaves acted against *Leish-*

mania major with IC_{50} values between 9.8 to 26.2 μ M [46]. EOs from *Thymus capitellatus* are evident to produce strong anti-leishmaniasis activity within the IC_{50} between 35 to 62 μ g/mL [47]. Otherwise, Morais et al. founded a few thymol and eugenol derivatives having potent anti-leishmaniasis activity [48].

Conclusion

Consistent with the obtained results, we observed a significant number of scientific papers and patent deposits involving monoterpenes and nerol. Although, there are links with neglected diseases, but found evidences in databases are firmly deficient with specific activities, despite of a number of essential oils are evident to have activity against neglected diseases. More research is requested in this field of study.

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Conflict of interest

We have no conflict of interest from any point of view.

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