



Trade of Medicinal Plants and Herbal Products with Teratogenic Potential and their Consumption during Pregnancy

Yvis Silva De Castro¹, Juliana Silva Pereira Santos¹, Stela Bersan Faustino¹, Cristhian Gomes Cardeal Martos¹, Gabriel Bastos Teixeira² and Aline Oliveira da Conceição^{3*}

¹Departamento de Ciências da Saúde, Colegiado de Medicina - Universidade Estadual de Santa Cruz, Rodovia Jorge Amado, Bahia, Brazil

²Departamento de Ciências da Saúde, Pós-Graduação em Ciências da Saúde - Universidade Estadual de Santa Cruz, Rodovia Jorge Amado, Bahia, Brazil

³Departamento de Ciências Biológicas, Universidade Estadual de Santa Cruz, Rodovia Jorge Amado, Bahia, Brazil

*Corresponding Author: Aline Oliveira da Conceição, Departamento de Ciências Biológicas, Universidade Estadual de Santa Cruz, Rodovia Jorge Amado, Bahia, Brazil.

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Abstract

The indiscriminate use and market of medicinal plants and herbal products is a reality in Brazil. Despite the preventive measures that already regulate this use, they do not reach all the communities. Therefore, investigations on the use of medicinal plants or herbal medicines in pregnancy are of fundamental need to help in the establishment of pharmacovigilance norms. The objective of this study was to investigate the sale of medicinal plants and herbal medicines in the city of Ilhéus, Bahia and the consumption of plants by women served in the municipal maternity ward. A qualitative and descriptive study was carried out, through field research, using a semi-structured questionnaire that addressed socioeconomic and ethnobotanical aspects. Herbalists and sellers in the local market were also interviewed about the presence of medicinal plants and herbal products with teratogenic potential in their establishments. In total, 19 individuals were invited to participate in the research, six sellers of medicinal plants and 13 women who gave birth in the local maternity ward. The results showed that medicinal plants with teratogenic potential are easily marketed in the municipality of Ilhéus. However, no teratogenic effects related to medicinal plants or previous high consumption of medicinal plants were mentioned. Despite the low evidence of harmful effects in this study, the fact that the plants are being sold freely in the local market shows the need of pharmacovigilance and education in natural products for professionals in local public health.

Keywords: Toxicity; Pregnancy; Over-The-Counter; Natural Products; Vulnerability

Introduction

Brazilian popular medicine consumption is the result of ethnic miscegenation among different immigrants and the different indigenous culture, who were responsible for spreading the knowledge of local herbs and transmitting it from generation to generation [1]. In addition, in the Brazilian natural products belief there is the conception that "natural" products do not cause problems to

the organism, which favors the propagation of the sometimes irrational consumption of medicinal and herbal plants [2].

In Brazil, studies report the use of medicinal plants and herbal medicines by the population both informally and in health units [3-6]. Ethnobotanical surveys conducted in the municipality of Ilhéus, Bahia, identified the use of different native and exotic plants

for medicinal purposes, such as jenipapo (*Genipa americana*), eucalyptus (*Eucalyptus* sp.), cashew (*Anacardium occidentale*) and other non-arboreal species such as sapé (*Imperata brasiliensis*) and chives (*Trimezia caulosa*) [7,8]. Covering the axis between the municipalities of Ilhéus-Itabuna, in the southern region of Bahia, there was the incorporation of practices with medicinal plants in the context of the Unified Health System (SUS), both in terms of its use by the population and its prescription by health professionals [9]. In addition, the sale of open-air markets of some toxic plants is a reality in Brazil [10].

It is well reported that most herbal medicines in use do not have their toxic profile determined [2,11,12]. Moreover, it is known that the inadequate use of a product, even of low toxicity, can induce serious problems in the presence of risk factors or in the concomitant use of other medicines [12], which constitutes a risk to human health - especially when considering the absence of scientific evidence on the action and toxicity of these products.

Taking into account the popular commercialization of medicinal plants, other aspects are considered important, such as incorrect identification of the plant species of interest, the possibility of adulteration of the merchandise, besides effects caused by over-dosage or allergic reactions [2]. It is also worth mentioning that the penal code in force in Brazil, created by the Decree Law nº 2.848, of December 7, 1940, as well as the Law nº 9.677, of July 2, 1998 [13], consider crimes against public health the falsification, corruption, adulteration or alteration of substances, food products and products destined to therapeutic or medicinal purposes, including also the commercialization or storage of these products. Furthermore, Article 7 of Law 5.991, of December 17, 1973 [14] establishes that "the dispensing of medicinal plants is private to pharmacies and herbalists, observing the proper packaging and botanical classification".

As for the use of herbal medicines and medicinal plants in pregnancy, the theme deserves even more attention. At this stage of the female life cycle, according to the popular idea that plants do not harm health, consumption can be stimulated. However, the active principles of certain plants are able to pass through the placental barrier and cause damage to the development of the fetus [15]. Furthermore, the indiscriminate use of medicinal plants by

pregnant women constitutes a public health problem, since many of these women can make use of these natural resources without knowing the possible effects brought about by this type of therapeutic practice [16].

In Brazil, a set of resolutions and ordinances guide the instruments and actions for the implementation of the National Policy on Medicinal Plants and Herbal Medicines [17], highlighting the National List of Medicinal Plants of Interest to the Unified Health System – RENISUS [18] and the Collegiate Directors Resolution RDC nº 26/2014 of National Health Surveillance Agency (ANVISA), which defines the categories "Herbal Medicine" and "Traditional Herbal Product" and establishes the minimum requirements for registration and notification of them. In this context, medicinal plants in the form of plant drugs - known as "medicinal teas" - dispense register and fall into the category of "Traditional Herbal Product", on the other hand, the registration of "Herbal Medicines" is mandatory. In addition, it should be noted that all "Traditional Herbal Products" can be marketed without a medical prescription, but this does not apply to all "Herbal Medicines" [19,20].

Aim of the Study

Thus, this study aimed to investigate aspects related to the sale of medicinal and herbal plants in the city of Ilhéus, Bahia, Brazil and the consumption of plants by women served in the municipal maternity hospital.

Methods

Design

This is a qualitative and descriptive study, through field research, using a semi-structured questionnaire, in which socioeconomic and ethnobotanical aspects of women attended at the Santa Helena maternity hospital in Ilhéus, Bahia and the over-the-counter sale of medicinal plants with teratogenic potential in this city were addressed.

Ethical aspects

The present work had the approval of the Ethics Committee (CEP) of the State University of Santa Cruz – UESC, under number CAAE 57404012.9.0000.5526, safeguarding the ethical principles of research involving human beings supported by Resolution 466/2012 of the Brazilian National Health Council (CNS).

After inviting the subjects, explanation of the research (objectives, benefits, and risks) and clarifications about the free participation in the study, volunteers have read and signed the Free and Informed Consent Term (TCLE) in case of acceptance to participate. One signed copy of TCLE was provided to the participant.

Methodological trail

Initially, a systematic review of medicinal/food plants in the scientific and popular literature (non-scientific printed or electronic sources that contained ethnobotanical information) with teratogenic potential was performed. From which, an illustrated catalog containing 25 potentially teratogenic plants identified by their scientific name and common names, according to known variations in Brazilian popular culture, was produced. The use of the catalog was in order to standardize terms and images among the interviewees, avoiding misinterpretation of popular names between the interviewer and the interviewed individuals.

Next, visits were made to herbalists and natural product establishments in the city of Ilhéus to check the free sale of medicinal/food plants with teratogenic potential. The identification of the volunteers took place from visits to the market places in Ilhéus near bus terminals and food supply centers. Seven individuals were identified and invited to participate in the survey. Of the seven, six agreed to respond to the form, being three street vendors (herbalists) and three vendors in commercial establishments.

In an individual interview that lasted around 10 minutes the plants present in the catalog were shown and asked to the interviewee if they were sold or not such plants in the establishment. At the same time, the questionnaire was filled out by the interviewer and if the answer was yes about the sale of some plant, it was asked how it was used.

In order to have access to mothers, the newborn's clinical records were evaluated to select the participants through the following aspects: maternal history at gestation, birth history and conditions and physical examination of the newborn. Based on information that provided evidence of birth alterations (low birth weight, malformation problems with absence of known underlying illnesses, APGAR less than three and drug consumption).

For the interviews, an interview script was used taking into consideration three aspects: the socioeconomic situation of the mothers, natural history, and the use of medicinal/phytotherapeutic plants.

Data were transcribed and organized in tables, using Microsoft Office Word 2016® and Excel 2016®, where a simple descriptive analysis of absolute and relative frequencies was performed.

Results and Discussion

Based on toxicological risk such as potential abortifacient effect in the course of pregnancy, uterine stimulants, emmenagogue or genotoxic criteria, 25 plant species from different families (Table 1) were selected to add to the catalog. The elaboration of the catalog provided better adherence of volunteers, made the process more dynamic and reduced the interview time, facilitating data collection.

In this study, of the six establishments visited, four of them offered for sale more than 10 species of 25 species included in the catalog. Among the plants, nine were most identified by herbalists and sellers in commercial establishments (Table 1 and 2), all of which having reports in the scientific literature of toxicological associated risk on pregnancy: (Stone Breaker), available for sale in the six places visited.

Besides the difficulty in detecting teratogenic effects during pregnancy, the toxic effects of plants at this stage are diverse. For example, *Schinus terebinthifolia* (Brazilian peppertree), *Cinnamomum verum* (Cinnamon), *Syzygium aromaticum* (Clove) have the potential to increase uterine contractions, causing abortion or premature birth [21]. This study is part of a larger survey on perinatal care in the City of Rio de Janeiro, Brazil. The type of hospital (public, contracted out by the Unified National Health System, or private. On the other hand, *M. chamomilla* (Chamomile) has a recognized calming and antispasmodic action, but its consumption is contraindicated during pregnancy because it provokes the relaxation of the uterus, stimulating bleeding and spontaneous abortion [22].

In addition, some toxic effects are contradictory in the scientific literature. *Zingiber officinale* (Ginger) causes higher than normal embryonic loss when administered to rats during pregnancy, but

there has also been an increase in the weight of remaining fetuses [23]. Also, when the ethanolic extract of this plant administered to pregnant rats it did not cause harm to the mother or the develop- ing fetus [24]. Despite this, ginger constituents are pointed out as potential inducers of apoptosis in human cells [25].

Family	Species	Brazilian Popular Name*	N _h	N _s	N _t
<i>Amaranthaceae</i>	<i>Dysphania ambrosioides</i>	Mastruço; Mastruz; Erva-de-Santa Maria	1	0	1
	<i>Pfaffia glomerata</i>	Ginseng-brasileiro	0	0	0
<i>Anacardiaceae</i>	<i>Schinus terebinthifolia</i>	Brazilian peppertree	3	3	6
<i>Apiaceae</i>	<i>Pimpinella anisum</i>	Erva-doce ou Funcho	3	2	5
<i>Asphodelaceae</i>	<i>Aloe vera</i>	Babosa	2	0	2
<i>Asteraceae</i>	<i>Matricaria chamomilla</i>	Camomila	3	3	6
	<i>Achyrocline satureioides</i>	Marcela	3	3	6
	<i>Arnica Montana</i>	Arnica	2	1	3
	<i>Artemisia absinthium</i>	Losna	2	1	3
<i>Celastraceae</i>	<i>Maytenus ilicifolia</i>	Espinheira Santa	3	3	6
<i>Cucurbitaceae</i>	<i>Momordica charantia</i>	Melão-de-São-Caetano	1	0	1
<i>Fabaceae</i>	<i>Senna alexandrina</i>	Sene	3	2	5
<i>Lamiaceae</i>	<i>Salvia rosmarinus</i>	Alecrim	3	3	6
	<i>Plectranthus barbatus</i>	Boldo	2	2	4
	<i>Mentha spicata</i>	Hortelã	2	1	3
	<i>Mentha pulegium</i>	Poejo	0	0	0
<i>Lauraceae</i>	<i>Cinnamomum verum</i>	Canela	3	3	6
<i>Linaceae</i>	<i>Linum usitatissimum</i>	Linhaça	1	2	3
<i>Myrtaceae</i>	<i>Syzygium aromaticum</i>	Cravo	3	3	6
<i>Phyllanthaceae</i>	<i>Phyllanthus niruri</i>	Quebra-Pedra	3	3	6
<i>Poaceae</i>	<i>Cymbopogon citratus</i>	Capim-cidreira; Capim-santo, Capim-limão	1	1	2
<i>Punicaceae</i>	<i>Punica granatum</i>	Romã	1	2	3
<i>Rubiaceae</i>	<i>Cinchona officinalis</i>	Quina-verdadeira	1	1	2
<i>Rutacea</i>	<i>Ruta graveolens</i>	Arruda	2	1	3
<i>Zingiberaceae</i>	<i>Zingiber officinale</i>	Gengibre	3	3	6

Table 1: Species listed and illustrated in the brochure for sale in Ilhéus, BA which were identified by herbalists and sellers at trading houses.

*Popular name used in the catalog. N_h – number of herbalists that recognized the plant species; N_s – number of sellers at the trading house that recognized the plant species. N_t – number of subjects that recognized plant species. Species in bold format were the most cited. Scientific names were validated at <http://www.splink.org.br/>.

Species	Effect	Reference
<i>Schinus terebinthifolia</i> (Brazilian peppertree)	Abortifacient	[11,21,26,27]
<i>Salvia rosmarinus</i> (Alecrim)	Emmenagogue and abortifacient	[28-30]
<i>Matricaria chamomilla</i> (Camomila)	Emmenagogue and abortifacient	[11,21,26,27]
<i>Cinnamomum verum</i> (Canela)	Abortifacient	[11,26,27]
<i>Syzygium aromaticum</i> (Cravo)	Abortifacient	[11,21,26,27]
<i>Maytenus ilicifolia</i> (Espinheira Santa)	Abortifacient	[31-34]
<i>Zingiber officinale</i> (Gengibre)	Abortifacient	[23,35]
<i>Achyrocline satureioides</i> (Marcela)	Abortifacient	[11,26,27]
<i>Phyllanthus niruri</i> (Quebra-Pedra)	Abortifacient	[36]

Table 2: Medicinal plants most cited by herbalists and sellers at trading houses with scientifically reports of toxicological associated risk during pregnancy.

Of the selected plants, most of interviewers reported the use in the form of “tea”/“powder” (n=72/96) while other less frequent forms were “seasoning”, “leaves”, “bark”, “honey”, “juice”, “oil”, “grain” and “syrup” (Figure 1). It should be noted that some terms, such as “leaf”, were not clarified by the interviewees and, therefore, the form of use by consumers after the sale cannot be specified.

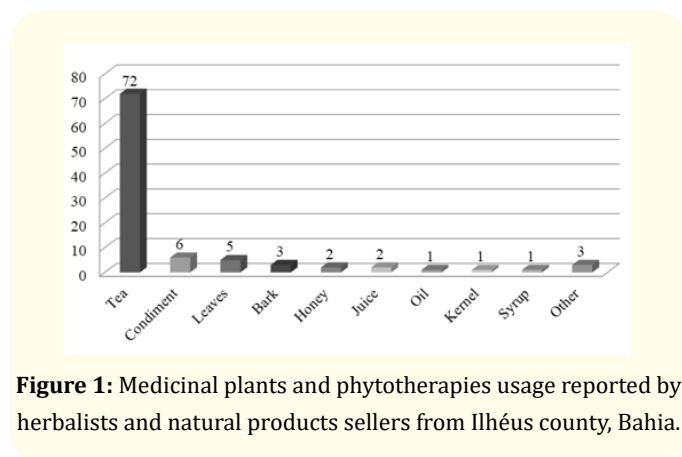


Figure 1: Medicinal plants and phytotherapies usage reported by herbalists and natural products sellers from Ilhéus county, Bahia.

During the visits, the observation of the places allowed us to see plants kept packed in plastic bags arranged on shelves or stored in acrylic jars. Two selling points for herb sellers were little brightness and situated in passageways. Plant identification by herbalists was rudimentary, but a tag with only a popular name of the plant could be seen in natural products establishments. In all places visited one or more failures in the control of sanitary surveillance

agencies (products with no labels, improper packaging, improper storage, unspecified origin, etc.) could be observed. Therefore, potential risk in the sale of medicinal plants and herbal medicines in the city of Ilhéus can be identified considering that among the main risks in the use of medicinal plants is keep them in improper containers/places which may lead to loss of real therapeutic actions or cause organic complications to users [37].

Physiological jaundice (n=3/13), premature birth (n=1/13) and the need for phototherapy (n=3/13) were the only reports found in the newborn in the period evaluated (12/01/2019 to 15/01/2020). The mother’s natural history showed that one mother tested positive for toxoplasmosis before pregnancy, nine were multiparous, none had a history of abortion, previous malformation, diabetes, hypertension or developmental problems of their previous children. However, two had problems at delivery, referred to as early placental detachment and pre-eclampsia.

The use of medication during pregnancy was restricted to three mothers, who reported using Dipyrone and Paracetamol for headache and a medicine for the treatment of urinary infection, under medical supervision. In contrast, all mothers reported the use of folic acid started at four months of gestation (n = 12/13), and at six months (n = 1/13) due to lack of previous medical follow-up.

All the women interviewed were from the state of Bahia, being from the city of Ilhéus itself (n = 6/13), Itacaré (n = 5/13) and from the city of Ubaitaba (n = 2/13), both cities located about 70 km

away from Ilhéus. It should be noted that in these cities there are no maternity clinics or pediatric reference centers, so as reported, women chose to give birth at the Maternidade Santa Helena, in Ilhéus, the only maternity clinic in the city of Ilhéus. Furthermore, Maternidade Santa Helena is part of the State Hospital Reference System for Secondary Care to High Risk Pregnant Women since 2012 [38].

Socio Economic profile of the interviewees during the survey period was of young pregnant women, with low schooling and in a situation of social vulnerability, characterized by single mothers, 3 - 5 people living in the same household, low level of schooling and very low-income (Figure 2).

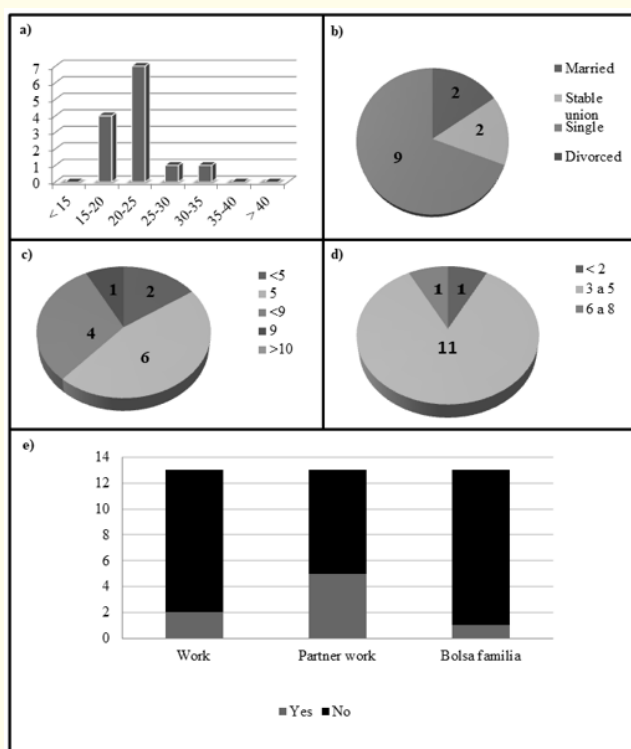


Figure 2: Sociodemographic profile of mothers interviewed in the Santa Helena's Maternity in Ilhéus, Bahia during the period of December 1st, 2019 to January 15th, 2020. Mothers were analyzed in relation to: age at time to give birth (a), marital state (b), schooling (c), number of people living in the same house (d) and if they were *Bolsa familia* recipients (e).

Regarding medicinal plants/herbs consuming, most of the puerperas reported not having consumed it during pregnancy. However, some reported have used *Aloe vera* twice as a hair moisturizer and consumed *Plectranthus barbatus* and *Cymbopogon citratus* in the form of tea once during pregnancy and *Salvia rosmarinus*, *Cinnamomum verum* and *Syzygium aromaticum* in the form of seasoning. *A. vera* and *C. citratus* were obtained in the backyards of the houses while the other plants were obtained in the local market. None of the plants consumed during pregnancy was through medical indication as stated.

The popular choice for medicines of plant origin involves different reasons, among them the reduced access and high cost of modern medicines, the scarcity of medical professionals, commercial availability of medicinal plants and herbal medicines, the common sense that "natural products" are absolutely safe for consumption, the great amount of adverse effects of modern treatments, placebo effect, cultural beliefs, religious beliefs, educational level, absence of effective treatments and family influence [39].

Despite the wide adherence to the use of medicinal plants, there are also barriers to this type of medicine: the great potential for interactions, difficulties in correctly identifying ingredients and plant species, less knowledge of the adverse effects, and lack of good production practices [39]. Therefore, the indiscriminate use of medicinal plants by the population is a point of concern from the public health point of view. So, it is also the challenge for health professionals to recognize and notify adverse effects associated with the use of herbal medicines. In addition, one can cite the absence of information from patients regarding the use of plants at the time of clinical care [40,41].

In this context, the main objectives of pharmacovigilance is the early detection of unknown undesirable effects of drugs through systematic monitoring of the occurrence of adverse reactions in the population, which contributes to reducing the risks related to their use [42,43]. Pharmacovigilance is therefore a crucial tool to support the development of reliable information on the safety of drugs marketed by society and due to the growing importance of this issue worldwide [44] and it should be improved in place with people living in situations of vulnerability.

In a positive way, it is observed that the practice of phytotherapy represents a sociocultural fact that has been accepted and incor-

porated by physicians from all over the world, even though these professionals have carried out their academic training according to the biomedical-pharmacological logic of health care [45]. Traditional medical knowledge has two great potentialities: 1) to encourage the use of easily accessible and low-cost medications for Primary Health Care and 2) to serve as a reference in the search for clues that may lead to the development of new medications through scientific research [39].

In view of the above, different countries started to create or improve their pharmacovigilance services, contributing to the identification of the effects of medicinal plants and herbal medicines already catalogued in the world. One example is Germany, which since 1978 has submitted more than 400 herbal products to pharmacovigilance, many of them withdrawn from the market due to important toxic effects and risk for human use [46]. In Italy, there is an advanced regulation, with emphasis on a program of “phyto-vigilance” (pharmacovigilance of medicinal plants). In Australia, adverse reactions to medicinal plants are now published in the “Therapeutic Goods Administration” [47].

In Brazil, regulatory measures at the local level have guided this use. In Rio de Janeiro state, for example, physicians are recommended to not prescribe medicinal plant drugs in general by internal use, during the first trimester of pregnancy and lactation, whose toxicological studies are not concluded drawing attention to the need for more studies and cautious use of medicinal plants by pregnant women [48]. However, the prescription, indication and preparation of medicinal plants and herbal medicines are a mixture of popular and medical-scientific knowledge and that this transversalism needs to be better studied in the Brazilian reality, mainly in the areas of phytochemistry and ethnopharmacology [49].

For the majority of medicinal plants there are no data regarding the safety of their use during pregnancy and as for herbal remedies, it is important to take into account that in many cases they are complex mixtures being difficult of distinguishing adverse reactions from events related to the quality of the herbal product, adulteration, contamination, incorrect preparation, inadequate storage and/or inappropriate use [50]. Nevertheless, it is important to recognize that if, on one hand, some plants can be harmful to the health of the pregnant woman and the growing fetus, others are indicated in this period, helping to improve the discomfort of mothers caused by pregnancy [22].

Therefore, the detection of the use of natural products by pregnant women and their availability on the market places is of fundamental importance for the health of current and future generations. The relevance of communication with the population in order to encourage spontaneous reports that give subsidies to health professionals to prevent damage caused by the consumption of medicinal plants or herbal medicines has been pointed out as an important aspect in reducing the toxic effects caused by the irrational use of medicinal plants [51].

Conclusion

We conclude that medicinal plants with teratogenic potential in the municipality of Ilhéus are easily traded. However, despite more robust research must be performed in the local community, no teratogenic effects related to medicinal plants or high previous consumption of medicinal plants by pregnant women was mentioned.

Despite the results, the importance of training in medicinal plants and herbal medicines by health professionals is still needed, so that they can correctly guide their patients and evaluate the risk and benefit that the use of these plants and/or medicines brings to the mother and fetus, if their use is necessary.

Finally, research on toxicity or undesirable reactions in certain plant species from ethnobotanical and ethnopharmacological surveys should be stimulated, as they can help the pharmacovigilance of medicinal plants and herbal medicines, contributing to the health of the population.

Authorship

YSC and JSPS share co-first authorship; YSC, JSPS, SBF and CGCM participated in the conception and design of the work; YSC, JSPS and GBT participated in the analysis and interpretation of data; drafting the article and revising it critically. AOC participated in all stages of the project and manuscript process. All authors approved the version to be published.

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