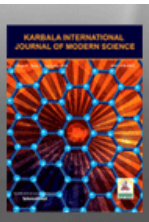

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A Review on the Ethnobotanical, Phytochemistry, and Pharmacological Activities of Aristolochia longa L.

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Abstract

Aristolochia longa L. is a plant native to Algeria and Morocco that has been used by the locals to combat different arrays of infections and diseases found among them. This particular plant is well-known for its therapeutic qualities that could be traced back to the presence of many effective phytochemicals that have been extrapolated from the different parts of the plant, like the leaves and roots: flavonoids, saponins, tannins, 4-hydroxybenzoic acid, β-carotenes, limonenes, and palmitic acids. This plant has been identified in different research articles to be able to manage diseases effectively because it possesses some pharmacological attributes such as; antitumor/anti-inflammatory, anti-cancer, anti-diabetic, anti-microbial, anti-fungal, as well as antioxidant properties. This review covers the ethnobotanical, phytochemical, and pharmacological activities of A. longa as well as its toxicological aspects. A thorough review of scientific literature published in a number of databases, including Scopus, Web of Science, and PubMed, was used to acquire relevant data for A. longa. The plant includes phytochemicals that have been proven to alleviate a variety of diseases. As a result, it's safe to claim that this plant is a good source of traditional medicine, which could be useful in medication development, bearing in mind that it could also be toxic depending on its consumption rate locally.

Keywords

Aristolochia longa L, ethnobotanical, medicinal plant, pharmacological, phytochemistry

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RESEARCH ARTICLE

A Review on the Ethnobotanical, Phytochemistry, and Pharmacological Activities of *Aristolochia longa* L

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Abstract

Aristolochia longa* L. is a plant native to Algeria and Morocco that has been used by the locals to combat different arrays of infections and diseases found among them. This particular plant is well-known for its therapeutic qualities that could be traced back to the presence of many effective phytochemicals that have been extrapolated from the different parts of the plant, like the leaves and roots: flavonoids, saponins, tannins, 4-hydroxybenzoic acid, β-carotenes, limonenes, and palmitic acids. This plant has been identified in different research articles to be able to manage diseases effectively because it possesses some pharmacological attributes such as; antitumor/anti-inflammatory, anti-cancer, anti-diabetic, anti-microbial, anti-fungal, as well as antioxidant properties. This review covers the ethnobotanical, phytochemical, and pharmacological activities of *A. longa* as well as its toxicological aspects. A thorough review of scientific literature published in a number of databases, including Scopus, Web of Science, and PubMed, was used to acquire relevant data for *A. longa*. The plant includes phytochemicals that have been proven to alleviate a variety of diseases. As a result, it's safe to claim that this plant is a good source of traditional medicine, which could be useful in medication development, bearing in mind that it could also be toxic depending on its consumption rate locally.

Keywords: *Aristolochia longa* L, Ethnobotanical, Medicinal plant, Pharmacological, Phytochemistry

1. Introduction

In recent years, the trend of using plants with medicinal properties cannot be ignored, as they have formed the basis for drug manufacturing and development [1,2]. There has been a significant increase in the recognition and open interest in orthodox treatments in third-world nations. With contemporary medical research in demand, the healthiest alternatives to existing synthetic pharmaceuticals with various unfavorable and health-hazardous consequences are medicinal plants, which are moving from marginal utilization to widespread use [1]. These locally-made pharmaceuticals are widely available in drug stores, grocery stores, and shopping malls. In African countries and in certain developed nations, about 80% of the population relies on alternative medications to cure ailments due to the ease with which they can be obtained and, most likely, the low cost factor associated with them when compared to contemporary drugs [3]. Many people in developing countries, including but not limited to Asia and Africa, rely heavily on traditional remedies to treat various illnesses and ailments [4,5]. The ability to obtain these plants without stress and with little or no money has been a major reason for their widespread use [4–6]. Several diseases have been treated and managed as a result of the various combinations of compounds and phytoconstituents (which are known to operate synergistically) to produce a new array of compounds that will act as essential herbal extracts [5,6].

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Recently, there has been a push to use novel components and treatments in food and drug manufacture to replace the contemporary ones, which have been proven to have side effects that limit their use among individuals [7,8]. Free radicals have been shown to be scavenged by the synergistic ability of phytoconstituents found in plants used as medications. According to [8], a good source of compounds high in pure antioxidants effectively treats a variety of disorders or diseases with minimal or no negative effects on the human system.

Plants and human beings have a shared relationship in traditional cultures, which is a study known as ethnobotany. Since the beginning of human existence as well as civilization, the use of medicinal plants has been a necessity to fully perform daily activities [9]. Recently, ethnobotanical studies have proven to be an important means of determining novel plants that are good for medicines or revisiting previously discovered bioactive substances [10]. The first step in the quality assurance of indigenous medicine is to use them for formulating new drugs from the archives of previously studied plants. This usage is known as ethnobotanical identification, and the knowledge of the identification helps in the proper utilization of the available biological resources. In other words, indigenous plant consumption has enormous potential socioeconomic advantages [11].

Aristolochia is a plant that belongs to the Aristolochiaceae family. The native plant utilization technique is used in the treatment of ailments such as inflammation, skin disorders, and purgatives. The antibacterial activity has been taken into account in the research that led to the extraction of the root [12]. The Aristolochiaceae are magnoliids, which are angiosperms that do not fall into the big groups of monocots or eudicots. According to the Angiosperm Phylogeny Group, the family Aristolochiaceae belongs to the order *Piperales* (Table 1). Based on anecdotal evidence, Aristolochia plants (Aristolochiaceae) are known to be utilized in all parts of the world for a variety of diseases [10]. The primary goal of this review is to comprehensively access the vast and common traditional uses of *Aristolochia* species, as well as to investigate their phytochemistry and pharmacological activities. Based on ethnopharmacological data, *Aristolochia* species are used medicinally in numerous parts of the world, but they also pose some risks (from a public health perspective). An organized review of the aristolochic acids that are produced in its utilization is required to determine a potential health risk. *Aristolochia* species have been linked to nephropathy, mostly in China and Europe. The review covers the utility of tackling the sickness (nephropathy) across all parts of the world [10]. There is significant evidence suggesting that this species of *Aristolochia* is well-known as a traditional medicine frequently used in India and Central America [10,12].

Table 1. Scientific classification of Aristolochia longa L.

SCIENTIFIC CLASSIFICATION	
Kingdom:	Plantae
Clade:	Tracheophytes
Clade:	Angiosperms
Clade:	Magnoliids
Order:	Piperales
Family:	Aristolochiaceae
Genus:	*Aristolochia*
Species:	*A. longa*
Binomial name	
Aristolochia longa L.	

1.1. Botanical description

Fig. 1 depicts the spindle-like shape of the root, which ranges in length from 5 cm to 3 cm and has a thickness of 2 cm. It is grayish in color externally, highly brittle, fleshy, brownish-yellow in color (inside), bitter, and has an awful odor when fresh. The taste of the plant's root is very bitter, and its leaves are long and thin, with violet-colored flowers [13].

2. Research methodology

As a keyword, the name of the plant, *Aristolochia longa* L., was used. Data for this review on *A. longa* L. was gathered from internationally recognized scientific databases via an electronic search (Wiley, SciFinder, Google Scholar, Springer, Web of Science, Francis & Taylor, Elsevier, PubMed, and The PlantList database). Furthermore, the medical books and PhD and MSc theses associated with *A. longa*, have been thoroughly examined and excerpts from them have been added to this review.

Fig. 1. A pictorial image of Aristolochia longa L.

3. Ethnobotanical study

An ethnobotanical survey was conducted in the northwest part of Algeria in a remote province called Mascara Province. They have a Mediterranean climate in the province, with about 450 mm of annual precipitation. There were approximately 826,334 people (both males and females) living there at the time, accounting for 1.04% of the population. Archives for information preservation were created through one-on-one conversations as well as semi-structured interviews [14]. A statistical report was also created to detail the portions of the plant that were most frequently used, and the results were as follows: roots (89%), leaves (9%), and the utilization of the complete plant (2%). Another study was evaluated to examine how the plant is prepared and used, and the results were as follows: mixing the crushed roots with honey and taking it orally ranked first at about 63%, followed by the combination of crushed roots with milk at 13%, which was also taken orally, followed by mixing the crushed roots with other known plants that have medicinal potential at 12%, and finally, by boiling parts of the plant in water and taking it orally at 11%. Skin illnesses such as infections and rheumatism have been treated by using the plant's paste, which is made by pulverizing the plant with olive oil or water and applying it to the skin's surface [15,16].

Another study was undertaken in the east of Algeria, at a town called Setif, roughly 300 km from Algiers. The study included one hundred (100) local volunteers, including elderly people and traditional healers, and some of the questions asked were about plant parts that were utilized in the cure of illnesses, ailments cured by the plants, how the plants were prepared, and how they were used, and all the responses gotten were carefully recorded. As a result of research in several areas of Setif (East Algeria), people confirmed the proposed thought that *A. longa* has been utilized in medicine for a number of purposes. Based on the information gathered and presented, it was discovered that only 50% of the group was able to identify the plant and knew how to use and prepare it, while the other 50% did not. *A. longa* has been used to cure a variety of diseases and health problems [17].

4. Phytochemistry

According to a study, *A. longa* extracts contain a wide range of phenolic constituents. However, citric acid was found to be the major phytochemical present in the aqueous fraction extracts of the root. When a different solvent (ethyl acetate) was utilized as a fraction, 4-hydroxybenzoic acid was the main component of the compounds. Furthermore, the inconsistency of phenolic constituents in the ethyl acetate fraction extraction is linked to the extraction solvents.

Some of the bioactive chemicals depicted in Fig. 2 have been found to be abundant in extracts of *A. longa*, including β-carotene, limonene, tannin, flavonoid, citric acid, catechin, rutin, quercetin, kaempferol, 4-hydroxybenzoic acid, chlorogenic acid, gallic acid, quinic acid, pyrogallol, and palmitic acid, and have been shown to have pharmacological effects [18] as shown in Table 2 [12].

5. Pharmacological activities

5.1. Antioxidant activity

The ability of a substance to inhibit the oxidation of other substances or even deactivate free radicals indicates that it has antioxidant qualities. A study by Attou et al. [19], examined the antioxidant activity of flavonoids and polyphenols isolated from *A. longa,* demonstrated that the plant has the potential to have a biological effect due to the presence of some chemicals (bioactive constituents), for example, flavonoids, polyphenols, and tannins (markers of antioxidant activity) [19]. Many studies have been conducted to evaluate the potential effect that the extracts of this plant would have on DPPH [20], ABTS [21], FRAP [22] scavenging activities as they aid in the neutralization of generated ROS. *A. longa's* ability to scavenge free radicals has been determined using various parts of the plant. The strongest inhibition of plant root extracts was observed in a study conducted by Merouani & Belhattab [14]. The aerial part of the plant was also investigated, and it was reported that methanol extracts demonstrated strong DPPH activity in a dose-dependent manner [14]. [19,20] reported the antioxidant capacity, reducing power, and radical scavenging activity (DPPH) of the methanolic leaf extracts of *A. longa*. According to [24,25], in research carried out, lead acetate was employed to create reactive oxygen species. But due to the existence of these compounds, they played a vital function in scavenging the produced free radicals. The ability of plant extracts to neutralize free radicals is solely related to the increasing levels of phenolic compounds (14.22 and 11.76 mg GAE/g, respectively). According to another study, *A. longa* has a greater amount of phenolic compounds to scavenge free radicals (such as hydroxyl radicals (OH.), superoxide radicals (O2.), and other ROS). The primary use of *A. longa's* antioxidant ability is to reduce oxidative stress by

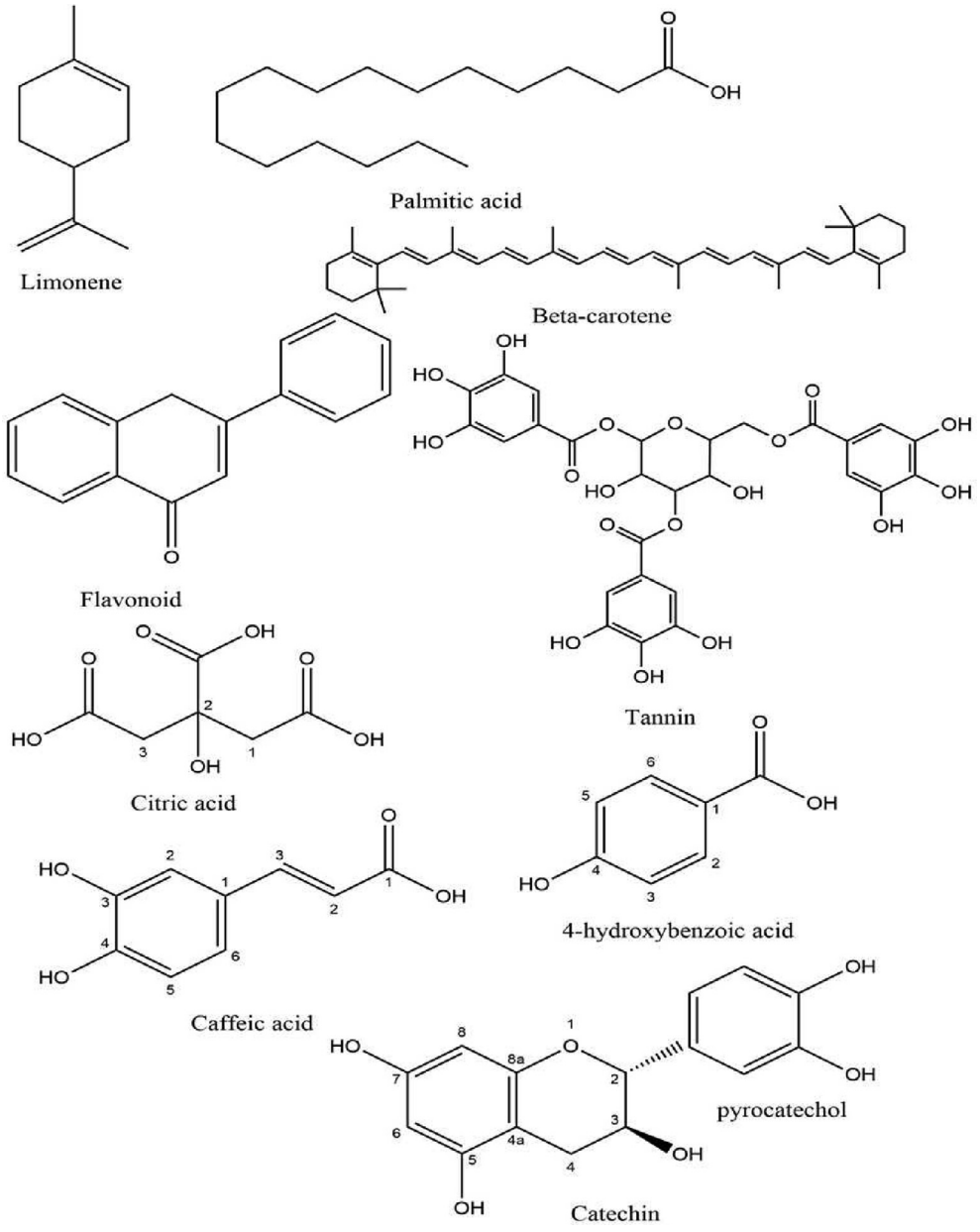

Fig. 2. Some selected bioactive compounds identified from A. longa extract.

scavenging radicals, which are the main cause of lipid peroxidation [26].

5.2. Antitumor/anti-inflammatory activity

According to [27], the study's data shows that applying the plant extract at a saturation limit dosage of 10% to the gingival topical, promotes inflammatory reactions to various oral cavity tissues (e.g., tongue, lips) as well as lung tissues, and is not limited to only the focused treated tissues. As a result, there were strong peribronchiolar hyperplastic lymphoid follicles as well as inflammatory interstitial polymorphic congestion and infiltration. This plant's rhizome included two primary components, AA-I, and AA-, both of which had stimulatory immunological activities [28]. An earlier *in vivo* investigation revealed that the aqueous extract of *A. longa* might induce an immune-stimulatory response in mice by enhancing both the humoral and cellular immune responses when supplied orally (through the mouth) [26,27]. This reaction was observed as a result of the plant's immunostimulant effect, which allows it to express its pro-inflammatory property.

Patients with systemic immunologic indications of tumors typically have suppression, which can be

Table 2. Some phytochemical Constituents of Aristolochia longa extracts [12].

S/N	Phenolic acids
1	Quinic acid
2	Malic acid
3	Pyrogallol
4	Citric acid
5	Succinic acid
6	Gallic acid
7	Chlorogenic acid
8	3,4-Hydroxybenzoic acid
9	Pyrocatechol
10	4-Hydroxybenzoic acid
11	3-Hydroxybenzoic acid
12	Catechin
13	Caffeic acid
14	Epicatechin
15	Benzoic acid
16	Epigallocatechin gallate
17	Syringic acid
18	Vanillic acid
19	4-Hydroxycinnamic acid
20	Rutin
21	Sinapic acid
22	3-Hydroxycinnamic acid
23	Ferulic acid
24	Quercitin
25	2-Hydroxycinnamic acid
26	Salicylic acid
27	Naringin
28	Rosmarinic acid
29	Luteolin
30	Resveratrol acid
31	Quercitrin
32	Kaempferol

measured as a reduction in the activity of the outer layer of lymphocytes as well as a reduction in their number [27]. These tumors play a role in mediating suppression by secreting substances. But it is not the only interaction between the host environment and the increasing metastasizing tumor [27,29]. The mystery of the anti-tumor [29,30] activity of *A. longa* can be attributed to the extracts of the plant, which induce the ability to combat tumor infections by their immune-stimulating activity, followed by the generation of inflammatory reactions and the development of tissue necrosis through a high level of cytotoxicity. *A. longa* revealed an increase in the number of mononuclear cells when used to treat experimental animals, as well as the lymphoid follicles and nodes that infiltrate the mononuclear cells. It was also discovered that an expanding number of different tissues containing eosinophils were all investigated. Following AA activation, it was explained by a series of pathways involving the inflammatory reaction and its cytotoxicity, that the NADPH oxidase catalyzes the reduction to superoxide from oxygen, releasing the ROS as quick-acting mediators [27,29].

5.3. Antidiabetic activity

Several *A. longa* extracts have been tested for antidiabetic efficacy [10]. This activity was assessed using two separate *in vitro* assays, α-glucosidase, and β-galactosidase uptake tests. Both enzymes examined were inhibited by *A. longa* extracts. Their findings are consistent with previous studies that have found that two of its species, aerial portions of *Aristolochia indica* [31] root extracts, reduced increased blood glucose levels in animal models. Inhibitory activities (α-glucosidase and β-glucosidase) have been examined via an *in vitro* analysis, and it was found that the fraction (ethyl acetate) shows the highest inhibitory effect [10,30].

5.4. Antimicrobial/antifungal activity

The antifungal medications that are now being manufactured are insufficient because of the inhibition in drug selection as well as the side effects that come with it, and the ability of pathogens (fungals) to resist them [31]. The aqueous extract of *A. longa* increases the level of inhibition of *Saccharomyces cerevisiae* cells. As a result, the plant is classified as a medication that is effective in the treatment of microbial infections [32]. *E. coli*, *P. aeruginosa*, *S. faecalis*, *S. aureus*, and *S. epidermidis* were all re-strained by the plant's aristolochic acid [33]. Pathogenic bacteria present are acted on by metabolites produced by a series of biological reactions contained in plant materials, and as a result, have become a good source of therapy [34]. When plants have medicinal potential, they ultimately have a close relationship with their components [35]. The plant of choice in this study, based on research, has extremely good antifungal activity and this conclusion is drawn based on the compounds identified in the *A. longa* aqueous extract [18].

5.5. Anticancer activity

An ethnobotanical study of *A. longa* revealed that the herb has been utilized to treat cancer patients. According to past studies, cancer therapy in Algeria has focused on *A. longa* due to its wide range of applications [18,36,37]. Several countries have documented the benefits of utilizing this herb to cure and control cancer, including Morocco [38] and Mexico [27]. The study clearly shows that the presence of saponins and flavonoids in *A. longa* extract produces dose-dependent cell death in a Burkitt's lymphoma cell line (BL41). Burkitt's lymphoma experiences an apoptotic process after being exposed to the plant extract, which results in the loss of mitochondrial

membrane potential and the activation of caspases-9 and -3 [39]. Previous researchers have found that increasing serum creatine, urea, and even uric acid levels with 1 g of *A. longa* could be harmful to kidney function in breast cancer patients [40–42].

6. Toxicity

Aristolochia is exceedingly lethal. It contains aristolochic acid, which is carcinogenic and detrimental to the kidneys. According to Gadouche et al. [43] and Grollman et al. [44], the toxicity of *A. longa* is mostly due to aristolochic acid, a poisonous chemical found in virtually all species of Aristolochia that is responsible for nephropathic syndromes. Furthermore, lysis of red blood cells was observed when treated with the plant extract, indicating severe toxicity. Saponins, which are secondary metabolites, were identified in aqueous extracts of the plant, and this may lead to the stimulation of hemolysis as well as apoptotic erythrocyte death. Consumption of dietary polyphenols may result in undesirable effects such as hemolytic anemia. Therefore, it is recommended that before using these polyphenols for therapy, they be evaluated for safety [45].

The use of *Aristolochia* can cause renal damage, necessitating dialysis or a kidney transplant. It also significantly raises the risk of bladder cancer and other urinary tract malignancies. Cherif and his colleagues investigated the toxicological profile of *A. longa*. They reported that *A. longa* (2.5 g/kg/day b. wt) treatment for 28 days had an effect on the biochemical indices of Wistar rats [46]. An *in-vivo* study reported that oral administration of the root aqueous extracts for 21 days at different doses shows toxic effects on both the liver and kidney functions in a dose-dependent trend [47]. Many studies have found that consuming *A. longa* (2.5 g/kg/day) produces histological damage to the hepatic and renal tissues [47,48].

7. Application of *A. longa*

Aristolochia species have been employed in traditional therapies for obstetrics and the treatment of intestinal affections, cutaneous disorders, wound healing, heart palpitation or snakebite, festering wounds, and tumors [27,49].

8. Limitations/drawbacks in the usage of *A. longa*

Despite its importance in treating or healing diseased processes, this herb includes aristolochic acid (AA) [25,50], a toxin responsible for the

Fig. 3. Schematic representation of pharmacological properties of A. longa L.

development of clinical syndromes such as nephropathy [51]. The major limitation of this plant is its toxicity. Being a potent nephrotoxic, aristolochic acid (AA), one of the major constituents of the plant, is still being extensively investigated for its pharmacological properties [47]. did a toxicological study on *A. longa* extract and concluded that *A. longa* could be toxic since it caused renal, liver, and intestinal toxicity. However, even at large dosages, the herb did not create substantial harmful effects at the start of the experiment, implying that, in addition to the AA, there may be other key constituents in *A. longa* dominating the intensity of toxicity, action speed, and possessing immunomodulatory properties able to involve immune responses in induced lesions. Further studies should be conducted to determine the effects of this plant on pregnant animals and their fetuses over longer study periods to complete the toxicity profile of this plant.

9. Conclusions

The ethnobotanical study concluded that this plant was widely used by the local population of Western Algeria to treat many illnesses and disorders, particularly the roots and leaves. However, as demonstrated in Fig. 3, the plant has many properties, including anticancer, antidiabetic, antifungal/antimicrobial, antitumor, antioxidant etc. The potency of this plant (*A. longa*) is due to the presence of bioactive components such as β-carotenes, limonenes, tannins, flavonoids, and palmitic acids or saponins. However, from the critical evaluation of this plant, it could very well be very toxic to the body system (liver, kidneys, intestines, etc.) depending on the consumption rate. It will be important to learn more about its effects on pregnant women and the developing fetus in the future.

Author's contribution

Conceptualization, O.A.O.; methodology, A.B.O.; validation, O.A.O. and A.B.O.; investigation, B.A. and M.I..; resources, A.B.O., B.A. and M.I.; data curation, M.I. and B.A.; writing—original draft preparation, M.I., A.B.O. and O.A.O.; writing—review and editing, A.B.O. and O.A.A..; supervision, O.A.O.; project administration, M.I., B.A. and A.B.O.; All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors have declared that they have no conflicts of interest.

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