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REVIEW ARTICLE

MEDICINAL PROPERTIES OF *RICINUS COMMUNIS* AND THE NEED FOR NOVEL FORMULATION OF THE EXTRACTS: A REVIEW

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Abstract

Some drugs from plant and animal sources have proven to be efficacious, safe, and effective therapeutically. They are potential alternatives to synthetic and semi-synthetic drugs in treating diseases, especially the chronic types. *Ricinus communis* is one such plant that has been used traditionally for centuries as a medicinal plant in the treatment of a wide range of ailments and disorders like stomach aches, flatulence, constipation, and gallbladder pain. Others include dysmenorrhea, rheumatism, arthritis, backache, muscle aches, and toothache. In addition, other uses include chronic headaches, insomnia, placenta expulsion, and anti-fertility. However, there is a deficiency of novel formulations of the extracts to maximize their therapeutic benefits. The phytochemicals in *Ricinus communis* are extracted via direct expression of the seed and solvent of both the seed and the different plant parts. Some solvents used for extraction include ethanol, petroleum ether, methanol, ethyl acetate, toluene, benzene, hexane, and chloroform. The constituents of the extracts depend on the plant part used, the solvent employed, and contact time. The phytochemicals found in the various extracts include tannins, saponins, phenols, alkaloids, glycosides, phytate, fatty acids, steroids, oxalate, and volatile constituents. These extracts are found to elicit a wide range of pharmacological activities against bacteria, fungi, cancer cells, worms, conception, constipation, pain, and malaria. In addition, some of the pharmacodynamic activities are laxative, uterine contraction, antiasthmatic, antidiabetic, anti-inflammatory, and anticonvulsant. The extracts are also useful in bone regeneration, wound healing, liver protection, and a host of other pharmacological actions. Novel products of *Ricinus communis* are not available. Subjecting the extracts to advanced drug delivery formulations such as lipid-based drug delivery technologies would accentuate the dissolution, absorption, and bioavailability of the extracts of *Ricinus communis* just like other herbal formulations currently in the market. Therefore, there is a crucial need for formulation scientists to explore novel nano-drug delivery technology to formulate extracts into medicines for the improvement of public healthcare.

Keywords: Bioactive, extracts, nano-formulation, phytochemicals.

INTRODUCTION

Ricinus communis L. popularly known as the castor oil plant taxonomically belongs to the family of Euphorbiaceae[1-4]; native to India and Africa (Ethiopia)[3], though widely distributed in tropical, subtropical, and warm temperate climates of the world[1,3,4]. It is known locally as Endi (Hindi), Errandi (Marathi), Zurma (Hausa), Jada (Oriya), Kherwal (Saudi Arabia), Diveli (Guajarati)[1,4-6]. Its botanical name was given by Carlos Linnaeus, a Swedish botanist[4]. There are more than 17 varieties of *R. communis* which are classified into trees and shrubs with the trees producing large seeds while the shrubs have smaller seeds[1,4,7]. The plant has pest and drought resistance, growing to a height of 10 to 12 meters high[3]. The wild varieties of the plant which are about 1-2 meters tall are abundant in North Central Nigeria, where they are being used in traditional medicine for diverse medicinal purposes[1,3,4,7]. Each tree or shrub bears male and female flowers, and they exist in clusters, with the male positioned at the upper and the female flowers at the lower position[2].

R. communis is highly adaptable and can grow in a wide range of climates, from warm temperate to tropical regions[4,8,9]. According to Salihu *et al.*,[8] they prefer aerated, moderately fertile, well-drained, and retentive loamy soil with a pH of 4.5 to 8.3. *R.*

communis can survive a wide range of temperatures and rainfalls, but they thrive in annual temperatures ranging from 7 to 27.8ºC and a yearly precipitation ranging from 20 to 429 cm[8].

A. Plant **B: Leaves** **C: Unripe fruits**

D: Ripe fruits **E: Seeds**

Figure 1: *R. communis.*

The castor seeds are smooth and elliptical-shaped. They manifest diverse variations in size and color which may be grey, black, or light brown[2,3]. Of the 17 varieties of the plants, the seed is categorized into 3 varieties namely, variety major (large seed variety), variety intermedia (medium seed variety), and variety minor (small seed variety)[2]. The seed contains 20% shell and 80 % kernel, and the average oil content for all the castor seed varieties is about 45–55% by weight, but the actual yield depends on the variety, geographical location, and the oil extraction methods[2,3]. Castor plants are generally cultivated to produce ricinoleic acid-rich castor oil[7].

Botanically, *R. communis* belongs to the Euphorbiaceae family, having the genus *Ricinus*, while the species is *R. communis* L[3,6,8]. Figure 1 shows pictures of *R. communis* and its parts.

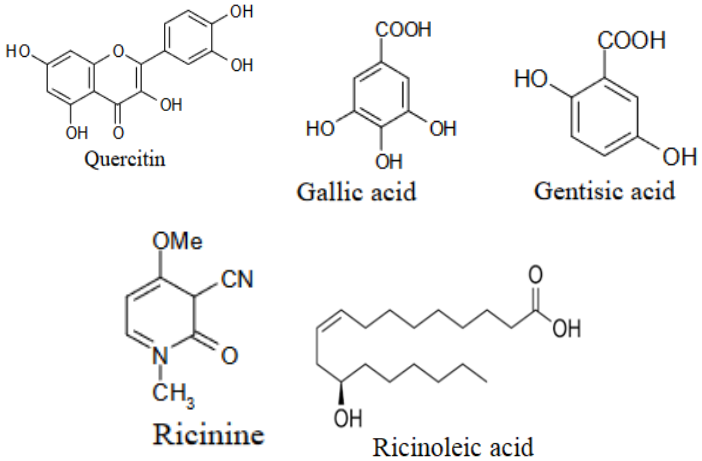

Figure 2: Chemical structure of some bioactive constituents of *R. communis.*

Phytochemicals found in *R. communis* plant

R. communis has been investigated to contain alkaloids, ricinoleates, steroids, tannins, glycosides, phenolics, flavonoids, saponins, and terpenes, among which are essential oils[4-6]. McNeil *et al.*,[2] Akpan *et al.*,[3] Abdul *et al.*,[4] and Elkousy *et al.*,[6] have documented that the

following phytochemicals are found in *R. communis*. They include alkaloids, mineral elements, flavonoids, proteins, globulins, tannins, sterols, enzymes, glycoproteins, and amino acids. In the same vein, they reported some bioactive compounds that have been isolated from *R. communis* extracts which include ricin, quercetin, ricinine, gallic acid, kaempferol, rutin, ricinoleic acid, gentistic acid, camphor, ellagic acid, lupeol, and a host of others[2-4,6]. Some of the chemical structures are shown in Figure 2.

Impact of extraction methods on oil yield

The oil from *R. communis* seed is extracted from the matured, sun-dried seed by removing the coat, cleaning, and milling[3,9]. The oil is extracted either by mechanical expression of the seed or solvent extraction[3,10]. Hexane is the first choice of solvent for the extraction process due to its low boiling point and is less corrosive, but other polar and non-polar solvents such as petroleum ether, ethyl ether, pentane, toluene, ethyl acetate, cyclohexane, acetone, chloroform, and ethanol[10]. It has been reported that the solvent type and extraction duration affect the oil yield from the seed[10]. Thus, effective extraction is dependent on the type of solvent, the temperature, the particle size of the milled *R. communis*, the contact time, the ratio of solute to solvent, and the procedure for extraction.

Researchers have adopted various extraction methods for different parts of *R. communis* plants, depending on the facilities available. To obtain crude oil extract from castor seeds, one common method is to subject 100 g of finely ground seeds to exhaustive Soxhlet extraction using 150 ml of methanol for 75 minutes to obtain 70.0 ± 2.8 g of crude extract[1,2]. Another method is to use petroleum ether at 5-20 mg/kg, which produces 15% w/w of the oil[11]. In another research, 8.42 kg of *R. communis* bean paste was wrapped in a cloth and mechanically cold-pressed below 45 °C using a manual extractor to obtain 3.20 liters of fresh yellow oil which is clear and viscous[3].

The castor seed oil

Castor oil is extracted from the matured seed of the castor plant after sun-drying, dehulling, removal of the coat, winnowing, sorting, cleaning, milling and mechanical expression, solvent extraction, or by applying both methods[3]. The oil is a triglyceride, which is non-volatile; it is viscous, pale yellow, and biodegradable. It has high resistance to oxidation and has a boiling point of 313°C[3,5].

Castor oil is composed of approximately 90% ricinoleic acid[3]. It also contains smaller amounts of linoleic acid, palmitic acid, oleic acid, dihydrostearic acid, and other fatty acids[3,5,7]. In addition to fatty acids, the following are also contained in castor oil: Phenol, Alkaloid, Lauric acid, Cyanogenic glycosides, Globulin, Vitamin E, B-sitosterol, Glycosides of fatty acids, Tannin, Cholesterol, Lipase, Phytate, Oxalate, Saponin, Cholesterol, Lipase, limonene, cineole, Flavonoids, trace amount of essential oil[5,7]. The extracted oil has diverse uses in fields including medicine, cosmetics, and industry[3].

Traditional uses of *R. communis*

R. communis has been a therapeutic agent as herbal medicine for the treatment of various ailments, disorders, and infections for the past 4,000 years, by the utilization of the leaves, roots, bark, flowers, fruits, stems, and seeds[4]. The plant has a long history of ethno-pharmaceutical use in the treatment of stomach aches, arthritis, flatulence, backache, muscle aches, toothache, bilharziasis, sciatica, chronic headache, constipation, gallbladder pain, dysmenorrhea, rheumatism, emetic in opium poisoning, and insomnia. It has also been used for the expulsion of the placenta and as a laxative[4,7]. The powdered leaves have been used to increase milk production in cows by feeding them with the leaves[4]. *R. communis* has a long history of being used by the Bassa people of Plateau state, Nigeria, as an antifertility agent[12].

Medicinal properties of *R. communis*

There are many studies that revealed the biological activities of *R. communis*. These activities are largely due to the crude extracts and the isolated bioactive molecules resulting from any of the solvent extraction methods[4]. Some of the key medicinal properties are described below.

Antibacterial/antifungal activity

The surfactant properties of *R. communis* oil which is due to sodium ricinoleate damage the cell membrane resulting in the loss of the content of the cytoplasm and subsequent death of the cell[4,7]. *R. communis* and its phytochemicals have been reported to have antimicrobial activity against various micro-organisms which include *S. aureus*, *E. coli*, *S. mutans*, *S. progenies*, *K. pneumonia*, *E. faecalis*, and methicillin-resistant *S. aureus*[4,6]. A study by Inayor and Ibraheem[13] shows that the phenolics and saponin extract of the leaves of *R. communis* hindered the growth of gram-negative bacteria, *Klebsiella halize*, and gram-positive *S. aureus* totally at a dose of 5mg/mL of the leaf extract. This shows that *R. communis* extract of the leaf could be a potential broad-spectrum antibiotic agent that can be used to treat multidrug-resistant bacteria infections. Therefore, this extract needs to be further investigated.

Methanolic and aqueous extracts of the root, leaf, and stem have been shown to have antifungal activity against many fungal cells[4,14]. In a study that tests the antifungal property of *R. communis*, the maximum antifungal activity was shown against *C. albicans*, while the least was on *Alternaria solani*[4]. This shows potent inhibitory activity against *A. niger* and *Aspergillus fumigatus* and less activity against *Aspergillus flavus*[4]. Again, this research has confirmed the antifungal and antibacterial activities of *R. communis*. This could be a potential new drug candidate for the treatment of fungal infections.

Anti-cancer activity

R. communis extract has been valuable in hepatitis, skin, and breast cancer therapy[15]. Fruit extract from the *R. communis* plant is very effective at killing breast cancer cells, including both estrogen-positive MCF and triple-negative breast cancer cells (MDA-MB-231 cell line)[16]. The extract stops cancer cells from spreading by preventing them from sticking to other cells, moving around, and breaking down the tissue around them; also, it kills the cancer cells[16]. Studies have shown that ethanolic, methanolic, and aqueous extract

of *R. communis* has anti-cancer activity against many types of cancer cells, including melanoma, breast cancer, liver cancer, pancreatic cancer, and cervical cancer[4,15].

According to Kumar[17], ricin isolated from *R. communis* exerts more toxic activity on tumor cells than normal cells. These findings preclude *R. communis* extracts and some of their isolates can be explored for cancer chemotherapy for better healthcare given the toxicity level of the synthetic and marketed anticancer drugs.

Anti-fertility property in male and female

Rana *et al.*,[18] and Okwasaba *et al.*,[1] observed that the ether-soluble portion of the methanol extract of *R. communis* produced anti-implantation, estrogenic, and contraceptive effects in rats and mice via subcutaneous route. They alluded to the fact that the activities emanate from different sites, which include direct effects on the endometrial implantation site, fallopian tube, or/and disruption on the estrogen/progesterone balance[1,18]. Furthermore, in another research, when 2.3 -2.5 g of de-coated seeds of *R. communis* was administered to 50 women volunteers as a single dose, it produced reversible anti-conceptive and anti-implantation activities in women for 12 months without side effects[4,12]. In the research conducted by Okwuasaba *et al.*,[11] the administration of different doses of petroleum ether extract (2-20 mg/kg) induced a dose-dependent contraceptive effect over 5 successive gestation periods.

Research has discovered that the common side effects that attend the conventional hormonal contraceptive agents such as weight gain, nausea, vomiting, prolonged amenorrhea, irregular bleeding, abdominal pain, headache, dysmenorrhea, depression, and hypertension were absent[11,12]. Research conducted using petroleum ether (PE) extract of *R. communis* seed not only shows a dose-dependent contraception for 5 successive gestation periods, but also indicated that its antifertility efficacy and pretreatment with PE altered the activity profile of the uterus and oviduct as well as their response to oxytocin, ergometrine, and acetylcholine in a characteristic manner[11]. According to another study, the presence of phytosterols, a steroid in the methanol extract of the seed of *R. communis* may be responsible for the antifertility activity[17].

Furthermore, giving male rats 50% ethanol extract of *R. communis* produced a reversible antifertility by reducing the sperm count, the sperm motility, changing the morphology and movement of the sperm cells, and reducing fructose levels[2,4,16]. A study was performed with the aqueous, acetone, petroleum ether, and ethyl acetate extract of the stem bark of *R. communis*, and it was discovered that at the highest concentration of aqueous extract (100 mg/ml), there was a 100 % reduction in sperm motility in 60 seconds and 100% immobility within 30 minutes of incubation[19]. Therefore, this plant extract drastically inhibits the motility of spermatozoa. The above findings make castor seed and its extracts a potential antifertility agent. The ricinoleic acid from the castor oil is used in contraceptive creams and jellies[3].

Antidiabetic activity

Chouhan *et al.*,[16] observed that giving 500mg/kg body weight of 50% ethanol extract of *R. communis* roots for 10-20 days significantly lowers blood glucose levels in both diabetic and normal animals, and improves lipid profile, kidney, and liver function. Also, administering diabetic rats with ethanolic extract and aqueous extract of *R. communis* leaves at doses of 300 mg/kg and 600 mg/kg body weight, respectively, caused them to lose weight and have lower blood glucose levels[16]. These prove the capacity of *R. communis* as a potential therapeutic agent in diabetes treatment and management. When 600 mg/kg of the drug was administered orally, there was no change in the levels of total protein, total bilirubin, albumin, urea, and creatinine, indicating the drug is a good option for therapy of diabetes mellitus[6,16].

Antioxidant Activity

Antioxidants help significantly in keeping body cells alive and ensuring their optimal health[4]. The antioxidant capacity of *R. communis* varies depending on the extraction methods and the plant part used. However, the leaves and seeds have the most antioxidant power[16]. Ricinoleic acid, its methyl esters, and 12-octadecadienoic acid isolated from *R. communis* seeds are strong antioxidants, even in low concentrations[6]. Tocopherols and tocotrienols from castor oil extract also possess good antioxidant properties[6]. It has been documented that ethanol has the highest free radical scavenging activity at 95%, followed by acetone which is 91%, dichloromethane (62%), and n-hexane which stands at 50%[16].

Other studies ascribed the antioxidant activity of *R. communis* to constituents like gallic acid, quercetin, gentisic acid, rutin, epicatechin, and ellagic acid in leaves[4]. Flavonoids have been discovered to be responsible for the strong antioxidant properties of *R. communis* extracts when compared with tannins[4]. The stem extract of the castor plant is rich in flavonoids which are beneficial against carcinogenesis as they inhibit oxidative cell damage[16]. The antioxidant property makes the oil extract have a long shelf-life of up to 12 months[7].

Antiulcer Activity

Studies have shown that *R. communis* has significant anti-ulcer properties which are due to the cytoprotective action and strengthening of the gastric mucosa that ultimately results in the enhancement of mucosal defence[4]. *R. communis* seed oil has antiulcer properties at a dose of 500 and 1000 mg/kg, it is more effective against ulcers caused by pylorus ligation, aspirin, and ethanol in rats at a dose of 1000 mg/kg[6].

Ophthalmic activity

R. communis oil is employed as a lubricant to treat dry eyes to maintain hydration and it also reduces muscular strain in the eyes to accentuate better vision[5,16]. In addition, the oil is utilized to remove accident-mediated foreign body particles in the eyes, and for eye cleansing for better vision[5]. Castor oil administered as an eyedrop thickens and changes the composition of the tear film lipid layer and it stays in the eye longer than conventional eyedrops[5].

According to studies, when castor oil is applied to the eyelids twice a day for four weeks it significantly reduces the symptoms of blepharitis, an eye condition that causes inflammation of the eyelids. The castor oil also improved several signs of blepharitis, including thickened eyelids, widened blood vessels, matted eyelashes, loss of eyelashes, dandruff-like scales on the eyelids, crusting on the eyelashes, and damage to the cells that line the eyelids[5,20].

Anthelmintic activity

R. communis leaf extracts in aqueous, ethanol, ethyl acetate, methanol, and chloroform at concentrations of 50, 75, and 100 mg/ml were effective in killing pheretima posthuma (long cylindrical worms)[16]. *R. communis* extracts paralyzed and killed worms, but the aqueous extract worked faster and better than the ethanolic extract at 100 mg/ml[4]. This is a clear indication that it has more anthelmintic properties. This shows that *R. communis* extracts are potential new chemical entities in worm therapy.

It can be inferred from several works that extracts of *R. communis* have numerous medical benefits that cannot be accounted for in a single article. Some medical benefits include antinociceptive, antiasthmatic, antihistaminic, hepatoprotective, wound healing, lipolytic, anti-inflammatory, bone regeneration activity, anticonvulsant activity, analgesic activities, and a lot more[4,6,7,13,16,18].

Toxicology of *R.communis*

The castor seeds are widely known for containing the toxic glycoprotein called ricin (5%), the alkaloidal ricinine, and toxic castor beans allergen, which are eliminated during the extraction processes[3,4,6,9]. Ricin is a type 2 ribosome-inactivating protein that irreversibly inactivates ribosomes and stops protein synthesis thus leading to the death of the cell[4,9,16].

Some studies have observed that the methanolic leaves extract of *R. communis* administered to rats at a dose of 100 mg and 200 mg/kg body weight showed the extract was non-toxic and caused no damage to the vital organs[16]. The presence of ricin and ricinine has resulted in accidental toxic effects with *R. communis*[4]. Some studies have shown that ricin toxicity in mice may vary from hyperactivity to seizure formation and even death at a dose greater than 340 mg/kg intraperitoneally and 3 g/kg orally[4]. Ricin poisoning can cause a range of symptoms, depending on amount of exposure of ricin. These symptoms can include abdominal pain, vomiting, muscle pain, difficulty breathing, low blood pressure, dehydration, muscle cramps, kidney, and liver problems[4].

According to Ahmad *et al.*,[21] *R. communis* seed is very toxic to humans, and other animals due to the 2.8 – 3% ricin content it contains. They further observed that 2.5 -20 seeds kill a human adult when chewed and swallowed, but only one seed can kill a child. Similarly, they reported that 4 seeds can kill a rabbit, 11 will kill a dog, it takes 6 seeds to kill a horse when chewed and swallowed, and it takes 5 to kill a sheep, but 80 seeds to kill a chicken and duck[21]. The presence of these toxic substances limits adequate benefits from the traditional method of using *R. communis* seeds for therapeutic purposes. This has necessitated writing this article to mobilize formulation scientists to take advantage of nanotechnology and nanobiotechnology approaches and formulate medicines out of *R. communis* extracts for clinical use.

Formulation of *R. communis* extracts

Medicinally, the *R. communis* plant is a great gift by nature to mankind. It's a plant that is highly endowed with numerous bioactive substances sufficient to meet therapeutic needs and accentuates public healthcare globally. However, the medicinal benefits of *R. communis* are not being harnessed as maximally as they ought to be. This is because we cannot derive maximal pharmacological benefits from the traditional methods of drug delivery due to several limitations. These bioactive constituents or crude extracts need to be converted into medicines via formulation technologies.

Medicines are drug delivery systems employed to administer drugs to the body in a safe, efficient, reproducible, and convenient manner[22,23]. The objective of designing a drug delivery system is to have a product with a predictable therapeutic response to the Active Pharmaceutical Ingredients (API) and possesses reproducible quality when manufactured on a large scale[15].

The major challenge for the delivery of several herbal drug preparations is low solubility, low oral bioavailability, poor absorption, and poor stability, which hinder their effective clinical application[25-29]. When the extracts from *R. communis* are subjected to novel drug delivery approaches the solubility, dissolution, absorption, and bioavailability of both the crude extracts and bioactive chemical entities will be enhanced[30,31]. Many phytochemicals offer satisfactory *in-vitro* activity but less efficacy *in vivo*, due to their poor aqueous solubility and inappropriate molecular size that give rise to poor absorption and poor bioavailability[24,29,32]. Therefore, the right drug delivery carriers must simultaneously ameliorate the challenge of solubility of the bioactive substances, diminish the degradation process, reduce toxicity, enhance the bioavailability, mask any bad taste, and improve site targetting[29,32].

Utilizing a nano drug delivery approach to the delivery of herbal bioactive extract increases the drug stability, reduces drug-protein binding, lengthens the drug half-life, minimizes toxicity, bypasses the first-pass effect, increases bioavailability, and accentuates patient compliance[24,26,29,31,33]. Nanotechnology-based drug delivery technology has made available effective drug delivery carriers to incorporate many bioactive molecules[28,31,32,34].

Nanotechnology has brought a significant solution to subdue the solubility challenges militating against herbal formulations[35]. For instance, artemisinin sourced from *Artemisia annual* L has been formulated into an emulsion solvent evaporation as an anticancer product; cinnamon oil from *C. verum* was formulated as a microemulsion for wound healing as an antimicrobial; oleanolic acid from plant extracts was formulated as nanoprecipitation for cancer treatment; salvianolic acid from *Salvia miltiorrhiza* was also

formulated as liposome used for bone fracture union[29,36,37].

Similarly, extracts of *R. communis* such as oil can be formulated using nano drug delivery technologies, such as self-nano drug delivery systems (SNEDDS), for enhanced solubility, absorption, stability, bioavailability, and reduced toxicity[37]. However, there is a gap in the literature concerning the nano formulations of castor seed oil extract or extracts from other parts of the plant into novel pharmaceutical products. This calls for step-up research by formulation scientists to develop novel pharmaceutical products from castor plant extracts to improve healthcare delivery. Currently, *R. communis* oil is being used as a pharmaceutical excipient for the formulation of other API such as the anticancer paclitaxel and docetaxel[9], and in ophthalmic preparations[7].

CONCLUSIONS

R. communis plant is a medicinal plant well distributed across the globe and is widely used traditionally for the treatment of a vast spectrum of ailments. Research has also shown the extracts from the roots, stem, leaves, fruits, and seeds have multiple pharmacological (medicinal) activities against various diseases and disorders, due to the presence of many bioactive phytochemicals such as alkaloids, glycosides, tannins, essential oils, saponins, steroids, fatty acids, phenols, phytate, oxalate, and volatile constituents. Even though *R. communis* is rich in multiple bioactive substances with pleasant pharmacological properties, there are very few formulated products for clinical use. This has limited the immense medicinal benefits of *R. communis* from being tapped maximally. Therefore, there is a great need for the active involvement of formulation scientists in developing nano-formulations of *R. communis* extracts from the different parts of the plant to produce drugs of natural origin that are safe, efficacious, effective, and have a wide spectrum of acceptance. This would greatly boost the economy and global public health systems.

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AUTHOR'S CONTRIBUTION

Ekoja A: data collection, writing: preparing the first draft. **Audu-Peter JD:** leadership and oversight of the design and implementation of the research activity. Every author gave their approval to the manuscript's final draft.

DATA AVAILABILITY

The data and material are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

None to declare.

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