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Phytomelatonin content in *Valeriana officinalis* L. and some related phytotherapeutic supplements

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ABSTRACT

The use of medicinal plants as an alternative phytotherapeutic remedy against mild illnesses and dysfunctions is increasingly embraced by people. Among these dysfunctions, episodes of nervousness and anxiety due to lack of sleep and insomnia are becoming more and more frequent among the population. To remedy these problems, several plants with sedative activity are recommended. In particular, valerian root (*Valeriana officinalis* L.) is the most recommended and studied with a significant difference. This study presented a quantification of the phytomelatonin contents in valerian root and several related and recommended herb supplements against nervousness, anxiety, and insomnia. The results showed the presence of phytomelatonin in all the samples analyzed. The high phytomelatonin contents in valerian root and its supplements indicated that, in addition to the known constituents of valerian root such as valerenic acid, phytomelatonin also contributed to the phytotherapeutic activity of this plant since the relaxing and sleep-inducing activity of melatonin is well documented. The recommended daily doses of valerian are analyzed according to their phytomelatonin content, and recommendations are given on the possible synergistic action of the components of valerian as a relaxant and sleep inducer in patients with these dysfunctions. It is also recommended to document the phytomelatonin contents in phytotherapeutic preparations.

1. Introduction

A medicinal herb is a plant containing some part/extract that can be used to treat an affectation or disease. The different presentation forms of herb supplements are worldwide products used for the treatment of minor human pathologies or dysfunctions. In the USA, these food supplements are regulated by the American Food and Drug Administration (FDA), which uses the term dietary supplements for products that have not been subject to control or evaluation and stipulate that these dietary supplements must be labeled with the annotation that they have not been evaluated by the FDA. In the European Union (EU), more restrictive legislation is applied by the European Medicines Agency (EMA) (EMA-HMP, 2018; Vanaclocha and Cañigueral Folcara, 2019).

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Generally, medicinal herbs and nutraceuticals of plant origin tend to be more accepted by consumers than others. In this sense, nutrition-based healthcare during the history of humankind can be explained by the funny commentary of Rowe (1999):

2000 B.C. - Here, eats this root.
1000 A.D. - That root is heathen. Here, says this prayer.
1850 A.D. - That prayer is superstition. Here, drinks this potion.
1940 A.D. - That potion is snake oil. Here, swallow this pill.
1985 A.D. - That pill is ineffective. Here, takes this antibiotic.
2000 A.D. - That antibiotic is artificial. Here, eats this root.

The trend of using pharmaceutical preparations of natural origin is increasing owing to the better knowledge of its efficacy and safety. Due to increased stress and sleep difficulties leading to episodes of anxiety, many people consider the consumption of medicinal plants as a possible alternative solution. Some medicinal plants have the property of being sedatives acting on the central nervous system, decreasing nervous excitement, being used as a treatment against anxiety, insomnia, and nervousness (Hadley and Petry, 2003; Wheatley, 2005; Singh and Sharma, 2020).

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Valeriana officinalis L. (valerian) is one of the plants on which more clinical studies have been published, demonstrating its effectiveness as a mild tranquilizer in cases of generalized nervousness, insomnia, restlessness, and moderate anxiety states. Its non-toxicity has been demonstrated in therapeutic doses. Valerian root is used as a sedative or sleep aid. It is worldwide available as a food supplement. Valerian supplements, with *V. officinalis* roots as the main component, were used to improve sleep quality and minimize anxiety, stress, or moderate nervousness, all thanks to its sedative and anxiolytic properties. Among the recommendations for valerian root, approved by the European Scientific Cooperative on Phytotherapy (ESCOP), are the relief of mild nervous tension episodes and difficulty falling asleep. In addition, EMA approves its traditional use to relieve mild mental stress symptoms and fall asleep (HMPC-EMA, 2016; Hadley and Petry, 2003).

Multiple studies of valerian roots and their possible effects on the improvement and induction of sleep have been conducted in recent decades. Generally, randomized and double-blind clinical trials have shown that extracts of valerian root and valerian supplements allow a higher quality in sleep parameters, facilitating relaxation, reducing the time needed to fall asleep, and deeper sleep phases than placebo. Nevertheless, some difficulties in interpreting the results appear because of the different dosage, origin, and purity of the herbaceous extracts used. However, the effects are not immediate, and treatment of 2-4 weeks is required to achieve a significant improvement, without risk of dependence or adverse effects, which differentiates the action of valerian roots from that of synthetic hypnotics and benzodiazepines (Tammadon et al., 2021; Shinjyo et al., 2020; Palmieri et al., 2017; Taavoni et al., 2011; Barton et al., 2011; Dimpfel and Suter, 2008; Miyasaka et al., 2006; Bent et al., 2006).

Furthermore, melatonin supplements are also used to improve sleep quality and sleep disorders, including insomnia, and avoid jet lag. Also, to prevent or treat states of anxiety or depression (Dahlitz et al., 1991; Ferracioli-Oda et al., 2013; Herxheimer, 2005; Jan et al., 2000; Xie et al., 2017). Melatonin supplements are made with synthetic melatonin, which is cheap and easy to synthesize chemically (He et al., 2003; Thomson et al., 2003; Bartolucci et al., 2016). These supplements can be found in the market in a wide range of form presentations such as tablets, pills, liquid, sublingual, etc. The regulations for these melatonin supplements are different depending on the country, being more strongly regulated in the EU and more laxly by the FDA in the USA (Coppens et al., 2006; Finley et al., 2014). In recent years, it has been proposed that obtaining phytomelatonin (discovered its presence in 1995) from plants (Pérez-Llamas et al., 2020; Arnao and Hernández-Ruiz, 2018) could be a natural alternative in the making of melatonin supplements since, in some cases, by-products of certain toxicity have been detected in synthetic melatonin preparations (Mayeno and Gleich, 1994; Naylor et al., 1999; Williamson et al., 1998). Phytomelatonin is present in all the plants studied, generally at low concentrations, being its most relevant content in aromatic and medicinal plants (Arnao, 2014; Arnao and Hernández-Ruiz, 2015; 2018; Cheng et al., 2021).

In this paper, a relationship between the sedative capacity of valerian roots and supplements and phytomelatonin content was studied. Valerian dry roots and herb supplements with/without valerian root were analyzed to know its phytomelatonin content and establish a possible synergic effect of traditional valerian components and the novel phytomelatonin determination in plants. A study of the recommended maximum daily dose of herb supplements and the phytomelatonin content was presented.

2. Materials and methods

2.1. Chemicals

The chemicals, solvents (methanol, acetonitrile, ethyl acetate), and reagents used were from Sigma-Aldrich Co. (Madrid, Spain). Milli-Q system (Milli-Q Corp, Merck, Darmstadt, Germany) ultra-pure water was used.

2.2. Plant material

Dried roots of *V. officinalis* were obtained from Murciana de Herboristeria S.A. (Cobatillas, Murcia, Spain), a specialized company in medicinal and aromatic herbs. Table 1 shows the technical sheet of valerian root used.

Table 1. Physico-chemical and microbiological characterization of *V. officinalis* samples

Product	Valerian roots
Denomination	The healthy, clean, and dried root of *V. officinalis*
Origin	Poland
Organoleptic characteristics	
Aspect:	Correct
Smell:	Characteristic, without the presence of strange odors
Color:	Brown
Physico-chemical characteristics	
Humidity (%)	12,00 Máx.
Total ash (%)	12,00 Máx.
Insoluble ash (%)	5,00 Máx.
Microbiological characteristics	
Escherichia coli (ufc/g)	≤100
Salmonella spp.	Absence / 25 gr
Total aerobics (ufc/g)	≤10.000.000
Molds and yeasts (ufc/g)	≤100.000

Moreover, three herbal supplements with sedative properties obtained from a local pharmacy office were used in the study. These herb supplements are commercialized in Spain and many other products with similar compositions in the EU. The supplements were: Valeriana Eladiet from Eladiet Lab. (Barcelona, Spain), Valeriana Deliplus from Korott Lab (Alicante, Spain), and Neuro Balance from Salus Lab (Bruckmühl, Germany), all recommended as sedatives and as a sleep aid. Table 2 shows the ingredients and composition of these herb supplements.

Table 2. Ingredients and composition of the herb supplements studied

Product	**Ingredients**	**Deck ingredients**
Valeriana Eladiet	60 pills (330 mg)	
	Valerian officinalis root (257 mg)	Hydroxypropylmethylcellulose
	Silicon dioxide	Microcrystalline cellulose
	Hydroxypropylcellulose	Stearic acid
	Magnesium stearate	Erythrosine
	Polyethylene glycol 6000	Indigo carmine
		Titanium dioxide
Valeriana Deliplus	60 pills (520 mg)	
	Valerian officinalis root (400 mg)	Gelatin
	Magnesium stearate	
Neuro Balance	10 ml	
	Aqueous extract of:	Juice concentrates of:
	Lemon balm leaves	Mango puree
	Lavender flowers	Guava puree
	Mint leaves	Ashwagandha root extract
	Passiflora grass	Carob flour
	Rosemary leaves	
	Vitamin C, Vitamin B12	
	Natural flavorings	

2.3. Extraction of phytomelatonin

Samples for phytomelatonin analysis were prepared according to Hernández-Ruiz and Arnao (2008) and Arnao and Hernández-Ruiz (2009). Briefly, samples of valerian roots and herb supplements (0.3 g DW) were placed in vials containing ethyl acetate (5 ml). After leaving overnight (15 h) at 4 °C in darkness with shaking, the tissue was discarded after being washed with the respective solvent (0.5 ml). The extract and washing solution from each sample was evaporated to dryness under vacuum using a SpeedVac (ThermoSavant SPD111V, Thermo-Fisher Sci, Waltham, MA, USA) coupled to a refrigerated RVT400 vapor trap. The residue was redissolved in acetonitrile (1 ml), filtered (0.2 µm), and analyzed using liquid chromatography with fluorescence detection (LC-FLUO) and by LC with time-of-flight mass spectroscopy (LC-QTOF/MS). The procedures were carried out in artificial dim light.

2.4. Phytomelatonin analysis

Phytomelatonin content in valerian roots and herb supplements was determined by liquid chromatography with fluorescence detection (LC-FLUO) and by LC with time-of-flight mass spectroscopy (LC-QTOF/MS), according to our previous studies (Arnao and Hernández-Ruiz, 2009). A Jasco liquid chromatograph Serie-2000 (Tokyo, Japan) equipped with an online degasser, binary pump, auto multi sampler, thermo-stated column, and a Jasco FP-2020-Plus fluorescence detector were used to measure phytomelatonin levels. An excitation wavelength of 280 nm and an emission wavelength of 350 nm were selected. A Waters XBridge-C18 (5 µm of particle size), 100 x 2.1 mm LC column (Sigma-Aldrich, Barcelona, Spain), and thermo-stated at 40 °C were used. Solvents A (MilliQ water with 0.1% formic acid) and B (acetonitrile with 0.1% formic acid) in isocratic mode, at a flow rate of 0.2 ml/min, were used for the compound separation. The data were analyzed using the Jasco ChromNAV v.1.09.03 Data System Software (Tokyo, Japan). For correct identification, an in-line fluorescence spectral analysis using the Jasco Spectra Manager Software (Tokyo, Japan) compared the excitation and emission spectra of standard melatonin with the corresponding peak of phytomelatonin in the samples. Identification of phytomelatonin in plant extracts was also confirmed using an LC/QTOF-MS system consisting of an Agilent 1290 Infinity II Series LC (Agilent Technologies, Santa Clara, CA, USA) equipped with an automated multi sampler module and a high-speed binary pump and connected to an Agilent 6550 Q-TOF Mass Spectrometer using an Agilent Jet Stream Dual electrospray (AJS-Dual ESI) interface. Experimental parameters for LC and Q-TOF were set in MassHunter Workstation Data Acquisition software (Agilent Technologies, Rev. B.08.00). The set parameters and signal corresponding to phytomelatonin were extracted and quantified with an m/z of 233.1285, according to (Hernández-Ruiz and Arnao, 2008).

2.5. Statistical analysis

For collecting all data, differences were determined using the SPSS 10 program (SPSS Inc., Chicago, USA), applying the LSD multiple range tests to establish significant differences at $p < 0.05$. The results are expressed as mean ± standard error (SE, $n = 5$).

3. Results and discussion

A peak corresponding to phytomelatonin was detected by LC-FLUO in the described conditions at ~ 12.3 min, as can be seen in Figure 1A, where a chromatogram of standard melatonin appears. Also, a calibration curve of standard melatonin in the range used is shown (Figure 1B). In the same conditions, the presence of phytomelatonin in a valerian root sample was indicated by its peak retention time (Figure 2) and from the respective excitation and emission spectra, including a comparison of the first- and second-order derivatives from each spectrum (Arnao and Hernández-Ruiz, 2009). The presence of phytomelatonin in the samples was confirmed by spiking the standard (at ng levels) into the root sample extracts and observing the increase in the putative melatonin peak. Also, confirmation was obtained by LC/QTOF-MS analysis (Hernández-Ruiz and Arnao, 2008).

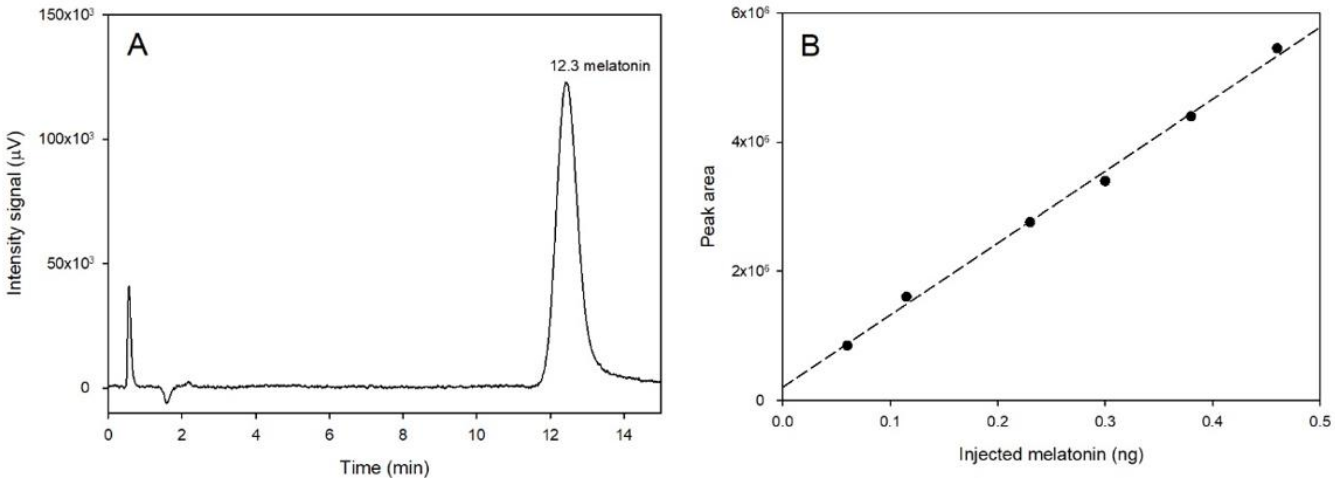

Figure 1. Panel A: Representative chromatogram of standard melatonin (116 pg) measured by LC with fluorescence detection with λexc = 280 nm and λemi = 350 nm. The melatonin peak at the retention time of 12.3 min is marked. Panel B: Linear regression curve of standard melatonin. Circles represent the means of three replicates; SE is included in the size of the symbols.

Table 3 shows the phytomelatonin quantitation in each studied sample. All the samples contained significant amounts of phytomelatonin. Phytomelatonin levels in edible plants range from nanograms to micrograms per gram of plant tissue. In general, seeds, leaves, stems, seedlings, and roots show the highest phytomelatonin levels and fruits the lowest. Medicinal/aromatic plants have significantly higher levels than seeds and fruits. Additionally, growing conditions and harvesting, among other

factors, affect phytomelatonin levels in plant tissues (Arnao, 2014; Arnao and Hernández-Ruiz, 2013; 2014; 2015).

Valerian root samples showed a high phytomelatonin content. Herb supplements containing valerian also presented similar contents. The differences between them (from 0.96 to 2.09 in Table 3) can be explained due to the variability of valerian root sources, a common aspect in herb supplements. When the phytomelatonin content is calculated by pill, considering the valerian dosage in each herb supplement (see technical sheets in material and methods), Valeriana Deliplus showed the highest dose (0.8 µg/pill).

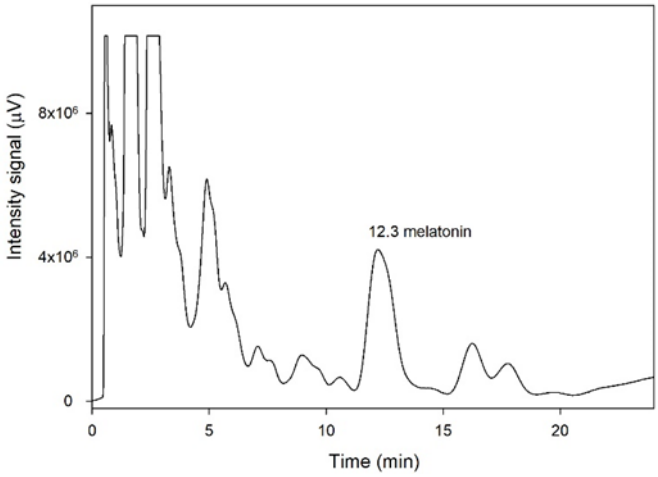

Figure 2. Representative chromatogram of valerian root samples measured by LC with fluorescence detection with λexc = 280 nm and λemi = 350 nm. The melatonin peak at the retention time of 12.3 min is marked.

According to a meta-analysis study on thirteen valerian products commonly used in the USA, which were evaluated by a reference laboratory, the recommended doses ranged from 75 to 3000 mg per day (Bent et al., 2006). In the EU, EMA recommends a daily dose of 400-600 mg of extract to relieve nervous tension, 1-3 times a day. Therefore, an MRDD is 1200-1800 mg of valerian extract (HMPC-EMA, 2016). However, ESCOP recommends up to 1-3 g of the dry herb of MRDD in infusion. Considering these approximate data, with ESCOP recommendation (MRDD of 3 g), the intake of phytomelatonin from valerian root infusion can become 4.68 µg/day. In the case of herb supplements, considering the recommendation by each lab, phytomelatonin intake in Valeriana Deliplus was higher than Valeriana Eladiet and higher than in valerian roots (Table 3).

Table 3. Content of phytomelatonin in the four studied samples

Samples	Phytomelatonin content		
	µg/g DW	µg/pill	µg/MRDD**
V. officinalis (root)	1.56 ± 0.068*	-	4.68
Valeriana Eladiet	0.96 ± 0.051	0.25	0.75
Valeriana Deliplus	2.09 ± 0.087	0.8	6.27
Neuro Balance	0.36 ± 0.008	3.6	7.2

*Average data ± SE (*n* = 5); **Maximum Recommended Daily Dose

According to the European Pharmacopoeia, the main constituents of valerian root are essential oils (0.3-1.1 %) and amino acids such as gamma-aminobutyric acid (GABA), glutamine, and arginine, in relatively high proportions. It also contains flavonoids (hesperidin and 6-methyl-apigenin), lignans (8'-hydroxypinosinol), traces of alkaloids (valerianine, methylpyrrolyl ketone), and several acidic compounds such as valerenic, formic, acetic, etc. Regarding pharmacological activity, valerian root preparations have a sedative and sleep-inducing action through a mechanism that would increase GABA transmission by increasing the concentration of GABA in the synaptic space due to an inhibition of its catabolism and reuptake. The cause of the inhibition of GABA catabolism could be valerenic acid, a sesquiterpenoid present in valerian essential oil (Figure 3). Most of the commercialized extracts were standardized to 0.8 % valerenic acid (Boonstra et al., 2015; Trauner et al., 2008; Vanaclocha and Cañigueral Folcara, 2019).

As is known, melatonin is a hormone that the brain produces in response to darkness to help the body fall asleep. It is also applied to prevent sleep disturbances from jet lag to improve insomnia and sleep efficacy/quality. Curiously, in valerian products (dry roots and supplements) the phytomelatonin contents never appear described. This is because phytochemical laboratories do not have the analysis of melatonin of plant origin among their routines since it is a relatively new molecule in the field of phytotherapy. Certainly, the phytomelatonin contained in valerian preparations could play an important role in the sedative and sleep-inducing action, hitherto attributed exclusively to valerenic acid. Although structurally, phytomelatonin and valerenic acid are not very similar (Figure 3), it is possible that both molecules contribute to the phytotherapeutic activity, and even with possible synergistic effects.

As an example of the importance of phytomelatonin in herb supplements, Table 3 also shows the phytomelatonin content of Neuro Balance samples. As it can be seen in the technical sheet (see material and methods), it is a natural multicomponent supplement based on juices and herbs, highlighting among its components the presence of Passiflora (*Passiflora incarnata* L.) and Ashwagandha (*Withania somnifera* L.) herbs. Ashwagandha root, also known as Indian ginseng or sleep herb, is used to induce and improve the quality of sleep in people suffering from insomnia and stress. Passiflora is also recommended in the case of insomnia and to help sleep-in. The analysis shows that Neuro Balance contains a low level of phytomelatonin (0.36 µg/ml), but considering the recommended daily dose (20 ml), a person can intake up to 7.2 µg of phytomelatonin a day, possibly enough to induce sleep-in. The exact origin of the phytomelatonin in this supplement is difficult to know, possibly from Passiflora and Ashwagandha but also from the other plant components of the mixture. In any case, this would be a good

example that herb supplements "designed to aid sleep" tend to contain phytomelatonin and that consumers should be made aware of this fact.

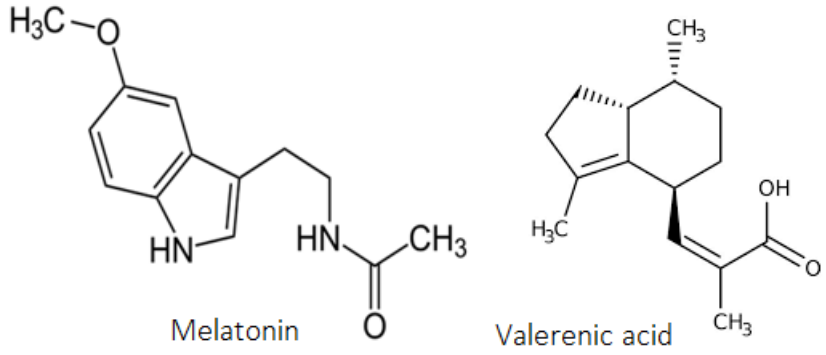

Figure 3. Chemical structures of melatonin and valerenic acid

Currently, studies with valerian focused on treating anxiety and insomnia continue to advance with very positive results (Das et al., 2021; Borrás et al., 2021). Also, in trials in patients with neuropathies (Soltani et al., 2021), mental disorders such as Alzheimer's (Marde et al., 2022), and in pregnancy (Kennedy et al., 2013), the beneficial effects of valerian extracts, as well as other phytotherapeutics, have been proven with interesting results. Another attractive line of research with valerian is the studies against skeletal muscle atrophy, of great interest in athletes (Kim et al., 2022). Also, in *in vitro* studies, no harmful effects have been detected at high doses of tranquilizing herbs, including valerian (Spiess et al., 2021). However, some recent studies suggest that these herbs can alter the pharmacokinetic response to drugs (Matura et al., 2021).

4. Conclusions

Our recommendation, considering the results, is that the phytomelatonin content in valerian supplements and other sleep-in inductors/improvers be determined and reported in the prospectuses or technical sheets of the product so that the consumer is aware that other compounds contained in the preparations can help you in therapeutic treatment. Also, research on valerian preparations should be promoted to understand the possible synergistic interaction of valerenic acid and phytomelatonin to establish and quantify the role of each of them. Finally, the design of herb supplements to improve sleep with plant components rich in phytomelatonin may be a future strategy of great interest. Currently, new research on the possible role of phytomelatonin in other herb supplements related to anxiety and sleep quality is in perspective.

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None.

Conflict of interest

The author confirms that there are no known conflicts of interest.

CRediT authorship contribution statement

Marta Losada: Formal analysis, Writing original draft, Writing-reviewing & editing
Antonio Cano: Methodology, Writing-reviewing & editing
Josefa Hernandez-Ruiz: Data curation, Supervision, Writing-reviewing & editing
Marino B. Arnao: Conceptualization, Formal analysis, Methodology, Writing original draft, Supervision, Writing-reviewing & editing

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Supplementary File

None.

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