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A Review: Pharmacological Activities of Quinoline Alkaloid of *Cinchona* sp.

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Abstract: *Cinchona* is a plant used in traditional malaria treatment. This review aims to examine pharmacological activities to increase the benefits and uses of the bioactive compounds found in the bark of the *Cinchona* trees as medicine and cosmetics. A literature search was conducted through the internet database https://pubmed.ncbi.nlm.nih.gov/; https://scholar.google.com/; https://www.sciencedirect.com/; https://www.wiley.com/en-us from 1998-2022. The main phytochemical content of *Cinchona* bark is quinoline alkaloids (quinine, cinchonidine, cinchonine, and cinchonidine), with total alkaloid concentrations varying between 6 and 15% (*Cinchona succirubra* ranging from 5-7%, *Cinchona calisaya* 4-7% and *Cinchona ledgeriana* 5-14%). *Cinchona* quinoline alkaloids have the same active site on the nitrogen atom in the quinuclidine ring and the methylene alcohol functional group, which plays an essential role in their pharmacological activity. Besides being used as an antimalarial, *Cinchona* alkaloids are currently being developed as their anticancer, antioxidant, antidiabetic, antifungal, muscle cramps, hair growth stimulant, antimicrobial, antiobesity, antiplatelet, antiviral, anesthetic, and antipyretic properties. Conclusion: Quinoline alkaloids of *Cinchona sp* have various pharmacological activities that have the potency to be developed as drugs and cosmetics.

Keywords: *Cinchona*; cinchonine; quinoline alkaloids.

1. Introduction

Cinchona is a plant native to South America [1–3]. *Cinchona* has been known in Europe since the 1640s and has been used in treating malaria since the 1820s [4]. The extraction, isolation, and purification of quinine (QN) and cinchonine (CN) was first carried out in 1820 by Joseph Pelletier and Pierre Caventou [5–7]. In 1860, the German pharmaceutical industry began researching and isolating the bioactive content of *Cinchona* [8], the first clinical trials for the treatment of malaria were conducted in 1866 and 1868 [9]. *Cinchona* arrived in Indonesia in 1855 and was first grown in 1865 in Bandung, West Java, Indonesia [10,11]. *Cinchona* alkaloids have many benefits. Therefore, plant culture increases production in a relatively short time [12].

The genus *Cinchona* belongs to the Rubiaceae family, Monocotyledonae class, Gentianales order, Asteranae Superorder, with the most cultivated species being *C. ledgeriana*, *C. officinalis*, and *C. succirubra* [13]. *Cinchona* is a large shrub or small tree with a height of 5-15 m [13]. Characteristics of the tree *C. ledgeriana* has a height of 6 - 16 m, grows well at 1000 – 1900 m above MSL, and a bark thickness of 2 – 5 mm, *C. officinalis* has a height of 6 – 10 m, grows well at 1200 – 2000 m above MSL, and the thickness of the bark is around 1.5 mm, and *C. succirubra* has a height of 18 – 20 m, grows well at 1200 – 2000 m above MSL and a bark thickness of 2 – 6 mm [13].

The widely known species of the genus *Cinchona* sp include *C. calisaya*, *C. ledgeriana*, *C. officinalis*, and *C. pubescens* (*C. succirubra*), which contain many alkaloid bioactive compounds [14]. *Cinchona* alkaloids are composed of 4 main alkaloids (quinoline alkaloids), namely quinine (QN), quinidine (QD), cinchonine (CN), and cinchonidine (CD) [15]. Secondary ethanol groups (methylene alcohol) and the quinuclidine ring play important roles in pharmacological activity in *Cinchona* alkaloids so that all *Cinchona* alkaloids have identical and synergistic pharmacological activities [16,17]. *Cinchona* alkaloids have pharmacological activities as antimalarial [18–21], anticancer [22], antioxidant [23–25], anti-diabetic [26–28], antifungal [29], muscle anti-cramp [30–32], hair growth stimulant [33,34], antimicrobial [35], antiobesity [36], antiplatelet [37], antivirus [38], anesthetic and antipyretic [39]. This review aims to examine the pharmacological activity to increase the benefits and uses of the bioactive compounds found in the bark of the *Cinchona* trees.

2. Materials and Methods

All of the articles in this review were retrieved from the internet database https://pubmed.ncbi.nlm.nih.gov/; https://scholar.google.com/; https://www.sciencedirect.com/; https://www.wiley.com/en-us from 1998 to 2022. Article searches were conducted using several keywords such as "*Cinchona*" or "*Cinchona* alkaloids" or "*Cinchona*, biological activity" or "*Cinchona*, anticancer" or "*Cinchona*, antioxidants" or "*Cinchona*, antidiabetic" or "*Cinchona*, antibacterial" or "*Cinchona*, antifungal" or "*Cinchona*, cramps" or "*Cinchona*, hair follicles", with some inclusion criteria, such as quinoline alkaloids, *Cinchona*, Quinine, Quinidine, Cinchonine, and Cinchonidine.

Reference search process through internet database https://pubmed.ncbi.nlm.nih.gov/; https://scholar.google.com/; https://www.sciencedirect.com/; https://www.wiley.com/en-us with the keywords "*Cinchona*, pharmacological activity" obtained 163 articles, "*Cinchona* alkaloids, pharmacological activity" obtained 171 articles, "*Cinchona*, biological activity" obtained 65 articles, "*Cinchona*, anticancer" obtained 8 articles, "*Cinchona*, antioxidants" obtained 18 articles, "*Cinchona*, antidiabetic" obtained 3 articles, "*Cinchona*, antibacterial" obtained 31 articles, "*Cinchona*, antifungal" obtained 5 articles, "*Cinchona*, cramps" obtained 6 articles, and "*Cinchona*, hair follicles" obtained 5 articles. The inclusion criteria were narrowed down to 84 articles from all articles.

3. Results and Discussion

3.1. Ethnopharmacological uses of Cinchona.

Cinchona became known as traditional medicine in the 17th century and became the only effective antimalarial drug for more than 400 years [40]. *Cinchona* alkaloids are found in the bark of the *Cinchona* bark [41]. *Cinchona* bark is an essential natural medicine because it

contains the main content of quinoline alkaloids, including QN, QD, CN, and CD. *Cinchona* alkaloids were first isolated in 1820, and the *Cinchona* quinoline alkaloids have been used to treat malaria caused by the protozoan (Plasmodium falciparum) [40]. *Cinchona* alkaloids have also been used in treating muscle cramps since the 1940s [42–45].

3.2. Phytochemistry/bioactive compounds of Cinchona trees.

The content of alkaloids in the *Cinchona* tree (from twigs, stems, and roots) ranges from 6 to 10% [46], 7 to 12% [41], 15% [47], and its leaf ranges from more than 1% (young leaves have a higher alkaloid content) [25]. *Cinchona* bark contains varying concentrations of total alkaloids, the total concentration of *Cinchona* alkaloids in *C. succirubra* ranged from 5 to 7%, *C. calisaya* from 4 to7%, and *C. ledgeriana* 5 to 14% [48]. *C. succirubra* was extracted with ethanol before being isolated using silica gel column chromatography [49]. The extract was characterized by determining the Rf value, adding 1% $FeCl_3$, 5% H_2SO_4, Vanillin-HCl, vapor I_2, Dragendorff, and spectral data using a UV-visible spectrophotometer and FTIR [49]. The analysis showed that the extract of *C. succirubra* contained alkaloids, amino acids, flavonoids, glycosides, phenolic organic acids, saponins, tannins (±3-10%), steroids, and terpenoids [49]. *Cinchona* extract contains 4 main alkaloids known as *Cinchona* quinoline alkaloids, including QN, QD, CD, and CN (Figure 1). The main quinoline content (QN, QD, CD, and CN) accounts for more than 50% of the total alkaloid content [43].

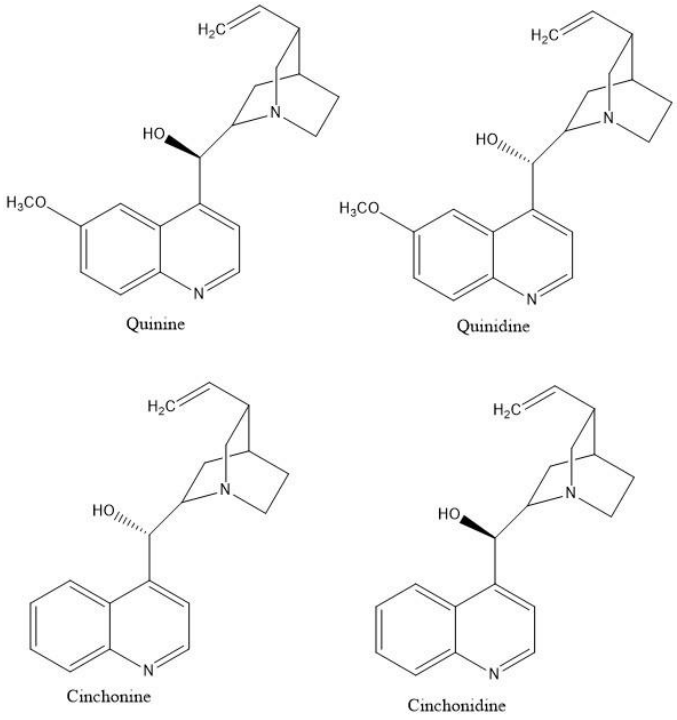

Figure 1. Chemical structure of *Cinchona* Alkaloids [image source: personal documentation - created using ChemDraw app].

Cinchona alkaloids are characterized by one or more nitrogen atoms linked to two carbon atoms in a heterocyclic ring system [15]. *Cinchona* alkaloids are composed of 3 main molecular groups: an aromatic quinoline ring, a quinuclidine ring, and a methylene alcohol group [17]. The nitrogen atom in the ring of quinuclidine and methylene alcohol is a functional group that plays an important role in pharmacological activity [50]. *Cinchona* alkaloids are aryl amino alcohols with a quinoline ring as the aryl group (amino alcohol quinoline) [51]. C-8 and C-9 in *Cinchona* alkaloids allow for configuration changes which can result in changes in

characteristics and pharmacological activity [52–54]. *Cinchona* alkaloids are ultraviolet (UV) light-sensitive and fluoresce when exposed to direct sunlight [7]. A quinoline ring is a functional group that plays a role in anticancer, antimalarial, and anti-inflammatory activities [55]. QN and its derivatives have autophagic effects, which involve the breakdown of intracellular components by lysosomes [55]. Because of its autophagic ability, the compound has cytotoxicity (causing death in cancer cells) [55]. Based on the literature search results above, the location of the active site that plays an essential role in the pharmacological activity of *Cinchona* alkaloids is the same, so each *Cinchona* alkaloid (QN, QN, CN, CD) will have the same and synergistic activity. This can have a positive impact. For example, to increase its pharmacological effectiveness, *Cinchona* alkaloids can be combined. However, this can also have a negative impact because increasing the number and variety of *Cinchona* alkaloids can also increase the risk of side effects.

3.3. Pharmacological activities of Cinchona.

3.3.1. Antimalarial.

In the Amazon region, malaria incidence is related to demographic, ecological, socioeconomic, and cultural changes [56]. Malaria is a deadly infectious disease caused by *Plasmodium falciparum* [57]. In 2019, more than 229 million malaria cases killed 409,000, about 94% of the global malaria cases, and 95% of the deaths were recorded in Africa [58]. The activity of *Cinchona* alkaloids as antimalarials is influenced by the methylene alcohol group [55]. The methylene alcohol group can decrease antimalarial activity and increase its toxicity [55]. Antimalarial activity is also affected by the quinoline ring [55]. The response test of *Cinchona* alkaloids against *Plasmodium falciparum* (IC_{50}: 36,1 nM to 8,72 μM) [59,60] showed that the isomeric form inhibited heme crystallization in the digestive vacuole of the parasite [52]. The stereospecific potential of *Cinchona* alkaloids is related to changes in charge and hydrophobicity which will affect the antimalarial activity of *Cinchona* alkaloids [52]. QN, the first antimalarial drug used, remains efficacious worldwide and does not cause resistance [61]. The Heck reaction examined the structure-activity relationship, modification of the vinyl group on QN resulted in good antiplasmodial activity with a lower IC_{50} value than QN [61]. QN and CN are included in the class of natural antimalarial agents [62]. Treatment of malaria with QN (≥ 50 μM) causes eryptosis, due to the struggle for phospholipids and the entry of Ca^{2+}, causing damage to the erythrocyte cell membrane, increasing oxidative stress, and making ceramide and casein kinase sensitive D4476 [63]. From these reviews, QN is effective as an antimalarial, but in the use of QN must pay attention to the dose to prevent the side effects of eryptosis.

3.3.2. Anticancer.

Quinoline alkaloids are active ingredients with anticancer properties: including leukemia (K562/ADM) [64], mouth cancer (KB and Hep-2), breast cancer (MCF-7), liver cancer (HepG2), lung cancer, colon cancer, and neuroblastoma (SH -SY5Y) [43]. *Cinchona* alkaloids isolated from *C. succirubra* and *C. legeriana* were found to have anticancer activity against 5 different types of cancer cells (human myeloid leukemia HL-60, hepatocellular carcinoma SMMC-7721, lung cancer A-549, breast cancer MCF-7 and colon cancer SW480) [43]. The anticancer activity of the isolated alkaloids from *Cinchona* was investigated and compared to those without a quinoline ring or quinuclidine and cisplatin as a positive control

[43]. *Cinchona* alkaloids (isolated from *C. succirubra*), liriodenine (another type of alkaloid), and cinchophylline (isolated from *C. legeriana*) significantly inhibited human myeloid leukemia HL-60 with IC_{50} values of 4.4, 6.4 and 5.8 M belonged to the moderate inhibitor group when compared to the positive control [43]. CN is a superior candidate as an anticancer with IC_{50} 1.22 ppm [55].

The computational docking program for *Cinchona* alkaloids showed that the major quinolines (QN, QD, CN, CD) effectively bind to the TRAF6 ring and block the interaction between TRAF6 and the Ubc13 protein [65]. Blocking this interaction impacts the early induction of apoptosis and reduces the proliferation of cancer cells [66]. In addition, *Cinchona* alkaloids are relatively safe and have no side effects on the immune system [67,68]. *Cinchona* alkaloids can increase levels of TNF-α, IFN-γ, and IgG [67,68]. In addition to binding to TRAF6, CN also binds to A-549 cells, thereby inhibiting growth and inducing apoptosis of cancer cells [47]. The bond between O and H (OH) with amino acid residues of Asp-57, can effectively prevent the formation of a salt bridge between Asp-57 from TRAF6 and Lys-10/Arg-6 from Ubc13 [47]. As an anticancer, CN ($C_{19}H_{22}N_{20}$) has much lower toxicity and a higher level of activity than QN, QD, and CD [47].

The mechanism of CN as an anticancer is the reversal of multidrug resistance (MDR) [69–71], which increases the percentage of success of chemotherapy [72] and synergistic apoptotic effects with paclitaxel (TAX) in uterine MES-SA/DX5 sarcoma cells (combination therapy) [37,66,73]. QN, QD, CN, CD (100 M), and added doxorubicin (DOX) (5μg/mL) were shown to significantly increase the induced cell death in HeLa and HepG2 cells [22]. The combination of DOX with QN, QD, CN, or CD was able to reduce the viability of HeLa cells to 11.7 ± 3%, 19.8 ± 3%, 42.3 ± 0.4%, or 43 ± 0.6%, while the cell viability of HepG2 ranged from 52 ± 3% to 63 ± 0.2% compared to cells exposed to DOX alone [22,74,75]. This study showed that QN, QD, CN, and CD were able to increase the sensitivity of cancer cells, thereby increasing their ability to induce apoptosis due to DOX.

3.3.3. Antioxidant.

C. ledgeriana leaves were extracted using the maceration method and 70% ethanol. The content of *C. ledgeriana* leaf extract includes alkaloids, flavonoids, terpenes, tannins, saponins, glycosides, quinones, and anthraquinones [10,25]. The antioxidant activity test was carried out using the DPPH method. The ethyl acetate fraction and insoluble in water have high antioxidant activity with IC50 values of 23.57 μg/mL and 17.63 μg/mL [10,25]. According to its high antioxidant activity (IC50 < 50 g/mL), *Cinchona* alkaloids have the potential to be developed as cosmetic preparations such as anti-aging.

3.3.4. Antidiabetic.

Antidiabetic activity test *C. ledgeriana* leaf extract was carried out using the Kim method, which was then analyzed with a UV-Vis spectrophotometer at a wavelength of 400 nm. Kim's method measures the inhibitory ability of the α-glucosidase enzyme activity [10,46]. Extracts and all fractions of *C. ledgeriana* showed antidiabetic activity with IC50 values of 14.44 to 61.56 μg/mL and toxicity with LC50 values of 14.79 to 120.22 μg/mL [10,46]. Therefore *C. ledgeriana* leaf extract has antidiabetic potential, but further isolation is needed to reduce its toxicity.

3.3.5. Antifungal.

Cinchona alkaloids and their derivatives were tested for antifungal activity against 8 plant pathogenic fungi, including P. zeae, R. solani, B. cinerea, F. graminearum, M. melonis, M. oryzae, F. oxysporum f.sp.vesinfectum, and S. sclerotiorum using the mycelium growth rate method [29]. QN, QD, CD, and CN had weak antifungal activity against 8 different types of fungi with inhibition levels ranging from ± 0 to 55.7% at a concentration of 100 μg/mL [29]. However, there was no reduction in the antifungal activity of the simplified quinone and quinotoxine compounds (which tend to increase the antifungal activity) [29]. This indicates that changes in the configuration of quinine and quinuclidine have little effect on antifungal activity.

3.3.6. Muscle cramps.

The use of QN in treating muscle cramps is still a matter of debate regarding its efficacy and safety [76]. *Cinchona* bark, in low doses, has been used to treat leg cramps since the 1940s [40]. *Cinchona* alkaloids work as a muscle anti-cramp by blocking the response of acetylcholine in Xenopus laevis oocytes [40]. The concentration of *Cinchona* alkaloids strongly influences the response-blocking activity of acetylcholine, such as QN (IC50: 1.70 μM) and QD (IC50: 3.96 μM) [40]. The response of the blocking mechanism is not affected by acetylcholine concentration [40]. It is thought that *Cinchona* alkaloids have neuromuscular and muscle effects, resulting in a reduced response to repeated stimulation [77].

3.3.7. Hair growth stimulant.

Cinchonine with a noisome delivery system has been shown to have pharmacological activity as a hair growth stimulant, as indicated by an increase in hair length of about 17 - 43% compared to controls [34]. The pharmacological activity of *Cinchona* extracts in stimulating hair growth by stimulating hair follicles and dermal papilla so that it enters the anagen phase more quickly by activating the Wnt/b-catenin pathway, increasing the production of VEGF (Vascular Endothelial Growth Factor), which is important in hair growth and regeneration [33]. *Cinchona* extract contains quinoline ring compounds, such as QN, QD, CN, and CD, that have the activity/potential to protect hair cells from hair loss (hair cell death) [78]. Based on this review, to increase the pharmacological activity of *Cinchona* alkaloids as hair growth stimulants, *Cinchona* alkaloids require a delivery system that can facilitate and increase penetration into hair follicles and dermal papillae.

3.3.8. Antimicrobial.

The agar well diffusion method was used to test antimicrobial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus pumilus*, *Candida albicans*, and *Escherichia coli* [49]. Holes were made with a size of 10 mm, and 0.1 mL of sample was added to each hole [49]. The diameter of the inhibition zone was measured after 24 hours of incubation at 27°C. With an inhibition zone of ± 20 - 33 mm (MIC *E. coli*: 33 mm), *C. succirubra* extract was effective for treating diseases caused by microorganism infections such as diarrhea, dysentery, and skin infections [49]. The disk diffusion method was used to test QN antibacterial activity against *E. coli*; *P. aeruginosa*; *S. aureus* and *B. substilis* performed , the results obtained Minimum Inhibitory Concentration (MIC) and Minimum Lethal Concentration (MLC) are respectively 0.25 - 0.5 and 0.5 - 0.125%; 0.5 – 1.25 and 2.5 –

5%; 0.25 – 0.5 and 2.5 – 1.25%; 2.5 – 5 and 2.5 – 5% [79–81]. This shows that *Cinchona* extract containing quinoline alkaloids has the potential to be developed as an infectious drug because it can inhibit the growth of bacteria.

3.3.9. Antiobesity.

Research on the activity of CN as an antiobesity was carried out by analyzing the reduction in adipogenesis induced by a high-fat diet and inflammation in rat epididymal fat tissue [36]. The results showed that rats fed a high-fat diet and given a 0.05% CN treatment for 10 days reduced weight gain by -38%, visceral fat weight by -26%, plasma levels of triglycerides, free fatty acids, cholesterol total, and glucose compared with mice fed only a high-fat diet [36].

3.3.10. Antiplatelet.

The activity of CN as an antiplatelet has been reported through the mechanism of inhibiting human platelet aggregation [37,82]. The aggregation inhibition is due to the inhibition of the entry of Ca2+ and protein kinase C (PKC) [37,82].

3.3.11. Antivirus.

Chloroquine phosphate (analog of quinine, originally extracted from the bark of the *Cinchona* tree) has broad-spectrum antiviral activities [83]. QN has antiviral activity against SARS-CoV-2 in Vero cells [38]. QN at a concentration above 50 μM inhibited SARS-CoV-2 infection as seen from the endogenous expression of ACE2 and TMPRSS2 in Calu-3 lung cells with IC50 values ranging from 3.7 to 50 μM. Therefore, QN has the potential as an antiviral drug for SARS-CoV-2 with lower toxicity [38]. Based on this review shows that QN has the potential as a promising antivirus in the future.

3.3.12. Anesthesia and antipyretics.

Herbal medicine has been using anesthetics for centuries based on their properties and can also be categorized as local anesthetic herbs and general anesthetic herbs based on their mechanism of action [84]. Local anesthetic herbs interact with voltage-gated Na+ channels, whereas general anesthesia interacts with membranes and protein receptors to inhibit sensory and motor function [84]. The aqueous extract of *C. officinalis* at a concentration of 10-20% had an anesthetic effect ($p < 0.001$) of 72.12 and 88.08%, with an onset of 6.44 ± 0.68 minutes compared to the anesthetic effect of 2% xylocaine. Single doses of *C. officinalis* extract (100, 200, and 400 mg/kg) provided an antipyretic effect comparable to aspirin's positive control [39].

Table 1. The pharmacological activity of *Cinchona* alkaloids.

No	*Cinchona* Alkaloids	Pharmacological activity	Models - Methods	Ref
1	Quinine, Cinchonine	Antimalarial	*In vivo*	[52,56,61]
			In vitro	[56,59,63]
2	*Cinchona* Alkaloids, Cinchonine	Anticancer	*In vivo*	[37,67,70]
			In vitro	[20,22,43,55,64,66,73,74]
			Molecular docking	[21,65,67]
			Clinical trial	[69]
3	*Cinchona* leaves extract	Antioxidant	DPPH	[10,46,49]

No	*Cinchona* Alkaloids	Pharmacological activity	Models - Methods	Ref
4	*Cinchona* leaves extract	Antidiabetic	Kim method	[10,46]
5	Quinine, Quinidine, Cinchonine, Cinchonidine.	Antifungal	*In vivo*	[29]
6	Quinine	Muscle cramp	*In vitro*	[40,76,77]
7	*Cinchona* extract, Cinchonine	Hair growth stimulant	*In vitro*	[33]
			In vivo	[34,78]
8	*Cinchona* extract	Antimicrobial	Agar well diffusion method	[49]
			Disk Diffusion Method	[79,80]
			Bacterial biofilms (biomass and resazurin Assay)	[81]
9	Cinchonine	Antiobesity	*In vivo*	[36]
10	Cinchonine	Antiplatelet	Clinical trial	[82]
11	Quinine	Antivirus	*In vitro*	[38,83]
12	*Cinchona* extract	Anesthesia and antipyretics	*In vivo*	[39,84]

4. Conclusions

This review conducted on the genus *Cinchona* sp showed that *Cinchona* contains the main phytochemical content of the quinoline alkaloids QN, QD, CN, and CD, with the active site located on the nitrogen atom functional group in the quinuclidine ring and methylene alcohol. Therefore, each *Cinchona* alkaloid will have the same or synergistic pharmacological activity. The pharmacological activity of *Cinchona* sp is very varied and has the potential to be developed as a drug or cosmetic product. To be a superior product with good effectiveness, stability, and safety, *Cinchona* alkaloids require an appropriate delivery system. Therefore, further research is needed to develop a delivery system to increase the benefits and uses of *Cinchona* alkaloids.

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Conflicts of Interest

The authors declare no conflict of interest.

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