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Spectrum of biological properties of cinchona alkaloids: A brief review

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Abstract
Cinchona which belongs to family Rubiaceae, got its importance from the centuries because of its anti-malarial activity. Alkaloids present in this herb, Quinine, Chichonine, Quinidine and Cinchonidine are the main, but percentage may vary in species to species. Since the early 17th century, these alkaloid are frequently used in Indian ayurvedic, sidha and traditional folk medicine to treating fever and Still now in modern medicine cinchona alkaloids are used for the treatment of malaria as well as for other diseases and became the well-known drug after the treatment of malaria caused by *Plasmodium* Sp. Literature study revealed that along with the antimalarial activity the cinchona alkaloids has other potentiality like anti-obesity, anti-cancer, anti-oxidant, anti-inflammatory, anti-microbial activity. These article reviews the biological activities of cinchona alkaloids along with its toxic effect.

Keywords: Cinchona, Alkaloid, biological activity, toxicity, anti-obesity, anti-cancer, anti-oxidant, anti-inflammatory, anti-microbial

Introduction
Cinchona, commonly known as Peruvian bark, belongs to the family Rubiaceae, is native to South America specifically from the Andes mountain range. It can also be found in India, Java, Cameroon, and Vietnam and in some other Asian and African countries. In India it is mainly found in hilly areas as a result of plantation or cultivation. Indonesia becomes the largest producer of cinchona throughout the world. Cinchona is a 10 to 20 m tall trees with straight trunk about 30 cm in diameter, It has a dense and irregular globular crown, darkly green, oval shaped leaf with a thick central nerve with full margin, the color of flower is white or pinkish with white hairs found in panicles and the fruit is dark brown 2-4 cm long with 3-4 seeds. The main part of the plant which is mainly used for medicinal and other purpose is the bark that can be upto 30cm long and 2- 6 cm thick. The brown bark of cinchona is looked like a tube which is arched or curved during aging. Bark are usually visible in trunk or branches and after immediate collection, the outside has a brown grayish color while the inside has a reddish brown. *Cinchona calisaya* d *Cinchona ledgeneria,* commonly known across the globe as the yellow cinchona and *Cinchona succirubra* popularly known as in trade as Red cinchona.
More than 20 alkaloids containing 15% amount, preferentially as quinine, quinidine, cinchonidine and cinchonine are found in the bark of cinchona combined with principle active compounds such as tannins (3-10%) [1]. Along with these ingredients the bark also contains acids, essentials oils and minerals, such as triterpine (quinovic acid), organic (quinic acids), phenolic (caffeic acid), flavonoids (psoanthycyanidine), phytosterols [2]. These alkaloids are collectively known as quinoline alkaloids mainly derived from tryphan by the modification of terpenoids indole [3]. And the terpenoid indole alkaloids are very common in the genus cinchona. In different species under genus cinchona, more than twenty types of alkaloids have been isolated. However, it has been revealed that an average commercial yield of the cinchona alkaloids from the dry bark materials plant are as follows: quinine (5.7%); quinidine (0.1-0.3%);cinchonine and cinchonidine (0.2-0.4%)[4]. Among these, the most popular quinoline alkaloids known as are quinine, cinchonine, quinidine and cinchonidine.

Alkaloids mainly responsible for anti-malarial activity of Cinchona
i). Quinine ($C_{20}H_{24}N_2O_2$): The most important and characteristic alkaloids of cinchona contain 16% [3] of quinine (Figure 1) in the bark but the percentage varies (6-10%) according to the species variety. The cinchona representative sample of dried cinchona or cinchona bark is found to be containing 0.4-4% [3]. It is frequently used as anti-malarial agent along with some other uses as a flavor in carbonated beverages [4], skeletal muscle relaxant, treats hemorrhoids and varies vein and also used as oxytoxic agent [3].

Quinine is supposed to be prophylactic for flu [3]. Quinine got its antimalarial [5] properties with interference in the synthesis of DNA in the merozoite phase of protozoa of the genus *Plasmodium* [6] Quinine generally known as "a general protoplasmic poison" [7] affects variety of biological systems. Its curare like action on skeletal muscle and toxic effects on bacteria and unicellular organisms such as plasmodium are the basis for its therapeutic use in man for muscle cramps and malaria, respectively [7].

i.a. Toxicity of Quinine

Quinine has a toxic effect due to the overdose. The nervous system including optic and auditory nerve were the primary site of damage by quinine toxicity and secondary to both vascular and neural injury [7]. Quinine causes fever, delirium and increased ventilator rate by an initial generalized stimulation of the central nervous system, which is followed by coma and respiratory depression. Quinine also causes myocardial depression, peripheral vasodilatation, and electro physiologic effects including an Increase in action potential duration and effective refractory period and a decrease in membrane responsiveness and automaticity. In addition, renal failure, hemolytic anemia, hypo-prothrombinemia, and gastrointestinal symptoms of both central and local origin are reported [7].Literature study revealed that, papillary dialation is a consistent feature of quinine toxicity which occurs due to the prolong use of the alkaloid to treat severe malaria sometimes creates bilateral blindness [8]. And fatal cardiac arrest [9] has been described in which the intravenous drug (heroin) is altered with quinine.

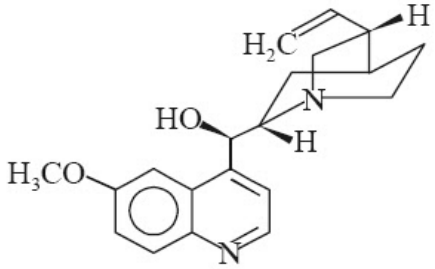

Fig 1: Chemical formula/structure of Quinine

ii. Cinchonine ($C_{19}H_{22}N_2O$): The next important alkaloid present within cinchona after quinine is cinchonine (Figure 2) which is also used as an anti-malarial agent [10] and has a lower toxicity than quinine and having a higher activity compared to that of other quinine related compounds [11]. But the exact percentage of the cinchonine present in cinchona is controversial to the researcher. It is mainly used as antimicrobial agent and broadly used for schizonticide, amoebiasis, flu, dysentery and fever. It acts as mild stimulant of gastric mucosa [3].

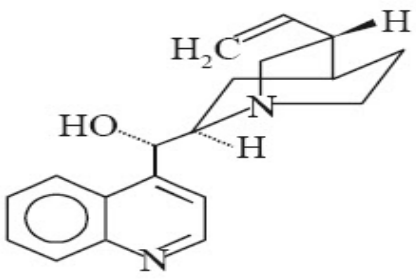

Fig 2: Chemical formula of Cinchonine

iii. Quinidine: The another important alkaloid is quinidine (Figure 3) mainly present in cinchona bark ranging from 0.25%-3.0% [4]. It is a dextrorotatory stereoisomer of quinine. The main function is it act as anti-malarial agent but it is also used as good anti-arrhythmic agent [12], when the anti-arrhythmic metabolism is accomplished through membrane stabilization. It helps to treat atrial flutter, AV junction and ventricular constructions, atrial and ventricular tachycardia and atrial fibrillation and premature atrial condition [3]. The anti—arrhythmic property of quinidine is due to the direct interference with the electrophysiological properties of cardiac cells, which causes rapid sodium influx and decrease of the atrial and intraventricular condition velocity [6].

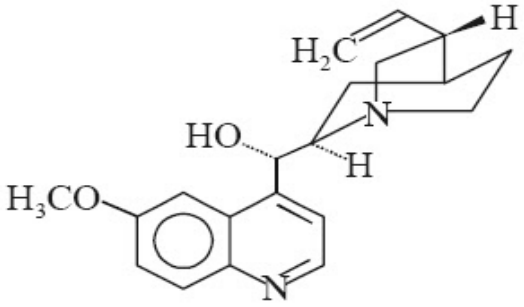

Fig 3: Chemical formula of Quinidine.

iv. Cinchonidine ($C_{19}H_{22}N_2O$): Cinchonidine (Figure 4) is obtained in most of the varieties of cinchona bark especially in the bark of *C. pusescensval*and *C. pitayensis*and it is mostly used as an anti-malarial agent. It is a stereoisomer and pseudo-enantiomer of cinchonine and used chiefly as a substitute of quinine. Epicinchonidine is mostly used as an antimalarial agent [4].

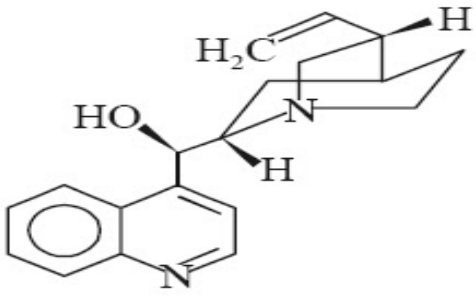

Fig 4: Chemical formula of Cinchonidine.

3. Cinchona Alkaloids responsible for some other important functions:

i. Anti-obesityproperty

Cinchonine, the potent alkaloids in cinchona bark, is widely used for anti-malarial activity. But, it could be a potential agent that can solve the concerns related to obesity. According to Jung *et al.* 2012 cinchonine effects dramatically than other phyto-chemicals that have been known to exert anti-obesity effects [13]. Even the supplemented dose was higher than or same, cinchonine showed higher rate of final body weight reductions compared to EGCG (epigallocatechin gallate) and curcumin [14] where 0.32% EGCG supplementation showed 9.4% decrease in final body weight in high fat died fed mice [15] and 0.05% curcumin supplementation is also known to lower the body weight by 11% in the same model [16]. Along with cinchonine's effect on

body weight reduction, cinchonine decreases the plasma level of lipid in mice fed on the HFD (High fat diet). Cinchonine effectively ameliorated hyperlipidemia and hyperglycemia induced by the HFD; cholesterol, LDL+VLDL cholesterol, HDL cholesterol, TG, and the plasma glucose levels. Cinchonine affect the HFD-mediated hyperlipidemia and hyperglycemia that are early symptoms of the metabolic syndrome and associated disorders. So, finally cinchonine has a dramatic suppressive effect on adipogenesis through the down-regulation of WNT and galanin-mediated adipo genesis signaling pathway, and it also attenuates inflammation by repressing TLR2- and TLR4-mediated pro-inflammatory signaling pathways in the adipose tissue [13].In several literature studies, it was demonstrated that cinchonine is a useful dietary phyto-chemical for the prevention of not only obesity, but also adipose inflammation.

ii. Anti-cancer agent

According to Krishnavedi and Suresh,2015, quinine is more potent to inhibit the cell proliferation and induce apoptotic cell death in cancer cell line in a dose and time dependent manner [17], the IC50 values obtained after 24hr treatment of different concentrations of quinine (125.23 μM/mL for 24 hr). ROS (Reactive oxygen species) is critical for the metabolic and signal transduction pathways associated with cell growth and apoptosis [18]. Several anticancer agents, including anthracyclines, cisplatin, bleomycin, and irradiation currently used for cancer treatment have been shown to cause increased intracellular ROS generation. The results of this study showed that the intracellular ROS levels were significantly increased in cancer cell line treated with quinine at time and dose dependent manner. Induction of cell death through indirect activation of the mitochondria dependent pathway is the conventional anticancer treatment but sometimes it is altered in drug resistant cancer cells. Effect of quinine induce typical morphological change as the signal of apoptosis like cell shrinkage, membrane blebbing, chromatid condensation, nuclear fragmentation, apoptotic bodies and loss of adhesion [19]. So quinine may be a strong anticancer agent in future due to its huge apoptotic activities in cancer.

iii. Antioxidant properties

As described by Ravishankara et.al cinchona exhibit efficient antioxidant properties due to presence of phenolic compounds [20]. The biological properties of phenolics include like anti-tumor, anti-viral, anti HIV and also inhibition of lipid peroxidation [21, 22]. The study was mainly concentrated on three major radicals – superoxide hydroxyl and nitric oxide radicals as these are the main radicals responsible for the oxidative damage of cellular components of the human body [23, 24, 25, 26]. Methonalic and water extract showed a concentration dependent antiradical activity by inhibiting DPPH, with the EC50 value of 8.08μg/ml and 64.19μg/ml respectively. And also the extract of cinchona shows the inhibition of erythrocytes hemolysis induced by phenyl hydrazine which was done in dose dependent manner and as a result Methanolic extract showed a better protection than α-tocopherol which revels the ability of the cinchona extract to scavenge the free radical.

iv. Antimicrobial property

According to Pankaj et.al cinchona alkaloids showed the antibacterial activity against the *Staphylococcus aureus* with the inhibition zone ranged from 8-18mm done by the disc diffusion method [27]. It has been studied that antimicrobial activity increases according to the concentration of the cinchona alkaloids. Extraction of cinchona alkaloids is found effective against amebiasis. Dried bark is used to treat disease caused by a pathogenic strain like *P.falciparum* and herpes [28]. Rojas J.J *et al.* confirmed that cinchona was active against the several microorganisms which are harmful to the human body [29].

v. Antiparasitic activity

In this modern world of medicine still the protozoan parasites causes the infectious disease and remain as major health problem. Among the disease, leishmaniasis, malaria and trypanosomiasis are the major health problem caused by the *leishmaniasp*, *Plasmodium sp*. and *Trypanosome sp*.

Moreover the main major problem in the treatment of these diseases is due to the increase of resistant strains to the medicine and the toxic effects and relative efficacy of some of the drugs used for treatment nowadays. Among the drug used for the treatment of malaria is quinine, the major alkaloid of cinchona and still remain the drug of choice. According to Aurelie Leverrier *et al.*, compound possessing a quinolone nucleus display a variety of biological properties and can be used as anti-parasitic such as for malaria, leishmania and trypanosomiasis [30]. By the means of a Barton-Zard decarboxylation reaction a series of Cinchona alkaloids and bile acids was prepared. The alkaloids of cinchona i.e., quinine, quinidine, cinchonine, cinchonidine were functionalized at C-2 of the quinoline nucleus by radical attack of norcholane substituent. The hybrid compounds showed promising trypanocidal activity with IC_{50} values in the same range as the suramin(a commercial anti trypanosomal drug). As well as the hybrid showed antiplasmodial activity ($IC_{50} \leq 6\mu g/ml$), particularly those containing a nor-chenodeoxycholate moiety with IC_{50} values comparable to those of the natural alkaloids and selectively indices in the range of 5.6 – 15.7.

vi. Anti-inflammatory

Apart from treating malaria, quinine is also used to treat nocturnal leg cramps and arthritis, and there have been attempts (with limited success) to treat prion diseases. It is also use as ingredient of tonic drinks for its bitter taste. Infusions of the bark of the Peruvian cinchona tree have been used for centuries for medicinal purposes and were observed to have both antimalarial and anti-inflammatory properties. The active agents, quinine and cinchonine were isolated and used as early as 1894 to treat lupus [31]. As slow acting, low toxicity drugs they are useful in combination therapy, especially for SLE (systemic lupus erythematous), since their mode of action is quite different to other anti-inflammatory drugs. They act by inhibiting lysosomal and endosomal function, thus limiting the release of secreted proteins, including cytokines. Antigen processing and presentation, and thus T cell activation are also inhibited [32].

Table 1: Major reviewed article about alkaloids of cinchonina regarding present study.

Research article	Activity	Author
Cinchonine Alkaloids	Anti obesity	JungS. A. *et.al,* 2012,
Cinchona calisaya bark	Antimicrobial activity	Kushwah P. *et.al*, 2016
Cinchona officinalis stem bark	Antioxident property	Ravishankara M.N.*et.al,* 2012
Cinchona sp bark extract	Antimicrobial agent	Tyagi R.*et.al,* 2016
Cinchona alkaloids	Antiparasitic activity	Leverrier A. *et.al,* 2013
Quinine Alkaloids	Apoptosis properties	Krishnaveni &Suresh K, 2015
Quinine Alkaloids	Toxic due to overdose	Coldenbermg A. M.1988
Rapid and Green Analytical Method for the Determination of Quinoline Alkaloids from *Cinchona succirubra* Based on Microwave-Integrated Extraction and Leaching (MIEL) Prior to High Performance Liquid Chromatography		Anne-Sylvie Fabiano-Tixier *et.al* 2011
Quinoline Alkaloids	Classification of Quinoline	Phar macognogy. 2012

Conclusion

Nature provides huge medicinal agents for thousands of years and a significant number of human drugs are developed from herbal sources. From ancient periods cinchona bark was traditionally used as anti-malarial drug to cure several health problems associated with malaria. The most important property of cinchona is due to the presence of several types of alkaloids. Researcher shows that the combinatorial effects of more than twenty alkaloids are the key source of its medicinal property rather than one of them. Among these twenty alkaloids four are mainly responsible for its anti-malarial property and contain maximum percentage of the alkaloids present. But the other alkaloids found in cinchona have not only an anti-malarial activity but also have other important biological properties and has been vital tool for pharmacologist and molecular biologist. In the present study, extensive literature review revealed that cinchona also have potential property of anti-obesity, anti-cancer, anti-oxidant, anti-microbial, anti-parasitic and anti- inflammatory activity. So, the trace amount of remaining alkaloids could be the major effective molecules for the mentioned characteristic of this wonder herb. But few researcher shows that the use of cinchona have mild to moderate side effects in a dose dependent manner. Cardiotoxicity and neurotoxicity are the major problem discouraging the medical use of this vital drug. However, a closer look in data of cinchona alkaloids clearly indicates that the toxicity is dose dependent. Thus, a well-controlled use of it can help to reduce its toxicity. Furthermore, a new drug with greater potency and significantly reduced toxicity can be designed from cinchona alkaloids. Without doubt a modification in alkaloids in a proper way may likely produce a lead drug in treatment of more diseases. So, there is an urgent need to developed new drug with better bioactive potential and without or less side effects.

Competing Interests Statement

The authors declare that they have no competing interests.

Data Sharing Statement

We cannot share any unpublished data with other laboratory or person

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