Available Online at http://www.journalajst.com

ASIAN JOURNAL OF SCIENCE AND TECHNOLOGY

ISSN: 0976-3376

Asian Journal of Science and Technology
Vol. 13, Issue, 11, pp.12255-12263, November, 2022

RESEARCHARTICLE

A REVIEW ON PHARMACOGNOSTIC AND PHARMACOLOGICAL ACTIVITY OF QUINOLINE AND IMIDAZOLE ALKALOIDS

Sachin Mendhi[1,*], Sachin More[1], Krutika Sawarkar[2], Vidushi Kaushik[3] and Shreya Joshi[4]

[1,2]Faculty, Department of pharmacology, Dadasaheb Balpande College of pharmacy Besa, Nagpur 4400037, Maharashtra; [3,4]Students, Bachelor of pharmacy, Dadasaheb Balpande College of pharmacy Besa, Nagpur 4400037, Maharashtra

ARTICLE INFO

Article History:
Received 19th August, 2022
Received in revised form
20th September, 2022
Accepted 14th October, 2022
Published online 30th November, 2022

Keywords:
Alkaloids, Quinoline, Cinchona, Camptotheca, Imidazole, Pilocarpine.

ABSTRACT

Alkaloids are pharmacologically active containing two or more fused organic compound including heteroatom in it. The quinoline alkaloids from higher plants are best classified according to their biogenetic derivation from either anthranilic acid or tryptophan Cinchona which belongs to family Rubiaceae, got its importance from the centuries because of its antimalarial activity. Alkaloids present in this herb, Quinine, Chichonine, Quinidine and Cinchonidine are the main alkaloids of this class. Another major important plant of this class is camptotheca which belongs to family nyssceae having the antitumor property. Alkaloids containing the imidazole nucleus which is the smallest groups of alkaloids in terms of number of known compounds. This class of alkaloids is synthesized by precursors derived directly from the amino-acid histidine. This class of alkaloids contain Pilocarpine, Alchornine, and White sapote. Pilocarpine belongs to family Rutaceae which shows muscarinic receptor agonistic property.Alchornine is from family Euphorbiaceae which is used to treat bacterial infections .White sapote belongs to family Rutaceae which shows anti-inflammatory sedative and mildly narcotic action.

Citation: ***Sachin Mendhi, Sachin More, Krutika Sawarkar, Vidushi Kaushik, Shreya Joshi*, 2022.** "A review on pharmacognostic and pharmacological activity of quinoline and imidazole alkaloids", *Asian Journal of Science and Technology*, 13, (11), 12255-12263.

INTRODUCTION

Quinoline alkaloids*:* A good number of very prominent and noteworthy samples of the 'quinoline-alkaloids' derived from tryphphan are nothing but the modifications of the terpenoid indole alkaloids commonly found within the asterid dicot genus belonging to the universe Rubiaceae. Interestingly, over twenty alkaloids are isolated and characterized from the bark of chinchona and Cinchona officinalis, very commonly known across the world because the Yellow Cinchona; besides the opposite equally well-known species Cinchona succirubra, popularly known in trade because the Red Cinchona. However, the four long prized and most well-liked quinoline alkaloids known for his or her antimalarial activities are namely: quinine, cinchonine, quinidine, and cinchonidine. These alkaloids shall now be described individually within the sections that follow

CINCHONA

Biological Source*:* Is the dried bark of the cultivated trees of Cinchona calisaya Wedd.

Corresponding author:** ***Sachin Mendhi,
Faculty, Department of pharmacology, Dadasaheb Balpande College of pharmacy Besa, Nagpur 4400037, Maharashtra.

C. ledgeriana Moens, C officinalis Linn, Csuccirubra Pav, exklotzsch, or hybrids of one of the last two species with one of the first two. Cinchona belongs to family Rubiaceae. It contains not less than 6 per cent of al alkaloids of cinchona.

Macroscopic characteristics*:* Cinchona bark has a slight and characteristic odour, but somewhat astringent and intensely taste. In general, the bark is available in quills and curved pieces.

Stem bark*:* It has a maximum length of 30 cm and a thickness between 2 and 6 mm. The outer surface nows dull brown grey or grey colour and many a time, shows presence of mosses and lichens owing to its growth in heavy rainfall areas. The bark is rough and has transverse cracks. These sures are different in different species. It is furrowed or wrinkled longitudinally. The outer bark in me varieties shows exfoliation. The inner surface is pale yellowish-brown to deep reddish-brown and the colour depends on the species. The fracture is short in external layers and fibrous in the portion.

Root bark*:* It occurs in length of 2 - 7 cm. The bark is curved, twisted or irregularly channelled the outer and inner surfaces are similar in colour. The outer surface is scaly and shows

depressions. The inner surface is striated. The different commercial varieties have some special characters. C. succirubra is also called as is referred to as yellow bark. C. robusta is the hybrid between C. succirubra and C.officinalis .

Microscopic Characters: Cinchona exhibits the typical histological characters of the bark. The cork cells are thin walled, followed by phelloderm. The cortex consists of several secretory channels and phloem fibres.There are medullary rays with radially arranged cells.Calcium oxalate idioblast is the specificity of cinchona bark. Starch grains are present in the parenchymatous tissues. Stone cells are scarcely present in the structure. A few of the cork cells are lignified. Medullary rays are 2 to 3 cells wide.

Chemical constituents: Alkaloids are quinine, quinidine, cinchonine and cinchonidine. The less important alkaloids are quinicine, cinchonicine, hydroquinine, hydrocinchonidine and homocinconidine. C. succirubra contains 5-7 per cent of total alkaloids, of which 30 per cent is quinine. C. ledgeriana yields from 6 -10 per cent and, in some cases, upto 14 per cent of total alkaloids, with upto 75 per cent is quinine. C. salisaya has 6-8 per cent total alkaloids (about 50 per cent quinine). Quinine and Quinidine are stereoisomers of each other. Quinidine is also obtained commercially from cuprea bark i.e. Ramijia pendunculata Fluckiger belonging to family Rubiacea or by isomerization of quinine more significant. Cinchonine and cinchonidine are also isomers of each other. Apart from alkaloids, cinchona also contains quinic acid and cinchotannic acid. In the plant, the alkaloids are present as salts Cinchotannic acid decomposes into insoluble cinchona red, due to its phlobatannin nature. Cinchona bark also contains a glycoside called quinovin tannins and bitter essential oil.

The alkaloid quinine occurs as bitter white crystals and it darkens when exposed as light and has fluorescent properties. It shows a strong blue fluorescence in ultra-violet light. This fluorescence is enhanced in presence of dilute sulphuric acid. Quinine forms salts with different acids Quinine sulphate IC 20 H 24 N 2 O 2) 2 .H 2 SO 4. 2H2O is important from pharmaceutical point of view the very less solubility in water (1 in 810 parts of water), due to which, it is suitable for oral use. Quinidine (C20H 24 N2O2) is similar to quinine in its physical and chemical properties and h higher water solubility. The free base is soluble in water, ethyl alcohol, methyl alcohol and chloroform.

Chemical Tests

- Heat the powdered drug in a dried test tube with little glacial acetic acid, purple vapours are produced at the upper part of test tube.
- **Thalleoquin test:** The powdered drug gives emerald green colour with bromine water and dute ammonia solution. 3. Quinidine solution gives a white precipitate with silver nitrate solution, which is soluble in nitric acid.

Phamracological activity

In cinchona: alkaloids mainly responsible for its antimalarial activity

QUININE

The most important and characteristic alkaloids of cinchona contain 16%3 of quinine 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[2], skeletal muscle relaxant, treats hemorrhoids and varies vein and also used as oxytoxic agent [1] Quinine is meant to be prophylactic for flu [(1)]. Quinine got its antimalarial properties with interference within the synthesis of DNA within the merozoite phase of protozoa of the genus Plasmodium [(3)] Quinine generally referred to as “a general protoplasmic poison affects style of biological systems. Its curare like action on striated muscle and toxic effects on bacteria and unicellular organisms like plasmodium are the premise for its therapeutic use in man for muscle cramps and malaria, respectively [(4).]

Toxicity of quinine*:* Quinine consists of a toxic effect due to the surplus. The sensory device along with optic and hear-capin a position nerve had been the critical web website online of damage via way of means of quinine harmfulness and auxiliary to each vascular and neural injury (4). Quinine reasons fever, daze and improved ventilator price via way of means of an underlying summed up incitement of the focal sensory device that is trailed via way of means of unconsciousness and breathing discouragement. Quinine likewise reasons myocardial despondency, fringe vasodilatation, and electro physiologic affects remembering a upward thrust for hobby viable duration and feasible cussed duration and a lessening in movie responsiveness and automaticity. Moreover, renal disappointment, hemolytic frailty, hypo-prothrombinemia, and gastrointestinal aspect results of each focal and close by motive are accounted for (4). Literature take a look at exposed that, papillary dialation can be a dependable element of quinine harmfulness which occurs due to the do away with usage of the alkaloid to deal with extreme intestinal illness as soon as in a completely at the same time as makes respective visible impairment(5). Furthermore, deadly coronary heart failure(6) has been depicted at some stage in which the intravenous medication (heroin) is adjusted with quinine.

The subsequent essential alkaloid is gift inside cinchona after quinine is cinchonine which is likewise used as an anti-malarial agent(7) and has a decrease toxicity than quinine and having a better hobby in comparison to that of different quinine associated compounds(8). But the precise percent of the cinchonine found in cinchona is arguable to the researcher. It is in particular used as antimicrobial agent and widely used for schizonticide, amoebiasis, flu, dysentery and fever. It acts as moderate stimulant of gastric mucosa1.

Quinidine*:* The another important alkaloid is quinidine mainly present in Jesuit's bark starting from 0.25%-3.0%[(2)]. it's a dextrorotatory stereoisomer of quinine. the most function is it act as anti-malarial agent but it's also used nearly as good anti-arrhythmic agent[(9)], 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 fibrillation and premature atrial condition[(1).] The anti—arrhythmic property of quinidine is thanks to the direct interference with the electrophysiological properties of cardiac cells, which causes rapid sodium influx and reduce of the atrial and intraventricular condition velocity [(3).]

Table 1. Description of plants coming under quinoline alkaloids

Plants with its alkaloids (Synonym)	Biological source	Chemical constituent	Activity
Cinchona **A)quinine** (Jesuit bark ,peruvian bark)	The cinchona species (Rubiaceae) specifically contains quinine in the bark upto 16% (mostly 6-10%) in a variety of its species, namely: Cinchona calisaya Wedd.; C. ledgeriana Moens ex Trimen; C. officinalis Linn. f.; C. robusta How.; and C. succirubra Pavon ex Klotzsch.	0.4 to 4% quinine.	1.It is used as an antimalarial agent. 2. It is also employed as a skeletal muscle relaxant. 3. It has been used to treat hemorrhoids and varicose veins. 4. Quinine is also used as an oxytocic agent.
B) Cinchonine	Cinchonine especially occurs in the bark of Cinchonamicrantha R &P. belonging to the natural order Rubiaceae.	Cinchonine	1. It is used as an antimalarial agent.

Table 2. Different barks of cinchona

Character	C.calisaya	C.ledgeriana	C.officinalis	C.succirubra
Size	Diameter is from 12-25mm and thicknes from 2-5mm	Diameter is 12-25mm and thickness varies from 2-5mm	Diameter is upto 12mm and thickness is upto 1.5mm	Diameter is from 20-40mm and thickness from 2-5mm
Other features	Broad longitudinal fissure with transverse cracks	Broad longitudinal fissure and cracks more in number ,but less deep .some piece show longitudinal wrinkles and reddish warts	It shows a number of transverse cracks	Well marked longitudinal wrinkles ,but less number of transverse cracks .only some pieces show reddishwarts
Powder	Cinnamon	Cinnamon brown	Yellow	Reddish brown

Fig No 1 Cinchona bark

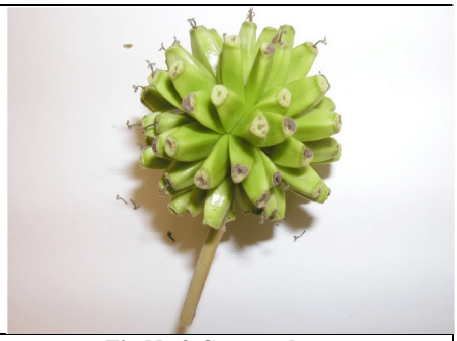

Fig No 2 Camptotheca

Fig. 3. Pilocarpine

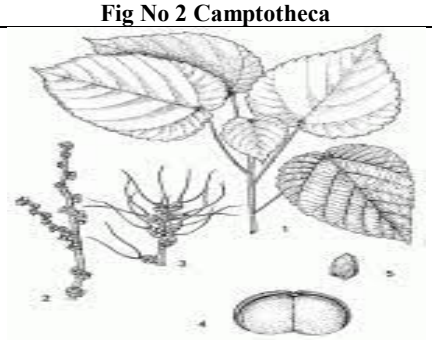

Fig. 4 . Alchornine

Fig. 5. white sapote

Sr.No	Alkaloids	Biological Source	Chemical constituents	Pharmacological activity
1.	Pilocarpus	It consits of leaflets of Pilocarpus jaborandi P.microphyllus belonging to family Rutaceae.	Pilocarpine, Isopilocarpine, Pilosine, Isopilosine	It acts as muscarinic receptor agonist.
2.	Alchornine	It is obtained from bark and leaves of Alchornea cordifolia belonging to family Euphorbiaceae	Terpenoids, steroid glycosides,flavonoids, imidazopyrimidine, alchorneidine etc.	It is used to treat bacterial infections.it is also used in diarrohea ,ulcer etc.
3.	White Sapote	Obtained from fruits of Casimiroa edulis belonging to family Rutaceae.	Methylhistamine, Zapotin, Zapotinine	Anti-inflammatory, sedative and mildly narcotic (hypnotic) action.

***Anti-obesity activity of cinchona**:* Hyperlipidemia is defined through raised serum stages of general ldl cholesterol (TC), low- density lipoprotein (LDL), Very low -density lipoprotein (VLDL), and faded serum stage of excessive density-lipoprotein (HDL). hold with American coronary heart incorporation, a excessive stage of fat known as hyperlipidemia. These fat comprises LDL cholesterol and triglyceride. Lipids and fatty materials in the blood and is probably a extra chance don't forget the growth of atherosclerosis and coronary heart diseases (10). Cinchonine, the effective alkaloids in bark, is broadly used for anti-malarial activity. But, it must fairly be a probable agent that could clear up the worries associated with weight problems. Consistent with Jung et al. 2012 cinchonine outcomes dramatically than different phyto-chemical compounds which might be acknowledged to exert anti-weight problems effects13.

Even the supplemented dose became on pinnacle of or same, cinchonine confirmed better charge of last weight discounts in comparison to EGCG (epigallocatechin gallate) and curcumin (11) in which 0.32% EGCG supplementation confirmed 9.4crease in very last weight in excessive fats died fed mice (12) and 0.05% curcumin supplementation is moreover acknowledged to decrease the weight through 11% in the equal model (13). In conjunction with cinchonine's impact on weight reduction, cinchonine decreases the plasma stage of lipid in mice ate up the HFD (High fats diet). Cinchonine efficaciously ameliorated hyperlipidemia and hyperglycemia caused through the HFD; ldl cholesterol, LDL+VLDL ldl cholesterol, cholesterin, TG, and as a consequence the plasma glucose stages. Cinchonine have an effect on the HFD-mediated hyperlipidemia and hyperglycemia which might be early signs and symptoms of the metabolic syndrome and related disorders. So, subsequently cinchonine consists of a dramatic suppressive impact on adipogenesis via the down-law of WNT and galanin-mediated adipo genesis signaling pathway, and it additionally attenuates irritation through repressing TLR2- and TLR4-mediated pro-inflammatory signaling pathways in the adipose tissue (10). In numerous literature studies, it were proven that cinchonine should also be a beneficial nutritional phyto-chemical for the prevention of now no longer handiest weight problems, however additionally adipose irritation.

***Anticancer property**:* According to Krishnavedi and Suresh,2015, quinine is less assailable to inhibit the cell proliferation and induce apoptotic necrobiosis in neoplastic cell line in an exceedingly dose and time dependent manner[(14)], the IC50 values obtained after 24hr treatment of various concentrations of quinine (125.23 μM/mL for twenty-four hr). ROS (Reactive oxygen species) is critical for the metabolic and signal transduction pathways related to cell growth and apoptosis18. Several anticancer agents, including anthracyclines, cisplatin, bleomycin, and irradiation currently used for cancer treatment are shown to cause increased intracellular ROS generation. The results of this study showed that intracellular ROS levels were significantlyincreased in neoplastic cell line treated with quinine at time and dose dependent manner. Induction of death through indirect activation of the mitochondria dependent pathway is that the conventional anticancer treatment but sometimes it's altered in drug resistant cancer cells. Effect of quinine induce typical morphological change because the signal of apoptosis [(15)] like cell shrinkage, membrane blebbing, chromatid condensation, nuclear fragmentation, apoptotic bodies and loss of adhesion [(16)]. So quinine is also a robust anticancer agent in future thanks to its huge apoptotic activities in cancer.

Antioxidant agent: As described by Ravishankara et.al cinchona exhibit efficient antioxidant properties thanks to presence of phenolic compounds [(17)]. The biological properties of phenolics include like anti- tumor, anti-viral, anti HIV and also inhibition of lipid peroxidation [(18, 19)]. The study was mainly targeting three major radicals – superoxide hydroxyl and gas radicals as these are the most radicals chargeable for the oxidative damage of cellular components of the human body [(20, 21, 22, and 23)]. Methonalic and water extract showed a degree 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 tired dose dependent manner and as a result Methanolic extract showed an improved protection than α- tocopherol which revels the power of the cinchona extract to scavenge the atom.

Antimicrobial activity: According to Pankaj et.al cinchona alkaloids be seen the antibacterial pastime towards the Staphylococcus aureus with the inhibition region ranged from 8-18mm executed through the disc diffusion method[(24)]..it is been studied that antimicrobial pastime will increase consistent with the attention of the cinchona alkaloids. Extraction of cinchona alkaloids is determined powerful towards amebiasis. Dried bark is hired to deal with sickness resulting from a pathogenic pressure like P.falciparum and herpes28. Rojas J.J et al. showed that cinchona became lively towards the numerous microorganisms which can be dangerous to the human body [(25)]

***In angina pectoris**:* The cinchona alkaloids are powerful in angina pectoris due to a vasodilator motion. Thus, they're greater powerful in sufferers who reply to nitroglycerin and are least powerful in sufferers who fail to reply to nitroglycerin. Furthermore, whilst those tablets are powerful additionally they save you or lower the electrocardiographic proof of anoxia precipitated with the aid of using exercise. That quinine have a vasodilating motion is indicated with the aid of using coronary blood float research in laboratory animals [(27)]it is likely that the cinchona alkaloids owe their effectiveness in angina pectoris to the presence of the quinoline ring. This could provide an explanation for why chloroquine and pentaquine also are powerful at the same time as chlorguanide, which has a phenol as opposed to a quinoline ring, is of no price. In this regard, it's far of hobby to observe that papaverine, ethaverine, and pavril additionally incorporate the quinoline ring and also are of price in angina pectoris despite the fact that the latter 3 are tons much less powerful in angina pectoris than are the cinchona alkaloids[(28)]

Amebicidal activity: A number of Cinchona alkaloids are studied for his or her amebicidal activity (I 72). The quinoline alkaloids quinine, quinidine, and quinidinone showed some activity, almost like the indole alkaloids cinchonamine (9a), 10-methoxycinchonamine (9b), epiquinamine (7b), and aricine [(5)].However, these activities were detected at concentrations approximately 100,200 times higher than those of the model drug emetine. Extracts of Cinchona Eedgeriana leaves were more active than may well be explained on the premise of the abovementioned alkaloids.

Other pharmacological activities of quinine

In nocturnal leg cramp: Quinine is effective inside the prevention of nocturnal leg cramps. However, given 38 instances of first rate detrimental activities related to quinine pronounced among April 2005 and October 2008, the Food and Drug Administration (FDA) warned in opposition to the usage of quinine for 'off label' use of this situation in July 2010[29].

Antipyretic: Quinine has long been thought to possess antipyretic actions. Although by itself it's not been found to own an effect on fever, it produces a more rapid come by temperature if administered after acetaminophen.

Antileukemic agents: Quinine together with some cancer chemotherapeutic agents, like mitoxantrone and cytarabine, has been found to be beneficial within the treatment of acute leukemias compared with use of those agents alone.

Sclerosing agent: A combination of quinine with urea hydrochloride has been used as a sclerosing agent for the remedy of inner haemorrhoids, hydrocele, varicose veins, and pleural cavities after thoracoplasty. Flavouring agent: Quinine is hired in tonic to supply a sour taste. Tonic contains as heaps as a hundred mg l1 quinine sulphate [30].

Synonym

Cancer tree, happy tree. Biological Source. Camptotheca consist of the dried stem wood of Camptotheca acuminata Decne, Camptothera lowreyona S.Y.Li. belonging to family Nyssaceae (Cornaceae). Geographical Source It is distributed in China and Tibet. It is indigenous to southern China. Camptothecin, was discovered by National Institute of Health, U.S.A. during the antitumor screening programme for this plant.

Macroscopic Characters: Leaves are dark green in colour with reddish petiale. Leaves are entire, accuminate, ovate and lanceolate. 8-10 cm in length and 3-5 cm in width. Flowers are red coloured.

Taste: Bitter

Chemical constituent: Camptotheca plant contains 0.004 - 0.03 per cent of quinoline alkaloid camptothecin. Other minor constituents of the drug are Irinotecan, topotecan, 9 aminocamptothecin, 10-hydroxy camptothecin and 10-methoxy camptothecin. All plant parts leaves, bark, fruits, and twigs also contain camptothecin, young leaves have highest concentration. Camptothecin has yellow needle shaped crystals. It is a weak weak basic alkaloid and does not form stable salts with mineral acids. It does not respond Dragendorff's and Mayer's reagent test. The other or constituents are 10-hydroxycamptothecin and 10-methoxycamptothecin.

Pharmacological activity: camptotheca acuminate: Cancer may be a global health concern and one among the leading causes of death worldwide. in step with the globe Health Organization, 18 million people suffer from cancer globally, and 9.5 million cancer deaths were reported in 2018 [31].

Unfortunately, cancer chemotherapy is usually related to severe adverse effects and, in most cases, poor patient outcomes [32]. Therefore, there's an urgent need to discover effective anticancer agents with minimal toxicity and side effects. Nature comprises a wealth of natural products representing a source of chemotherapeutic agents that inspires chemists to develop novel lead drug candidates [33]. In fact, natural products represent a chic source of first-in-class drugs; hence drug developers are constantly developing new natural-products analogues to boost their pharmacokinetic and pharmacodynamic properties by modifying their chemical structures through diversity-oriented synthesis and employing late-stage ring-distortion strategies.

Mechanism of action of CPT: The anticancer mechanism of action of CPT was uncovered and located to result to the inhibition of Topoisomerase I (Top I) [34]. The latter is crucial for the replication of DNA (DNA). Additionally, it had been found that CPT inhibits Top1-DNA complex rather than the free Top1 enzyme [35]. The invention of this molecular target of CPT led to promising advances within the chemistry and SAR of CPT, allowing the synthesis of analogues with improved potency, higher selectivity, so reduced toxicity [36]. The expression of Top I enzyme in cancer cells is significantly higher as compared to healthy cells, with target selectivity [37]. CPT sensitivity is directly proportional to the Top1 concentration within the body [38]. Thus, cells with higher concentrations of Top I are more tuned in to the cytotoxic effect of CPT. Unfortunately, CPT's clinical use is expounded to varied side effects, including vomiting, diarrhoea, and haemorrhagic cystic disease [38]. Mechanism of movement of CPT becomediscoveredvia the molecular function of its goal enzyme, Top1 Top I. The double-helical shape of DNA is subjected to supercoiling throughout the system of replication below the effects of DNA and RNA polymerases [39]. .Top1 is responsible forthe relaxation of supercoiled DNA, with the aid of using regulating DNA topology [40]. It hyperlinks with the DNA phosphate spinethru a phosphotyrosine bond and cuts the supercoiled part of the DNA, inflicting a single-strand destroy[41]. Then Top I covalently binds to the nicked 30 end. Thisallows the 5-nicked strand to unwind and rotate spherical the intact strand, observedwith the aid of using Top I catalysing the inverse reactionvia religation of the reduce strand, relieving the supercoils torsional pressureconsequently Top I is without delayworried in DNA replication, recombination, transcription, and repair [42]. In contrast, Topoisomerase 2 (Top2) cuts supercoiled DNA, inflicting a double-strand destroy into the DNA in preference to the single-strand destroywithinside the case of Top I. CPT has no pastimetowards The complicated of Top I and DNA, stateddueto the fact the "Top I covalent complicated", is that theprimarygoal of CPT . CPT integrates itself into this complicated, forming a ternary complicated. Under regular physiological circumstances, the equilibrium among unbound Top I and Top I -DNA complicated shifts towards the unfastenedenzyme, butbelow the impact of CPT, this equilibrium strongly shifts in the direction of the formation of the ternary complicated, reducing the variety of unfastened Top I and sooner or later inhibiting its impact The ternary complicated is taken under consideration an obstruction to the DNA replication fork. CPT binds to each the Top I and DNA via hydrogen bonds, stopping the religation of the nicked DNA breaks, ensuing in neoplastic mobileular apoptosis throughout the S-section of the mobileular cycle (43).

Specifically, with the inhibition of Top I movement, the DNA supercoil are prominent, interfering with the moves of the RNA and DNA polymerase (43). CPT as an anticancer (camptotheca acuminata): likewise due to the fact the departure of the best I from the DNA [43] . This finally ends upwithinside the buildup of DNA strand. The first-era of CPT analogues Camptosar (irinotecan or CPT-11) and Hycamtin (topotecan) are water-soluble derivatives with an intact lactone ring that have been authorised to be utilized by the United States Food and Drug Administration (FDA) in 1996. These tablets are advertised in the u. s. via way of means of Pharmacia (Pfizer) and GlaxoSmithKline, respectively. Topotecan has modest interest in sufferers handled formerly with ovarian and small mobileular carcinoma and is presently authorised to be used in the USA as second-line remedy in those diseases. Preliminary proof for interest in opposition to hematological malignancies is moreover promising. Irinotecan can be a pro-drug that undergoes enzymatic conversion to the biologically energetic metabolite 7-ethyl-10-hydroxy-CPT. Irinotecan have become commercially to be had in Japan in 1994, wherein its authorised warning signs have been cancers of the lung (smallcell and non-small mobileular), cervix and ovaries. Later, it become authorised in Europe in 1995 as a second-line agent for colon most cancers. it is currently the remedy of desire while applied in aggregate with fluoropyrimidines as first-line remedy for sufferers with superior colorectal most cancers or as one agent after failure of 5-fluorouracil-primarily based totally chemotherapy. Encouraging initial outcomes recommend that irinotecan might also additionally have an growing position in the remedy of different strong tumors, inclusive of small and non-small mobileular carcinoma, cervical most cancers, ovarian most cancers, gastric most cancers, and malignant gliomas (Garcı´a-Carbonero and Supko, 2002(44)). The mixed income of irinotecan and topotecan in 2003 have been anticipated to attain nearly $1 billion (Oberlies and Kroll, 2004[45].

Other pharmacological action of Camptotheca: Although the antitumor interest of CPT and its derivatives has been the maximum recognition of studies for businesses in each the enterprise and educational arenas, CPTs have additionally been studied as robust inhibitors of replication, transcription, and packing of double stranded DNA-containing adenoviruses, papovaviruses, and herpesviruses, and consequently the single-stranded DNA-containing independent parvoviruses (reviewed in Pantazis et al., 199946). CPT inhibits viral features through poisoning topo I, the host mobileular enzyme required for initiation and fulfilment of viral features. If well developed, CPTs should convince be effective antiviral pills for numerous DNA viruses, that are causative marketers for an oversized wide variety of diseases. In the mid-1990s, CPT became additionally proven to personal promising interest in opposition to parasitic trypanosomes and Leishmania (Bodley and Shapiro, 1995[47]). More lately, researchers on the National Cancer Institute screened 2000 numerous compounds for practical inhibition of the hypoxia-inducible element 1 (HIF-1), a grasp regulator of the most cancers cells cappotential to live to tell the tale beneathneath oxygen deprivation. Only 4 compounds exhibited HIF-1 inhibitory interest, and 3 of these had been CPTs (Rapisarda et al., 2002[48]). Hence, those pills might also additionally have other suited sports in opposition to strong tumors which can be unbiased of topo I poisoning.

Imidazole Alkaloids: Imidazole alkaloids contain an imidazole ring and are derived from histidine. Found in various species of Pilocarpus ,Rutaceae and fungi egergothioneine and hercynine A number of imidazole alkaloids found in sea spongeswere reviewed Pilocarpine, the only naturally occurring imidazole alkaloid, is used in clinical drugs to treat glaucoma.. It is isolated from the leaves of Pilocarpus microphyllus. The medicinally importantjaborandi are species of Pilocarpus but the vernacular name is also applied to the other rutaceous and piperaceous plants.A review on jaborandi alkaloids has been published and have reported a number of pilocarpine biogenetic and biosynthetic pathways[49]

Pharmacognostic Characteristics of Imidazole Alkaloids:

Pilocarpine: The Jaborandi Alkaloids comprise a group of closely related alkaloids that occur in South American plants belonging to family of the Rutaceae [50]. The first samples of the shrubs were investigated interalia for their pharmacological properties in their third quarter of the 19thcentury[50].These samples came from Pilocarpus Jaborandi Holmes. Pilocarpus naturally occurring Imidazole alkaloid that is used in clinical medicine. Inspite of many references to Pilocarpus jaborandi holmes in ethnological and botanical sources and suggestions of its employment for variety of diseases. The medicinally important Jaborandi's are species of Pilocarpus but it should be remarked and this vernacular name is commonly applied to the other rutaceous and numerous piperaceous plants as well. [50].

Alchornine: Alchornea cordifolia is a shrub or small tree widespread throughout tropical Africa, it can reach 8 meters in height. The plant is used in traditional African medicine. The Common name is the Christmas bush. .[53]Theleaves, roots and stem bark contain terpenoids, steroid glycosides, flavonoids, tannins, saponins, carbohydrates and the imidazopyrimidine alkaloids alchorneine, alchornidine,and several guanidine alkaloids. The leaves also contain a number of hydroxybenzoic acids: gallic acid and its ethyl ester, gentisic acid, anthranilic acid, protocatechuic acid, and ellagic acid (alizarine yellow). A C20 homologue of vernolic acid named alchornoic acid can be found in the seed oil..[53] Alchornea cordifolia is commonly known as Christmas bush. It is staggling laxly branched evergreen dioecious shrub or small tree growing up to 8 metres tall. .[53] It is mainly harvested from the wild. It also supplies dye, wood etc and occasionally it can also be used as food. The plant is cultivated for its medicinal uses. The root bark, leaves and fruits are sold for medicinal purposes in local markets. .[53]

Chemical constituents : The leaves, roots and stem bark contain terpenoids, steroid traditional medicine and much pharmacological research has been carried out into it's antibacterial, antifungal, antiprotozoal properties as well as it's anti-inflammatory activities with positive significant results. .[53]Alchornine is obtained from Alchornea cordifolia.

White Sapote : The genus Casimiroa of the Rutaceae family was named in honor of Cardinal Casimiro Gomez de Ortega, Spanish botanist of the 18th century. Embraces 5 or 6 species of shrubs or trees. White sapote trees range from 15 to 20 ft (4.5-6 m) up to 30 to 60 ft (9-18 m) in height[61]. They have light-gray, thick, warty bark and often develop long, drooping branches.

The leaves, mostly evergreen are alternate, palmately compound, with 3 to 7 lanceolate leaflets, smooth or hairy on the underside. The odorless, small, greenish-yellow flowers are divided into 4 or 5 parts, and borne in terminal and axillary panicles.They are hermaphrodite or occasionally unisexual because of aborted stigmas. [(61).] The fruit is round, oval or ovoid, symmetrical or irregular, more or less distinctly 5-lobed; 2 1/2 to 4 1/2 in (6.25-11. 25 cm) in width and up to 4 3/4 inches (12 cm) in length; with thin green, yellowish or golden skin coatedwith a very fine, tender, but inedible flower; and creamy white or yellow flesh that shines with numerous tiny, showy, yellow oil glands(61). The flavor is sweet with a hint or more of bitterness and sometimes distinctly resinous. There may be 1 to 6 plump, oval, hard, white seeds, 1 to 2 in (2.5-5 cm) long and 1/2 to 1 in (1.25-2.5 cm) thick, but often some seeds are under-developed (aborted) and very thin. The grains are bitter and narcotic. [(61).] C. edulis has leaves usually composed of 5 leaflets, glabrous to slightly pubescent on the underside, and 5 divided flowers. The fruit looks somewhat apple-like on the outside, usually smooth, fairly symmetrical, and 2 1/2 to 3 inches (6,257.5 cm) wide.C. sapota is very similar but the leaves usually have only 3, slightly smaller, leaflets. The fruit looks somewhat apple-like on the outside, usually smooth, fairly symmetrical, and 2 1/2 to 3 inches (6,257.5 cm) wide C. edulis and velvety-white on the underside, and all the parts of the flowers are in 4's. The fruits are usually 4 to 4 1/2 in (10-11. 25 cm) wide, ovoid, irregular and knotty, with a rough and pitted skin, and granular particles are often present in the pulp. [(61)]

Chemical constituents: It involves chemical constituents N-methylhistamine, N-Ndimethylhistamine and histamine.It also contains 2,5,6-trimethoxyflavone, 2',6',5,6-tetramethoxyflavone (zapotin), and 5-hydroxy_2'6,7-trimethoxyflavone (zapotinin)[(61)].

Pharmacological characteristics:

Pilocarpine*:* Pilocarpine is widely studied peripheral stimulant of the parasympathetic system. It is topically act as a myotic to counteract the mydriatic effect of atropine and other parasympatholytic drugs. It has clinical value in the treatment of glaucoma when used as eyedrop solutions ranging from 0.5-10% in concentration . Pilocarpine is reported to stimulate the growth of hair and therefore was employed in hair lotions[(50).] Internally it was used as a diphoretic in the treatment of Nephritis. Pilocarpine is unique among the cholinergic agents in that it is a tertiary amine derivative whereas the majority of the members of this class are quarternary ammonium compounds. It has been demonstrated that Pilocarpine looses its activity when it is measured at pH 9 whereas acetylcholine does not suggesting that pilocarpine acts in its ionised form i.e its activity decreases its activity on increasing pH. [(50).]

Alchornine*:* It is used incoughs, gonorrhoea, infertility, prostatitis, bacterial infections, diarrhoea, ulcers, pain, inflammation, fever and bronchial troubles.

White Sapote: It shows anti-inflammatory activity. It also shows sedative and mildly hypnotic action. They also posses anti- spastic and anticonvulsive actions. It's leaves have an anti-inflammatory action. [(61)]

CONCLUSION

- In this review literature we have discussed on quinoline and imidazole alkaloids which are the important class of alkaloids in terms of pharmacological activities , of which major important alkaloids in quinoline class are obtained from cinchona bark belonging to family rubiaece from which four different alkaloid are obtained quinine ,quinidine ,cinchonine and cinchonidine .
- 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.
- Second major important alkaloid of this class is camptotheca its chemical constituent Camptothecin is a potent natural product based anticancer agent isolated from an organic extract of the bark of a Chinese tree.
- Along with the antitumor property is shows the property as parasitic trypanosomes and in Leishmania.
- Another class of alkaloid is imidazole plants like pilocarpine, white sapote and alchornine these alkaloids signifies various pharmacological actions which includes anti-cholinergic, anti-bacterial, anti-protozoal, anti-diarroheal and anti-inflammatory activity.

REFERENCES

1. Kacprzak KM. Chemistry and Biology of Cinchona Alkaloids. Springer Publication. 2013, 605-641.
2. Anonymous, Wealth of India, Raw materials, CSIR, New Delhi. 1950, 188-209.
3. Committee for Veterinary Medical Products, Cinchona Cortex, the European Agency for the Evaluation of medical Products, Veterinary Medicine and information Technology Unit, January, 2000.
4. Goldenberg AM, MD LF Wexler MD Quinine Overdose: Review of Toxicity and Treatment, 1988.
5. Verner N. Orish, Ilechie A Alex. Acute Blindness in a child after quinine treatment for severe malaria.
6. Levine LH, Hirsch CS, White LW. Quinine Cardioxicity: A mechanism of sudden death in narcotic addicts. J Forrensic Sci. 1971, 17, 167.
7. Tracy JW, Webster LT. Drugs used in chemotherapy of protozoal infections," The Pharmacological Basis of Therapeutics. 1996; 9: 80-808.
8. Genne P, Duchamp O, Solary E, *et al.*, comparative effects of quinine and cinchonine in reversing multidrug resistence on human leukemic cell line K562/ADM, Leukemia. 1994; 8(1): 160-164.
9. Munther K, Homoud MD. Tufts-New England Medical Center, Introduction to Antiarrhythmic Agents, Spring 2008.
10. Dubey Anubhav, Tiwari Mamta, Kumar Vikas, Srivastava Kshama, Singh Akanksha. Investigation of Antihyperlipidemia Activity of Vinpocetine in Wistar Rat. International Journal of Pharmaceutical Research. 2020; 12, (2) 1879-1882.
11. Sung A. Jung, Miseon Choi, Sohee Kim, Rina Yu, Taesun Park. Cinchonine Prevents High-Fat-Diet- Induced Obesity through Down regulation of Adipogenesis and Adipose Inflammation, Hindawi Publishing Corporation. 2012.
12. Sae-Tan S, Grove KA, Kennett MJ, Lambert JD. (-)-Epigallocatechin-3-gallate increases the expression of

genes related to fat oxidation in the skeletal muscle of high fat-fed mice, "Food and Function. 2011; 2(2): 111- 116.
13. Desvergne B, Wahli W. Peroxisome proliferator-activated receptors: nuclear control of metabolism, Endrocrine Reviews. 1999; 20(5): 649-688.
14. Ejaz A, Wu D, Kwan P, Meydani M, Curcumin inhibits adipogenesis in 3T3-L1 adipocytes and angiogenesis and obesity in C57/BL mice, Journal of Nutrition. 2009; 139(5)919-925.
15. Krishnaveni1 M, Suresh K. Induction of apoptosis by quinine in human laryngeal carcinoma cell line (KB), International Journal of Current Research and Academic Review, Int. J Curr. Res. Aca. Rev. 2015; 3(3): 169-178.
16. hannickal VJ, Fanburg BL. Reactive oxygen species in cell Tsignaling, Am J Physiol. 2000; 279: 1005- 1028.
17. Kampa M, Alexaki VI, Notas G, Nifli AP, Nistikaki A, *et al.* Antiproliferative and apoptotic effects of selective phenolic acids on T47D human breast cancer cells, potential mechanisms of action, Breast Cancer Res. 2004; 6: 63-74.
18. Ravishankara MN, Harish Padh, Rajani M. Antioxidant activity of Cinchona officinalis stem bark extracts Oriental Pharmacy and Experimental Medicine. 2003; 3(4): 205-211.
19. Haslam E. Natural polyphenols (vegetable tannins) as drugs: Possible modes of action. J Nat. Prod. 1996; 59205.
20. Bagul MS, Ravishankara MN, Harish Padh, RajaniM. Phytochemical evaluation and free radical scavenging properties of rhizome of Bergenia ciliate (Haw) Sternb. Forma ligulata Yeo. J Nat. Remed. 2003; 3(1): 83-89.
21. Halliwell B, Gutteridge JMC. Free radicals, ageing, and disease, Free radicalsin Biology and Medicine, 2ndedition, Clarendron Press, Oxford. 1985, 279- 315.
22. Marletta MA. Nitric oxide: biosynthesis and biological significance. Trends Biol. Sci. 14, 488-492
23. Moncada A, Palmer RMJ, Higgs EA. (1991) Nitric oxide: Physiology, Pathophysiolgy and Pharmacology. Pharmacol. Rev. 1989; 43: 109-142.
24. Moncada A, Palmer RMJ, Higgs EA. (1991) Nitric oxide: Physiology, Pathophysiolgy and Pharmacology. Pharmacol. Rev. 1989; 43: 109-142.
25. Miyake T, Shibamoto T. Antioxidant activitiesof natural compounds found in plants. J Agri. Food Chem. 1997; 45: 1819-1822.
26. Moncada A, Palmer RMJ, Higgs EA. Nitric oxide: Physiology, Pathophysiolgy and Pharmacology. Pharmacol. Rev. 1991; 43: 109-142.
27. 1 HEDBOM, K.: Ueber die Einwirkung verschiedener Stoffe suf das isolirte Saugethierherz. Skandinav. Arch. f. Physiol. 8: 169, 1898. 32 S
28. GRAY, W., RISEMAN, J. E. F., AND STEARNS, S.: Papaverine in the treatment of coronary artery disease. New England J. Med. 232: 389, 1945.
29. Achan, J., Talisuna, A.O., Erhart, A., Yeka, A., Tibenderana, J.K., Baliraine, F.N., Rosenthal, P.J., D'Alessandro, U., 2011. Quinine, an old anti-malarial drug in a modern world: role in the treatment of malaria. Malaria J. 10, 144. http://dx.doi. org/10.1186/1475-2875-10-144.
30. Ballestero, J.A., Plazas, P.V., Kracun, S., et al., 2005. Effects of quinine, quinidine, and chloroquine on alpha-9 alpha-10 nicotinic cholinergic receptors. Mol. Pharmacol. 68, 822–829.
31.) World health organization, cancer. https://www.who.int/news-room/facts
32. G.H. Lyman, Impact of chemotherapy dose intensity on cancer patient outcomes, J. Natl. Compr. Canc. Netw. 7 (2009) 99e108, https://doi.org/10.6004/ jnccn.2009.0009.
33. G.H. Lyman, Impact of chemotherapy dose intensity on cancer patient outcomes, J. Natl. Compr. Canc. Netw. 7 (2009) 99e108, https://doi.org/10.6004/ jnccn.2009.0009.
34. D. Lorusso, A. Pietragalla, S. Mainenti, V. Masciullo, G. Di Vagno, G. Scambia, Review role of topotecan in gynaecological cancers: current indications and perspectives, Crit. Rev. Oncol. Hematol. 74 (2010) 163e174, https://doi.org/ 10.1016/j.critrevonc.2009.08.001.
35. F. Li, T. Jiang, Q. Li, X. Ling, Camptothecin (CPT) and its derivatives are known to target topoisomerase I (Top I) as their mechanism of action: did we miss something in CPT analogue molecular targets for treating human disease such as cancer? Am. J. Canc. Res. 7 (2017) 2350e2394
36. V.J. Venditto, E.E. Simanek, Cancer therapies utilizing the camptothecins: a review of the in vivo literature, Mol. Pharm. 7 (2010) 307e349, https:// doi.org/10.1021/mp900243b.
37. L.F. Liu, S.D. Desai, T.K. Li, Y. Mao, M. Sun, S.P. Sim, Mechanism of action of camptothecin, Ann. N. Y. Acad. Sci. 922 (2000) 1e10, https://doi.org/10.1111/ j.1749-6632.2000.tb07020.x
38. E. Martino, S. Della Volpe, E. Terribile, E. Benetti, M. Sakaj, A. Centamore, A. Sala, S. Collina, The long story of camptothecin: from traditional medicine to drugs, Bioorg. Med. Chem. Lett 27 (2017) 701e707, https:// doi.org/10.1016/ j.bmcl.2016.12.085.
39. J. Zou, S. Li, Z. Chen, Z. Lu, J. Gao, J. Zou, X. Lin, Y. Li, C. Zhang, L. Shen, A novel oral camptothecin analog, gimatecan, exhibits superior antitumor efficacy than irinotecan toward esophageal squamous cell carcinoma in vitro and in vivo, Cell Death Dis. 9 (2018) 661,.
40. L.R. Ferguson, B.C. Baguley, Mutagenicity of anticancer drugs that inhibit topoisomerase enzymes, Mutat. Res. 355 (1996) 91e101, https://doi.org/ 10.1016/0027-5107(96)00024-3
41. C.H. Shen, Nucleic Acids: DNA and RNA, Diagnostic Molecular Biology, 2019, pp. 1e25.
42. J.L. Nitiss, E. Soans, A. Rogojina, A. Seth, M. Mishina, Topoisomerase assays, Chapter 3, Curr. Protoc. Pharmacol. (2012), https://doi.org/10.1002/ 0471141755.ph0303s57. Unit 3 3.
43. F. Li, T. Jiang, Q. Li, X. Ling, Camptothecin (CPT) and its derivatives are known to target topoisomerase I (Top I) as their mechanism of action: did we miss something in CPT analogue molecular targets for treating human disease such as cancer? Am. J. Canc. Res. 7 (2017) 2350e2394
44. Garcı´a-Carbonero, R., Supko, J.G., 2002. Current perspectives on the clinical experience, pharmacology, and continued development of the camptothecins. Clin. Cancer Res. 8, 641–661.
45. Oberlies, N.H., Kroll, D.J., 2004. Camptothecin and taxol: historic achievements in natural products research. J. Nat. Prod., 67,129– 135
46. Pantazis, P., Han, Z., Chatterjee, D., Wyche, J., 1999. Water-insoluble camptothecin analogues as potential antiviral drugs. J. Biomed. Sci. 6, 1–7.
47. Bodley, A.L., Shapiro, T.A., 1995. Molecular and cytotoxic effects of camptothecin, a toposiomerase I

inhibitor, on trypanosomes and Leishmania. Proc. Natl. Acad. Sci. USA 92, 3726–3730.
48. Rapisarda, A., Urachimeg, B., Scudiero, D.A., Selby, M., Sausville, E.A., Shoemaker, R.H., Melillo, G., 2002. Identification of small molecule inhibitors of hypoxia-inducible factor I transcriptional activation pathway. Cancer Res. 62, 4316–4324
49. IUPAC Compendium of Chemical Terminology 2nd Edition (1997).
50. R.H.F Manske. The Alkaloids Chemistry and Physiology Volume VIII New York 1965.
51. Robert Alan Lewis, Lewis dictionary of toxicology CRC Press, 1998.
52. Roberts M.F. (1998), Alkaloids, Biochemistry, Ecology & Medicinal Applications Wink, Miachel Boston , MA Springer US.
53. Virginie Ebessa , Gesquiere Laure, M.Tiani, Joseph Tchamgoue Alchornic acid derivatives from the fruits of Alchornea Cordifolia (Schumach & Thonn) , Muell Arg. (Euphorbiaceae) Volume 23 , February 2018 Page No:62-65
54. Mavar-Manga, H., Lejoly, J., Quetin-Leclercq, J., Schmelzer, G.H., 2007. In: Schmelzer, G.H., Gurib-Fakim, A. (Eds.), Alchornea cordifolia (Schumach. & Thonn.) Müll.Arg. (Internet) Record from Protabase. PROTA (Plant Resources of Tropical Africa/ Ressources végétales de l'Afrique tropicale), Wageningen, Netherlands.
55. Pone, K.B., Sabrina, B.F., Carlos, R.K., 2016. Recent trends in phytochemistry: ethnobotany and pharmacological significance of Alchornea cordifolia (Schumach. &Thonn.) Muell. Arg. J.Ethnopharmacol. 191, 216–244. Rezanka, T., 2002. Glycosides of polyenoic branched fatty acids from myxomycetes.
56. Morton, J.F., 1987. White sapote. In: Dowling, Jr., C.F. (Ed.), Fruits of Warm Climates. Media Incorporated, NC, USA, pp. 191–196.
57. .Essentials of Medical Pharmacology K.D Tripathi, Seventh Edition, Pg No 104
58. Trease and Evans Pharmacognosy William C Evans, 16th Edition, Pg No 407-408
59. A textbook of Pharmacognosy by S.B Gokhale, C.K Kokate,
60. Neelam Mishra , Sushil Kumar, Rajesh Luthra, Kiran L Singh Recent Advances in Biosynthesis of Alkaloids.
61. Virginie Ebessa, Joseph Tchamgoue, Muhammad I. Chaudhary, Pierre Tane Alchornoic acid derivatives from fruits of Alchornea cordifolia.
62. T.R. Ahlawat, N. L Patel, C.R Patel and Roshni Agnihotri White Sapote (Casimiroa edulis Llave & Lex).
63. Ogungbamila, F.O., Samuelsson, G., 1999. Smooth muscle relaxing flavonoids from Alchornea cordifolia. Acta Pharmaceutica Nordica 2, 421–424.

****