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Therapeutic Values of Pyridine Molecules from Natural Sources: A Comprehensive Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Reason for the Study: Many commercial pharmacologically interesting medicinal plant species and their formulations are used in more communities and often in more countries around the world, for their multiple uses of Active compounds from the natural sources. It should be need to extensively explored to get their properties and their benefits. The costs of drugs for resistance of common infective diseases are increased especially bacterial infections and sexually transmitted diseases. The therapeutic approach of herbal medicines is an option for concerted search for new chemical entities for new drugs development. So searching of valuable medicinal plants with their longest track record for their use and their location and distribution is must and essential.

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Aim: This study aims to provide an overview and documentation about pyridine alkaloids and their phytopharmacological activity related some medicinal plants.
Methodology: By using the key words, the literatures were collected from Science Direct, PubMed and Google Scholar search engines. This review will create a platform to harmonizing the traditional medicine practice in the country, create a synergy between herbal medicines and modern medicine and more harmonized integrated traditional medicine practices in future. It gives an insight into the strategic plan and route map for the development of new formulations and research platform for the practice and development of herbal medicines. The pharmaceutical industry has come to consider traditional medicine as a source for identification of bio-active agents that can be used in the preparation of semi synthetic medicine in different novel formulations.
Conclusion: This article focused some medicinal plants which contain different types and derivatives of pyridine alkaloids with their therapeutic applications. Further research needs to be done to make Novel pharmaceutical preparations with patent drugs and appropriate therapeutic documentation.

Keywords: Documentation; herbal medicines; pyridine alkaloids; phytopharmacology; traditional medicine.

1. INTRODUCTION

Alkaloids are produced by a large variety of living organisms including bacteria, fungi, plants, and animals. They can be purified from crude extracts of these organisms by different methods of extraction like acid-base extraction or solvent extractions followed by silica-gel column chromatography. Alkaloids have a wide range of pharmacological activities. Most of the alkaloids are contributing therapeutic value but some are producing toxic effect (e.g., atropine, tubocurarine). Although alkaloids act on a diversity of metabolic systems in humans and other animals, they almost uniformly have a bitter taste [1,2,3].

Pyridine alkaloids are a class nitrogen containing chemical compounds with pyridine ring widely found in plants. Pyridine alkaloid is a basic heterocyclic organic compound with the chemical formula (C_5H_5N). It is structurally related to benzene with one methane group (=CH-) replaced by a Nitrogen atom, an isostere of benzene. Initially it was isolated by Anderson in 1846 from picoline. Then the pyridine structure was elucidated by Wilhelm Korner (1869) and James Dewar (1871). Pyridine molecule is one of the most important molecule of more than 7000 existing pharmaceutical drug products. Pyridine based natural products consist of a variety of interesting compounds with diverse structures that originate from the five kingdoms of life. Nicotine, niacin (vitamin B_1) or (nicotinic acid), and pyridoxine (vitamin B_6) are extreme recognized compounds with an aromatic $\boldsymbol{\pi}$ electron pyridine moiety [4].

The pyridine alkaloids are highly flammable, weakly alkaline, water miscible liquid with a distinctive, unpleasant fish like smell. Mostly they are colorless, but older to impure samples may appear yellow. Alkaloids with a pyridine partial structure are further subdivided according to their occurrence and their biogenetic origin. In plants, they are mostly originated as alkaloids. In biological systems, a redox reaction of nicotinamide adenine dinucleotide (NAD) reduces its pyridine moiety into dihydropyridine compounds, rendering NADH Related redox reactions also exist in anabolic reactions involving NAD phosphate ($NADP^+$, NADPH) inter conversion [5].

Pyridine Derivatives can be classified into four main groups. [6,7,8] they are 1. Simple Pyridine Derivatives for example Nicotinic Acid, Trigonelline, Ricinine, Arecoline, 2. Polycyclic noncondensing pyridine derivatives for example Nicotine, Nornicotine, Anabasine, Anatabine. 3. Polycyclic condensed pyridine derivatives for example Actinidine, Gentianine, Pediculinine, 4. Sesquiterpene pyridine derivatives Isoleucine, Evonine, Hippocrateine, Triptonine. Generally the pyridine alkaloids are having therapeutic activity towards central nervous system and GIT, antimicrobial activity, anthelmintic activity [9,10].

2. MATERIALS AND METHODS

The method used to collect literature is the Extensive literature survey like Google search, Elsevier, Wiley online library, Springer, American Chemical Society, Science direct, Royal Society of Chemistry and Research Gate, Science Direct, and Pub Med search engines with keywords.

2.1 Therapeutic Activity Important Pyridine Molecules

2.1.1 Arecoline [11-15]

It was isolated from Arecanut Palm, its biological name is *Areca catechu* belongs to the family Arecaceae. The chemical name of arecoline is methyl 1-methyl-3,6-dihydro-2*H*-pyridine-5-carboxylate. It is a tetrahydropyridine that is 1,2,5,6-tetrahydropyridine with a methyl group at position 1, and a methoxycarbonyl group at position 3. It acts as an agonist of muscarinic acetylcholine and an agonist at nicotinic acetylcholine receptors. It showed potent anti-oxidative, free radical scavenging, and anti-hyaluronidase activity. Antioxidative effect of the extract was similar to tocopherol and higher than ascorbic acid. Arecanut extract showed free radical scavenging activity in DPPH method and against superoxide anion radical (O_2) evaluated by electron spin resonance (ESR) technique. It shows Anti-inflammatory and Anti-Melanogenesis Activity. Areca nut extract inhibits hyaluronidase activity, may work on immune regulatory and anti- inflammatory on skin problem. Skin whitening effect of arecanut extract showed through inhibitory activity on mushroom tyrosinase activity and melanin synthesis in B16 melanoma cells. Fatty acids from areca nut (myristic and oleic acids) and procyanidine were showing major antibacterial principles against a primarily cariogenic bacterium, *Streptococcus mutans*, and the major inhibitory activity against Glucosyl transferase from S. mutans. It shows Vascular-relaxation Activity. Areca catechu extract found to have relaxed aortic ring preparations. It is showing antidepressant activity and it was evaluated in rodents using the forced swimming and tail suspension tests. The ethanol extract caused a significant reduction in the immobility time without effecting spontaneous motor activity.

Topical application of arecanut extract inhibits hyaluronidase activity in vivo on delayed hypersensitivity and croton-oil induced ear edema in mice. It suggest that arecanut extract may reduce immune- regulatory, inflammatory on skin problem. Betel nut may cause Central Nervous System stimulant and euphoric effects and some conditions used for relaxation. The arecoline, a cholinergic, use in the managing neurological disorder in humans. Areca catechu reported to have most potent inhibitor of antigen induced degranulation in mast cells.

Arecoline is reported as a partial agonist of acetylcholine muscarinic receptor and to exert favourable effects against the schizophrenic symptoms. It possess efficacy against schizophrenia by directly targeting the OLs and prevents the demyelination of white matter. It enhances to protects the myelin damage in cortex by facilitating oligodendrocyte precursor cells (OPC) differentiation through dephosphorylating the activated protein kinase AMPKα. Five subtypes (M1-M5) of muscarinic receptor are widely distributed in the CNS which are chiefly involved in nociception, cognition, and movement regulation**.**

2.1.2 Trigonelline [16-23]

Trigonelline occurs in many plants. It has been isolated from fenugreek seeds *Trigonella foenum-graecum*. Higher levels of trigonelline are found in *Coffea arabica*. The molecule trigonelline is also obtained from the plant *Raphanus sattivus* belongs to the family Brassicaceae. The molecule trigonelline is chemically, 1-methylpyridin-1-ium-3-carboxylate. N-methylnicotinate is an betaine that is the conjugate base of N-methylnicotinic acid, arising from deprotonation of the carboxy group. Trigonelline (*N*-methyl-nicotinate) is a derivative of vitamin B6. It is functionally related to a nicotinate with a conjugate base of a N-methylnicotinic acid. It has been evaluated and reported that it showed diverse biological activities, such as hypoglycemic, hypolipidemic, neuroprotective, antimigraine, sedative, memory-improving, antibacterial, antiviral, and anti-tumor activities**.**

The seed extract exhibit antimicrobial activity against both gram-positive and gram negative bacteria such as *Bacillus species*, *Staphylococcus aureus*, *Enterococcus species*, *R. sativus*. *Klebsiella pneumonia*, *Staphylococcus aureus, Pseudomonas aeruginosa* and *Escherichia*.

The extract of *R. sativus* leaves showed the presence of a histaminergic component plus a weak spasmolytic factor supporting its traditional use for constipation. It shows the Histaminergic; spasmolytic activity and the gut stimulatory activity. And extract contain hepatoprotective constituents.

Study evaluated the anti-carcinogenic effect of *Raphanus sativus* in combating chemically (DMH) induced colon cancer. It reduced serum

CEA ($p<0.01$) and CA19-9 ($p<0.01$) as evidence of anticarcinogenic effect and showed the galactan polysaccharide of RS has pronounced cytotoxic effects on colon cancer cell line and might be a suitable candidate as chemo preventive and adjuvant therapy for colon cancer. Trigonelline has exhibited acetyl cholinesterase inhibitory effect and has been claimed to be able to regenerate dendrites and axons and improve memory functions. Trigonelline reduces blood glucose concentrations in human. It protects ß-cells of the pancreas and increases insulin sensitivity index as well as insulin content.

2.1.3 Mimosine [24-30]

Momosine is chemically known as 2-amino-3-(3-hydroxy-4-oxopyridin-1-yl) propanoic acid found in *Leucaena leucocephala* plant belonging to the family Fabaceae. L-mimosine is a rare plant amino acid extracted from Mimosa or Leucaena species and it has been reported to exhibit antitumor activity in a number of types of cancer. Mimosa pudica ethanolic extract of leaves showed anti-inflammatory activity. Immunofluorescene in fibroblasts and biochemical detection of native type I collagen in culture serum revealed a strong inhibition of synthesis and secretion of triple helical mature collagens. Treatment of fibroblasts with 200 Mm mimosine showed elevation of matrix metalloproteinase (MMP)-9 activity.

Mimosine acts as a hypoglycemic agent by selective regeneration of beta-cells of STZ-damaged pancreas while also protecting the beta-cells from the necrotic effect of STZ.

Mimosine act as an antioxidant by its potent iron-binding activity a chelator of fe(III). For antioxidant Activity was attributed to the phenolic content. The seed extract did not produce mortality or acute toxicity in rats with doses up to 2000 mg: kbw. Study of seed extract showed antidiabetic and antioxidant activities. There was an increase in the level of serum insulin in diabetic-LLSE treated rats.

The stem bark extract of *Mimosa pudica* has been reported for the treatment of hyperglycemic patients.. Seed aqueous extracts showed the most active fraction contain polar polyphenols, providing the anthelmintic therapy in veterinary practice. *L. leucocephala* had a detrimental effect on nematode eggs, which could be attributed with the high protease and chitinase activity of the extracts.

2.1.4 Ricinine [31-35]

Chemically it is 4-methoxy-1-methyl-2-oxopyridine-3-carbonitrile obtained from the plant *Croton tiglium* belong to the family Euphorbiaceae. Fifty percent of ethanolic extract of the root, stem and leaves of this plant showed hypoglycemic activity. The replacement of the O-methyl group of ricinine with acetyl group greatly affected its antimicrobial activity to the most active ricinine derivative against bacterial strains and the pathogenic fungus, *C. albicans*.

It consists of vitamin C and reduces the risk of coronary heart diseases and cancer. It is possible to reduce the risk of chronic diseases and to prevent disease progression by either enhancing the body's natural antioxidant defense or by supplementing with proven dietary antioxidant. The subcutaneous application of the extracts of seed of the plant showed significant anticonceptive effect. It also reduced response to oxytocin, ergometrine, acetylcholine, and transmural electrical stimulation.

Study on *Croton tiglium* oil showed Gastrointestinal Motility Modulation and it might modulate gastrointestinal motility, induce intestinal inflammation related to immunological milieu and motor activity results in gastrointestinal disorders.

A methanol extract of seeds of *Croton tiglium* yielded five phorbol diesters , that inhibit an HIV-induced cytopathic effect (CPE) on MT-4 cells and to activate protein kinase C (PKC) associated with tumor-promoting action. 12-O-Tetradecanoylphorbol-13-acetate (TPA) was one of the most potent inhibitor of HIV-1-induced CPE also the most potent activator of PKC.

2.1.5 Wilfortine [36-44]

The molecular formula of wilfortine is $C_{41}H_{47}NO_{20}$, and its chemical name is [(1S,3R,18S,19R,20R,21R,22S,23R,24R,25R)-20,22,23,25-tetraacetyloxy-21-(acetyloxymethyl)-15,26-dihydroxy-3,15,26-trimethyl-6,16-dioxo-2,5,17-trioxa-11-azapentacyclo-hexacosa-7(12),8,10-trien-19-yl] furan-3-carboxylate. It is a member of pyridines and a methyl ester. It is obtained from the plant *Tripterygium wilfordii* belongs to the family Celastraceae.

Alkaloids from *T.wilfordir* were shows inhibition of cytokine production in human peripheral mononuclear cells, which include B and T-cells among other types. Wilforonide, a C13 compound, inhibited T cell proliferation and IL-2 production from T cells**.** It showed anti-inflammatory activity. Wilforine was effective in treating idiopathic pulmonary fibrosis (an inflammatory lung condition), and arthritis. Wilfortine inhibited growth of murine leukemia cells *In vivo*. The alkaloids wilfordsine, wilfordconine, and wilfornine were reported to be immunosuppressive and wilfortrine, euonine and wilforine inhibited the humoral immune response (antibody-mediated responses) in animals. It was effective in treating idiopathic pulmonary fibrosis (an inflammatory lung condition) in rats, and arthritis. It inhibited the functioning of B cells from lupus patients as well as proliferation of peripheral blood mononuclear cells.

2.1.6 Triptonine [45-48]

Triptonine is isolated from the plant *Tripterygium wilfordii* it belongs to the family Celastraceae and its Molecular Formula is $C_{45}H_{55}NO_2$. It is a terpene lactone, a sesquiterpene alkaloid, a macrocyclic lactone, an acetate ester, a member of pyridines and a methyl ester.

It has been used medicinally in china for the treatment of rheumatoid arthritis and other autoimmune disease for centuries. A dose dependent activity in a particular cellular component, with cytotoxicity, and effective treatment option for the HIV-1 infections. It showed insecticidal activities.

2.1.7 Evonine [49-55]

Evonine is isolated from the plant *Euonymus alatus* and belongs to the family Celastraceae. Its Molecular Formula is $C_{36}H_{43}NO_{17}$. It is one of the important alkaloid among the 5 alkaloids isolated from this plant. Aplication for treating skin disorders such as wounds, eizema, bacterial infection, swelling and an infection caused by tiny lice like insects. It is used as anti-inflammatory agent in joint pain caused by arthritis or rheumatism. It is also used for urinary tract and genital tract disorders, antihypertensive, antitumor, sedative, and regulation of blood lipid and immune functions.

It is effective against hyperglycemia, chronic nephropathy, cor pulmonale, bronchial asthma, anaphylactic disease, urinary tract infection, and prostate diseases. The stem and branches are alterative, analgesic, anodyne, anthelmintic, anticoagulant, antiphlogistic, antipruritic, astringent blood tonic, carminative and purgative.

2.1.8 Haplophyllidine [56-59]

The furopyridine alkaloid haplophyllidine was isolated from the seeds of *Haplophyllum perforatum*, belongs to the family Haplophyllum. The Molecular Formula is $C_{18}H_{23}NO_4$. This alkaloid is also present in the stems and leaves of the plant. The Structure of Haplophyllidine is (7R,8R)-4,8-dimethoxy-8-(3-methylbut-2-enyl)-6,7-dihydro-5H-furo[2,3-b] quinolin-7-ol.

Different extracts derived from the areal parts of *H. tuberculatum* plant showed promising potential source for antioxidant and antimicrobial activity and potential to alleviate diseases neurodegenerative disorders induced by reactive oxygen species.

It showed good antimicrobial activities against *Bacillus subtilis, Klebsiella pneumoniae, Morganella morganti,* and *Staphylococcus aureus,* antiviral activity against *Fusarium culmorum*, Rhizoctoniasolani, and toacco mosaic virus (TMV) because of high concentration content in resveratrol kaempferol, myricetin, rutin, quercetin and rosmarinic acid.

Haplophyllidine showed a potent CNS depressant and synergizes the effects of narcotic; hypnotic drugs in mice, rats, and rabbits. Moreover, a Molecules prepared from the aerial parts of *H. perforatum* is used to relieve severe toothaches. The alkaloids perforine and khaplamine isolated from this species have been reported to have sedative action. The antagonism properties of haplophyllidine reported against analeptic agents, including corazol, camphor, strychnine and caffeine. Haplophyllidine exhibits pronounced sedative and anti-analeptic properties.

2.1.9 Gentianadine and Gentianine [60-64]

These molecules are isolated from the plant *Gentiana lutea* belongs to the family Gentianaceae. The molecule Gentianine formula is (C10H9NO2) ,its chemical nature is 5-ethenyl-3,4-dihydropyrano [3,4-c] pyridin-1-one Gentianine is also a pyranopyridine, a lactone and a pyridine alkaloid . The formula for the molecule Gentianadine is C8H7NO2 and its

chemical nature is 3,4-dihydropyrano[3,4-c] pyridin-1-one .Gentianadine is a pyranopyridine.

Gentianine is applied to the skin for treating wounds and cancer and sorrel for treating symptoms of sinus infections (sinusitis). It might be partly based on the notable reduction of prostaglandin $\mathbf{E_2}$ (PG $\mathbf{E_2}$) and nitric oxide (NO) levels. It has been reported as having anti inflammatory activity. Antidiabetic effect of gentianine by regulating the gene expression of PPAR-γ, GLUT-4 and adiponectin was recently proven. It also has the other activities such as anti-inflammatory, antipyretic, sedative-hypnotic and diuretic effects.

2.1.10 Cerpegin [65-67]

Cerpegin was isolated from flesh stem the plant *Ceropegia juncea* belongs to the family Apocynaceae with the chemical structure of 1,1-dimethyl-5H-furo[3,4-c] pyridine-3,4-dione. Cerpegin is a naturally occurring a pyridine alkaloid consisting of a 2-pyridone fused with a 2-furanone ring.

It acts as astringent and are used for treating insectinal disorders and they have antimicrobial and antioxidant drugs. Cerpegin exhibits a dose related analgesic effect against acetic acid induced writhing in mice without automatic or behavioral changes upto a dose of 20 mg/kg but doses of more than 400 mg/kg produce excitation, convulsions and respiratory paralysis in mice. The alkaloidal fraction of the ceropegid plant extract exhibits promising tranquilizing properties, used to treat mental illness behavioral disorder that are characteristic of the psychores like Schizophrenia. Decoction of tubers of *Ceropegia bulbos* (L) is used to remove urinary bladder stone and inhibition of stone formation or dissolution of preformed stones.

2.1.11 12’ hydroxy–7-multijuginol [68-73]

This phytoconstituent isolated from the plant *Senna multijuga* belongs to the family Fabaceae. The chemical nature is 12’ hydroxy–7-multijuginol is $C_{18}H_{31}NO_3$ with the name of 12-(5-hydroxy-6-methylpyridin-2-yl) dodecane-1,6-diol. Traditionally the leaf and flower decoctions are used in treatment of intestinal worm infestation and stomach disorder. The aqueous and organic extracts of the roots and leaves has significant antimicrobial activity against Gram negative and Gram positive bacteria. The extracts and the isolated bio-active compounds from different genus senna provide an significant antiviral and anti-protozoal activities.

2.1.12 Anatabine [74-77]

Anatabine isolated from *Nicotiana tabacum* plant belongs to the family Solanaceae. Anatabine is naturally occurring member of bipyridines and most active enantiomer of nicotine. Pyridine alkaloids are present in tobacco as free bases and salts. The molecular formula for anatabine is $C_{10}H_{12}N_2$ with the molecular formula 3-[(2S)-1,2,3,6-tetrahydropyridin-2-yl] pyridine. Methanol and aqueous extracts of Nicotina tobacum exhibited dose-dependent anthelmintic activity against adult fleas (*Ctenocephalidesfelis*), blowfly (*Luciliacuprina*) larvae, nematodes (*Caenorhabditis elegans*) and ticks (*Rhipicephalus sanguineus*) larvae and adults (*Xodesricinus nymphs*). In vitro antibacterial activities of various extracts of *N. tobacum* effective towards controlling *Basillus cereus* and *Erwinia carotovora*, *Staphylococus aureus* and *Agrobacterium tumefaciens*.

Anatabine reduces ß-amyloidosis, neuro inflammation and alleviates some behavioral deficits in 7g Es 1/APRS and exploration of anatabine as a possible disease modifying agent for the treatment of AD. It acts as a phytogenic insecticide against pests of industrial crops such as cotton, sugar beet (aphids, spider mites), tobacco (tobacco thrips or aphids) fruit trees, etc, a teratogenic agent, a neurotoxin, an anxiolytic drug, a nicotinic acetylcholine receptor agonist, a biomarker, an immunomodulator, a mitogen, a peripheral nervous system drug, a psychotropic drug, and a xenobiotic. It is a conjugate base of a (S)-nicotinium (1+). It is an enantiomer of a (R)-nicotine.

Nicotine elucidates its potential efficacy in promoting the neuroprotection in Alzheimer’s by significantly up regulating the α4 and α7 nAChRs level. It has been stated as to constrain the formation of Aβ-peptide by binding to α-helical structure and also improve the memory and learning mediated via neuropeptide Y (NPY1) receptors.

2.1.13 Nornicotine and Nicotine [79-88]

Nornicotine is a 3-pyrrolidin-2-ylpyridine with the structure of $C_9H_{12}N_2$ obtained from the plant *Nicotiana tabacum* and belongs to the family Solanaceae. The (S)-nicotine is a 3-(1-methylpyrrolidin-2-yl) pyridine in which the chiral

centre has S-configuration or 3-[(2S)-1-methylpyrrolidin-2-yl] pyridine.

It is used for the treatment of obesity are associated with rebound weight gain, negative side effects and the potential for abuse. Tobacco shows the key effective antifungal mechanism through destroying the structure of the hyphal internal membrane to inhibit the growth of the mycelium..86 .Study on the aqueous extract of *N. tabacum* leaves showed significant decrease in RBC count, PCV, Hb and platelet count with increase in MCV and MCH. Results suggest the consumption of the aqueous extract of N tabacum may lead to some level of anemia despite its "pleasant effects."

2.1.14 Actinidine [89-93]

The actinidine was isolated from the plant *Actinidia polygama* belongs to the family Actinidiaceae. The actinidine having the formula $C_{10}H_{13}N$ with the chemical nature of (7S)-4,7-dimethyl-6,7-dihydro-5H-cyclopenta[c]pyridine. Actinidine is a member of the class of cyclopentapyridines that is 6,7-dihydrocyclopenta[c]pyridine bearing two methyl substituents at positions 4 and 7, used as a gamma source, indicator and neutron source**.**

Actinidia polygama (silver vine) has long been used to relieve pain, gout, rheumatoid arthritis, and inflammation. The extracts show anti-inflammatory and anti-asthmatic effects by reducing the levels of interleukin (IL)-4, interleukin (IL)-5, interleukin (IL)-13, and immunoglobulin E (IgE) in an ovalbumin-induced allergic airway inflammation mouse model. The actinidiamide, extracted from *A. polygama*, reduces allergy and inflammation by inhibiting NO production and ß-hexosaminidase release in lipopolysaccharide (LPS)-stimulated RAW264.7 cells and IgE-sensitized RBL-2H3 cells.

It has been shown to have antioxidant and anti-inflammatory activity in intestinal cells in patients suffering from Crohn's disease and in the mucosa of patients suffering from celiac disease. The extracts of Actinidia species containing protein-dissolving enzymes (actinidin) have been shown to be effective in wound healing, diabetic foot ulcers, burns, and pressure ulcers.

2.1.15 Valerianine [94-97]

It was isolated from *Valerian officinalis* belongs to the family Caprifoliaceae with the molecular formula $C_{11}H_{15}NO$ and the structure is (7S)-4-(methoxymethyl)-7-methyl-6,7-dihydro-5H-cyclopenta[c]pyridine. Traditionally being used as an antispasmodic and antidiarrheal besides its culinary use as spice, relief of cramping, neuralgias and intestinal colic. It showed the Reduce writhing response on Abdominal constriction, Hind limb stretching, antidepressant activity symptoms like Attenuate stress, Improve depression symptoms. Valerianine showed Anti-inflammatory activity, Inhibit inflammation mediators, Potent suppression of acute edema with analgesic activity. Its root extract is one of the most effective herbal sedatives and tranquilizers, where the plant is also used for the treatment of gastrointestinal spasms. It is used in the treatment of brain disorder and also used for the treatment of varied nervous disorders, antispasmodic, anthelmintic, diuretic, diaphoretic, and emmenagogue, and hysteria.

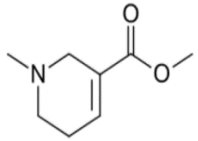
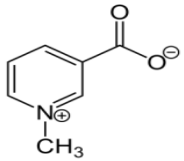
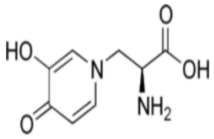
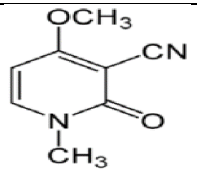
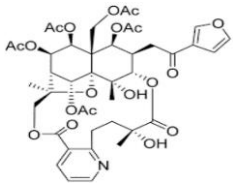
2.1.16 Aconitine [98-99]

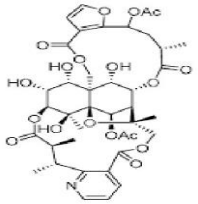
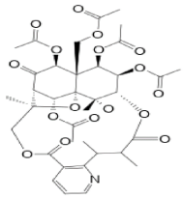
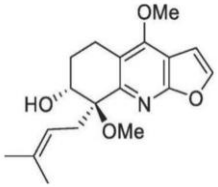
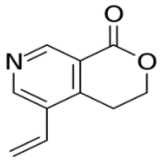
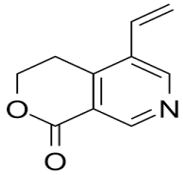
The molecule Aconitine isolated from the plant *Aconitum lycoctonum* belongs to the family Ranunculaceae. Its molecular formula is $C_{34}H_{47}O_{11}N$, with the chemical name of 20-ethyl-3alpha,13,15alpha-trihydroxy-1alpha, 6alpha, 16beta-trimethoxy-4-(methoxymethyl)aconitane-8,14alpha-diol having acetate and benzoate groups at the 8- and 14-positions respectively. . It is functionally related to an aconitane. The first alkaloid identified from Aconitum species was aconitine (AC), which was isolated by Geiger et al. in 1833. Aconitine has shown excellent efficacy in anti-inflammation for instance, in the treatment of rheumatoid arthritis by regulating 1L-b and TNF-α cytokine levels and inhibiting the activation of NF-KB signaling pathway.It has shown antiarrythmogenic activity by delaying the final repolarization phase of action potential in cardiac cells, which initiates premature or triggered excitations. The marked cardiac activity of this alkaloids is mainly due to their effect on the voltage-gated Na+ channels.The anti-epileptic activity of alkaloids is in line with the blockade of the Na+ channels which involved in the genesis of abnormal activity in epilepsy. These alkaloids posses antiproliferative effects of several alkaloids against *Leishmania infantum*, antiprotozoal activity and some diterpene alkaloids exhibits anti parasiteic effect without being toxic to the host cells.

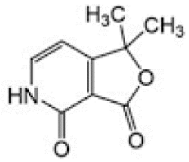
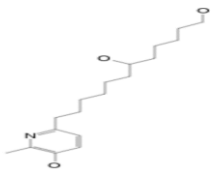
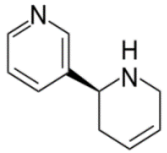
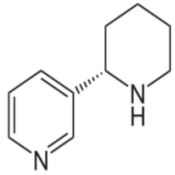
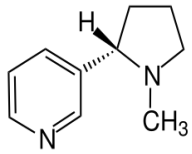
3. DISCUSSION

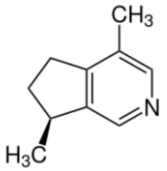
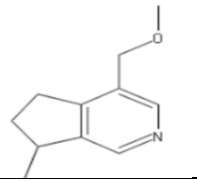
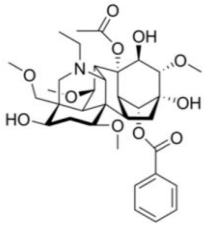
The following molecules were identified from different plant sources for their therapeutic

Table 1. Phytomolecules and their therapeutic applications

S. No.	Structure	Name	Therapeutic value	Reference
1		Arecoline	Antioxidant Activity, Anti-inflammatory, Anti-Melanogenesis,Antimicrobial Activity, Vascular-relaxation Activity, Antidepressant and Central Nervous System Stimulant, Anti-allergic Activity	[10-15]
2		Trigonelline	Gastroesophageal reflux, Antimicrobial Activity, Attenuation of PTZ-Induced Seizures, Antimicrobial Activity, Histaminergic; Spasmolytic, Hepatoprotective and Anticarcinogenic Activity.	[16-23]
3		Mimosine	Anti-Cancer Activity, Hypoglycemic Activity Antidiabetic , Antioxidant Activity Anthelmintic Effect	[24-30]
4		Ricinine	Purgative; Laxative Activity Tumor-Enhancing Activity Gastrointestinal Motility Modulation Anti-HIV.	[31 -35]
5		Wilfortine	immunomodulatory effects. Anti-inflammatory and autoimmune Activity Cancer	[36 -44]

S. No.	Structure	Name	Therapeutic value	Reference
6		Triptonine	anti-HIV activity	[45-48]
7		Evonine	antihypertensive, regulation of blood lipid	[49-55]
8		Haplophyllidine	antimicrobial activities, antifungal activity sedative and anti-analeptic properties	[56-59]
9		Gentianadine	Antidiabetic effect	[60-64]
		Gentianine	CNS stimulant	[63-64]

S. No.	Structure	Name	Therapeutic value	Reference
10		Cerpegin	analgesic, tranquilizing, anti-inflammatory, anti-ulcer, and anti-cancer properties	[65-67]
11		12’ hydroxy-7-multijuginol	Antibacterial and Antifungal Activity, Antiviral Activity	[68-73]
12		Anatabine	Anthelmintic Activity Antimicrobial Activity	[74-77]
13		Nornicotine	Anthelmintic Activity Antimicrobial Activity	[78-88]
14		Nicotine	Anthelmintic Activity Antimicrobial Activity Alzheimer’s	[78-88]

S. No.	Structure	Name	Therapeutic value	Reference
15		Actinidine	gout, rheumatoid arthritis, and inflammation	[89-93]
16		Valerianine	nervous disorders, antispasmodic, anthelmintic, diuretic, diaphoretic. To treat insomnia, migraine, fatigue, and stomach cramps. anxiety, depression, premenstrual syndrome (PMS), menopause symptoms, and headaches	[94-97]
17		Aconitine	Externally for trigeminal neuralgia, lumbago, sciatica, arthritis, gout, and rheumatic fever. Analgesic effect, Effects on the nervous system Anti-epileptiform effects, cardiac activity- anti-arrhythmic, Antimicrobial activity, Cytotoxic activity.	[98-99]

applications were listed out in the Table 1. Some of these Phyto molecules have been formulated and others are yet to be isolated for their new formulations. The compounds which have been formulated are Arecoline, Trigonelline, Mimosine, Triptonine, Gentianadine, Gentianine, Cerpegin, Anatabine, Nicotine, Lobeline, Valerianine, Cytisine, Hyperzine A and Anabasine. The Phyto molecules that have not been formulated are Ricinine, Wilfortrine, Evonine, Haplophylidine, Nornicotine, Actinidine, Aconitine, Coniine and 12'-hydroxy-7'-multijuguinol. Maximum of the compounds are having anti bacterial, antifungal activity also active on nervous system. Summarizing, the tabulated and argued data in the current review paper can attract the attention of the scientific community towards focusing their valuable time and knowledge on these particular alkaloids and prompt researchers in phytochemical, pharmaceutical, and related areas to design and develop more studies on these valuable herbal plants. From a phytochemical point of view, a large number of bioactive natural compounds in pyridine alkaloids, as well as their derivative bioactive compounds, are able to exhibit many pharmacological activities, among which the antimicrobial, Anthelmintic Effect, and act on Central Nervous System are the most important.

Some 2-pyridineformamide thiosemicarbazones were synthesized and evaluated towards pancreatic cancer. They showed cell death by inhibiting MAPK signaling and intrinsic pathway and confirms the anticancer activity. New compounds such as Zinc(II) complexes of 3-hydroxy-2-formylpyridine N(4)-methylthiosemicarbazone and 3-hydroxy-2-formylpyridine N(4)-pyrrolidinyl thiosemicarbazone respectively has been synthesized and investigated for their antiproliferative potential against PC3 (Prostate Cancer), DU145 (Prostate Cancer), A549 (Lung Cancer), A431 (skin cancer) and Hela (Cervical Cancer cell) cell lines. They showed good antiproliferative activity against the cancer cell lines [100,101,102]. These compounds can be added with the natural comounds to synergesise the effect and could be developed as a new semi synthetic molecule, future therapeutics agents to treat cancer.

4. CONCLUSION

In the current review work, the literature data has been systematically reviewed and different aspects relating to the numerous species contain pyridine alkaloids have been discussed. Regarding it further investigations are required to confirm the real therapeutic potential activities of these species and to represent their remarkable phytochemical and biological potency. So, the researchers can focus on research to isolate the compounds in bulk quantity and identify the particular activities of these pyridine alkaloids to go for suitable natural new poly herbal formulations for the benefit of the people.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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