

Review Article

Therapeutic Values of Pyridine Molecules From Natural Sources : A Comprehensive review

Abstract

Reason for the study: Many more commercial pharmacologically interesting medicinal plant species are used around the world and are employed in more communities, and often in more than one country, 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 like bacterial infections and other sexually transmitted diseases. These leads to the therapeutic approach to alternative traditional medicine as an option for concerted search for new chemical entities, So valuable medicinal plants are with the longest track record of use in most or wider locations or distribution.

AIM :The aim of this study is to provide an overview and documentation on pyridine alkaloids and their phytopharmacological activity related some medicinal plants.

Methodology: The method used to collect literature is the Science Direct, PubMed and Google Scholar search engines with keywords. 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 pharmaceutical preparations in the form of patent drugs with appropriate therapeutic documentation.

Key Words: Pyridine alkaloids, herbalmedicines, therapeutic activity

1.INTRODUCTION:

Alkaloids are produced by a large variety of organisms including bacteria, fungi, plants, and animals. They can be purified from crude extracts of these organisms by 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 evoke a bitter taste[1,2,3].

Pyridine alkaloids are a class of alkaloids, nitrogen containing chemical compounds widely found in plants,

which contain a pyridine ring. 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 is one of the important molecule reactants 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_3) or (nicotinic acid), and pyridoxine (vitamin B_6) are extreme recognized compounds with an aromatic π 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) interconversion[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 surveyed Google search, Google scholar, Wiley online library, Elsevier, Springer, Science direct, American Chemical Society, Royal Society of Chemistry and Research Gate, Science Direct, PubMed and Google Scholar 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-2H-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 arecanut (myristic and oleic acids) and procyanidine were showing major antibacterial principles against a primarily cariogenic bacterium, *Streptococcus mutans*, and the major inhibitory activity against Glucosyltransferase 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 affecting spontaneous motor activity.

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 protect the myelin damage in cortex by facilitating oligodendrocyte precursor cells (OPC) differentiation through dephosphorylating the activated protein kinase AMPK α . 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 arabica coffee. The molecule trigonelline is also obtained from the plant *Raphanus sativus* belongs to the family Brassicaceae. The molecule trigonelline is chemically, 1-methylpyridin-1-ium-3-carboxylate. N-methylnicotinate is a 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 reported that it has 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 β -cells of the pancreas and increases insulin sensitivity index as well as insulin content.

2.1.3. Mimosine [24-30]

Mimosine is chemically known as 2-amino-3-(3-hydroxy-4-oxypyridin-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. Immunofluorescence 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/kg bw. 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-oxypyridine-3-carbonitrile obtained from the plant *Croton tiglium* belong to the family Euphorbiaceae.

Roots and aerial parts are useful in the treatment of diabetes. 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 is such as vitamin C 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 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 [16.7.1.01,21.03,24.07,12] 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. wilfordii* show 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. Wilfortine 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 wilforine 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. Application for treating skin disorders such as wounds, eczema, 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 C₁₈H₂₃NO₄. This alkaloid is also present in the stems and leaves of the plant [60]. 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 morganii*, and *Staphylococcus aureus*, antiviral activity against *Fusarium culmorum*, *Rhizoctonia solani*, and tobacco 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 khapamine 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 E₂ (PGE₂) 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- α , 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 psychoses 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-multijuginolis $C_{18}H_{31}NO_3$ 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 *Nicotiana tabacum* exhibited dose-dependent anthelmintic activity against adult fleas (*Ctenocephalides felis*), blowfly (*Lucilia cuprina*) larvae, nematodes (*Caenorhabditis elegans*) and ticks (*Rhipicephalus sanguineus*) larvae and adults (*Xodes ricinus nymphs*). In vitro antibacterial activities of various extracts of *N. tabacum* effective towards controlling *Bacillus cereus* and *Erwinia carotovora*, *Staphylococcus aureus* and *Agrobacterium tumefaciens*.

Anatabine reduces β -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 phyto-genic 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 $\alpha 4$ and $\alpha 7$ nAChRs level. It has been stated as to constrain the formation of A β -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 β -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 familyCaprifoliaceae 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 [98-101]

The molecule Aconitine isolated from the plant *Aconitum lycoctonum* belongs to the familyRanunculaceae. Its molecular formula is $C_{34}H_{47}O_{11}N$, with the chemical name of [(1S,2R,3R,4R,5R,6S,7S,8R,9R,13R,14R,16S,17S,18R)-8-acetyloxy-11-ethyl-5,7,14-trihydroxy-6,16,18-trimethoxy-13-(methoxymethyl)-11-azahexacyclo [7.7.2.12,5.01,10.03,8.013,17] nonadecan-4-yl] benzoate. 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 IL-6 and TNF- α cytokine levels and inhibiting the activation of NF- κ B signaling pathway. It has shown antiarrhythmic 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 possess antiproliferative effects of several alkaloids against *Leishmania infantum*, antiprotozoal activity and some diterpene alkaloids exhibit anti parasitic effect without being toxic to the host cells.

3. DISCUSSION

The following molecules were identified from different plant sources for their therapeutic applications were listed out below 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, Haplophyllidine, 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.

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.

REFERENCES

1. Roberts J E, Speedie M K, Tyler V E Alkaloids pharmacognosy and pharmacobiotechnology. "chapter 9: Philadelphia, Lippiincott, Williams & Wilkins (1996); 143-185.
2. R.H.F. Manke. The Alkaloids. Chemistry and physiology. Volume VIII – Newyork; Academic press, 1965;673.
3. Kaur R., Arora S. Alkaloids – Important therapeutic secondary metabolites of plant origin J.crit. Rev 2015; 2:1-8.
4. Glasby J. Encyclopedia of the Alkaloids, Vol. 1. New York, London: Plenum Press, 1975; 15– 16.
5. Ashok kumar SK, Shah SK, Kazi S, et al. Pyridine: the scaffolds with significant clinical diversity. Rsc Advances. 2022; 12 : 15385 – 15406.
6. Aniszewski T. Alkaloids – secrets of life. Alkaloid chemistry, Biological significance, Applications and Ecological Role. First ed. Amsterdam, Netherlands: Elsevier science ; 2007; 85-92.
7. Lin SX, Curtis MA, Sperry J. Pyridine alkaloids with activity in the central nervous system. Bio org med chem. 2020; 28(24):15820.
8. Pollak N, Dove C, Ziegler M. The power of pyridine nucleotides-small molecules with a multitude of functions. Biochem.J.2007; 402(2): 205-218.
9. Nonaka, GI, Hsu, FL, Nishioka I: Structures of dimeric, trimeric, and tetrameric procyanidins from Areca catechu. J Chemical Soc Chemical Commutations 1981; 781-783.
10. Pathak SP, SS Mathur: The component acids and glycerides of areca-nut (Areca catechu) fat.

Journal of the Science of Food and Agriculture 1954; 5 (10): 461-465.

11. Kuk Kook, JJ Lee, J Cho, Park., JD Choi: The effects of Areca Catechu L Extract on Anti-Inflammation and Anti Melanogenesis. International Journal of Cosmetic Science; 1999; 21(4): 275.
12. Sumitra Hada, Nobuko Kakiuchi, Masao Hattori, Tsuneo Namba.: Identification of antibacterial principles against Streptococcus mutans and inhibitory principles against glucosyltransferase from the seed of Areca catechu L. Phytotherapy Research. 2006; (3)4:140 – 144.
13. Cotter D. Daniel, Mackay Gursh, Chana Clare Beasley, Sabine landau, Ian P. Everall Reduced Neuronal Size and Glial Cell Density in Area 9 of the Dorsolateral Prefrontal Cortex in Subjects with Major Depressive Disorder. Cereb Cortex. 2002;12(4):386–94.
14. Coppola M, Mondola R. Potential action of betel alkaloids on positive and negative symptoms of schizophrenia: A review. Nordic Journal of Psychiatry. 2012; 66: 73–78.
15. Nai-Shin Chu: Effects of Betel Chewing on the Central and Autonomic Nervous Systems. J Bio med Sci. 2001; 8:229–236.
16. P Namboodiripad, K Srividya; Can Coffee Prevent Caries? - An In-Vitro Study; The Internet Journal of Dental Science. 2008 ;7 (2).
17. Histological, Phytochemical and Antimicrobial Evaluation of Coffea Species; ÉvaBrigittaPatay; Ph.D. Dissertation; 2017; University of Pecs, Hungary.
18. Romualdo G.R., Rocha A.B., Vinken M., Cogliati B., Moreno F.S., Chaves M.A.G., Barbisan L.F. Drinking for protection . Epidermiological and experimental evidence on the beneficial effects of coffee or major coffee compounds against gastrointestinal and liver carcinogenesis. Food Res. Int. 2019; 123: 567-589.
19. Xue W.-L., Li X.-S., Zhang J., Liu Y.-H., Wang Z.-L., Zhang R.-J. Effect of Trigonella foenum-graecum (Fenugreek) extract on blood glucose, blood lipid and hemorheological properties in streptozotocin-induced diabetic rats. Asia Pacific Journal of Clinical Nutrition. 2007;16(1):422–426 .
20. Jiyin Zhou, Shiwen Zhiu, Shengya Zeng,. Experimental diabetes treated with trigonelline: effect on β cell and pancreatic oxidative parameters. Fundamental and Clinical Pharmacology. 2011; 27(3): 279-287.
21. Rosa Martha Pérez Gutiérrez and Rosalinda Lule Perez; Raphanus sativus (Radish): Their Chemistry and Biology; TheScientificWorld Journal. 2004; 4: 811–837
22. Surekha Shukla, Sanjukta Chatterji, Deepak Kumar Yadav, Geeta Watal; Antimicrobial Efficacy of Raphanus Sativus Root Juice; International Journal of Pharmacy and Pharmaceutical Sciences,2011, 3 (5).
23. Anwarul Hassan Gilani and M Nabeel Ghayur; Pharmacological basis for the gut stimulatory activity of Raphanus sativus leaves; Journal of Ethnopharmacology, 2004; 95 (2-3): 169-172.
24. Binh Cao Quan Nguyen, Shinkichi Tawata, The Chemistry and Biological Activities of Mimosine: A Review. Phytotherapy research .2016; 23(08): 1230-1242.
25. Chung L.C, Tsui KH, Feng TH, Lee SL, Chang PL and Juang HH. L-mimosine blocks cell proliferation

via up regulation of β - cell translocation gene 2 and N-Myc downstream regulated gene 1 in prostate carcinoma cells. Am J physiol cell physiol. 2012; 302: 676- 685.

26. Hsing-Tan Li, Syun - Wun Ruan, Jin - Cherng Huang, Hsin-Liang Chen and Chung-Yi Chen. Antioxidant and tyrosinase inhibitor from *Leucaena leucocephala* ; African Journal of Biotechnology . 2012 ;11 (77): 14182-14185.

27. .JU H, Hao J, Zhao S, Dixon I M. Antiprediferative and Antifibrotic effects of mimosine on adult cardiac fibroblasts. Biochim Biophys Acta. 1998 ; 1448(1): 51-60.

28.Si Thu Hein, Nadi Nwe Oo, Hnin Yi Soe, Khin Thida Khaing ,Effect of *Leucaena Leucocephala* Leaves on Microscopic Structure of Thyroid Gland of Sheep in Myanmar. International Journal of Novel Research in Life Sciences.2016; 3(1): 12-19 .

29.Darmono Syamsudin, Simanjuntak and Partomuan Simanjuntak; The Effects of *Leucaena leucocephala* (Imk) De Wit Seeds on Blood Sugar Levels: An Experimental Study; International Journal of Science and Research. 2006; 2(1): .49-52 .

30. Syamsudin, Ros Sumarny, Partomuan Simanjuntak , Antidiabetic Activity of Active Fractions of *Leucaena Leucocephala* (Imk) Dewit Seeds in Experiment Model;; European Journal of Scientific Research. 2010; .43 (3): 384-391.

31.Sandhya kumary K. Bobby RG and Indira M. Antifertility effects of *Ricinus Communis* (Linn) on rats. Phytother. Res., 2003; 17(5): 508-511.

32.Xin Wang. Effects of essential oil from *Croton tiglium* L. on intestinal transit in mice.

Journal of Ethnopharmacology, 2008; 117, (1): 102-107.

33.El-Mekkawy, S; Meselhy, M R; Nakamura, N; Hattori, M; Kawahata, T; Otake, T; Anti-HIV-1 phorbol esters from the seeds of *Croton tiglium*. Phytochemistry, 2000 53, 457-464.

34. B L Van Duuren, L Orris., The Tumor-enhancing Principles of *Croton Tiglium* L.; Cancer Research . 1965; 11 (1): 1871–1875.

35. B L Van Duuren. L Laangseth, A Sivak, L Orris., The tumor-enhancing principles of *Croton tiglium* L. II. A comparative study. 1966; 26(8): 1729-1733

36.Duan H, Takaishi Y, Momota H, Ohmoto Y, Taki T, Jia Y, Li D. Immunosuppressive sesquiterpene alkaloids from *Tripterygium wilfordii*. J Nat Prod. 2001b; 64:582–587.

37.Horiuch, M; Murakami, C; Fukamiya, N; Yu, D; Chen, TH; Bastow, KF; Zhang, DC; Takaishi, Y; Imakura, Y; Lee, KH . "Tripterygines A-C, sesquiterpene pyridine alkaloids from *Tripterygium wilfordii*, and structure anti-HIV activity relationships of *Tripterygium* alkaloids". J Nat Prod. (2006); 69 (9): 1271–4.

38. Beroza M and Botteger M. The insecticidal value of *Tripterygium Wilfordii*. J. Econ. Entomol. (1954). 47, 188-189.

39. M. Magrupova, I. Kamilov, N. Polievtsev; Synergy of the alkaloid haplophyllidin with sleep-inducing and narcotic drugs; Farmakol Alkaloidov, AkadNaukUz USSR, Inst KhimRastVeshchestv, (1962), 1. 160-168

40. Deng F, Cao J, Xia Z, Lin S, Wang X. Studies on the sesquiterpene alkaloids of *Tripterygium wilfordii* Hook. f. Zhiwu Xuebao. 1987a; 29:523–526.
41. Xue Tong, Yanheng Qiao, Yuanjian Yang, Haizhao Liu, Zhiyong Cao, Bo Yang, Lijuan Wei, Hongtao Yang, Applications and Mechanisms of *Tripterygium Wilfordii* Hook. F. and its Preparations in Kidney Diseases; Front Pharmacol.2022, 13. 846746.
42. Anita M.Brinker, junma, Peter E.Lipsky and Llya Raskin, Medicinal chemistry and pharmacology of genus *Tripterygium* (Celastraceae) . Phytochemistry; 200768(6):11-29
43. Yu H, Qin W, Wu H. Effect of wilfordine on systemic lupus erythematosus patients' B cell immune function in vitro. Zhongguo Mianyixue Zazhi. 1999; 15:27–28.
44. Zheng, YL; Xu, Y; Lin, JF. "Immunosuppressive effects of wilfortrine and euonine". Acta Pharmaceutical .1989, 24 (8): 568–72.
45. Horiuchi, M; Murakami, C; Fukamiya, N; Yu, D; Chen, TH; Bastow, KF; Zhang, DC; Takaishi, Y; Imakura, Y; Lee, KH . "Tripfordines A-C, sesquiterpene pyridine alkaloids from *Tripterygium wilfordii*, and structure anti-HIV activity relationships of *Tripterygium* alkaloids". J Nat Prod. (2006). 69 (9): 1271–4.
46. González AG, Tincusi BM, Bazzocchi IL, Tozuda H, Nishino H, Konoshima T, Jiménez IA, Ravelo AG. Anti-tumor promoting effects of sesquiterpenes alkaloid from *Maytenus cuzcoina* (Celastraceae) Bioorg Med Chem. 2000a; 8:1773–1778.
47. Duan H, Takaishi Y, Momota H, Ohmoto Y, Taki T, Jia Y, Li D. Immunosuppressive sesquiterpene alkaloids from *Tripterygium wilfordii*. J Nat Prod. 2001b; 64:582–587.
48. Hsing-Tan Li, Syun - WunRuan, Jin - Chheng Huang, Hsin-Liang Chen and Chung-Yi Chen. Antioxidant and tyrosinase inhibitor from *Leucaenaleuco cephal* ; African Journal of Biotechnology. 2012 ; 11 (77), 14182-14185.
49. Tabassum S., Mahmood S., Hanif J., Hina M., Uzair B. An overview of medicinal importance of *Swertia chirayita*. Int J Appl Sci Technol. 2012;2(1):298–304.
50. Vaidya H., Goyal R.K., Cheema S.K. Anti-diabetic activity of *Swertia marin* is due to an active metabolite, gentianine, that upregulates PPAR-gamma gene expression in 3T3-L1 cells. Phytother Res. 2012;27(4):624–627
51. Ishiwata H., Shizuri Y., Yamada K. Three sesquiterpene alkaloids from *Euonymus alatus* forma *Striatus*. *Phytochemistry*. 1983;22(12):2839–2841.
52. Yan Z.-H., Han Z.-Z., Hu X.-Q., Two new sesquiterpenes from *Euonymus alatus*. Helvetica Chimica Acta. 2013; 96(1):85–92.
53. The preliminary study on the pharmacological effects *Euonymus alatus*. Journal of Traditional Chinese Medicine. 1977; 4:28–30.
54. Huang D.B. Experimental research on inhibition of immediate and delayed type hypersensitivity by the 70% ethanolic extract from *Euonymus alatus*. Chinese Pharmacological Bulletin. 2003;19(6):686–688.
55. Lang S. M., Zhu D. N., Yu B. Y., Zhao J. L., Wang Q. J., Yang Y. Q. Hypoglycemic effects of extracts and constituents from *Euonymus alatus*. Journal of China Pharmaceutical University. 2003;34(2):128–131.

56. M. Magrupova, I. Kamilov, N. Polievtsev; Synergy of the alkaloid haplophyllidin with sleep-inducing and narcotic drugs; Farmakol Alkaloidov, AkadNaukUz USSR, Inst KhimRastVeshchestv, (1962), 1. 160-168.
57. M. Magrapova, I. Kamilov, N. Polievtsev, Antagonism between Haplophyllidin and Analeptics Farmakol Alkaloidov, Akad Nauk Uz SSR, Inst khim Rast Veshch, 1 (1962), 169
58. L. Avazmukhamedov, T. Shakirov, V. Tel'nov, The technology of the isolation of the alkaloids dubinidine and haplophyllidine, Chem Nat Compd., 1966) ;2 (8)
59. Mohammadhosseini, M.; Nekoei, M.; Mashayekhi, H.A.; Aboli, J. Chemical composition of the essential oil from flowers, leaves, and stems of *Haplophyllum perforatum* by using head space solid phase micro extraction. J Essent Oil Bear Plants 2012, 15, 506–515.
60. Tabassum S., Mahmood S., Hanif J., Hina M., Uzair B. An overview of medicinal importance of *Swertia chirayita*. Int J Appl Sci Technol. 2012;2(1):298–304.
61. Vaidya H., Goyal R.K., Cheema S.K. Anti-diabetic activity of swertiamarin is due to an active metabolite, gentianine, that up regulates PPAR-gamma gene expression in 3T3-L1 cells. Phytother Res. 2012;27(4):624–627.
62. Liu X.-w., Cao M., Liu S.-m. Study on antipyretic effect and its mechanism of gentianine. Chin J ExpTradit Med Formulae. 2011; 24:038.
63. Liu X.-w., Liu S.-m., Liu C.-f. Sedative-hypnotic effect of gentianine and its influence on the content of 5-HT, GABA in mouse brain. Lishizhen Med Materia Medica Res. 2012; 2:063.
64. Mihailovic V., Katanic J., Misic D. Hepatoprotective effects of secoiridoid-rich extracts from *Gentiana cruciata* L. against carbon tetrachloride induced liver damage in rats. Food Funct. 2014;5(8):1795–1803
65. Adibatti, P., Thirugnanasambantham, C., Kulothungan, S., Viswanathan, A pyridine alkaloid from *Ceropegia juncea*. Phytochemistry, (1991) ; 30 (7), 2449-2450.
66. Gupta and Kohli., Phytochemical screening of *Sarcostemma acidum* W. &Ar. IJPLS, (2010). 1(3) 170-173.
67. Fargo K. Alzheimer's Association Report: Alzheimers disease facts and figures. Alzheimer's Dement; 2014. 10. (2); 47-92.
68. Wellington Francisco, Marcos Pivatto, Amanda Danuello, Luis O Regasini; Pyridine Alkaloids from *Senna multijuga* As Acetylcholin esterase Inhibitors; J Nat Produc., 2012, 75(3): 408-413 .
69. S. Thabit, H. Handoussa, M. Roxo, N. S. el Sayed, B. Cestaride Azevedo, and M. Wink, "Evaluation of antioxidant and neuroprotective activities of *Cassia fistula* (L.) using the *Cae-norhabditis elegans* model," Peer J. 2018, 13(6).
70. M. N. Abubacker, R. Ramanathan, and T. S. Kumar, "In vitro antifungal activity of *Cassia alata* Linn. Flower extract," Nat-ural Product Radiance, 2008, vol. 7, 1, 6–9.
71. A.T. de Castro, A. P. Castro, M. S. Silva; "In vitro evaluation of the schistosomicidal effect of the

extracts, fractions and major 3-hydroxy-2,6-dialkyl-substituted piperidine alkaloids from the flowers of *Senna spectabilis* (Fabaceae),” *Bioorganic & Medicinal Chemistry Letters*, 2016, 26, 17, 4197–4204.

72.M. Villaseñor, A. P. Canlas, M. P. Pascua, M. N. Sabando, and L. A. Soliven, “Bioactivity studies on *Cassia alata* Linn. Leaf extracts,” *Phytotherapy Research*, 2002, 16, S1, 93–96.

73.S. Thabit, H. Handoussa, M. Roxo, N. S. El Sayed, B. Cestaride Azevedo, and M. Wink, “Evaluation of antioxidant and neuroprotective activities of *Cassia fistula* (L.) using the *Caenorhabditis elegans* model,” *Peer journal* 2018, vol. 6.

74.Lee YC, Kim SH, Seo YB, Roh SS, Lee JC. Inhibitory effects of *Actinidia polygama* extract and cyclosporine A on OVA-induced eosinophilia and bronchial hyperresponsiveness in a murine model of asthma. *Int Immuno Pharmacol*. 2006;6(4):703-713.

75.Sashida, Y., Ogawa, K., Mori, N., & Yamanouchi, T. Triterpenoids from the fruit galls of *Actinidia polygama*. *Phytochemistry*, 1992,31(8), 2801–2804.

76. McGuffey JE, Wei B, Bernert JT, Morrow JC, Xia B, Wang L, Blount BC, Validation of a LC-MS/MS method for qualifying Urinary Nicotine, Six Nicotine metabolites and the minor tobacco alkaloids – anatabine and anabasine in smokers Urine. *PLOS one*. 2014; 9(7):1-13.

77.Evaluation of the Antibacterial Potential of Some Plants Against Human Pathogenic Bacteria; S Satish, M P Raghavendra, and K a Raveesha; *Advances in Biological Research* 2008, 2 (3-4): 44-48,.

78. Samane Sattar, Gholamreza Asghari, Ali Akbar Ehsanpour; *Biotechnological Reduction of Tobacco (Nicotiana Tabacum L.) Toxicity; Iranian Journal of Toxicology*, 2012, 6(18). 699-703.

79. Choudhury B, Saytode P, Shah V. Neurodegenerative Disorders: Past, Present and Future. *Int J Appl Pharm Biotechnol*. 2014;5(2):14–28.

80. Akaike A, Takada-Takatori Y, Kume T, Izumi Y. Mechanisms of neuroprotective effects of nicotine and acetylcholinesterase inhibitors: Role of $\alpha 4$ and $\alpha 7$ receptors in neuroprotection. In: *Journal of Molecular Neuroscience*; 2010.40(1-2)211–6.

81. J.P. Dzoyem and J.N. Eloff , Anti-inflammatory, anticholinesterase, and antioxidant activity of leaf extracts of twelve plants used traditionally to alleviate pain and inflammation in South Africa;; *Journal of Ethnopharmacology*, 2015; 3(160): 194-201.

82.Zafar Iqbal; In vitro and In vivo anthelmintic activity of *Nicotiana tabacum* L. leaves against gastrointestinal nematodes of sheep; *Phytotherapy Research*. 2005,20,1,46 - 48

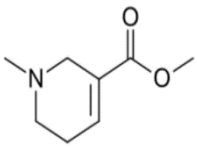
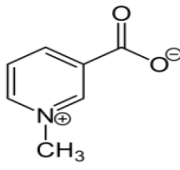
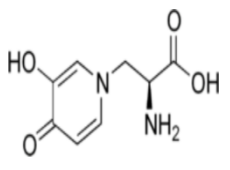
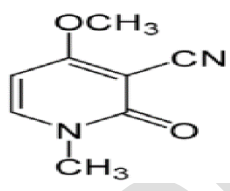
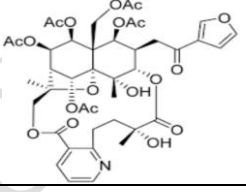
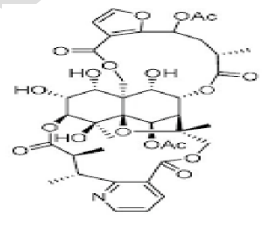
83.Abrar M Tamboli, Rukhsana A Rub, Pinaki Ghosh, SL Bodhankar , Antiepileptic activity of lobeline isolated from the leaf of *Lobelia nicotifolia* and its effect on brain GABA level in mice; *Asian Pacific Journal of Tropical Biomedicine*, 2012; 2(7): 537–542.

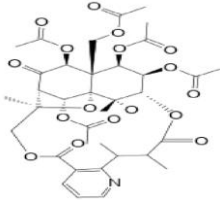
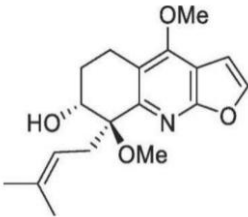
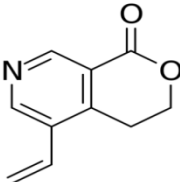
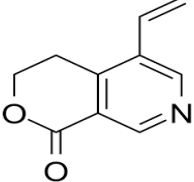
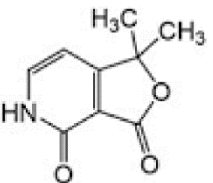
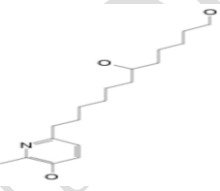
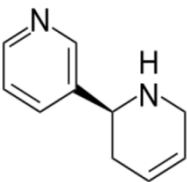
84.S. Kunchari Kalaimathi, G. Muthu and K. Manjula, Antibacterial Activity of *Lobelia Nicotianifolia* Against Various Bacterial Strains;; *International Journal of Life Science & Pharma Research*, July 2015; 5(3) ; 19-25.

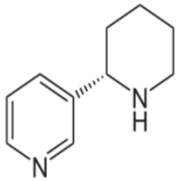
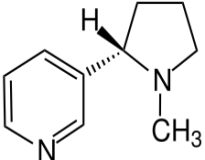
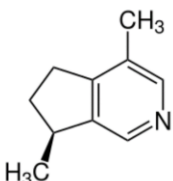
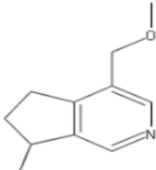
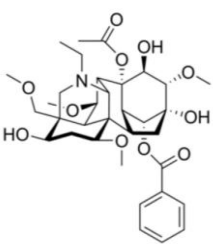
85.Roth E & S; Imran Khan Systematic Review on Phytochemical and Pharmacological Profile of *Lobelia Nicotianaefolia*; *Pharmacology Online* ;2011; 3:7-22

86. Adeniyi Philip, Adeyemi Olu'seun, Ghazal Kamal Olaide, Jimoh Olusegun Rabi, David Joan Adejoke, Adefolaju Gbenga A., and Caxton-Martins Ezekiel Ademola. The Cytoarchitectural alterations in the neocortex of Wistar rats: Effects of aqueous tobacco (*Nicotiana tabacum*) leaves extract exposure. 2010; 9(44), 7539-7543.
87. Madaan R, Kumar S. screening of alkaloidal fraction of *conium maculatum* L., aerial parts of analgesic and anti-inflammatory activity. Indian journal of pharmaceutical sciences. 2012; 74(5): 457-460.
88. Mukusheva GK, Zhasymbekova AR, ZhumagalievaZZ, Seidakhmetova RB, Nurkenov OA, AkishinaEa, Petkevich SK, Bikusar EA, Potkin VI. Synthesis and Biological activity of N-acyl Anobasine and cytosine derivatives with Adamantane,, Pyridine and 1,2-Azole fragments, molecules. 2022 Oct 31; 27(21): 73-87.
89. Lee YC, Kim SH, Seo YB, Roh SS, Lee JC. Inhibitory effects of *Actinidia polygama* extract and cyclosporine A on OVA-induced eosinophilia and bronchial hyperresponsiveness in a murine model of asthma. Int Immunopharmacol. 2006;6(4):703-713.
90. Ciacci C, Russo I, Bucci C; The kiwi fruit peptide kissper displays anti-inflammatory and antioxidant effects in in-vitro and ex-vivo human intestinal models. Clin Exp Immunol. 2014;175(3):476-484.
91. Sashida, Y., Ogawa, K., Mori, N., & Yamanouchi, T. Triterpenoids from the fruit galls of *Actinidia polygama*. Phytochemistry, 1992,31(8), 2801–2804.
92. Yuan CS, Mehendale S, Xiao Y, Aung HH, Xie JT, Ang-Lee MK. "The gamma-aminobutyric acidergic effects of valerian and valerenic acid on rat brainstem neuronal activity". Anesth Analg. 2004, 98 (2): 353–8
93. Wills, R.B.H. & Shohet, D. "Changes in valerenic acids content of valerian root (*Valeriana officinalis* L. s.l.) during long-term storage". Food Chemistry. 2009,115 (1): 250–253.
94. Marder M, Viola H, Wasowski C, Fernández S, Medina JH, Paladini AC. "6-methylapigenin and hesperidin: new valeriana flavonoids with activity on the CNS". Pharmacol Biochem Behav. 2003,75 (3): 537–45.
95. Fernández S, Wasowski C, Paladini AC, Marder M. "Sedative and sleep-enhancing properties of linarin, a flavonoid-isolated from *Valeriana officinalis*". Pharmacol Biochem Behav. 2004,77 (2): 399–404.
96. Singh, MK, Vinod M, Lyer SK, Khare G, Sharwan G, Larokar Y. Aconitum: a pharmacological update. Int. J. Res. Pharmaceut. Sci. 2002, 3:242-246.
97. Ameri A. The effects of Aconitum alkaloids on the central nervous system. Prog Neurobiol 1998; 56: 211– 235.
98. Friese J; Aconitum sp. alkaloids: the modulation of voltage-dependent Na⁺ channels, toxicity and antinociceptive properties. Eur J Pharmacol 1997; 337: 165– 174.
99. Gonzalez P; In vitro activity of C20-diterpenoid alkaloid derivatives in promastigotes and intracellular amastigotes of *Leishmania infantum*. Int J Antimicrob Agents 2005; 25: 136– 141.

Table .1. Phytomolecules and their therapeutic applications

S.No	Structure	Name	Therapeutic value	Referen ce
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		Ricine	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]
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]
10		Cerpegin	analgesic, tranquilizing, anti-inflammatory, anti-ulcer, and anti-cancer properties	[65-67]
11		12' hydroxy- multijuganol	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]
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 of the nervous system Anti-epileptiform effects, cardiac activity- anti-arrhythmic, Antimicrobial activity, Cytotoxic activity.	[98-101]