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A Comprehensive Review on Pharmacological Activities of Alkaloids: Evidence from Preclinical Studies

Review Article

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Abstract

Plant alkaloids are a broad range of chemical entities that make up one of the biggest classes of natural goods. Even though man has used alkaloids-containing plants for at least 3000 years as medicines, teas, and potions, the chemicals implicated for their action were not determined till the 19th century. Alkaloids' essential nature causes them to form salts when mixed with alkaline solutions or organic acids. Except in extraordinary circumstances, alkaloids salts are generally soluble in water and dilute alcohols, but not in organic solvents. They are classified using a variety of markers, such as natural origins or chemical composition. The distribution of alkaloids according to their primary structure, the major C-N skeleton, is the most correct and frequent categorization. Alkaloids, which are compounds isolated from natural sources, exhibit promising pharmacological activity, including pharmacological activity for the curing of neurogenerative illnesses like vascular dementia, which currently treated with a variety of medications. As a result, the article focuses on the technological prospecting of alkaloids with important properties for curing the illness, such as antioxidant, anxiolytic, anti-inflammatory, antiviral, antiemetic, antifungal, antihyperlipedemic, antihypoglycemic, muscle relaxant, antiulcer, antitussive, expectorant, anticancer, antimicrobial, antimalarial, immunosuppressant, antidepressant.

Key Words: Alkaloids, Pharmacology, Antioxidant, Anticancer, Antimalarial, Expectorant.

Introduction

Chemical compounds having at least one nitrogen atom in a heterocyclic ring are known as alkaloids. They're difficult to recognize since they don't reflect a consistent collection of molecules from any perspective, including chemical, biological, and physiological. Even though they're all nitrogen-based materials, alkaloids do not have a single definition (1). Lower plants have fewer alkaloids. Gliotoxins are lysergic acid analogues and sulfur-containing alkaloids found in fungus, for example. Lycopodium, ephedra, and Taxus are all alkaloids found in pteridophytes and gymnosperms that have therapeutic properties. The distribution of alkaloids in angiosperms is unequal. The alkaloids-rich orders that have been reported are as follows, Rosales Gentiles (Apocynaceae, Loganiaceae, Rubiaceae), and Tubiflorae (Boraginaceae, Convolvulaceae, Solanaceae). However, there have been no reports of alkaloids in the dicot orders Salicales, Fagales, Cucurbitales, or Oleales (2).

Classification of alkaloids

Alkaloids are classified into various classes based on their basic chemical structure. oxindoles, quinolines, quinazolines, phenylethylamines, piperidines, purines, pyrrolidines, ephedras, ergots, imidazoles, indoles, bisindoles, indolizidines. One of the most fascinating and significant aspects of bioorganic chemistry is the chemistry of alkaloids. The term "alkaloid" was first used to describe N-containing molecules with a markedly basic character that were found in plants. This phrase is now applied to a considerably broader range of situations. Plants, micro-and marine creatures, and fungus create a diverse range of natural N-containing chemical compounds known as alkaloids Unlike other natural chemicals, structural frameworks are essentially endless, and its molecules contain an N atom, making them very changeable (3). They are classified using a variety of markers, such as their biological origin or synthetic composition. The most important, common classification of alkaloids is based on their basic arrangement, the major C-N skeleton. Alkaloids are categorised as indole, quinazoline, diterpenoid, pyrrolidine, pyridine, quinoline, isoquinoline, steroidal, and other alkaloids, according to contemporary research. Each of these groupings is subdivided based on the structural characteristics of its individuals (4).

Pharmacological Action of Alkaloids

Herbivore activity, vertebrate toxicity, cytotoxicity activity, alkaloids' molecular targets, Antibacterial, antifungal, and antiviral capabilities, as well as their potential role as phytoalexins, have all been taken into consideration. Most of the alkaloids are poisonous to animals and can kill them if they consumed. Insecticides such as nicotine and anabasine are alkaloids. The neurological system is affected by several alkaloids in one of two ways (4). In Chinese traditional medicine, plants containing protoberberine alkaloids are claimed to be utilised as anesthetics, sedatives,

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disinfectants and stomachics. Antiseptics, sedatives, stomachics, uterine muscle depressants, as well as antiseptics, sedatives, stomachics, and uterine muscle depressants, are all used in Indian and Islamic traditional medicine for bleeding issues and eye diseases... Both quaternary alkaloids and their tetrahydro derivatives have a broad variety of biological and medical applications; palmatine, jatrorrhizine, and tetrahydropalmatine, for example, have been proven to have antimalarial activity in vitro. Tetrahydropalmatine is a Chinese analgesic that is said to have bradycardic, hypotensive, and sedative characteristics.

Table 1. Classification of alkaloids (5)

S No.	Chemical Group of Alkaloids	Parent Compounds	Examples
1	Pyrrolidine alkaloids	Pyrrolidine	Cuscohygrine, Hygrine
2	Tropane alkaloids	Tropane	Scopolamine/hyoscine, Atropine, Cocaine, Hyoscyamine
3	Pyrrolizidine alkaloids	Pyrrolizidine	Acetyl Iycopasamine, acetyl intermedine Meteloidine, Retronecine
4	Piperidine alkaloids	Piperidine	Sedamine, Piperidine, Piperine, Piperidine, Lobeline, Lobelanine, Anaferine.
5	Quinolizidine alkaloids	Quinolizidine	Cystisine , Lupanine , Spartenine
6	Indolizidine alkaloids	Indolizidine	Swansonine, Castanospermine
7	Phenylethyl aminoalkaloids	Phenylethyl amine	Dopamine, Adrenaline, anhalamine, tyramine.
8	Simple tetrahydroisoquinoline alkaloids	Benzyltetra-hydro-iso-quinoline	Tetrandrine, Thebaine, Tubocurarine, Codeine, Morphine, Norcoclaurine, Papaverine, Tetrandrine, Thebaine, Tubocurarine
9	Phenethylisoquinoline alkaloids	Amaryllidaceae alkaloids	Haemanthamine, Lycorenine, Maritidine, Vittatine, Oxomaritidine, Autumnaline, Crinine , Floramultine, Galanthine.
10	Indole alkaloids	Indole Simple indole alkaloids	Serotonin, Tryptamine, Zolmitriptan , Arundacine , Arundamine, Psilocin
11	Quinoline alkaloids	Quinoline	Chloroquine, Cinchonidine, Quinine, Quinidine.
12	Pyrroloindole Alkaloids	Indole	Corynantheidine, Dihydrocoryn A-yohimbine, Chimonantheine, Antoine Corynanthine. Chimonantheine, Corynantheine.
13	Imidazole alkaloids	Imidazole	Pilocarpine, Pilosine, Histamine.
14	Manzamine alkaloids	Xestomanz- amine	Xestomanz- amine A, Xestomanz- amine B.
15	Marine alkaloids	þ-carboline	Saxitoxin, Tetrodotoxin.
16	Quinazoline alkaloids	Quinazoline	Peganine.
17	Quinoline alkaloids	Quinoline	Acetylfolidine, Acutine Bucharine, Dictamnine Dubunidine, ç-figurine, Flindersine Foliosidine, Glycerine. Haplophyllidine, Haplopine Helietidine, Kokusaginine Maculosine, Perfamine Perforin, Polifidine Skimmianine.
18	Acridone alkaloids	Acridine	Acronycine, Rutacridone
19	Pyridine alkaloids	Pyridine/ Pyrrolidine	Anabasine, Cassinine, Celapanin Evoline, Econoline, Evorine Maymyrsine, Nicotine, Regelidine Wilforine,
20	Terpenoid indole alkaloids	Indole	Yohimbine.
21	Sesquiterpene alkaloids	Sesquiterpene	Cassinine, Celapanin, Evonine Evonoline ,Evorine ,Maymyrsine, Regelidine Wilforine.
22	Ephedra alkaloids	Phenyl C	Cathine Cathinone Ephedrine Norephedrine.
23	Aromatic	Phenyl	Capsaicin
24	Purine alkaloids	Purine	Caffeine, Theobromine, Theophylline.

Muscle relaxant activity

It is generally known that alkaloids have a muscle-relaxing effect. d-tubocurarine has an anti-paralytic effect because it inhibits the areas of the acetylcholine receptor that help muscles relax at neuromuscular junctions. When compared to KCl, is thebaine, isocorydine, magnoflorine, and Corstubenne, all isolated from *Mahonia aquifolium*, were shown to cause moderate contractions in isolated aortas (6).

Anticancer activity

Red algae contain martefragin A, an indole alkaloid. NADPH-dependent Catharanthus roseus (Apocynaceae) contains the alkaloids vinblastine and vincristine, which are extensively used in leukaemia and Hodgkin illness. These alkaloids have a chemopreventive impact by depolymerizing the protein microtubules that form the mitotic spindle during cell division. It lowers the risk of cancer by preventing tumour cell growth and differentiation. The divalent calcium cation (Ca2+) is proven to regulate energy generation and cellular metabolism by functioning as a primary molecule during cell signal transduction. Benzyisoquinoline, have been recognized to reduce lipid peroxidation mediated by Fe^{2+}/ cysteine in rat liver microsomal fractions. There are phenolic hydroxyls or other reactive classes that are found. Martensia fragilis inhibits lipid peroxidation in rat liver microsomes (7). Majus helidonium Linn's alkaloids have phenanthridine-like properties. Imidazole compounds have antibacterial action in addition to their medicinal potential. It has similarly shown that drugs with an imidazole moiety suppressed p38 MAP kinase and 5-Lipoxygenase. In addition to their cytotoxic potential, cycleanine and cocsoline, two bisbenzylisoquinoline alkaloids found in Albertisia villosa, exhibit antibacterial, antifungal, and antiplasmodial properties. Delphinium Spp was used to isolate diterpenoid

alkaloids. Spodoptera littoralis and Leptinotarsa decemlineata, two insect species, were shown to exhibit antifungal and anti feed properties. Indole alkaloids have been linked to a unique oxathiazepine and Eudistomin, the ring containing alkaloids derived by Eudistoma olivaceum that has been shown to be effective against RNA viruses like CoxsachieA-21 and equine rhinovirus, as well as DNA viruses like HSV-1, HSV-2, and Vaccinia virus (8).

Antimicrobial and Amoebicidal Activity

Clinical drug-resistant yeast isolates were used to test the antifungal activity of phenanthridine natural alkaloids produced from Chelidonium majus Linn. (9). According to De Luca (2006), imidazole compounds offer a lot of therapeutic potentials as well as antibacterial activity. Drugs having an imidazole moiety have also been demonstrated to inhibit p38 MAP kinase and 5 lipoxygenases (10). According to Lohombo-Ekomba and colleagues, the bisbenzylisoquinoline alkaloids cycle nine and cocsoline discovered in Albertisia villosa have antiplasmodial, antifungal and antibacterial action, as well as cytotoxic potential (11).

Antidiabetic activity

For ages, the roots of Aerva lanata Linn. (Amaranthaceae) (AL) have been utilised in Ayurvedic medicine as an antihyperglycemic. Different solvents were used to fractionate the methanol extract of the roots. Alkaloids were found in the partially purified alkaloid basified toluene fraction (PPABTF). At a dose of 20 mg/kg, PPABTF drastically decreased type II non-insulin-dependent diabetic Mellitus (NIDDM) produced by streptozotocin-nicotinamide in rats. The activity might be explained by the presence of alkaloids such as canthin-6-one derivatives. (12).

Anti-diuretic activity

In Mexican folk medicine, spring water is used to heal kidney ailments. In this study, the diuretic effect of furosemide (4 mg/kg) was compared to an aqueous extract (200 mg/kg) and alkaloids from this plant at various concentrations (10, 40, and 100 mg/kg). Adult rats were investigated to see how extracts, alkaloids fraction, furosemide, and vehicles affected sodium, potassium. In comparison to the control group, the extract, the alkali fraction, and furosemide substantially increased urine salt, potassium, and water excretion. The dosage of the alkaloids fraction was dose-dependent, with the highest dose having the greatest impact. Potassium excretion increased, although not as much as furosemide-induced potassium excretion. These findings imply that S. lepidophylla's aqueous extract and alkaloid-rich fraction cause diuresis (13).

Antihyperlipidemic activity

The antihyperlipidemic effect of five main alkaloids in Rhizoma Coptidis was investigated using high-fat and high-cholesterol-induced hyperlipidemic hamsters. Epiberberine, palmatine, Coptisine, berberine, jatrorhizine and total Rhizoma Coptidis alkaloids were given to hyperlipidemic hamsters every day for 140 days at a dose of 46.7 mg/kg. Following alkaloid therapy, serum total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and total bile acids were measured. In hamsters, all treatment drugs lowered blood total cholesterol while increasing high-density lipoprotein cholesterol, according to the findings. In hyperlipidemic hamsters, jatrorrhizine, Berberine, and total Rhizoma Coptidis alkaloids reduced triglyceride levels, whereas coptisine, jatrorrhizine, palmatine, and total Rhizoma Coptidis alkaloids delayed the rise in Serum cholesterol. Total Rhizoma Coptidis alkaloids like jatrorrhizine, Berberine, palmatine and coptisine, and orlistat were all shown to significantly enhance bile acid excretion in the faeces. The total alkaloids in Rhizoma Coptidis have a far greater lipid-lowering effect than the pure alkaloids in Rhizoma Coptidis. Rhizome colpitis alkaloids reduce 3-hydroxy-3-methyl glutaryl coenzyme mRNA expression, which lowers cholesterol synthesis. According to quantitative reverse transcription-polymerase chain reaction tests, reductase improves lipid clearance by upregulating the low-density lipoprotein receptor, cholesterol 7-hydroxylase, and uncoupling protein-2 expression. The importance of Rhizoma Coptidis alkaloids in the treatment of hyperlipidemia is demonstrated by these studies. As a result, future therapy attempts must consider them (14).

Anti hypoglycemic activity

Tinospora cordifolia (TC) stems are commonly used in traditional Indian folk medicine to treat diabetes. The insulin-mimicking and insulin-releasing effects of isoquinoline alkaloid rich fraction (AFTC) produced from TC stem and three alkaloids, palmatine, jatrorrhizine, and magnoflorine, were investigated. Rat hepatocytes were studied to see how they affected hepatic gluconeogenesis. The RINm5F rat pancreatic-cell line was used to study insulin release in vitro. In fasting and glucose-challenged normal rats, AFTC and isolated alkaloids have also been studied for their effects on glycemia. Specifically, on rat hepatocytes, AFTC suppresses gluconeogenesis in the same manner as insulin does, and in RINm5F cells, it stimulates insulin secretion in the same way that tolbutamide does. In a 30-minute in vitro study, AFTC, jatrorrhizine, magnoflorine and palmatine boosted insulin production from the RINm5F cell line. Oral treatment of AFTC (50, 100, and 200 mg/kg), jatrorrhizine, palmatine and magnoflorine (10, 20, and 40 mg/kg), as well as palmatine, jatrorrhizine, and magnoflorine (10, 20, and 40 mg/kg) to normal rats reduced fasting serum glucose and stopped sugar levels from moving up after a 2 g/kg glucose loading greatly lower fasting glucose tolerance and stopped the blood. In vivo study, the capacity of glucose-fed rats to secrete insulin was further proven by increasing blood insulin levels. These data suggest that TC's alkaloid has a role in the antihyperglycemic activity. AFTC lowers postprandial hyperglycemia by exerting hypoglycemic effects through insulin secretion and insulin-mimicking pathways (15).

Antitussive activity

Using bioactivity-directed fractionation of the crude extract of Stemona tuberosa, four new stenine-type Stemona alkaloids, tuberostemonine, tuberostemonine H, epi-bisdehydrotuberostemonine, and neostigmine, as well as the existing neotuberostemonine, were found and reported. After cough induction by citric acid aerosol stimulation, these five alkaloids were tested for antitussive efficacy in guinea pigs. Compounds 1 and 5 were discovered to have considerable antitussive activity for the first time in this study. However according to further investigations on these extracted compounds and two synthesized derivatives, the injection of tricyclic pyrrolo [3,2,1-jk] The benzazepine nucleus is the most critical structure in antitussive action, and all cis configurations at the three-ring joints are the best structures for stenine-type antitussive action. Alkaloids in Stemona (16).

Antiulcer activity

Ulcer illness is a type of gastrointestinal erosion that affects a large mucosa breadth, such as muscular mucosa. A wide range of natural compounds, including this one, have been studied as treatments for several ailments. Alkaloids, flavonoids, terpenoids, tannins, and other active ingredients are commonly found in these products, which are derived from plant and animal sources. Alkaloids are nitrogen-containing secondary metabolites that are present in around 20% of plants and are largely produced from amino acids. The antiulcer action of these substances has been studied extensively in pharmacology. We evaluate the literature on antiulcer alkaloids, which contains around sixty-one alkaloids, fifty-five of which exhibit antiulcer activity when produced in animals (17).

Antidiarrhoeal activity

The separation of three bioactive carbazole alkaloids, Kuriyama (I), koenimbine (II), and koenine, from the n-hexane extract of Murraya koenigii Spreng's (Rutaceae) seeds, was led by a bioassay (III). The compounds' structures were verified using (1)H-, (13)C-, and 2D-NMR spectrum data. Castor oil-induced diarrhoea and PGE(2)-induced enter polling in rats were significantly inhibited by (I) and (II) of the three substances. In the charcoal meal test, the chemicals caused a substantial decrease in gastrointestinal motility in Wistar rats (18).

Antiemetic activity

The anti-emetic effects of reserpine and alseroxylon against apomorphine-induced emesis were evaluated in dogs. Emesis was caused by morphine, ergot (Hydergine), veratrum, and oral copper sulphate, and the Rauwolfia alkaloids were tested against it. Reserpine and alseroxylon are very efficient at preventing apomorphine-induced vomiting. They also protect against morphine and ergot-induced vomiting, although they are ineffective against veratrum and oral copper sulphate-induced emesis. The pattern of anti-emetic effect points to selective depression of the medullary emetic chemoreceptor trigger zone as the mechanism of action (19).

Antiviral activity

Herpes virus considers a common infection that may be found worldwide. Finding and developing innovative alternative medications for the treatment of HSV-1 infection is critical. In traditional Chinese medicine, Tripterygium hypoglaucum (level) Hutch (Celastraceae) is an anti-inflammatory, anti-tumour, and anti-fertility herb. The roots are the most often utilised medicinal part of the plant, with a 1% yield of alkaloids. T. repens roots were utilised to make a crude total alkaloids extract. A cytopathic effect (CPE) test, plaque reduction assay, and RT-PCR analysis were used to investigate Hypoglaucum's antiviral efficacy against HSV-1 in Vero cells. The alkaloids extract was shown to have low cytotoxicity (CC(50) = 46.6 g/mL) and a strong CPE inhibitory activity (IC(50) = 6.5 g/mL), which was much less than Acyclovir's (15.4 g/mL). The alkaloids extract efficiently decreased plaque formation at doses ranging from 6.25 g/mL to 12.5 g/mL, with a plaque speed reducer of 55 to 75, which was 35 percent higher than Acyclovir at the same dosage. The alkaloids extract inhibited transcription of two important delayed early genes, UL30 and UL39, and thus a late gene US6 of the HSV-1 genome, according to RT-PCR analysis; the utterance inhibiting potency was 74.6 percent (UL30), 70.9 percent (UL39), and 62.6 percent (US6), respectively, when compared to the control at a working concentration of 12.5 g/mL. According to laboratory findings, the alkaloids extract appears to have a powerful anti-HSV-1 effect (20).

Expectorant activity

The key objective of this review is to investigate antitussive and expectorant impacts of the alkaloids imperialine , chuanbeinone , verticinone , and verticine obtained from the Bulbus Fritillariae Cirrhosae using a phytochemical technique (BFC). In mice, all of the alkaloids reduced cough frequency and prolonged the latent duration of ammonia-induced cough. In an expectorant test, imperialize, verticinone , and verticine considerably improved tracheal phenol red output, while in an anti-inflammatory test, imperialine ,chuanbeinone , and imperialine , significantly lowered the advancement of ear oedema in an amount of the drug manner. Additionally, the structure-activity correlations among some of the four alkaloids differed significantly. The four alkaloids imperialize, chuanbeinone, verticinone, and verticine were discovered to be active components in Bulbus F. Cirrhosae (BFC) (21).

Antifungal activity

Sparteine, ammodendrine, and anagyrine, the most prevalent chemicals in alkaloids extracts of leaves and stems, may be responsible for their antifungal properties. The inactivity of R. monosperma seeds may be due to high levels of cytisine and its derivatives in the alkaloids extract (22).

Antidepressant activity

In a mouse model of serotonin-induced oedema, treatment with Aconitum baicalein diterpene alkaloids shortened the time of immobility in the tail suspension test and had an anti exudative impact. Alkaloids showed no influence on animals' overall motor activity, orientation and exploratory behaviour, or emotional reactions in an open field test. The diterpene alkaloids of Aconitum baicalensis have antidepressant qualities, according to the study, most likely owing to alterations in serotonin reactivity (23).

Antimalarial activity

Malaria is a severe global public health issue in nations. Every year, there are many people has been died because of this disease which led to so much cost to the nations. Sensitivity of the causal agent, the plasmodium parasite, to currently available therapies such as chloroquine, amodiaquine, and artemisinin-based combination therapy (ACT), is a severe problem in malaria treatment and control across the world. It needs a quick search for novel compounds, especially those originating from original resources like herbal plants. Alkaloids have been discovered as key phytoconstituents with intriguing biological characteristics over time. Quinine, an alkaloid derived from the Cinchona tree, was the first antimalarial drug to be effective. This review covers alkaloids that have recently been discovered and claimed to have antimalarial activity (from 2013 to 2019). Several kinds of alkaloids have been identified to have antimalarial activity, such as indole, quinolone, and isoquinoline alkaloids. It is anticipated that the review's findings would spur greater study into structural alterations and/or the development of new antimalarial drugs based on these intriguing molecules (24).

Immunostimulant activity

Trichopus zeylanicus Geert (Trichopodaceae) is also known as "Arogyappacha," which means "greener of health" in indigenous languages. This plant is used to treat the body as a tonic and rejuvenator. In a series of stages, the whole plant material of Trichopus zeylanicus is defatted and

extracted with methanol. Methanol extract has been used to remove the alkaloid component in Trichopus zeylanicus. At a dose of 2000 mg/kg, which would be given orally, there was no mortality or toxicity. The neutrophil adhesion test, the delayed type hypersensitivity response, and the impact on haematological measures including total white blood cells, RBCs, and haemoglobin, as well as the immunosuppressive effect in cyclophosphamide, were employed to test the immunomodulatory effect of Trichopus zeylanicus Gaertn's alkaloid fraction. Long-term administration of the alkaloid part of Trichopus zeylanicus (75, 150, and 300 mg/kg p.o.) led to substantial (P 0.001) rises in blood parameters including such total WBCs, RBCs, and haemoglobin. If rats were cured with cyclophosphamide (30 mg/kg, p.o.), the alkaloid component of Trichopus zeylanicus reduced myelosuppression. According to the current study, the alkaloid part of Trichopus zeylanicus activates the immune system by changing various immunological markers (25).

Antipsychotics activity

Co-morbidity between epilepsy and psychiatry is common, necessitating the prescription of both psychiatric and antiepileptic medications (AEDs). Although atypical antipsychotics are most active at lowering signs (particularly adverse signs) and have fewer extrapyramidal side effects, they produce the greatest seizures in schizophrenia patients. Traditional Nigerian psychiatrists employ the indol alkaloid alstonine as a fundamental component of anti-dementia treatments. The experimental profile of the alkaloid is very similar to that of clozapine, an atypical antipsychotic. The purpose of this study was to compare the pro-convulsant effectiveness of antipsychotic medications. Alstonine, unlike clozapine, does not have a pro-convulsant impact after repeated treatment over 30 days, according to a kindling model. The findings back up previous assertions that also nine should be investigated as perfect for the growth of fresher neuroleptics (26).

Sedative activity

Nervousness-induced sleeplessness, agitation, and/or anxiety are treated with the herbal medication Phytonoxon N (abbreviated as PN). It's made up of Corydalis cava (20%) and Eschscholtzia californica (20%) alcoholic medicine extracts (80 per cent). Isoquinoline alkaloids generated from tyrosine metabolism are abundant in both plants. According to recent studies, they may have an impact on neurotransmitter metabolism (27).

Hypnotic activity

Lotus leaves have long been used as a meal and a natural treatment in Asia. Open-field, sodium pentobarbital-induced sleeping, and light/dark box tests were used to evaluate the most of alkaloid compounds isolated from herbal plants for sedative-hypnotic action, The researchers used ultrafast LC and mass spectrometry to detect how much amounts neurotransmitters present in the brain. The effects of picrotoxin, flumazenil, and bicuculline on TA's hypnotic action and Cl (-) influx in cerebellar granule cells were examined. The hypnotic effect of TA was suppressed by bicuculline and picrotoxin, but not by flumazenil since it increased the quantity of (GABA) in the brain. In cerebellar granule cells, TA has also been demonstrated to enhance Cl (-) inflow. TA produced anxiolytic-like effects and consistently elevated serotonin (5-HT), 5-hydroxy indole acetic acid (5-HIAA), and dopamine levels at a dose of 20 mg/kg (DA). Those findings reveal that, through binding to the GABAA receptor, TA stimulates the monoaminergic system and has sedative-hypnotic and anxiolytic effects (28).

Antiparkinson's activity

The anti-efficacy of petroleum ether extract of Ficus religiosa (PEFRE) leaves against Parkinson's disease was investigated in experimental animal models produced using haloperidol and 6-hydroxydopamine (6-OHDA). In this study, rats were given Ficus religiosa (100, 200, and 400 mg/kg, p.o.) to see how it affected in vivo neurological measurements including catalepsy, muscular stiffness, and locomotor activity, as well as neurochemistry indicators like MDA, CAT, SOD, and GSH. Haloperidol was used to produce catalepsy, whereas 6-OHDA was utilised to create Parkinson's disease-like symptoms in the study. At doses of 200 and 400 mg/kg, the PEFRE substantially lowered the higher cataleptic scores (generated by haloperidol) (p.o.). 6-OHDA caused substantial motor dysfunction. The treatment with 6-OHDA resulted in a significant increase in lipid peroxidation, as well as decreased superoxide dismutase, catalase, and other antioxidant enzymes. PEFRE (400 mg/kg) was given once a day and was found to improve motor performance while reducing oxidative damage. According to the study, Ficus religiosa therapy restored motor deficits while also protecting the brain from oxidative stress (29).

CNS stimulant activity

Stimulants of the central nervous system (CNS) can help people feel less exhausted while also increasing alertness, competitiveness, and aggressiveness. They are more commonly employed in competitions, but they can also be utilised in training to boost the intensity of a workout. There are some risks associated with their usage in contact sports. This research examines the abuse of the three primary CNS stimulants, ephedrine, amfetamine, and cocaine, in sports (30).

Anaesthetic activity

At peripheral nerves, alkaloids extracted from Aconitum roots have anaesthetic properties. The current quantitative structure-activity relationship (QSAR) investigation was carried out to better get clear (MOA) of alkaloids such as 11 Aconitum alkaloids as local anaesthetics. The greatest anaesthetic alkaloids have an aroyl/aryloxy group at R14, whereas the lesser ones have one at R4. As local anaesthetics, the stable molecules outperformed the unstable ones. When compared to the reactivity indexes of atoms on the aromatic ring, C2' was the most reactive among the compounds with the strongest anaesthetic effect; C3' and C5', on the other hand, were less reactive. Between the two sets of alkaloids, the reactions of N, C1', C4', and C6' were comparable. In both groups, the PKA was around 7.3. In alkaloids, electronic energy, total energy, RI-C5', and heat of synthesis are all inversely related, although molecular weight, core-core repulsion energy, steric energy, and RI-C2' are all directly related. Finally, we discovered a collection of structural characteristics linked to Aconitum alkaloids' local anaesthetic activity. Our findings are important for getting an insight into the mechanism of action of these alkaloids, as well as providing a rationale for chemical modification of the compounds to develop powerful extracts with lower toxicity (31).

Anticholinergic activity

Alzheimer's sickness is a broad-minded illness marked by significant damage in the brain neurotransmitter acetylcholine, which causes a variety of cognitive and

behavioural symptoms. Metabolites originating from plants, such as alkaloids, it was created to inhibit neuroprotective action it might be probably safe, implying that they might be exploited to develop effective therapy molecules for brain diseases such as Alzheimer's disease. Oliver online, noroliveroline, pyridoxine, isoindoline, polyethene, and darienine (all from Polyalthia longifolia in the Apocynaceae family), Oliver online, noroliveroline, pyridoxine, isoindoline, polyethene, and darienine (all from Polyalthia longifolia in the Apocynaceae family), and Among the alkaloids, pilocarpine showed promising anti-cholinergic potential, with its amino derivative having a six-fold stronger anticholinergic potential than pilocarpine itself. Pleiocarpine and its amino analogue were found to be more effective AChE blockers than the commonly used drugs tacrine (brand name: Cognex) and rivastigmine (brand name: Exelon), indicating that these compounds might be examined as potential treatments in the future (32).

Anti-asthmatic activity

One of the most well-known Chinese citrus herbal medicines is Pericarpium Citri Reticulate (PCR, Citrus reticulata 'Chachi', Guangchenpi in Chinese). The anti-asthmatic activity of 'Chachi' PCR was investigated in vivo using a histamine-induced experimental asthma paradigm in Guinea pigs. Synephrine and stachydrine, two alkaloid-like substances, were investigated and detected in the fraction of alkaloids ('Chachi' PCR). In a dose-dependent way, Guinea pigs were protected from histamine-induced experimental asthma by the alkaloid fraction and synephrine. The PCR alkaloid component "Chachi" raised specific airway resistance by 284 per cent, 328 %, and 355 %, respectively, and reduced dynamic compliance by 57 per cent, 67 per cent, and per cent at high, moderate, and low dosages. Synephrine had a similar transformation. When compared to the control group, the 'Chachi' PCR alkaloid fraction and synephrine significantly reduced eosinophil expression in BALF as well as serum IgE, IL-4, and IL-5 levels, whereas stachydrine had no statistically significant effect on the expression of tested inflammatory cells (leukocytes, eosinophils, neutrophils, and lymphocytes) or immunoglobulin levels in histamine-induced experimental (IL-4 and IL-5). One of the pathological changes in lung tissues in each treatment group was the infiltration of inflammatory cells around the bronchia (33).

Nootropic activity

Alzheimer's disease (AD) is the most common cause of dementia in those over the age of 65. Nootropics are a sort of psychotropic drug that helps laboratory animals enhance their learning, memory, and learning impairments. Traditional medicine has used a range of botanicals to address cognitive disorders. Passiflora incarnata Linn (Family: Passifloraceae) had been used as an old drug such as sedative, anxiolytic, antispasmodic, analgesic, anticonvulsant, and homicidal. As of yet, no evidence of Passiflora incarnate nootropic action has been found**.** As a result, the current work used an elevated plus maze and an object recognition test to explore the nootropic effect of the n-butanol extract of P. incarnata leaves (BEPI). According to the findings, a flavonol-rich n-butanol extract of P. incarnata leaves exhibited a nootropic effect, as demonstrated by a decrease in transfer latency (TL) and a rise in discriminating index. The rats were protected against scopolamine-induced memory deficits by BEPI pretreatment. BEPI's nootropic effect is mediated by stimulation of brain cholinergic neurotransmission, according to the current study's findings, and significant phytoconstituents including flavonoids, alkaloids, and phenolic compounds may be responsible for P. incarnate's nootropic activity (34).

Anti-epileptic activity

Epilepsy is a potentially fatal neurological condition that affects more than 50 million people worldwide. It stays a puzzling problem, Spites the fact that newer anticonvulsant medications are becoming more widely available. However, these drugs are effective in controlling epilepsy, the remaining one-third of patients are resistant to therapy. This has generated a lot of research into novel anti-epileptic medications. Medicinal herbs have been an important source of novel anticonvulsant medications in this area (35). Berberine is an isoquinoline alkaloid that has been used for ages in Ayurvedic and Chinese medicine. Berberine has been proven to have a wide range of pharmacological effects, making it a promising treatment for coronary heart disease Alzheimer's, diarrhoea, cancer. Antiplatelet, antiviral, antibacterial, and immunostimulant activities are also present (36). Although numerous pharmacological studies on berberine have been published in the past, there is increased interest in the compound due to its potential advantages in several psychiatric and neurological conditions. Berberine has been revealed to have anxiolytic, analgesic, depressive, anti-amnesic, promise in the treatment of drug addiction, and neuroprotective properties, according to a recent study (37).

Oxytocic activity

Piperidinomethyl and related naphthol derivatives, substituted phenols, and indoles were studied in vitro and in vivo. Many substances had levels of activity that were higher than ergometrine. There was no structural relationship to the ergot alkaloids that were related to the activity. The highest activity was found in 2-piperidinomethyl phenol derivatives, with the greatest potency obtained by replacement of methyl or ethyl at both the 4- and 5- positions, or by linking these locations to generate an indane compound. Piperidinomethyl compounds were substantially more active than those synthesised with other bases in all series, and methylation of both piperidine and morpholine analogues at the alpha-position to the nitrogen atom boosted their activity. The (-) form of 2'-methyl piperidinomethyl phenols was shown to be much more powerful than the (+) form. The action was unaffected by acylation or alkylation of the phenolic hydroxyl group. The oxytocic activity of the compounds was unique since they were less effective on other kinds of smooth muscle. A central nature effect on blood pressure and breathing was noted (38).

Uterine relaxant activity

The goal of this research was to find out more about *Cissampelos mucronata* root extract's uterine smooth muscle relaxant characteristics and how they relate to its traditional use in the protection of pre-term labour. Standard protocols were used to conduct phytochemical and pharmacological testing. The extract's effects on contractions generated by recognised uterine stimulants were tested in addition to its effects on gravid rat uterus non-gravid. The impacts of the extract on the amplitude and frequency of contractions in the uterus of pregnant rats were also studied. The impact of the extract on potassium channel opening was investigated using glibenclamide, an ATP-sensitive potassium channel blocker. Carbohydrates, glycosides, flavonoids, and alkaloids are among the phytochemical elements found in the root. In a time- and concentration-dependent manner, the extract relaxed the non-gravid rat uterus. Serotonin, oxytocin, acetylcholine, and prostaglandin E2-induced contractions were also suppressed. The extract potentiated the uterine relaxing effect of terbutaline (a selective Î22-receptor agonist used as a tocolytic medicine) while reducing the contractions caused by propranolol (a non-selective Î2-receptor

antagonist). In the absence and presence of the extract, the frequency and amplitude of contractions in the gravid uterine strips were substantially different (p0.05). Glibenclamide inhibited the extract's uterine relaxing activity, suggesting that potassium channels may be involved in the extract's effects. On the separated gravid and non-gravid rat uterine smooth muscles, an ethanolic root extract of C. mucronata showed considerable (p0.05) relaxant action. The findings support the plant's usage as a tocolytic (uterine relaxant) in traditional medicine (39).

Nephroprotective activity

The production of reactive oxygen species by cisplatin causes acute nephrotoxicity, which limits its usage in the treatment of many malignancies. Gelsemine, a gelsemium Elegans alkaloid, has been shown to have anti-inflammatory and anti-cancer properties. The purpose of this study was to explore if gelsemine could protect the kidneys against cisplatin-induced nephrotoxicity. Six groups of male Wistar rats were constructed, each with six animals. The vehicles were under the control of Group 1, For gelsemine and cisplatin, the control group (peanut oil for 14 days and 0.9 percent saline on day 14) was also used. On day 14, Group 2 was given a single intraperitoneal cisplatin injection. In addition to cisplatin, groups 3 and 4 got two different dosages of gelsemine, whereas groups 5 and 6 received only gelsemine. The actions of gelsemine on cisplatin-induced nephrotoxicity were studied using a well-established oxidative damage model in the kidneys, which includes anti-oxidant enzyme activity, lipid peroxidation, and DNA damage. The cisplatin-induced DNA and oxidative damage in rats were significantly reduced after pretreatment with gelsemine. The blocking of lipid peroxidation and xanthine oxidase activity was followed by increased production and/or activity of anti-oxidants, both enzymatic (catalase, glutathione peroxidase, glutathione reductase, and glutathione-S-transferase) and non-enzymatic (GSH) (40).

Cardioprotective activity

Plants have been utilised to relieve human pain since the dawn of civilization, and it has been documented that plants have been used for therapeutic purposes for thousands of years. Phytochemicals are natural bioactive molecules that are derived from medicinal plants, vegetables, and fruits and are used to treat a variety of illnesses. It's vital to look into plant biodiversity for medicinal and pharmaceutical applications. Placed much emphasis medicinal plants' cardioprotective effects were identified in Google Scholar, Medline, PubMed, and the Directory of Open Access Journals, among other databases. For the therapy of cardiovascular disorders, several compounds derived from a range of plant species are employed. Diosgenin, isoflavones, sulforaphane, carbonized, catechin, and quercetin, among other bioactive compounds present in cardioprotective plants, have been demonstrated to promote cardioprotection, decreasing the incidence of cardiac problems. The goal of this review article is to provide information on the use of medicinal plants, particularly in the treatment of cardiac illnesses, as well as to look into the molecules/ phytoconstituents found in plant secondary metabolites for their cardioprotective properties (41).

Neuroprotective activity

Alkaloid fractions from the Amaryllidaceae Rhodophiala pratensis, Rhodolirium speciosum, Phycella australis, and Phaedranassa lehmannii were studied for their chemical composition and neuroprotective effects. The technique of gas chromatography/mass spectrometry (GC/ MS) has been used to detect 41 known alkaloids. With IC50 values of 35.22 and 38.13 g/mL, respectively, Rhodolirium speciosum and Rhodophiala pratensis extracts were the most potent against acetylcholinesterase (AChE). These extracts were evaluated for their capacity to protect human neuroblastoma cells (SH-SY5Y) against rotenone/oligomycin A (R/O)-induced mitochondrial oxidative stress and okadaic acid-induced toxicity (OA). Only 0.75 and 1.5 g/mL of Phycella australis and Rhodophiala pratensis appear to prevent R/O-induced cell death by around 12%. In an OA test, alkaloid fractions from Phycella Australis and Phaedranassa lehmannii had a concentration-dependent effect (0.375-3.0 g/mL), with peak neuroprotective responses of 78 per cent and 84 per cent, respectively. The neuroprotective actions of Phycella australis (3 and 6 g/mL) in rat hippocampus slices exposed with oxygen-glucose insufficiency (OGD/R) showed over 14 percent protection. Finally, Phycella Australis (6 g/mL) increased cell viability from 65 to 90% in slices treated with OA, suggesting a 25% protection related to this species' alkaloids (42).

Adrenergic activity

Ephedra species have both good and negative impacts, which are mostly due to the presence of ephedrine alkaloids. Few studies have looked at the direct effects of ephedrine alkaloids on human adrenergic receptor subtypes (ARs). Ephedrine alkaloids' binding affinities on human alpha (1A), alpha (1B), alpha (1D), alpha (2A), alpha (2B), and alpha (2C)-AR subtypes expressed in HEK and Chinese hamster ovary cells were investigated in this study. The functional activity of ephedrine alkaloids at alpha (1A), alpha (2A), and alpha (2C)-ARs was determined using cell-based reporter gene experiments. Ephedrine alkaloids did not activate alpha(1)- or alpha(2)-ARs, and they blocked the agonist-mediated actions of phenylephrine and medetomidine on alpha(1)- and alpha(2)-ARs, correspondingly. The functional antagonist activity of 1R, 2R- and 1R,2S-ephedrine was higher in binding studies than that of the 1S,2R- and 1S,2S-isomers. 1R,2R > 1R,2S > 1S,2R The potencies of alkaloids with a 1R,2S configuration are ranked as follows: or = ephedrine > N-methylephedrine > norephedrine The direction of the beta-hydroxyl group on the ethylamine side chain, as well as the condition of N-methyl substitution, are both important for alpha-AR binding and functional activity of ephedrine alkaloids, according to these studies. Finally, while the investigated ephedrine isomers and analogues had no direct agonist action on cloned human alpha-ARs, they did have a strong antagonist impact. Blocking presynaptic alpha(2A)- and alpha(2C)-ARs may play a role in Ephedra alkaloids' direct effects (43).

Diuretic activity

The aerial parts of Selaginella lepidophylla (Hook. et Grev.) Spring are used to treat renal issues in Mexican traditional medicine. The goal of this study was to evaluate the diuretic response of an aqueous extract (200 mg/kg) and alkaloids from this plant at various doses (10, 40, and 100 mg/kg) to furosemide (4 mg/kg). The effects of extract, alkaloids fraction, furosemide, and vehicle on sodium, potassium, and water balance in adult rats were studied. In comparison to the control group, the extract, the alkaloids fraction, and furosemide all resulted in substantial increases in urine salt, potassium, and water excretion. The alkaloids fraction dosage was dose dependant, with the highest dose

having the greatest impact. Even though potassium excretion improved, it was less than furosemide-induced increases. These data suggest that S. lepidophylla's aqueous extract and alkaloids-rich portion elicit a diuretic effect (13).

Antiarrhythmic activity

Diterpenoid alkaloids are a wide category of natural chemicals generated by the Aconitum and Delphinium genera of plants. Some of these compounds have been discovered to have useful pharmacological effects, such as antiarrhythmic action. Allapinine (an alkaloid produced from lappaconitine) was authorised as a medication. The structure-activity link was investigated, and structural components responsible for arrhythmogenic and antiarrhythmic characteristics were discovered (44).

Antihypertensive activity

Ayurvedic medicine has long recognised the antihypertensive benefits of moringa oleifera leaves. In a preliminary investigation conducted in our lab, a water extract of this tree's leaves was found to be effective in reducing the chronotropic and inotropic effects on the isolated frog heart. The activity of the alkaloids obtained by fractionation of the aqueous extract of M. oleifera leaves, converted to their salt form, was examined on the isolated frog heart. The inotropic action of total alkaloidal salts on the frog heart has been discovered. An isolated guinea pig ileum was used to further characterise this action (45).

Antiplatelet activity

Alkaloids are nitrogen-containing chemical molecules that are often extracted from plants. Several alkaloids are respected therapeutic chemicals that may be used to treat a wide range of illnesses, including malaria, diabetes, cancer, and heart disease. Similarly, platelet aggregation for reasons other than homeostasis is the root cause of blood clotting disorders. This review, which is based on research from the preceding decade, gives a thorough understanding of alkaloids as antiplatelet agents, as well as a probable mechanism of action. This study will also include alkaloids' antiplatelet activity and clinical application as strong antiplatelet medicines, as well as a description of structural relation action and prospective toxic elements for future drug development (46).

Conclusion

Alkaloids are a type of secondary metabolite found in plants. They are nitrogen-containing natural bioactive chemicals that are well-known. Alkaloids are the subject of cutting-edge research to uncover potential medicinal techniques. Alkaloids have numerous biological actions, according to the literature, and certain alkaloids also change into active forms. So there are several pharmacological activities that have reported for alkaloids like antitussive, antifungal, anticancer, antimicrobial, antimalarial, antibacterial, Antiduretic, antidepressants, Antiepleptic, Antiplatele, antihypertensive, immunosuppressive, expectorant, antioxidant, muscle relaxant, sedative, hypnotic, hypoglycemic, urine relaxant, oxytotic, emitic, antiviral, Antiparkinson, CNS stimulants, Nootropic, antipsychotic, antipyretic, antiulcer, antihyperlipidemic, nephroorotective, neuroprotective, cardioprotective, Chilonergic, Antichonergic, antiasthmatic, activities have reported, so there are activities that haven't been reported like antigout, ion channel, carrier molecule, receptors, enzymes, Antilepral, mucolytic, anticoagulant, coagulant, cardiotonic, so this information has to be helpful to the other scientific researcher. We've compiled a list of documented alkaloids' origins and biological activity throughout the last few decades.

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