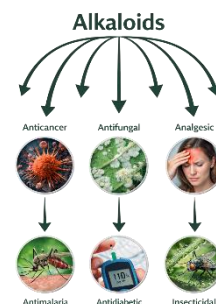


CHAPTER 06

Alkaloids: Nature's Potent Bioactive Compounds



EESHA RIAZ¹, TAHREEM FATIMA^{2*}, YUSHFA AKRAM², MUHAMMAD BILAL AMIN², BUSHRA AKRAM², AMNA IQBAL²

¹Department of Zoology, Wildlife and Fisheries, University of Agriculture, Faisalabad, Pakistan

²Department of Zoology, Government College University, Faisalabad, Pakistan

Corresponding author: t.fatima.uaf@gmail.com

ABSTRACT: Alkaloids are nitrogen containing heterocyclic metabolites predominantly found in plants and sporadically in some animals. Alkaloids can be classified on the basis of their structure (e.g. pyrrolidine, indole, isoquinoline and tropane), precursor molecule (e.g. tryptophan, lysine, tyrosine and ornithine) and pharmacological activity such as anticancer, analgesics, antimalarial, and antimicrobial. Alkaloids are key components of several modern anticancer drugs due to their ability to modulate critical signaling pathways involved in cell cycle regulation, proliferation, and metastasis. Vinblastine and vincristine act as anticancer agents by disrupting microtubule dynamics, which leads to cell cycle arrest and the induction of apoptosis. Alkaloids are also known for their neuroprotective and anti-inflammatory properties, as well as their ability to prevent cell death and oxidative stress. Future perspectives include advances in computational biology and artificial intelligence (AI), which are set to revolutionize alkaloid-based drug discovery. Additionally, synthetic biology offers innovative approaches to produce alkaloids in microbial systems, eliminating the reliance on plant extraction. Green chemistry principles, such as the use of renewable solvents and catalysts, are being adopted to make alkaloid extraction and synthesis more sustainable. These innovations can address both environmental and economic concerns.

Alkaloids are one of the largest classes of plant-derived secondary metabolites comprising of more than 20,000 compounds with diverse structural and biosynthetic attributes that exhibit useful bioactivities (Yang & Stöckigt, 2010). Alkaloids have been reported to be produced by living organisms including bacteria, fungi, flowering plants, and animals (insects, beetles, birds, and mammals). Microorganisms and marine organisms are promising sources of novel alkaloids, offering unique molecular structures with unparalleled medicinal potential (Mondal et al., 2019). The presence of nitrogen (N) as an essential chemical component enables alkaloids to readily interact with biological proteins, potentially leading to biological activity such as enzyme inhibition and receptor modulation. The non-bonded electron pair of nitrogen is the pharmacophoric feature of alkaloids responsible for its interaction with

biological receptors. In living things, the protonated nitrogen can then form a connection with the receptor's anion groups. The precursor amino acids for most alkaloids are ornithine, lysine, phenylalanine, tyrosine, and tryptophan, which are the building blocks of primary metabolism. Ornithine is the source of the pyrrolidine alkaloids, pyrrolizidine alkaloids, and the bicyclic tropane bases like atropine, scopolamine, and cocaine.

German chemist Wilhelm Sertürner was the first to isolate an alkaloid from a natural source. In a paper published in 1806, he described opium's "*Principium somniferum*" as an alkali, which he later named morphine. Alkaloids have been used in medicine for a long time, for example, morphine, extracted from *Papaver somniferum*, is still widely used as an analgesic (pain-relieving agent) (Pereira et al., 2016). Quinine from *Cinchona* species has also proven to be extremely helpful in treating

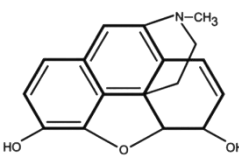
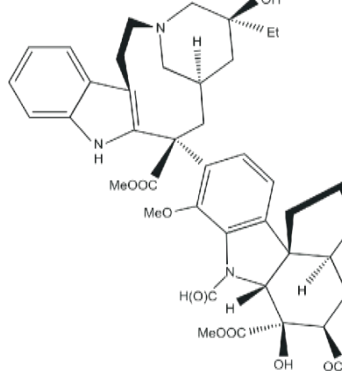
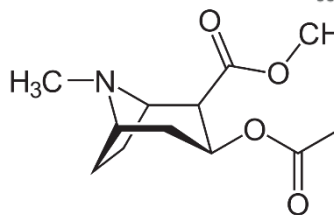
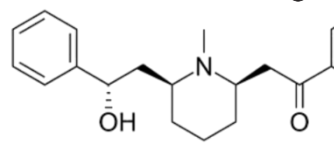
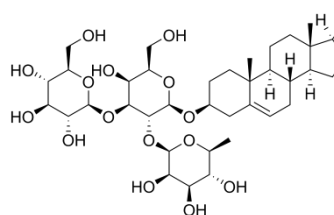
malaria (Kittakoop et al., 2013). These substances have served as the basis for numerous contemporary medications, illustrating the significant influence of natural products in pharmacotherapy, drug design, and the development of novel therapeutic agents (Christodoulou et al., 2019). Due to their high toxicity, alkaloids are typically sequestered in non-metabolically active cells to prevent damage to essential cellular functions. Although the production of alkaloids in plants may appear to be random, many plant alkaloids play a defensive role by repelling harmful organisms and predators. Their

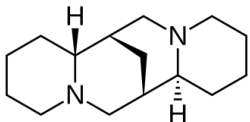
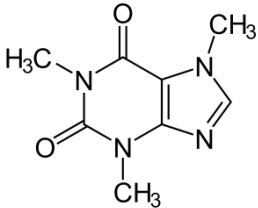
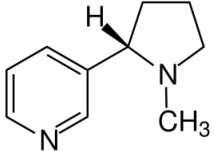
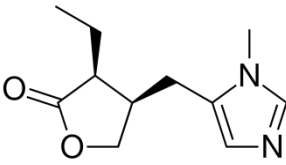
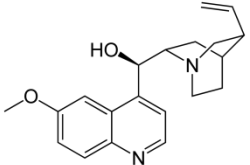
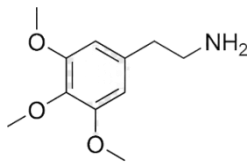
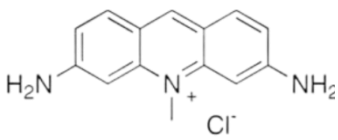
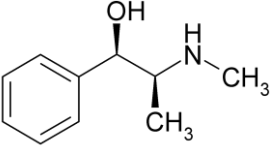
widespread use in medicine is largely attributed to their potent physiological effects. The current chapter discusses the biological activity and significance of alkaloids in detail.

BIOSYNTHESIS AND STRUCTURAL DIVERSITY OF ALKALOIDS

Alkaloids can be classified on the basis of their structure, biosynthetic origin, pharmacological activity, and natural source. Table 1 describes a detailed classification of alkaloids.

Table 1. Classification of alkaloids based on their biosynthetic origin, structure, pharmacological activity and representative compounds

Classes	Biosynthetic origin/Plant Source	Structure	Precursor molecule	Effect	Example
Isoquinoline Alkaloids	<i>Opium poppy</i>		l-tyrosine and tyramine	Pain relief	Morphine
Indole Alkaloids	<i>Madagascar periwinkle</i>		vindoline and catharanthine	Anti-cancer	Vincristine
Tropane Alkaloids	<i>Erythoxylon coca</i>		N-methyl-pyrrolinium	local anesthetic and vasoconstrictor	Cocaine
Piperidine Alkaloids	<i>Lobelia tupa</i> (Devils's tobacco)		Lobelanine	Respiratory stimulant, smoking cessation aid	Lobeline
Steroidal Alkaloids	<i>Solanum tuberosum</i> (Potato)		Solanidine	Anti-cancer, Anti-fungal, Contraceptives	Solanine

Quinolizidine alkaloids	<i>Cytisus scoparius</i>		lysine	Anticonvulsant, antiarrhythmic	sparteine
Purine Alkaloids	<i>Conium maculatum</i> (Hemlock)		Xanthosine	Stimulates Central Nervous System	Caffeine
Pyrrolizidine Alkaloids	<i>Nicotiana tabacum</i> (Tobacco)		Nicotinic acid	Stimulant, modulates neurotransmitters	Nicotine
Imidazole Alkaloids	<i>Pilocarpus</i> species		L-histidine	Stimulant for sweat and lacrimal glands, treat glaucoma	Pilocarpine
Quinoline Alkaloids	<i>Cinchona officinalis</i>		Cinchonidine	Antimalarial	Quinine
Phenylethylamine Alkaloid	<i>Lophophora williamsii</i> (Peyote Cactus)		<u>3,4,5-trimethoxyβ-phenethylamine</u>	Psychoactive, hallucinogenic	Mescaline
Acridine Alkaloid	Synthetic		3,6-diamino-10-methylacridinium chloride	Antibacterial, antiprotozoal	Acriflavine
Alkaloidal Amine	<i>Ephedra sinica</i>		methcathinone	Bronchodilator, treats asthma	Ephedrine

MECHANISMS OF ACTION IN BIOMEDICAL APPLICATIONS

Analgesic Effects of Alkaloids

Alkaloids such as morphine are characterized for their analgesic properties, some opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) are the alkaloids that have the consumption rate of up to 30% patients dependent for pain management

(Hewitt et al., 2009). Nociceptors respond to pain-inducing stimuli by triggering neurogenic pain in the early phase, while the late phase is characterized by a sustained (tonic) response resulting from the release of inflammatory mediators (Verma et al., 2005). Analgesics act through two primary mechanisms; centrally acting narcotic analgesics suppress nociception in both phases, whereas peripherally acting drugs, such as aspirin, impede prostaglandins synthesis and primarily target the

last phase of pain response (Mohammad et al., 2013). Ethnopharmacological and ethnobotanical studies have identified alkaloids in plants such as *Papaver somniferum*, *Erythroxylum coca*, *Solanum nigrum*, *Mitragyna speciosa*, *Corydalis yanhusuo*, and *Rauwolfia serpentina*, highlighting their traditional use in pain management (Yogesh et al., 2012).

Opioid alkaloids and their mechanisms of analgesia: Alkaloids can be naturally derived from poppy seeds, such as morphine, codeine, and thebaine, or produced as semisynthetic derivatives like oxycodone, hydrocodone, and buprenorphine. Additionally, fully synthetic opioids, such as phenylpiperidines (e.g., meperidine and fentanyl), are also developed to mimic their analgesic properties. Synthetic pseudopiperidines belong to the broad class of opioid analgesics (Chang et al., 2007) which exert their effect by interacting with the G-protein-coupled opioid receptors (μ , δ , and κ). Unpleasant stimulus typically activates these receptors by generating endogenous peptides such as endorphins, enkephalins, and dynorphins (Chen et al., 2014). The three receptors share a lot of structural similarities and link G-proteins to block adenylate cyclase activity, promote potassium efflux, reduce calcium influx, and control neurotransmitter release.

Opioid receptors are extensively expressed across the central nervous system (CNS) and within the dorsal horn of the spinal cord. These receptors are responsible for relaying nociceptive signals to the central mediator to produce analgesic effects of opioids. Descending pain-modulating pathways originate from several brain regions, including the periaqueductal gray (PAG), rostral ventromedial medulla (RVM), locus coeruleus, amygdala, and hypothalamus. Deep analgesia is achieved through the activation of opioid receptors, mediated by both presynaptic and postsynaptic actions. Presynaptically, opioid analgesics act on primary nociceptive afferents to inhibit calcium channel activity, thereby reducing neurotransmitter release. This suppression lowers the release of key neurotransmitters such as substance P and glutamate which plays a central role in nociceptive transmission. Additionally, by opening potassium channels, opioid analgesics hyperpolarize the

postsynaptic cell membranes, thereby directly inhibiting neuronal excitability and further dampening pain signaling. Other opioid actions, such as antitussive and gastrointestinal tract motility-reducing properties, can have useful therapeutic applications (Johnston, 2010).

Opioid analgesics: Opioid analgesic exhibit range of negative side effects such as, excitement, depression, anxiety, drowsiness, respiratory distress, reduced gastrointestinal motility, endocrine system suppression, cardiovascular abnormalities, convulsions, nausea, vomiting, and itching (Ballantyne & Mao, 2003). It is always recommended to start with a low dose and then increase it gradually to avoid these side effects, especially for patients who are not familiar with opioids (Von et al., 2013). Because long-acting opioids are thought to have fewer side effects, need fewer doses, and cause less variation in analgesic blood levels, short-acting opioids can be replaced by long-acting opioids for patients with chronic persistent pain. However, strong controversies are associated with the opioid dosing formula (Argoff & Silvershein, 2009).

Morphine: Morphine, a Schedule II controlled substance, is commonly prescribed for the management of moderately severe to severe pain. It primarily acts on mu (μ) receptors, also known as OP3, or MOR (mu-opioid receptors), which are distributed in the brainstem and medial thalamus. Activation of these receptors is associated with a range of physiological effects including analgesia, respiratory depression, euphoria or excitement, sedation, constipation and addiction (Trescot et al., 2008).

Morphine can adversely affect the respiratory and cardiovascular systems, significantly limiting its clinical and therapeutic applications (Witharana et al., 2022). It may induce histamine release which potentially result in bronchospasm and hypotension. Furthermore, morphine exerts a direct respiratory depressant effect by diminishing the CNS's response to arterial carbon dioxide tension, thereby limiting respiration (Baldo, 2021). Additionally, morphine may reduce the tone of the sympathetic nervous system, which could lead to venous pooling and orthostatic hypotension as well as decreased tone in peripheral veins (Watso et al., 2022). Morphine

affects the digestive tract by decreasing intestinal motility, leading to constipation, and by causing spasms of the sphincter of Oddi and biliary smooth muscle. Urinary retention is brought on by similar effects in the genitourinary system, which cause the bladder to spasm (Witharana et al., 2022). Morphine can cause nausea and vomiting by directly stimulating the chemoreceptor trigger zone in the fourth ventricle's floor. Peripheral vasodilation and skin flushing with urticaria are examples of cutaneous alterations that might happen as a result of morphine's histamine-releasing effects. In people with sulfa allergies, the sulfites present in parenteral morphine formulations may trigger anaphylactic reactions or potentially fatal hypersensitivity responses (Watso et al., 2022).

Codeine: Codeine is an opioid analgesic with a weak affinity for μ opioid receptors (OP3/MOR) and a moderate interaction with κ -opioid receptors (KOR/OP2), which are distributed throughout the brainstem, spinal cord, limbic system, and other diencephalic regions. Activation of these receptors can lead to respiratory depression, sedation, spinal analgesia, physical dependence, and dyspnea (Trescot et al., 2008). Codeine has a half-life of 2.5 to 3 hours, and its analgesic effect is considerably weaker than that of morphine. Its pain-relieving action is primarily attributed to its metabolic conversion into morphine via the CYP2D6 enzyme. Some evidence suggests that the metabolite codeine-6 glucuronide is pharmacologically active (Vree et al., 2000). The infants of breastfeeding mothers who take codeine may experience side effects, as some women are quick metabolizers of codeine. This leads to rapid and excessive conversion of codeine into morphine, resulting in elevated morphine concentrations in breast milk and increasing the risk of potentially fatal respiratory depression in nursing infants (Corsi et al., 2021).

Alkaloids in Cancer Therapy

Alkaloids serve as cancer treatments for different patients because they influence crucial cellular pathways which control apoptosis, angiogenesis, cell proliferation and metastasis. Scientists have conducted extensive research on alkaloids as anticancer agents because they demonstrate the ability to interfere with multiple biological pathways that drive tumor development and growth.

The chemotherapy drugs Camptothecin and its related compounds topotecan and irinotecan work by blocking topoisomerase I which serves as a vital enzyme for cancer cell DNA replication (Mondal et al., 2019). Paclitaxel serves as a treatment for breast, ovarian, non-small cell lung and prostate cancer (Saini et al., 2024). The drug Vincristine functions as an effective treatment for leukemia and various types of lymphoid cancers. The medical alkaloids, with anti-proliferative properties, used in clinical practice produce their therapeutic benefits through DNA damage induction which leads to apoptosis (Dey et al., 2017).

Recent advancements have also explored the potential of metalloalkaloid complexes, such as those derived from berberine and Lutein A, to enhance therapeutic outcomes in chemotherapy while mitigating drug resistance. Furthermore, steroidal alkaloids from Solanaceae family plants have shown selective anticancer activity, with *in vitro* and *in vivo* studies supporting their potential to inhibit various cancer cell lines (Vasas et al., 2010). Fig. 1 shows different protective effects on alkaloids against cancer and intestinal damage.

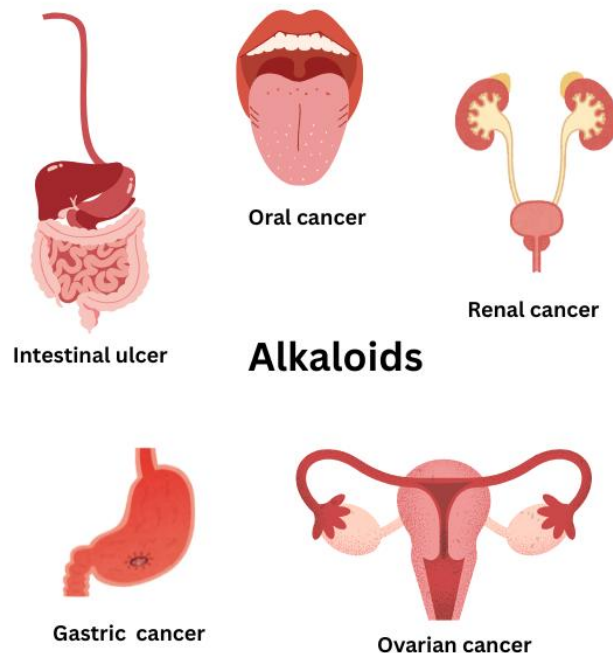


Fig 1. Protective effects of alkaloids on human health, including cancer development and gastrointestinal damage

Cytotoxic alkaloids and their apoptotic mechanisms:

In a self-amplifying cascade, caspases selectively break their substrate proteins at the aspartate residues during apoptosis. Caspases play a key role in the pathways leading to programmed cell death. The intrinsic and extrinsic pathways are the two main caspase activation pathways that have been identified (McIlwain et al., 2013). They combine the several apoptotic signals that are triggered by p53 activation, DNA damage, cytotoxic drugs, ROS generation, and abnormal oncogene expression. The apoptotic machinery is triggered upon detection of any of these signals (Prokhorova et al., 2015). Subditine, a monoterpenoid indole alkaloid, isolated from the bark of *N. subdita*, is found to activate apoptosis in human prostate cancer cells through the intrinsic pathway in a dose-dependent manner (Liew et al., 2014). Subditine therapy inhibits the anti-apoptotic activity of Bcl-2 and Bcl-xL by downregulating their expression and upregulating p53.

Role of alkaloids in apoptotic pathways:

Scutebarbatine A, a major alkaloid extracted from *Scutellaria barbata*, exhibited dose-dependent anti-proliferative activity against human lung carcinoma cells by cleaving caspases 3 and 9 and downregulating the expression of the Bcl-2 protein, as demonstrated by cytochrome c efflux to the cytosol (Yang et al., 2014). Tabernaelegantine C and tabernaelegantinine B that are obtained from the medicinal plant *Tabernaemontana elegans* activate caspase-8 in colon cells (Mansoor et al., 2013). Anticancer treatments exert their effects by modulating signaling pathways, thereby activating caspases that orchestrate and execute the apoptotic machinery to eliminate cancer cells. Newly discovered plant-derived alkaloids have very acceptable IC₅₀ values and activate a vast array of caspases. These alkaloids may exert potent inhibitory and pro-apoptotic effects when combined with conventional chemotherapy, particularly against multidrug-resistant (MDR) cancer cells, as the acquired suppression of caspase activation plays a key role in the development of chemoresistance.

Vinblastine and vincristine: microtubule-targeting antimitotic agents:

In order to minimize the adverse effects and systemic toxicities associated with cytotoxic chemotherapies, the

development of new targeted therapies has emerged as a significant advancement in cancer drug discovery (Lee et al., 2018). One approach utilized in targeted therapy involves disrupting microtubules during mitosis. Most microtubule-targeting agents (MTAs) halt the metaphase-anaphase transition by interrupting spindle assembly or spindle kinetochore attachment (Mollinedo & Gajate, 2003).

Vinca alkaloids including vinblastine and vincristine primarily target the tubulin by interrupting the microtubule network which proves effective in apoptosis induction and thus acting as a potent anticancer agent (Bates & Eastman, 2017). They disrupt microtubule by increasing oxidized glutathione, cAMP, disrupting lipid content and downregulation of Ca²⁺-calmodulin-activated cAMP phosphodiesterase. Vinblastine is primarily used in the treatment of breast cancer, bladder cancer, and lymphomas. Vincristine is mostly used to treat acute lymphoblastic leukemias and lymphomas. Similar to other microtubule-targeting agents (MTAs), plinabulin binds to the colchicine-binding site, leading to depolymerization of microtubule and anti-vascular effects (Bertelsen et al., 2011). It induces apoptosis, inhibits tumor growth, and shows enhanced efficacy when used in combination with other drugs, such as doxorubicin (Lee et al., 2018).

Neuroprotection Against Neurological Disorders

Alkaloids in the management of alzheimer's disease:

Alzheimer's disease is characterized by dementia, memory loss, and cognitive impairments. Its pathogenesis involves oxidative stress, tau protein aggregation, amyloid- β (A β) plaque deposition, and reduced acetylcholine levels (Kihara et al., 2004). Nicotine exhibits wide pharmacological properties in both CNS and PNS through stimulation of nicotinic acetylcholine receptors (nAChRs) (Ribeiro & Leite, 2003). Nicotine enhances synaptic plasticity and dopaminergic neuronal survival. Additionally, it reduces oxidative stress and neuroinflammation, thereby alleviating the severity of the pathological condition (Kharkwal et al., 2016). Nicotine contributes to neuroprotection in Alzheimer's

disease by significantly upregulating the expression of $\alpha 4$ and $\alpha 7$ nicotinic acetylcholine receptors (nAChRs) (Fargo, 2014). By attaching to the α -helical structure, it has been said to limit the synthesis of A β -peptide and enhance memory and learning through neuropeptide Y (NPY1) receptors (Girdhar et al., 2015). Through cotinine, one of its main metabolites, nicotine can reduce AD pathogenesis (Akaike et al., 2010).

Piperine inhibits acetylcholinesterase and β -secretase enzymes, thereby enhancing cognitive function and attenuating cognitive deficits and oxidative stress, as observed in Alzheimer's disease (Murata et al., 2015). Salsoline, an isoquinoline alkaloid, exerts protective effects against AD through its cholinesterase inhibitory activity (Tundis et al., 2009). Galantamine, an FDA-approved alkaloid from the Amaryllidaceae family, is derived from *Narcissus* species and *Galanthus nivalis* (commonly known as snowdrops). It is a selective, reversible Acetyl cholinesterase enzyme that increases cholinergic activity and has neuroprotective properties due to its antioxidant action (Kaur et al., 2022).

The Chinese plant toothed clubmoss (*Huperzia serrata*) yields huperzine A, an acetylcholinesterase inhibitor that impose neuroprotective effects by reducing free radical production, promoting synaptic remodeling, and controlling the excitotoxic effect of the neurotransmitter glutamate (Dall, 2013). Galantamine and huperzine A increase acetylcholine levels, thereby supporting memory and cognitive function in the brain. These alkaloids also reduce the generation of ROS and raise the levels of antioxidant enzymes like superoxide dismutase (Pasandideh & Arasteh, 2021).

Alkaloids and parkinson's disease:

neuroprotective roles: Berberine is an alkaloid that is extracted from Berberis species to treat neurological disorders through its ability to decrease oxidative stress, inflammation and mitochondrial dysfunction. Berberine activates autophagy which helps cells in eliminating their metabolic waste products. The compound protects brain health by lowering oxidative stress and reducing the level of inflammatory mediators. Berberine enhances cellular mechanisms responsible for the cleavage and clearance of misfolded proteins (Kartik et al.,

2023). Reserpine, an extract from *Rauwolfia serpentina*, limits dopaminergic levels by using vesicular monoamine transporters to help rebalance the dopaminergic link in the early stages of the disease (Bagde et al., 2014). The combination of reserpine and berberine aids to control dopamine neurotransmission which helps people with motor dysfunction.

Alkaloids in modulating neuroinflammation and oxidative stress:

Alkaloids exhibit significant anti-inflammatory and neuroprotective properties. According to Choudhury et al. (2014), Berberine has anticancer, anti-inflammatory, antihypertensive, antioxidant, anti-depressant, anti-microbial, anti-diarrheal properties along with the ability to decrease cholesterol and glucose. Fluctuations in inflammatory and oxidative stress markers indicate toxicity and can be used to assess the effectiveness of the compounds (Ijaz et al., 2023). Berberine is a promising option for treating chronic inflammation because it can inhibit COX-2 production and nuclear factor- κ B (NF- κ B) signaling (Sarbadhikary et al., 2021). Alkaloids like galantamine, which comes from the Galanthus species, function as acetylcholinesterase inhibitors in neurodegenerative illnesses, helping to alleviate the symptoms of Alzheimer's disease (Klochkov et al., 2021; Ahmed et al., 2025). Tetrahydropalmatine, a bis-benzylisoquinoline alkaloid, exerts neuroprotective effects by modulating dopamine and glutamate transmission, suggesting its potential as a therapeutic agent for Parkinson's disease and related neurodegenerative disorders (Chen et al., 2020).

Neuroprotective and antimalarial actions of

quinine: Quinine, an alkaloid derived from the bark of *Cinchona officinalis*, is now FDA-approved for the treatment of malaria (Eyal, 2018). It is used to treat neuropathy, restless legs syndrome, and muscle cramps (Houstoun et al., 2014), experimental Parkinson disease (PD), ischemic damage, and prion disorders. In both local and global models of cerebral ischemia, quinine stabilizes blood pressure, reduces inflammation, minimizes infarct size and inhibits neurodegeneration. In experimental Parkinson's disease, it shields dopaminergic neurons from neurodegeneration (Farooqui et al., 2005). The

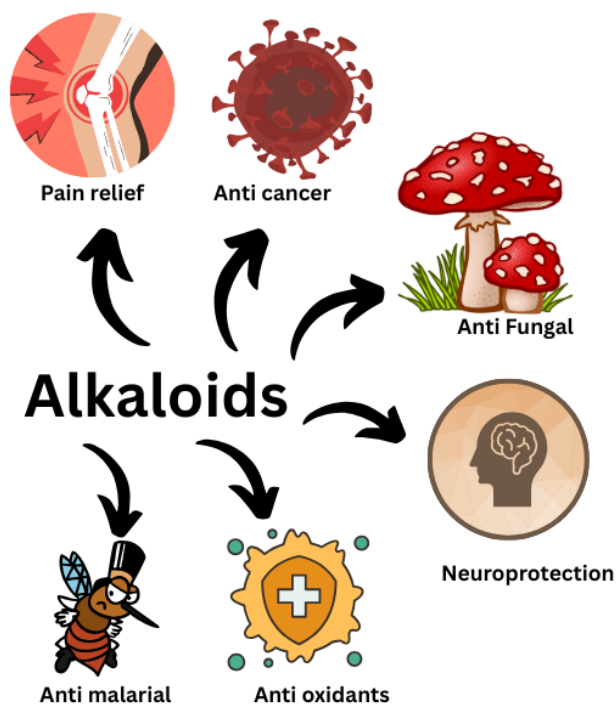


Fig 2. Pharmacological potential of alkaloids: diverse therapeutic activities including pain relief, anticancer, antifungal, neuroprotective, antimalarial, and antioxidant effects

vast therapeutic and pharmacological applications of alkaloids have been demonstrated in Fig. 2.

FUTURE PERSPECTIVES IN ALKALOID-BASED DRUG DISCOVERY

Artificial Intelligence and Computational Modeling in Alkaloid Research

Techniques such as virtual screening, machine learning, and molecular docking can be used to identify alkaloids. The multi-target activities of alkaloids become predictable through systems biology methods which allow researchers to understand how these compounds interact with complex disease systems. The combination of high-throughput screening with omics technologies (genomics, proteomics, and metabolomics) will speed up the discovery process for new alkaloids and their derivatives (Islam et al., 2024). Computational biology and artificial intelligence (AI) have brought a fresh perspective to alkaloid-based drug discovery through their recent advancements. AI algorithms enable scientists to conduct quick structure-activity relationship studies

and enhance lead compounds while predicting their binding strengths (Christodoulou et al., 2019).

Synthetic Biology and Metabolic Engineering for Sustainable Alkaloid Production

Natural alkaloids demonstrate strong biological effects but their medical applications face restrictions because of their poor absorption and metabolic processing and their harmful effects at elevated doses. The production of synthetic versions of these substances helps to overcome these restrictions. The modification of structural elements results in improved toxicity levels and better blood-brain barrier permeability and enhanced pharmacokinetic characteristics. Scientists have developed semi-synthetic galantamine derivatives which demonstrated better stability and effectiveness as proof of these advancements. Scientists can now generate perfect alkaloid analogues through synthetic biology methods which enable bacterial and plant production systems to maintain continuous production at scale (Isabel et al., 2024). Synthetic biology enables scientists to develop new methods for producing alkaloids through microbial systems which eliminate the need for plant extraction. Scientists achieve high production of complex alkaloids through genetically modified microorganisms which generate environmentally friendly results (Aryal et al., 2022).

Innovative Drug Discovery Approaches for Alkaloid Therapeutics

The role of alkaloids in personalized medicine is a prioritized approach that is shaping ongoing translational and therapeutic research. The main reason for this focus lies in the fact that alkaloids and their derivatives achieve their highest therapeutic potential when they are designed according to individual genetic and metabolic profiles (Laghezza et al., 2019). The green chemistry concept in alkaloid synthesis and extraction, such as the options of consumption of renewable solvents and catalysts is also a very advanced step towards the sustainable economy and the environment (Kar et al., 2022).

Research shows alkaloids provide strong medical benefits, yet their application needs more validation via multidisciplinary approaches. Synthetic biology may be combined with computational methods and

sustainability principles through an integrated approach to speed up drug discovery for modern healthcare needs (Mondal et al., 2019).

CONCLUSION

Alkaloids are the plant derivatives that consist of pain-relieving, anti-neoplastic and neuroprotective attributes. They got attention in pharmacognosy owing to their structural diversity and therapeutic benefits. In the past few decades, various derivatives of alkaloids, i.e., codeine, morphine, and berberine have been used as pain-relieving elements in health challenges, but these derivatives have various side effects that include addiction, euphoria, and depression. Current studies show that various novel alkaloids are emerging with improved efficiency and fewer side effects, and this has become possible due to the advancement in separation, novel computational techniques and synthetic biology and. It has been observed that the forthcoming time is suitable for alkaloid-based treatments if the interdisciplinary methods combine biology and green chemistry.

REFERENCES

- Ahmed Z, M Baig, LN Khan et al., 2025. Anti-inflammatory and antioxidant properties of herbal extracts: mechanism and therapeutic potential. *Chronicles of Biomedical Sciences* 2:50.
- Akaike A, Y Takada-Takatori, T Kume et al., 2010. Mechanisms of neuroprotective effects of nicotine and acetylcholinesterase inhibitors: Role of $\alpha 4$ and $\alpha 7$ receptors in neuroprotection. *Journal of Molecular Neuroscience* 20:211-6.
- Argoff CE & DI Silvershein, 2009. A comparison of long- and short acting opioids for the treatment of chronic noncancer pain: tailoring therapy to meet patient needs. *Mayo Clinic Proceedings* 84:602-12.
- Aryal B, BK Raut, S Bhattarai et al., 2022. Potential therapeutic applications of plant-derived alkaloids against inflammatory and neurodegenerative diseases. *Evidence-Based Complementary and Alternative Medicine*. 2022:7299778.
- Bagde SM, SG Mujbaile & PS Gangane, 2014. HPLC Stability indicating assay method for marketed herbal antihypertensive formulations containing rauwolfia serpentina benth. *Indian Journal of Physics and Natural Sciences* 4:1448-58.
- Baldo BA, 2021. Toxicities of opioid analgesics: respiratory depression, histamine release, hemodynamic changes, hypersensitivity, serotonin toxicity. *Archives of Toxicology* 95:2627-42.
- Ballantyne J & J Mao, 2003. Opioid therapy for chronic pain. *The New England Journal of Medicine* 349:1943-53.
- Bates D & A Eastman, 2017. Microtubule destabilising agents: far more than just antimetabolic anticancer drugs. *British Journal of Clinical Pharmacology* 83:255-68.
- Bertelsen LB, YY Shen, T Nielsen et al., 2011. Vascular effects of plinabulin (NPI-2358) and the influence on tumour response when given alone or combined with radiation. *International Journal of Radiation Biology* 87:1126-34.
- Chang G, L Chen & J Mao, 2007. Opioid tolerance and hyperalgesia. *Medical Clinics of North America* 91:199-211.
- Chen H, J Cao, L Zha et al., 2020. Neuroprotective and neurogenic effects of novel tetramethylpyrazine derivative T-006 in Parkinson's disease models through activating the MEF2-PGC1 α and BDNF/CREB pathways. *Aging* 12:14897-17.
- Chen KY, L Chen & J Mao, 2014. Buprenorphine-naloxone therapy in pain management. *Anesthesiology* 120:1262-74.
- Choudhury B, P Saytode & V Shah, 2014. Neurodegenerative disorders: past, present and future. *International Journal of Applied Biology and Pharmaceutical Technology* 5:14-28.
- Christodoulou MI, J Tchoumtchoua, AL Skaltsounis et al., 2019. Natural alkaloids intervening the insulin pathway: new hopes for anti-diabetic agents? *Current Medicinal Chemistry* 26:5982-6015.
- Corsi DJ & MS Murphy, 2021. The Effects of opioids on female fertility, pregnancy and the breastfeeding mother-infant dyad: A Review. *Basic & Clinical Pharmacology & Toxicology* 128:635-41.
- Dall S, 2013. Plant-derived acetylcholinesterase inhibitory alkaloids for the treatment of Alzheimer's disease. *Botanics: Targets and Therapy*. 11:19-28.
- Dey A, A Mukherjee & M Chaudhury, 2017. Alkaloids from apocynaceae: origin, pharmacotherapeutic properties and structure-activity studies. *Studies in Natural Products Chemistry* 52:373-488.
- Eyal S, 2018. The fever tree: from malaria to neurological diseases. *Toxins* 10:491-512.
- Fargo K, 2014. Alzheimer's Association Report: 2014 Alzheimers disease facts and figures. *Alzheimer's & Dementia* 10:200-16.
- Farooqui AA, WY Ong, ML Go et al., 2005. Inhibition of brain phospholipase A2 by antimalarial drugs: implications for neuroprotection in neurological disorders. *Medicinal Chemistry Reviews-Online* 2:379-92.
- Girdhar S, A Girdhar, SK Verma et al., 2015. Plant derived alkaloids in major neurodegenerative diseases: from animal models to clinical trials. *Journal of Ayurvedic and Herbal Medicine* 1:91-100.
- Hewitt DJ, RJ Hargreaves, SP Curtis et al., 2009. Challenges in analgesic drug development. *Clinical Pharmacology & Therapeutics* 86:447-50.
- Houstoun M, ME Reichman, DJ Graham et al., 2014. Use of an active surveillance system by the FDA to observe patterns of quinine sulfate use and adverse hematologic outcomes in CMS Medicare data. *Pharmacoepidemiology and Drug Safety* 23:911-7.
- Ijaz MU, T Fatima, M Batool, et al., 2023. Therapeutic efficacy of chrysoeriol on doxorubicin-induced liver

- damage by improving biochemical and histological profile in rats. *Journal of Food and Nutrition Research* 11:57-62.
- Isabel UV, AD Belen & GB Elena, 2024. A new frontier in neuropharmacology: recent progress in natural products research for blood–brain barrier crossing. *Current Research in Biotechnology* 100235-50.
- Islam MT, M Aktaruzzaman, A Saif et al., 2024. Identification of acetylcholinesterase inhibitors from traditional medicinal plants for Alzheimer's disease using in silico and machine learning approaches. *RSC Advances* 14:34620-36.
- Johnston S, 2010. Effectiveness and safety of high-dose opioids for chronic pain letter. *American Family Physician* 81:693-700.
- Kar S, H Sanderson, K Roy et al., 2022. Green chemistry in the synthesis of pharmaceuticals. *Chemical Reviews* 122:3637-710.
- Kartik S, R Pal, MJ Chaudhary et al., 2023. Neuroprotective role of chloroquine via modulation of autophagy and neuroinflammation in MPTP induced Parkinson's disease. *Inflammopharmacology* 31:927-41.
- Kaur J, Melkani I, AP Singh et al., 2022. Galantamine: a review update. *Journal of Drug Delivery and Therapeutics* 12:167-73.
- Kharkwal G, K Bрами-Cherrier, JE Lizardi-Ortiz et al., 2016. Parkinsonism driven by antipsychotics originates from dopaminergic control of striatal cholinergic interneurons. *Neuron* 91:67-78.
- Kihara T & S Shimohama, 2004. Alzheimer's disease and acetylcholine receptors. *Acta Neurobiologiae Experimentalis*. 64:99-105.
- Kittakoop P, C Mahidol & S Ruchirawat, 2013. Alkaloids as important scaffolds in therapeutic drugs for the treatments of cancer, tuberculosis, and smoking cessation. *Current Topics in Medicinal Chemistry* 14:239-52.
- Klochkov S & M Neganova, 2021. Unique indolizidine alkaloid securinine is a promising scaffold for the development of neuroprotective and antitumor drugs. *RSC Advances* 11:19185-95.
- Laghezza MV, S Bernardini, L Modesti et al., 2019. Medicinal plants as a source of alkaloids. *Medically Important Plant Biomes: Source of Secondary Metabolites* 2019:85-113.
- Lee IJ, M Lee, SJ Kim et al., 2018. Chemoembolization with vascular disrupting agent CKD-516 dissolved in ethiodized oil in combination with doxorubicin: A VX2 tumor model study. *Journal of Vascular and Interventional Radiology* 29:1078-84.
- Liew SY, CY Looi, M Paydar et al., 2014. Subditine, a new monoterpenoid indole alkaloid from bark of *Nauclea subdita* (Korth.) Steud. Induces apoptosis in human prostate cancer cells. *PLoS ONE* 9:87-100.
- Mansoor TA, PM Borralho, S Dewanjee et al., 2013. Monoterpene bisindole alkaloids, from the African medicinal plant *Tabernaemontana elegans*, induce apoptosis in HCT116 human colon carcinoma cells. *Journal of Ethnopharmacology* 149:463-70.
- Mcilwain DR, T Berger & TW Mak, 2013. Caspase functions in cell death and disease. *Cold Spring Harbor Perspectives in Biology* 7:26-71.
- Mohammad I, Y Mohamad, ZS Mohammad et al., 2013. Activity-guided isolation of bioactive constituents with antinociceptive activity from *Muntingia calabura* L. Leaves using the formalin test. *Evidence Based Complementary and Alternative Medicine* 2013:715074.
- Mollinedo F & C Gajate, 2003. Microtubules, microtubule-interfering agents and apoptosis. *Apoptosis* 8:413-50.
- Mondal A, A Gandhi, C Fimognari et al., 2019. Alkaloids for cancer prevention and therapy: Current progress and future perspectives. *European Journal of Pharmacology* 858:172-97.
- Murata K, S Matsumura, Y Yoshioka et al., 2015. Screening of β -secretase and acetylcholinesterase inhibitors from plant resources. *Journal of Natural Medicines* 69:123-9.
- Pasandideh S & A Arasteh, 2021. Evaluation of antioxidant and inhibitory properties of *Citrus aurantium* L. on the acetylcholinesterase activity and the production of amyloid nano–bio fibrils. *International Journal of Biological Macromolecules* 82:366-72.
- Pereira RM, GA Ferreira-Silva, M Pivatto et al., 2016. Alkaloids derived from flowers of *Senna spectabilis*, (–)-cassine and (–) spectraline, have antiproliferative activity on HepG2 cells for inducing cell cycle arrest in G1/S transition through ERK inactivation and downregulation of cyclin D1 expression. *Toxicology in Vitro* 31:86-92.
- Prokhorova EA, AV Zamaraev, GS Kopeina et al., 2015. Role of the nucleus in apoptosis: Signaling and execution. *Cellular and Molecular Life Sciences* 72:4593-612.
- Ribeiro RA & JR Leite 2003. Nantenine alkaloid presents anticonvulsant effect on two classical animal models. *Phytomedicine* 10:563-8.
- Saini A, K Seni , PA Chawla et al., 2024. An insight into recent updates on analytical techniques for bioactive alkaloids. *Phytochemical Analysis* 35:423-44.
- Sarbadhikary P, BP George & H Abrahamse, 2021. Inhibitory role of berberine, an isoquinoline alkaloid, on NLRP3 inflammasome activation for the treatment of inflammatory diseases. *Molecules* 26:6238.
- Trescot AM, S Datta, M Lee et al., 2008. Opioid pharmacology. *Pain physician* 11:133-53.
- Tundis R, F Menichini, F Conforti et al., 2009. A potential role of alkaloid extracts from *Salsola* species (Chenopodiaceae) in the treatment of Alzheimer's disease. *Journal of Enzyme Inhibition and Medicinal Chemistry* 24:818-24.
- Vasas G, G Borbely, P Nanasi et al., 2010. Alkaloids from cyanobacteria with diverse powerful bioactivities. *Mini Reviews in Medicinal Chemistry* 10: 946-55.
- Verma PR, AA Joharapurkar, VA Chatpalliwar et al., 2005. Antinociceptive activity of alcoholic extract of *Hemidesmus indicus* R.Br. in mice. *Journal of Ethnopharmacology* 102:298-301.
- Von Korff MR, 2013. Long-term use of opioids for complex chronic pain. *Best Practice & Research: Clinical Rheumatology* 27:663-72.
- Vree TB, RT van Dongen & PM Koopman-Kimenai, 2000. Codeine analgesia is due to codeine-6-glucuronide, not morphine. *International Journal of Clinical Practice* 54:395-8.

- Watso JC, LN Belval, FA Cimino 3rd et al., 2022. Low-dose morphine reduces tolerance to central hypovolemia in healthy adults without affecting muscle sympathetic outflow. *American Journal of Physiology - Heart and Circulatory Physiology* 323:H89-99.
- Witharana TN, R Baral, VS Vassiliou 2022. Impact of morphine use in acute cardiogenic pulmonary oedema on mortality outcomes: a systematic review and meta-analysis. *Therapeutic Advances in Cardiovascular Disease* 16:17539447221087587.
- Yang L & J Stockigt, 2010. Trends for diverse production strategies of plant medicinal alkaloids. *Natural Product Reports* 27:1469-79.
- Yang XK, MY Xu, GS Xu et al., 2014. In Vitro and in Vivo Antitumor Activity of Scutebarbatine A on human lung carcinoma A549 cell lines. *Molecules* 19:8740-51.
- Yogesh B, YV & C Sumitra, 2012. Brine shrimp cytotoxicity, anti-inflammatory and analgesic properties of *Woodfordia fruticosa* Kurz flowers. *Iranian Journal of Pharmaceutical Research* 11:851-61.