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Alkaloids and Their Utilization in Drugs

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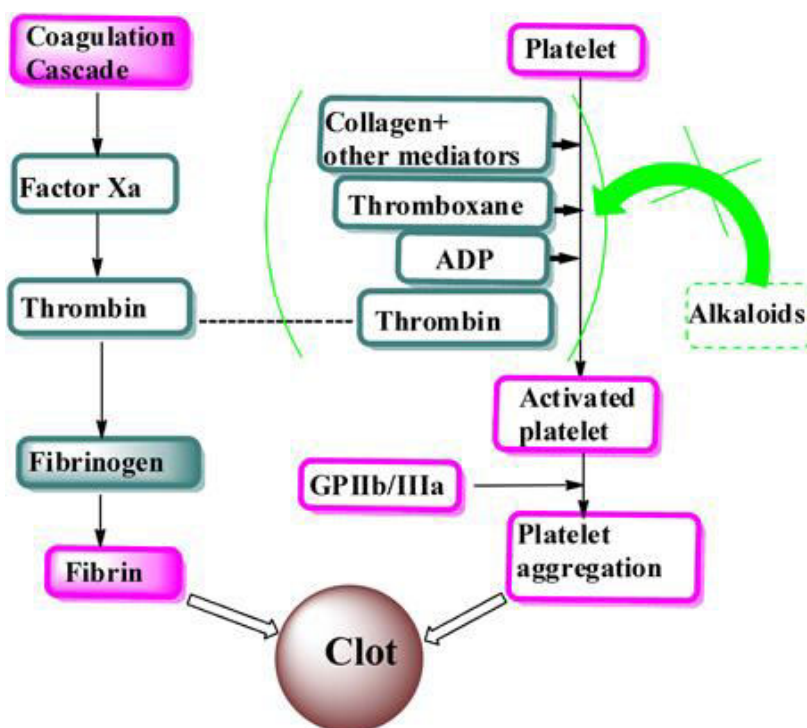
ABSTRACT: Alkaloids play an essential role in both human medicine and in an organism’s natural defence. Alkaloids make up approximately 20% of the known secondary metabolites found in plants. In plants, alkaloids protect plants from predators and regulate their growth. Therapeutically, alkaloids are particularly well known as anaesthetics, cardioprotective, and anti-inflammatory agents. Well-known alkaloids used in clinical settings include morphine, strychnine, quinine, ephedrine, and nicotine. Recently, there is a resurgence of interest in bioactive natural products, driven both by a very proactive development in the field of traditional medicines (ethnopharmacology) as well as their potential in drug discovery

KEYWORDS: alkaloids, morphine, ephedrine, nicotine, quinine, strychnine, medicines

INTRODUCTION

An alkaloid is a class of naturally occurring organic nitrogen-containing compounds that are frequently found in the plant kingdom. Many alkaloids are valuable medicinal agents that can be utilized to treat various diseases including malaria, diabetes, cancer, cardiac dysfunction etc. Similarly, platelet aggregation beyond the purpose of homeostasis is the underlying cause of blood clotting related diseases. This review presents a thorough understanding of alkaloids as antiplatelet agents with a possible mechanism of action based on the literature of the last decade. In addition, this review will address the antiplatelet activity of alkaloids and their medicinal usage as potent antiplatelet agents with a description of structural relationship activity and possible lead compounds for future drug discovery. [1,2,3]

Based on the literature, the alkaloids isolated from various sources provoked antiplatelet activity generally mediated through multiple mechanisms, different from aspirin which is a cyclooxygenase inhibitor and thus expressed their widespread potential as new effective agents of the class or as lead compounds.





Proposed mechanism of alkaloids as antiplatelet.

One would assume that with a 4000+ year history of use, often acting as remedies for a variety of illnesses, alkaloids and alkaloid containing taxa would play an important and visible role in modern drug development (Bruhn and Bruhn, 1973). Or in the words of G. Cordell (1981) focusing on local and traditional uses:[5,7,8] ‘For thousands of years, indigenous groups around the world discovered, through self-experimentation with locally available plant extracts, that they could provide materials for hunting prey, culinary enhancement, amelioration from disease, relief of pain, and healing...in this [last] 200-year period, many alkaloids became critical components of the global pharmaceutical armamentarium, and tremendous healing has resulted from their clinical application’ (Royal Society of Chemistry, 1971). Our search using the ‘Dictionary of Alkaloids (Buckingham, 2010) and other sources identified a total of 53 alkaloids used currently or within the last 50 years for pharmaceutical applications (Table 1). To date less than 0.002% (53/27,000) of alkaloids or alkaloid-based drugs are marketed for such uses internationally (Table 1). It is not surprising that such a diverse set of natural products and their derivatives yield medicines which are used in a variety of applications ranging from cough-suppressants to antimalarial agents. However, in the last 25 years only galanthamine and taxol were newly introduced into biomedicine.[9,10,11] and the former in essence through an extension of the therapeutic claims (i.e. from poliomyelitis to Alzheimer's disease, Heinrich and Teoh, 2004). There are only less than 200 others which are commonly used in industrial processes and the manufacturing of commercial goods (for example: N,N'-dioctadecanoylethanediamine is an antifoaming agent used in the polymer industry and methylamine hydrochloride is used in the tanning industry).[12,13,15]

Table 1. Record of alkaloids used in marketed medicines, drugs, and clinical environments (excluding additive used in extending the storage life of drawn blood) (Based on The Royal Society of Chemistry, 1971; Cordell, 1981, Schmeller and Wink, 1998, Buckingham, 2010). Derivatives not included.

Alkaloid name	Synonyms	Applications	Example product
Aconitine		Rheumatism, neuralgia, sciatica	Aconitysat™, Bronpax™, Pectovox™, Vocadys™
Adenine		Antiviral agent, pharmaceutical aid used to extend storage life of whole blood	Adenosine, An-syr®
Ajmaline	Ajmaline, Gilurytmal, Merabitol, Raugalline, Rauwolfine, Rytmalin, Tachmalin	Antiarrhythmic agent	Aritmina™, Gilurytmal™, Rauwopur™, Ritmos™
Atropine	Tropine tropate	Antispasmodic, anti-parkinson, cycloplegic drug	Abdominol™, Espasmo™, Protecortor™, Tonaton™
Berberine	Berbericine, Umbel-latine,	Eye irritations, AIDS, hepatitis	Kollyr™, Murine™, Sedacollyre™
Boldine		Cholelithiasis, vomiting, constipation	Boldoflorine™, Boldosal™, Ox-yboldine™, Sambil™
Caffeine		Neonatal apnea, atopic dermatitis	Agevis™, Anlagen™, Thomapyrine™, Vomex A™



Alkaloid name	Synonyms	Applications	Example product
Canescine	Harmony1, Raunormine, Recanescine, Reserpine	Antihypertensive agent	Deserpidine
Cathine	Norpseudoephedrine, Norisoephedrine	Anorectic drug	Amorphan™, Eetless™, Recatol™
Cinchonidine	Cinchonan-9-ol	Increases reflexes, epileptiform convulsions	Quinimax™, Paluject™
Cocaine		Local anesthetic	Used in highly regulated clinical environments
Codeine	Methylmorphine, Codecept, Codein, Tussipan	Antitussive, analgesic	Antituss™, Codicaps™, Tussipax™
Colchicine		Amyloidosis treatment, acute gout	ColBenemid™, Colgout™, Verban™
Diethanolamine	2,2'-Dihydroxydiethylamine, Diolamine	Base used in pharmaceuticals etc.	Menbutone Diethanolamine
Emetine	Ipecine, Methylcephaleine	Intestinal amoebiasis, expectorant drug	Cophylac™, Ipecac™, Rectopyrine™
Ephedrine		Nasal decongestant, bronchodilator	Amidoyna™, Bronchicum™, Peripherin™, Solamin™
Ergometrine	Ergonovine, Ergotrate, Ergobasine, Ergotocin, Ergostetrine	Postpartum/postabortal hemorrhage	Ergometron™, Ergotrate Maleat™, Syntometrine™
Ergotamine		Migrane treatment	Ergostat™, Lingraine™, Migral™, Virdex™
Eserine	Physostigmine	Ophthalmology, antidote/poisoning	Anticholium™, Antilirium™, Piloserine™
Galanthamine	Galantamine, Karantonin, coremine	Jilkon, Ly-Muscle relaxant, Alzheimer's	Nivalina™
Hydrastine		Gastrointestinal disorders	Gine Sedans™, Kollyr™
Hyoscine	Scopolamine	Motion sickness,	Buscopan™, Hyospasmol™,



Alkaloid name	Synonyms	Applications	Example product
			Lotanal™, Transcop™
Hyoscyamine	Daturine, Duboisine	Antispasmodic, anti-parkinson, cycloplegic drug	Bellatard™, Cystospaz™, Donnatab™, Urised™
Lobeline		Anti-smoking, asthma, cough	Citotal™, Lobatox™, Refrane™, Stopsmoke™
Morphine		Pain relief, diarrhea	Diastaf™, Durormorph™, Oramprph™, Spasmofen™
N,N-Diallylbisnortoxinerine	Alcuronium chloride	Short acting muscular relaxant	Alloferin
Narceine		Cough suppressant	Peneraj™
Nicotine		Anti-smoking	Nicabate™, Nicoderm™, Nicorette™, Stubit™
Noscapiene	Narcotine	Cough suppressant	Bequitusin™, Degoran™, Tossamine™, Tussisedal™
Papaverine	Papaveroline tetraethyl ether	Vasodilator, gastrointestinal disorders	Acticarbine™, Opdensit™, Pameion™, Vasocalm™
Pelletierine		Tenia infestations	Pelletierine tannate USP
Pilocarpine	Ocucarpine, Pilocarpol, Syncarpine	Miotic in treatment of glaucoma, leprosy	Frikton™, Piladren™, Salegen, Thiloadren™, Vistacarpin™
Quinidine	Conquinine, chinine, Pitayine	Con- Ventricular and supraventricular arrhythmias, malaria, cramping	Cardioquin™, Duraquin™, Quindex™, Rhythomochin 1™
Quinine	6'-Methoxycinchonan-9-ol, Chinin	Malaria, babesiosis, myotonic disorders	Adaquin™, Biquinate™, Quinoctal™, Zynedo-B™
Raubasine	Ajmalicine	Vascular disorders	Circolene™, Cristanyl™,



Alkaloid name	Synonyms	Applications	Example product
			Duxil™, Sarpan™
Rescinnamine	Reserpinine, Anaprel, Apoterin, Cinnaloid, Rescaloid, Moderil, Scinnamina	Hypertension	Detensitral™, Diuraupur™, Rauwopur™
Reserpine		Hypertension, psychoses	Abicol™, Briserin™, Sandril™, Terbolan™
Rotundine	Argemonine, Bisnorargemonine,	Analgesic, sedative, hypnotic agent	Rotundin-BVP, Transda
Sanguinarine		Antiplaque agent	Toothpastes and mouthwashes
Sparteine		Uterine contractions, cardiac arrhythmias	Anxoral™, Difucord™, Normotin™, Tachynerg™
Strychnine	Strychnidin-10-one	Eye disorders	Dysurgal™, Pasuma™, Retinovix™, Senirakt™
Synephrine		Vasoconstrictor, conjunctival decongestant, weight loss	Oxedrine, Sympatol
Taxol	Paclitaxel, Taxol A, Anzatax, Yewtaxan	Mamma and ovary carcinoma	Taxol™
Theobromine		Asthma, diuretic agent	Atrofed™, Circovegetalin™, Dynamol™, Urodonal™
Theophylline	Austyn, Elan, Elixophyllin, Euphyllin, Nuelin	Asthma, bronchospasms	Adenovasin™, Aerobin™, Euphyllin™, Theochron™
Turbocuranine	Tubarine	Muscle relaxant	Jexin™, Tubarine™
Vinblastine		Hodgkin's disease, testicular cancer, blood disorders	Periblastine™, Velban™, Velbe™, Velsar™
Vincamine		Vasodilator	Aethroma™, Angiopac™, Pervin™, Vincimax™
Vincristine		Burkitt's lymphoma	Norcristine™, Oncovin™, Vin-



Alkaloid name	Synonyms	Applications	Example product
Vindesine		Chemotherapy	DAVA, Eldesine, Eldisine
Yohimbine	Aphrodine, Corymbin, Corynine, Yohimex, Hydroergotocin, brachine, Yohimvetol	Aphrodisiac, urinary incontinence	Aphrodyne™, Pasuma™, Prowess™, Yohimex™

II.DISCUSSION

Alkaloids are secondary metabolites, which carry one or several nitrogen atoms, mostly in their ring structures. More than 30000 different alkaloid structures have been found in Nature. Most of them derive from amino acid precursors, such as phenylalanine, tyrosine, tryptophan, lysine, arginine, and ornithine.[15,17,18]

Alkaloids have evolved in nature as defence substances against herbivores, and to a lesser degree against microbes or competing plants. As a consequence, most alkaloids show a pronounced toxicity. Many alkaloids interact with elements of neuronal signal transduction, such as ion channels; ion pumps; neurotransmitter receptors; enzymes, which degrade neurotransmitters; and transporters. Cytotoxic alkaloids often interfere with DNA (via alkylation or intercalation) and microtubules and induce apoptosis.

As a consequence, plants with alkaloids are either known as toxic plants or as medicinal plants, because they can interfere with molecular targets that are relevant in health conditions. For example, morphine is still used as an analgetic drug; vinblastine, paclitaxel, and camptothecin as antitumor drugs; and galantamine and physostigmine as inhibitors of acetylcholine esterase.

The use of alkaloids in medicine (in the treatment of cancer, parasitic diseases, pathogenic bacteria, and neuronal disorders) and even in agriculture is an exciting field, because many alkaloids have not yet been discovered, and in most cases their exact mode of action has not been elucidated. New tools, such as Next Generation Sequencing, RNASeq, and high-resolution microscopy, offer the possibility to understand the activity of alkaloids at the DNA level.

Alkaloids are a type of natural compound possessing different pharmacological activities. Natural products, including alkaloids, which originate from plants, have emerged as potential protective agents against neurodegenerative disorders (NDDs) and chronic inflammations. A wide array of prescription drugs are used against these conditions, however, not free of limitations of potency, side effects, and intolerability. In the context of personalized medicine, further research on alkaloids to unravel novel therapeutic approaches in reducing complications is critical. In this review, a systematic survey was executed to collect the literature on alkaloids and their health complications, from which we found that majority of alkaloids exhibit anti-inflammatory action via nuclear factor- κ B and cyclooxygenase-2 (COX-2), and neuro-protective interaction through acetylcholinesterase (AChE), COX, and β -site amyloid precursor protein activity. In silico ADMET and ProTox-II-related descriptors were calculated to predict the pharmacological properties of 280 alkaloids isolated from traditional medicinal plants towards drug development. Out of which, eight alkaloids such as tetrahydropalmatine, berberine, tetrandrine, aloperine, sinomenine, oxymatrine, harmine, and galantamine are found to be optimal within the categorical range when compared to nicotine.[19,20,21] These alkaloids could be exploited as starting materials for novel drug synthesis or, to a lesser extent, manage inflammation and neurodegenerative-related[22,23,25] complications. Inflammation is a nonspecific and immediate response mechanism of the body's innate system against infectious (bacteria, viruses, fungi, and parasites) and noninfectious stimuli. Innate immune cells include white blood cells such as dendritic cells, neutrophils, natural killer cells, monocytes/macrophages, eosinophils, and basophils. Innate immune[25,27,28] cells can produce and release pro-inflammatory mediators such as NO, cytokines, chemokines, hormones, growth factors, and adhesion molecules to sustain their communication and orchestrate immune responses [29,30,31].

Nuclear factors, such as NF- κ B, a family of inducible transcription factors, play a significant role in the inflammatory process because they regulate genes involved in immunological and inflammatory responses [32]. NF- κ B is responsible for the transcriptional induction of several cytokines, chemokines, growth factors, cell adhesion molecules, and some acute-phase proteins. The activation of NF- κ B involves the phosphorylation and degradation of its inhibitory protein

via proteasomal degradation. As a result, free NF- κ B is released into the nucleus, where it binds to κ B binding sites in the promoter site of target genes, causing pro-inflammatory cytokine transcription. The major cytokines it regulates include tumor necrosis factor (TNF)- α , interleukin (IL)-1, IL-6, IL-8, and IL-12 IL-18. Furthermore, it also regulates the expression of chemokines, such as monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-2 (MIP-2), C-X-C motif chemokine ligand (CXCL)-1, and CXCL-10 [33]. NF- κ B also modulates the inflammasome, a multiprotein complex composed of pattern recognition receptors that act as an innate immune system sensor to infectious microorganisms and host inflammatory proteins [34].

Overall, positive feedback mechanism and inflammatory cytokines again activate NF- κ B in innate immune cells, thereby inducing cytokines and chemokines in greater quantity leading to further infiltration of inflammatory cells to disseminate the inflammation [35]. This reaction further helps on-site differentiation and infiltration of adaptive immune cells to eliminate microbes and harmful antigens [36]. Usually, inflammation and release of inflammatory mediators are beneficial to the host as it helps resolve the diseases; however, the dysregulation of the inflammatory responses results in severe tissue damages and contributes to the development of acute or chronic inflammatory diseases. Therefore, in the later case, the inhibition of inflammatory mediators or their receptors remains beneficial to prevent further tissue damage.

Prostaglandins are also important in inducing an inflammatory response. They are the lipids biosynthesized in inflamed and damaged tissue and, therefore, associated with the development of acute inflammation symptoms, swelling, and redness. The generation of prostaglandins from arachidonic acid, an essential fatty acid, involved cyclooxygenase (COX) isoenzymes. The prostaglandin synthesis is blocked by nonsteroidal anti-inflammatory drugs (NSAIDs), inhibiting COX activities [37]. Nitric oxide (NO) activates and regulates COX enzyme activity during the inflammatory condition [38], besides targeting prostaglandins. Hence, NO and/or COX are also common possible therapeutic targets to suppress the inflammatory pathogenesis of diseases.

III.RESULTS

Many modern pharmaceutical treatments are derived from traditional and natural remedies. Humans have relied on herbs and plants as sources of effective medicine for treating illness for thousands of years. In conventional medicine, more than 53,000 plant species from worldwide have been used [47]. For instance, *Berberis vulgaris*, rich in berberine alkaloids, is traditionally used as a herb that is effective in preventing coronary artery disease and shows anti-inflammatory and immunomodulatory effects. The trigonelline alkaloid, isolated from *Trigonella foenum-graecum* in China, is effective for curing diabetes and central nervous system (CNS) diseases [48]. Due to synergistic actions of secondary ingredients, such as oxindole and L-stachydrine from *Capparis tomentosa* has been traditionally used for inflammation in Tanzania [49]. Similarly, the traditional Chinese herbal plant *Lycoris radiata*, natural isoquinoline alkaloid, has different biological utilities, including anti-inflammatory-related activity [50]. Similarly, evolitrine, a key component identified in the leaves of *Acronychia pedunculata*, a traditional medicinal plant in Sri Lanka, was discovered to have NO inhibitory, anti-nociceptive, antihistamine, and antioxidant properties [51]. Anti-inflammatory and antioxidant activities have been revealed in alkaloids found in Malaysian and Thai *Erythroxylum cuneatum* leaf extract [52]. *Neolamarckia cadamba*, a plant traditionally used in China to treat inflammation, fever, and itch, contained 3-dihydrocadambine, a key chemical with anti-inflammatory efficacy in vitro and in vivo studies [53]. The acridone alkaloids obtained from the barks of *Citrus aurantium* have been reportedly used in Nigerian traditional medicine to treat inflammatory diseases and for the management of cancer [54]. Similarly, mistletoe, i.e., *Viscum album* L., a culturally significant plant in Europe, has been used to treat neurological conditions such as epilepsy, hysteria, nervousness, and Alzheimer's diseases [55]. Likewise, the aerial part of the plant *Sida acuta* (Malvaceae family), used in traditional Ayurvedic Indian medicine, contained a good quantity of cryptolepine, which has anti-inflammatory properties [56]. In addition, *Stephania rotunda* (Menispermaceae) has been utilized as a folk medicine in several Asian nations, which is prevalent in hilly regions of Cambodia and found to contain several bisbenzylisoquinoline alkaloids like 2-norcepharanthine, cepharanoline, and fangchinoline that is used for the management of inflammatory diseases [57]. Around 392 species of African plants have been found to possess isoquinoline alkaloids (19%) and have been used for the exclusive treatment of cancer and inflammation-related diseases [58]. *Sceletium* contains alkaloids of the mesembrine type, including Δ^7 mesembrenone, mesembranol, mesembrenone, mesembrine, and epimesembranol, which are used as a traditional medicine in South Africa to treat neurodegenerative disease [59]. In the Guangxi and Yunnan provinces of China, *Stephania cepharantha* has been widely used to treat stomach aches and snakebites, and the alkaloids present in it have been found to possess potential anti-neuroinflammatory agents [60].

IV. CONCLUSIONS

Alkaloids, one of the remarkable classes of natural compounds, exhibit extensive routes of structurally and/or functionally diverse molecules for the new potential preventative and/or therapeutical use in anti-inflammatory, AChE inhibition, and NDDs. Based on the literature survey and in silico ADMET analysis, alkaloids, namely, harmine, berberine, aloperine, oxymatrine, tetrandrine, sinomenine, tetrahydropalmatine, and galantamine, have the potential to serve as a lead compound against several anti-inflammation and NDDs. However, for further studies, it is imperative to explore extensively clinical trials, pharmacokinetic properties, health complications, and other important parameters before its medicinal applications. Many alkaloids are also toxic; thus, their safety profiles should be studied in detail. Collaborative research using alkaloids in combination with currently FDA-approved medicines could be investigated for improved and long-term anti-inflammatory and anti-AChE formulations. Hence, this review will be significant on medicinal chemistry, ethnopharmacological applications, and research on drug delivery regarding the alkaloids in the management of inflammation and NDDs.[60]

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