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Review Article

# ALKALOIDS-IMPORTANT THERAPEUTIC SECONDARY METABOLITES OF PLANT ORIGIN

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**ABSTRACT**

Plants are eminent source of new therapeutic agents that helps to alleviate human ailments and promote health. The noteworthy preventive and protective properties of these substances are related to their strong antioxidative, antimutagenic and anticarcinogenic potential. Among these, alkaloids are important secondary metabolites that are known to possess curative properties and are of prime importance for humankind. On the basis of their biosynthetic precursor and heterocyclic ring system, the compounds have been classified into different categories including indole, tropane, piperidine, purine, imidazole, pyrrolizidine, pyrrolidine, quinolizidine and isoquinoline alkaloids. These are important therapeutic molecules due to their efficacy to prevent the onset of different degenerative diseases by scavenging the free radicals or binding with catalysts of the oxidative reactions, such as some metal ions. These molecules also inhibit the growth and development of microorganisms including bacteria, fungi, protozoans etc. Due to their immense properties, these compounds are in great demand for pharmaceutical formulations and might emerge as valuable metabolite used to cure many lethal diseases like cancer. In this review, we aim to discuss about alkaloids, their biological activities and related mechanism of action for protective behaviour.

**Keywords:** Alkaloids, Secondary metabolites, Indole alkaloid, Anticancer activities.

## INTRODUCTION

Alkaloids constitute an important class of structurally diversified compounds that are having the nitrogen atom in the heterocyclic ring and are derived from the amino acids. The term 'alkaloids' was coined by the German chemist Carl F. W. Meissner in 1819 and the word is derived from the Arabic name *al-qali* that is related to the plant from which soda was first isolated [1]. These compounds are low molecular weight structures and form about 20 % of plant based secondary metabolites. Alkaloids have influenced the human history profoundly due to their wide range of physiological effects on animals and pharmacological properties such as antibiotic, anticancer along with their potential exploitation as narcotics, poisons and stimulants [2]. Till date, about 12,000 alkaloids are isolated from different genera of the plant kingdom.

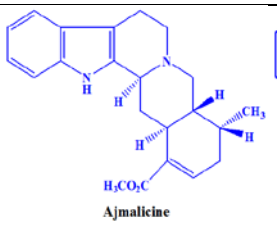
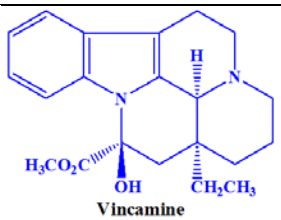
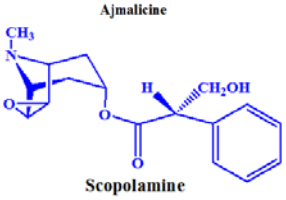
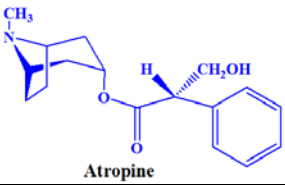
### Different alkaloids and their biological activities

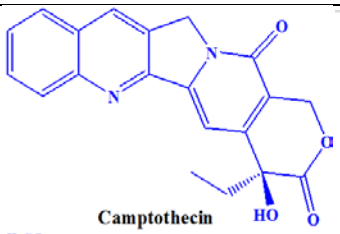
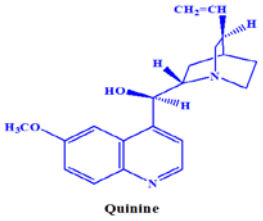
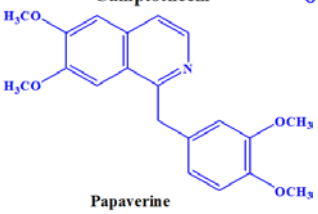
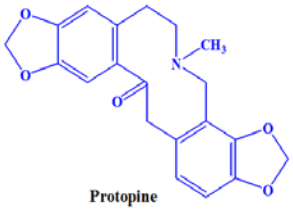
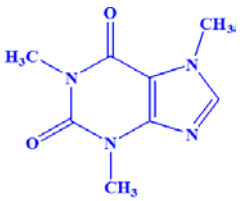
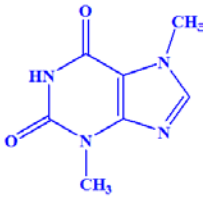
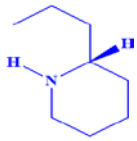
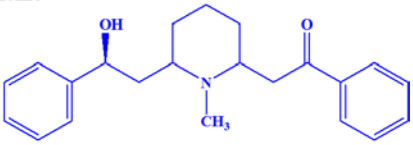
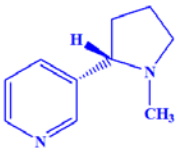
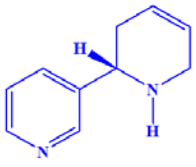
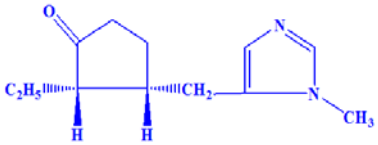
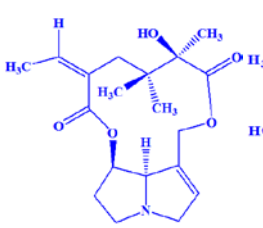
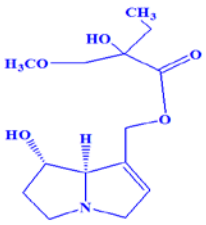
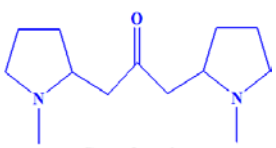
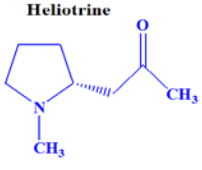
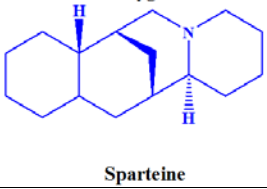
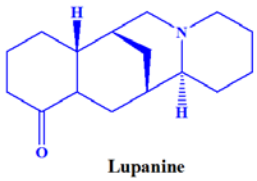
Depending upon their biosynthetic precursor and heterocyclic ring system, alkaloids have been classified into different categories including indole, tropane, piperidine, purine, imidazole, pyrrolizidine, pyrrolidine, quinolizidine and isoquinoline alkaloids. The chemical nature of these alkaloids along with their biosynthetic precursor and distribution are of primary interest. Alkaloids have been widely studied owing to their beneficial biological properties. The different alkaloids have their own specific properties and act useful for the medicinal purposes. The different alkaloids and their structures are given in table 1, and their biological activities have been mentioned in this section.

Indole alkaloids are characterized by the presence of serotonin, chemically known as 5-hydroxytryptamine or 5-HT and others of their kind. About 2,000 compounds are associated to this category of alkaloids with vincamine, vincristine, vinblastine, strychnine, ajmalicine and ajmaline as the most explored members for their biological and pharmacological properties. Vinblastine and vincristine, also known as spindle poison, are often used as anticancer drugs [3].

Tropane alkaloids belong to the families Erythroxylaceae, Convolvulaceae and Solanaceae. They have the 8-azabicyclo [3.2.1] octane nucleus and are derived from the amino acid ornithine. The alkaloids such as scopolamine, hyoscyamine, cocaine and atropine are the important members of this group and have several legitimate medicinal uses. The tropane alkaloids are known to have anticholinergic activities [2].

**Table 1: Different alkaloids and their structures**

| S. No. | Type of Alkaloids | Structures |
|---|---|---|
| 1. | Indole Alkaloid |  Ajmalicine  Vincamine |
| 2. | Tropane Alkaloid |  Scopolamine  Atropine |

| | | |
|---|---|---|
| **3.** | Quinoline Alkaloid |  Camptothecin  Quinine |
| **4.** | Isoquinoline Alkaloid |  Papaverine  Protopine |
| **5.** | Purine Alkaloid |  Caffeine  Theobromine |
| **6.** | Piperidine Alkaloid |  Coniine  Lobeline |
| **7.** | Pyridine alkaloids |  Nicotine  Anatabine |
| **8.** | Imidazole Alkaloid |  Pilocarpine |
| **9.** | Pyrrolizidine alkaloids |  Senecionine  Heliotrine |
| **10.** | Pyrrolidine alkaloids |  Cuscohygrine  (+)-Hygrin |
| **11.** | Quinolizidine alkaloids |  Sparteine  Lupanine |

Quinoline and isoquinoline are another important heterocyclic aromatic alkaloids formed due to the fusion of the benzene ring to the pyridine ring and are commonly known as benzopyridines. Quinine is an important member of quinoline alkaloids obtained from the bark of *Cinchona ledgeriana* and *C. officinalis*. It is found to be poisonous to *Plasmodium vivax* and three supplementary classes, including the single-celled organisms or protozoans that causes malaria. Other important examples of quinine alkaloids are camptothecin, echinopsine, homocamptothecin, chinidin, cinchonidin, folipdine and dihydroquinine. This class of compounds has been found to possess important biological activities *viz.* antimalarial, anti-bacterial, antifungal, anthelmintic, cardiotonic, anticonvulsant, anti inflammatory and analgesic activity [4].

Isoquinoline alkaloids, on the other hand, are the structural isomer of quinoline alkaloids. They are divided into many subclasses such as simple isoquinolines, benzylisoquinolines, morphine alkaloids, phthalide isoquinolines, protoberberines and ipecac alkaloids on the basis of an addition of groups. Many important alkaloids like narcotines, protopines, morphine, codeine and thebaine belong to this type of alkaloids. These alkaloids have the tendency to act as analgesic and narcotic drug (morphine), cough suppressant (codeine), muscle relaxant and also exert the antitumor properties associated with papaverine and noscapine respectively and antimicrobial activity linked to sanguinarine [5]. This class of alkaloids are also known to exhibit biological activities like antihyperglycemic, antitumor and antibacterial activity [6].

Purine alkaloids are obtained from purine i.e. adenine and guanine, and are commonly known as xanthenes. Caffeine, theobromine, theophylline and aminophyline are the most important members of this class of alkaloids. They have many beneficial properties such as antioxidant, anti-inflammatory, protects from diabetes, hyperlipidemia and obesity [7, 8].

Piperidine alkaloids occur widely in the plant as well as animal kingdom. It is highly studied and about 700 alkaloids of this structural type are known. The saturated heterocyclic ring, i.e., piperidine nucleus is the characteristic of piperidine alkaloids and these compounds are known for their toxicity. Apart from the toxicity, these compounds possess bactericidal, anti-histaminic, anticancer, central nervous system stimulant and depressant, herbicidal, insecticidal and fungicidal properties [9]. The best known piperidine alkaloid poisons are those of poison hemlock, *Conium maculatum*. The best known examples of piperidine alkaloids are coniine, lobeline, cynapine. Pyridine alkaloids are similar to piperidine alkaloids except that their heterocyclic nitrogen containing nucleus is unsaturated. The important examples of pyridine alkaloids are anabasin, nicotine, anatabin, anatabine, epibatidine. Pyridine alkaloids have been found to exhibit strong antimicrobial properties and are used for the same purpose [10].

Imidazole alkaloids are derived from amino acid L-histidine containing imidazole ring. Pilocarpine is an important alkaloid of this group and is obtained from *Pilocarpus jaborandi.* The product is valuable in ophthalmic practices and is used in the treatment of eye-disorders such as glaucoma [11].

The presence of pyrrolizidine alkaloids is restricted to plants belonging to families Boraginaceae, Compositae, Orchidaceae, Leguminosae, Convolvulaceae and Poaceae. Structurally, these alkaloids consist of two five membered rings (necine base) which share a common nitrogen at position 4. Senecionine, heliotrine and clivorine are the common examples of pyrrolizidine alkaloids. Pyrrolizidine alkaloids are produced constitutively in various plants as a defence against herbivores. These are hepatotoxic and may also cause hepatic veno-occlusive disease and liver cancer. Interestingly, their glycosidase inhibitory activity makes them an important compound for the treatment of diseases like cancer and diabetes [12].

Pyrrolidine alkaloids contain 5-membered, N-containing rings that are derived from amino acids ornithine (or arginine in some cases) and lysine with addition of acetate/malonate units. Putrescine, hygrine and cuscohygrine are some of the important examples of pyrrolidine alkaloids. A lot of research is being carried out on these compounds and they have shown to possess exceptional antibacterial, antifungal and antitubercular properties [13].

Quinolizidine alkaloids consist of two fused 6-membered rings that share nitrogen and show structural variations from simple to complex one. These alkaloids occur primarily in the genus *Lupinus* and are frequently referred as lupine alkaloids. However, in addition to lupinine and lupanine alkaloids, cytisine and sparteine are the two most widely distributed quinolizidine alkaloids. These alkaloids have been found to exhibit antimicrobial properties against a wide range of microorganisms [14].

**Extraction and estimation of alkaloids**

Due to the high interest in this valuable compound, researchers from all over the world have tried to find new and better techniques for the extraction and the estimation of alkaloids. Like all the other secondary metabolites, the extraction of alkaloids was also started with the paper chromatography (PC) [15]. It was the most easiest method for extraction, which was rapid and cheap. The whole sample could be analysed in a few minutes with the help of ultraviolet light. Chronologically, it was followed by the similar method of thin layer chromatography (TLC) [16]. This method was also rapid and required the $R_f$ values for the estimation of the alkaloids. It was a reproducible method and had a low detection limit as compared to PC.

High performance liquid chromatography (HPLC) method for the isolation of alkaloids has always been a widely preferred method. One of the earliest known methods for the isolation of alkaloids by HPLC was reported by Wu and Wittick [17]. It is highly accurate and has the ability to detect very small quantities of the compound. Gas chromatography (GC) was another highly appreciated method for the isolation and estimation of alkaloids. Brochmann-Hanssen and Svendsen [18], were the first to report the successful estimation of alkaloids by GC. Although, not as famous as HPLC, this method has been used for both the qualitative as well as quantitative analysis of alkaloids. The wonderful results even at low efficiency and the simple procedure were the main reasons for its acceptance. Other important methods used for the extraction of the alkaloids are microwave assisted method [19], ultrasound assisted method [20], supercritical carbon dioxide extraction method [21] and the combination of ultrasound and surfactants for the extraction of alkaloids [22].

Many methods for the estimation of alkaloids have been formulated. Both the physical and chemical methods are widely used. Among these, chromatographic methods are always of high interest, as these can be employed for both the extraction and estimation processes. The major chromatographic techniques employed for the estimation of alkaloids are PC, TLC, HPLC and GC [23-27]. Along with these methods, some important chemical methods are also used *viz.* ELISA and radio immuno assay [28]. But the major methods for the characterization of alkaloids are the spectroscopic methods involving mass spectroscopy and NMR [29-32]. These spectroscopic methods can be used either alone or in combination with the chromatographic techniques.

**Biological activities of alkaloids**

Alkaloids are known for a variety of biological activities and each having its own specific mechanism of action. Most of these mechanisms have been proved, but some have been hypothesised. Here we discuss the important biological activities of alkaloids.

**Muscle relaxant**

Alkaloids are known to have muscle relaxant property. D-tubocurarine is one such example that possesses the antiparalytic activity due to its ability to obstruct the acetycholine receptor spots which enable the muscles to unwind at neuromuscular intersections [33, 34]. The aporphine alkaloids including corstubenne, magnoflorine, isothebaine and isocorydine, isolated from *Mahonia aquifolium* were reported to relax the contractions induced by nor-adernaline as compared to those induced by KCl in isolated rat aorta [35].

**Antioxidant property**

The alkaloids are known to possess antioxidant activities due to their ability to act as scavenger of free radicals, metal chelating activity or electron or hydrogen donation ability. A quinoline alkaloid, obtained from the aleurone layer of *Oryza sativa* cv. *Heugjinmi*, was reported to

exhibit moderate antioxidative characteristics using 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals as substrate [36]. In 2004, Herraiz and Galisteo [37] examined the radical scavenging ability of twenty-nine indoles and their analogs against 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) radical cations and found the higher radical scavenging ability at physiological pH. The norditerpene alkaloids including linearilobin, linearilin, lycotonine browniine, isolated from the roots of *Delphinium linearilobum* (Trautv.), were reported to exhibit antioxidant activity using DPPH and metal chelating assays [38]. Moura *et al.* [39] reported the ROS scavenging ability, antimutagenic and antigenotoxic activities of beta-carboline alkaloids, found in medicinal plant and variety of foods, using *Saccharomyces cerevisiae* strains and comet assay in V79 cell line [39]. In another study, El-Desouky *et al.* [40] reported the strong DPPH radical scavenging ability of pyrrole alkaloid isolated from *Arum palaestinum* Boiss whereas Correche *et al.* [41] reported the antioxidant and cytotoxic effect of alkaloids such as berberine, canadine, anonaine and antioquine in a similar manner as were found for alpha-tocopherol and trolox.

**Anticancer activity**

The vinblastine and vincristine alkaloids obtained from *Catharanthus roseus* (Apocynaceae) are popularly used for the treatment of patients suffering from leukemia and hodgkin's disease. These alkaloids exert chemopreventive effect by terminating or causing depolymerisation of protein microtubules that forms the mitotic spindle in cell division. This results in hindrance in division and separation of tumour cells and reduces the incidences of cancer. Divalent calcium cation ($Ca^{2+}$) is known to regulate energy output and cellular metabolism by acting as a major signalling molecule during cell signal transduction. *Vinca* alkaloids are found to decrease calcium uptake rate and its amount into mitochondria and thus might lead to a change in cytoplasmic $Ca^{2+}$concentration that appears to enhance the cytotoxicity by selective release of cytochrome c or increasing the production of ROS [42]. Wani *et al.* [43] and Goto *et al.* [44] reported the cytotoxic effect of camptothecin alkaloids in B-388 leukemia system and human peripheral blood mononuclear cells due to the induction of tumour necrosis factor (TNF) and inhibitory activity on type I DNA topoisomerase. Likhitwitayawuid *et al.* [45] reported the cytotoxic and antimalarial activity of extracts prepared from tubers of *Stephania pierrei* due to the presence of isoquinoline and aporphine alkaloids. Similar activities, related to benzylisoquinoline alkaloids, obtained from *Stephania* spp., *Cyclea* spp. and *Berberis curare* were reported by Angerhofer *et al.* [46]. Gul and Hamann [47], in a review, concluded that marine sources including sponges, tunicates, red algae, acorn worms are rich in indole alkaloids and are known to show cytotoxic effects in a number of cancer cell lines including P-388, HCT-8 (human colon cancer cell lines), A-549 (human lung cancer cell lines), MDAMB (human mammary cancer cell lines), MCF7 (breast cancer cell lines), mouse neuroblastoma N-18 cells, human hepatoma Hep-G2 cells and murine lymphoma L-1210 cells. These alkaloids include dragmacidin, staurosporine, grossularine, halocyamine, hyrtiosins, gelliusines and kapakahines. The roots of *Aconitum yesoense* var *macroyesoense* and of *Aconitum japonicum* and *Delphinium elatum* are known to possess diterpenoid alkaloids like kobusine. Wada *et al.* [48] reported the cytotoxic effect of these alkaloids against A172 human malignant glioma cells. Sorbicillactone A was a novel type alkaloid isolated by Bringmann *et al.* [49] from the sponge derived fungus *Penicillium chrysogenum* and was also reported to exhibit cytostatic activity against murine leukemic lymphoblasts (L5178y). In addition, it also exhibit cytopathic effects against HIV-1 [49]. It was reported that the alkaloids isolated from the methanolic extract of the fresh ripe fruits of *Emblica officinalis* exhibited strong cytotoxic activity as well as inhibitory activity against gram positive and gram negative pathogenic bacteria [50]. The aporphine alkaloids of *Magnolia grandiflora* L. were reported to have cytotoxic activities against tumour cell lines including Hela (cervix tumour cancer cell lines), HEPG2 (hepato cellular carcinoma cell lines), U251 (brain tumour cell lines). These alkaloids have high to moderate antiviral activity against *Herpes simplex* and Poliovirus type-1 respectively [51]./fig. 1 depicts the mechanism of action of alkaloids at cellular level and their interaction with different transcription factors related to apoptosis, cell cycle arrest, DNA repair processes and ceramide accumulation. The effect of alkaloids on oxidative stress inducing agents could also be well understood from fig. 1. Umezawa *et al.* (1996) reported that conophylline, a vinca alkaloid isolated from the plant *Ervatamia microphylla,* exhibited tumor suppressing effect by effecting the *Ras* expressing genes [52]. It has been reported by Frederich *et al.* (2003) that Iso strychnopentamine-an indol monoterpenic alkaloid, isolated from *Strychnos usamberensis* exerted chemopreventive effect as a result of induction of apoptosis and cell cycle arrest. Induction in apoptosis is related by the translocation of phosphatidylserine from inner layer to an outer layer of plasma membrane, chromatin condensation, DNA fragmentation, activation of caspases 3 and 9 cascades and inhibition of RNA synthesis. These cytological modifications resulted in the arrest of cell cycle in G2-M phase [53]. *Scutellaria barbata* has been widely used as an antitumor agent in traditional Chinese medicine. Wang and co-workers (2011) reported that antiproliferative effects of alkaloids extract of *Scutellaria barbata* is due to the induction of apoptosis and cell cycle arrest in G2/M phase [54]. DNA damaging effect of deoxyamphimedine–a pyridoacridine alkaloid, isolated from *Xestospongia* sponges found in Philipines, is related to reactive oxygen species related phenomenon. Neoamphimedine–another member of this class, is reported to effect cytotoxicity *via* topoisomerase-2-dependent DNA aggregation/catenation. Deoxiamphimedine resulted in the production of ROS that attack DNA as a result of single strand breaks (SSB) and double strand breaks (DSB) [55].

Yin *et al.* (2005) reported the induction of apoptosis by the modulation of ROS synthesis by another alkaloid 6-methoxydihydrosanguinarine [56]. Similar type of mechanism of action was reported for quaternary benzo[c] phenanthridine alkaloids including sanguilutine and chelilutine [57]. TNF-α–a cytokine, is known to play a pivotal role in the regulation of inflammation. Conophylline was reported to down regulate the expression of the TNF-α receptors on the cell surface and in this way inhibit the TNF-α induced NF-κB activation [58]. Yui *et al.* (2001) reported that Amaryllidaceae alkaloids, lycorine and lycoricidinol inhibited the TNF-α production either by inhibiting the protein synthesis or by altering the cysteine/methionine incorporation into the macrophages [59]. Lycorine and its synthetic derivative are known to induce cell cycle arrest, up regulate the expression of pro-apoptotic proteins (caspase 3, 7 and 9) and down regulate the antiapoptotic proteins (Mcl-1, Bcl-2) [60].

Ceramide accumulation is another remarkable process associated with cancer chemoprevention. The increased availability of ceramide within the cell either by activating sphingomylinase or by blocking degradation of ceramide under the cytotoxic effect of chemotherapeutic agent resulted in modulation of associated cell signalling pathways. The resultant effect of this alteration is cell cycle arrest, terminal cell differentiation and apotosis [61]. Ceramide induced cell death is reported to be of two types depending on the dependency of transcription factors. The component alters the activity of apoptosis related proteins of BCl-2 family and its relation with preapoptotic proteins (Bax and Bad). The over expression of antiapoptotic proteins might block the ceramide mediated cell death without having an effect on its generation [62]. The much exploited role of *Vinca* alkaloids including vincristine and vinblastine in treatment of leukemia might be due to increased accumulation of ceramide in cells. Vinblastine has been reported to elevate the levels of cellular ceramide even at 1.5nM concentration that furthermore induced cell death in KB-3-1 human epidermoid carcinoma cells [62].

Nuclear factors such as NF-κB have an important role in the process of inflammation. Its presence is reported in cells that expresses cytokines, chemokines, growth factors, cells adhesion molecules and some acute phase proteins. The activation of NF-κB involves the phosphorylation of IκBs by serine residues (Ser32, Ser36) *via* the IκB kinase (IKK) signal-o-some complex. The phosphorylated IκB are ubiquitous and their degradation by 26s proteosome liberated free NF-κB that is translocated to the nucleus where it binds to κB binding sites in the promoter regions of target genes and induces the transcription of pro-inflammatory mediators e. g. iNOS, COX-2, TNF-α and IL-1B,-6 and-8 [63]. Another important factor iNOS (inducible Nitric Oxide Synthase) is expressed in response to interferon-γ, lipopolysaccharide (LPS) and various pro-inflammatory cytokines. NO

modulates acute and chronic inflammatory response by acting as potent vasodilator and thus maintain vascular homeostasis. The expression of COX-2 is induced in immune cells such as macrophages in various stress conditions that led to increase in prostaglandins (PGs) level. The elevated PGs level resulted in tumor growth due to angiogenesis and inhibition of apoptosis [63]. Poncirin isolated from the fruits of *Poncirus trifoliata* is a potent inhibitor of LPS-induced NO, $PGE_2$, TNF-α and IL-6 production in macrophages cells and it acts at transcription level. Inhibitory effect of Poncirin was found to be associated with NF-κB inactivation *via* the blockage of IκB-α phosphorylation. In addition to this, poncirin significantly declined the TNF-α and IL-6 release and their mRNA expression alongwith reduction of COX-2 and iNOS expression in macrophages cells in dose dependent manner [63]. Quinoline alkaloids isolated from *Evodia rutaecarpa* showed inhibitory effects against NF-κB activity [64].

In addition to this, Benzyisoquinoline alkaloids due to the presence of phenolic hydroxyls or similar reactive groups are reported to act as inhibitors of lipid peroxidation stimulated by $Fe^{2+}$/cysteine in rat liver microsomal fractions [65]. Martefragin A-an indole alkaloid, isolated from red alga *Martensia fragilis* has been reported to show inhibitory activity on NADPH-dependent lipid peroxidation in rat liver microsomes [66].

**Antimicrobial and amoebicidal activity**

The alkaloids of phenanthridine nature, isolated from *Chelidonium majus* Linn. were reported to exhibit antifungal activity against the clinical drug-resistant yeast isolates [68]. De Luca (2006) found the imidazole derivatives having an immense therapeutic potential and also reported their antibacterial activity. It was also found that the compounds with imidazole moiety act as p38 MAP Kinase and 5-Lipoxygenase inhibitors [69]. Lohombo-Ekomba and co-workers demonstrated that the bisbenzylisoquinoline alkaloids such as cycleanine and cocsoline isolated from *Albertisia villosa* have antibacterial, antifungal, antiplasmodial activities in addition to cytotoxic potential related to these alkaloids [70]. Diterpenoid alkaloids isolated from *Delphinium* spp. were known to possess moderate antifungal activity, along with antifeedent activity against the insect species *Spodoptera littoralis and Leptinotarsa decemlineata* [71]. Gul and Hamann, in their review on indole alkaloids, have mentioned the antiviral activities of Eudistomin, a novel oxathiazepine ring containing alkaloids isolated from *Eudistoma olivaceum* against RNA viruses such as Coxsachie A-21 and equine rhinovirus and against DNA viruses such as HSV-1, HSV-2, *Vaccinia* virus [47]. Wright *et al.* (1992) demonstrated that Dragmacidin alkaloids isolated from *Spongosorites* sp. were reported to inhibit *in vitro* replication of feline leukemia virus (FeLV) whereas Bokesch *et al.* (2000) showed the anti-HIV effect of Coscinamide alkaloids isolated from *Coscinoderma* sp [72, 73]. In 2000, Wright *et al.* assessed the antiplasmodial property against *Plasmodium falciparum*, antiamoebic against *Entamoeba histolytica* and cytotoxic activities against KB cells (human carcinoma of the nasopharynx) of twenty-one alkaloids including allocrytopine, columbamine, dehydroocoteine, jatrorrhizine, norcorydine, thalifendine, and ushinsunine [74]. Hymete and co-workers reported that the presence of alkaloids saponins and phenols in *Echinops ellebeckii* and *E. lingisetus*, and found them being the main factors contributing to their inhibitory activity against *Candida albicans*, earthworms, *Staphylococcus aureus* [75].

The quinoline alkaloids including skimmianine, kokisaginine and masculine isolated from *Raulinoa echinata* were reported to exhibit antifungal activity against *Leucoagaricus gongylophorus*, the symbiotic fungus of leaf cuttings ants (*Atta sexdens*) and *in vitro* against trypomastigote forms of *Trypanosoma cruzi* [76]. Wirasathien *et al.* demonstrated that aporphine alkaloids isolated from the aerial part of *Pseuduvaria setosa* were known to display antituberculosis activity against *Mycobacterium tuberculosis*, antimalarial activity against *Plasmodium falciparum* and cytotoxic activity against epidermoid carcinoma (KB), breast cancer (BC) and small cell lung cancer (NCI-H187) cell line [77]. Nibret *et al.* reported the *in vitro* inhibitory effect of four pyrrolizidine alkaloids including senecionine on bloodstream forms of *Trypanosoma brucei* and human leukaemia HL-60 cells. It was found that among the four alkaloids, senecionine showed moderate antitrypanosomal activity with an $IC_{50}$ value of 41.78µg/ml [78].

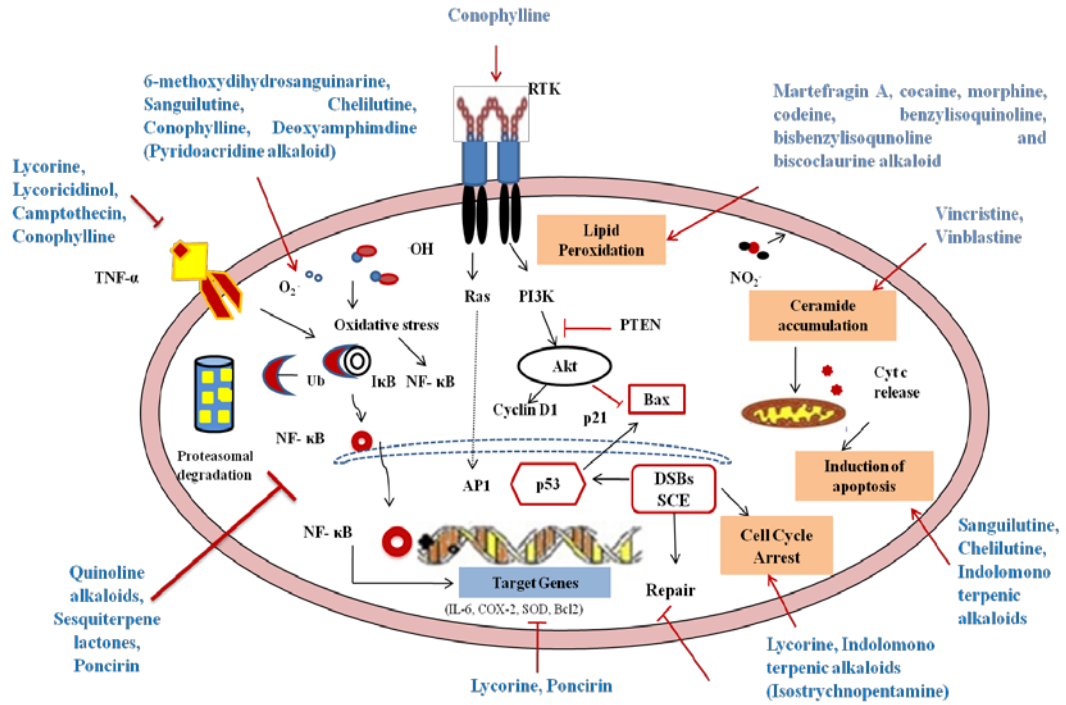



**Figure 1:** Mechanism of action of alkaloids at cellular level and their interaction with different transcription factors related to apoptosis, cell cycle arrest, DNA repair processes and ceramide accumulation and oxidative stress induc. Here, RTK = receptor tyrosine kinase; AP1 = poly(ADP-ribose) polymerase-1; NF-κB = Nuclear factor-κB; TNFα = Tumor necrosis factor α; Ub = Ubiquitin; Cyt c = cytochrome c; DSBs = double strand breaks; IκB = Inhibitor of kappa B; SCE = sister chromatid exhange; IL = interleukin; COX-2 = cyclooxygenase -2; SOD = superoxide dismutase; PTEN = phopshatase and tensin homolog; PI3K = phosphinositide-3-kinase; $NO_2$ = Nitric oxide (Modified and adopted from Nambiar *et al*., 2011 [67])

**Fig. 1**

**Other activities**

Berberine, an alkaloid isolated from *Berberis vulgaris* L., has been found to ameliorate type 1 diabetes due to the reduction in Th17 and Th1 cytokine secretion. The decreased secretion is achieved with the suppression of Th17 and Th1 differentiation by activating ERK1/2, and by inhibiting p38 MAPK and JNK activation (it down-regulated the activity of STAT1 and STAT4) respectively [79]. Cottam *et al.* demonstrated that compounds with purine, pteridine, quinazoline ring system were reported to inhibit the production of tumour necrosis factor–alpha (TNFα) in human peripheral blood monocytes and thus acts as an anti-inflammatory agents [80]. The powdered leaves and roots of *Mallotus oppositifolium* were reported to be rich in alkaloids and have been demonstrated to exhibit antioxidant and anti-inflammatory activities in beta-carotene linoleate model system and carrageenin induced rat paw oedema animal model [81]. In a review, Barbosa-Filho and co-workers evaluated the anti-inflammatory activity of 171 alkaloids of different structural groups in different models. It was concluded that Carrageenin-induced paw oedema was the most widely used model determining anti-inflammatory activity and about 137 alkaloids were effective against inflammation, with isoquinoline alkaloids being the most effective one [82]. The phenoxazone alkaloids isolated from red-orange bracket fungus *Pycnoporus cinnabarinus* was also reported to exhibit anti-inflammatory activity as well as antiviral and antimicrobial activities [83]. Hansch and Verma reported that camptothecin derivatives were found to act as DNA topoisomerase I (topo I) inhibitors whereas Motiur Rahman *et al.* related the cytotoxic activities of 2,2-dimethy-2H-pyran derived alkaloids with their potential to inhibit the topoisomerase I and II activities [84, 85].

**CONCLUSION**

These important class of secondary metabolites have been found to exhibit many important biological properties such as muscle relaxant, analgesic and antioxidant properties. These are used for the curative purposes and are helpful for the mankind. Interestingly, it has been found that alkaloids are not only beneficial to humans, but in certain cases may even be life threatening. Certain alkaloids have shown to cause paralysis, asphyxia or in some extreme conditions death of the patient. A large number of extraction and estimation methods of alkaloids have been formulated. These are developed to ease the researchers in the study of this metabolite and these methods are improvements to the previous methods.

With the advancements in the field of science and technology, alkaloids are being exploited for various purposes. Scientists have been able to synthesize halogenated alkaloids, which have made it easier to study the various gene clusters. Alkaloids have also been utilized for the pharmaceutical and curative purposes. It is hoped that this valuable metabolite may be used to cure many lethal diseases like cancer. We would like to conclude that alkaloids are useful for plants, animals, as well as humans. They can be employed for pharmaceutical purposes, due to its presence in almost all the vegetables and medicinal plants. Attention is required in testing this compound for the curative purposes of the human diseases.

**CONFLICT OF INTERESTS**

Declared None

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