



Anti-inflammatory activity of alkaloids: A twenty-century review

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RESUMO: "Atividade anti-inflamatória de alcalóides: Uma revisão do século XX". Muitas substâncias que interferem na resposta inflamatória têm sido isoladas de plantas. Esta revisão mostra alguns alcalóides de origem vegetal que no período de 1907-2000 foram avaliados quanto a uma possível atividade anti-inflamatória. Os alcalóides foram classificados em subgrupos de acordo com suas estruturas químicas e os dados farmacológicos foram obtidos de diferentes modelos experimentais. Dos 171 alcalóides avaliados, 137 apresentaram atividade anti-inflamatória, e, entre eles, os alcalóides do tipo isoquinolínicos foram os mais estudados. O modelo de edema de pata induzido por carragenina foi o mais empregado para avaliação da atividade anti-inflamatória. Nesta revisão 174 referências foram consultadas.

Unitermos: Alcalóides, atividade anti-inflamatória, inflamação, modelos experimentais.

ABSTRACT: Many substances which interfere with the inflammatory response have been isolated from plants. This review shows some alkaloids of vegetal origin which in the period of 1907 to 2000 were evaluated regarding a possible anti-inflammatory activity. The alkaloids were classified in sub-groups in accordance with their chemical structures and the pharmacological data were obtained from different experimental models. Of the 171 evaluated alkaloids, 137 presented anti-inflammatory activity, and among those, the isoquinoline type was the most studied. The Carrageenin-induced paw edema was the most used model for evaluating the anti-inflammatory activity. In this review, 174 references were cited.

Keywords: Alkaloids, anti-inflammatory activity, inflammation, experimental models.

INTRODUCTION

Inflammation can be defined as a generalized, nonspecific but beneficial response of tissues to injury. It comprises a complex array of adaptive responses to tissue injury which are both local and systemic. The local responses result in recruitment of phagocytic cells and removal of endogenous or foreign material. The systemic responses may alter the 'milieu interior' to allow these processes to occur more efficiently (Denko, 1992; Henson; Murphy, 1989). The cellular processes of inflammation fall into four major groups: changes in blood flow caused by changes in smooth muscle cell function causing vasodilatation, alterations in vascular permeability engendered by cytoskeletal contraction in endothelial cells, migration of phagocytic leukocytes to the site of inflammation, and phagocytosis (Denko, 1992; Evans; Whicher, 1992).

The main pathophysiological pathways for drug targeting at present are: arachidonic acid metabolism; the complement cascade; phagocytosis and other cell functions; auto-immune processes; protein kinase C and others enzymes involved in second messenger systems (Willianson, 1996). Early inflammation changes in damaged tissues are now known to involve the release of various biologically active materials from polymorph nuclear leukocytes, lysosomal enzymes and others. The vascular effects are primarily mediated by kinins, prostaglandins and vaso-active amines (e.g. histamine, released by mast cells), which cause increased vascular permeability leading to plasma exudation.

The inflammatory process involves a complex interplay between cells of the blood, the blood vessels themselves and the cells of the involved tissue. The process can be seen as a coordinated response of a large number of cells to an initial stimulus (Henson; Murphy,

1989).

The immigrating cells themselves exert little effect by their presence alone, but initiate all the complex reaction of inflammation as a consequence of the materials that they secrete or release to the extra cellular environment. Such materials include molecules that exacerbate the response by attracting further inflammatory cells, inhibitors that serve to reduce the severity of the reactions, histotoxic agents such as proteases, oxygen metabolites and cations, as well as signals to the surrounding inflammatory and tissue cells to implement some or all of the complex reactions which they are capable (Henson; Murphy, 1989).

Uncontrolled inflammation is undesirable. The reversible features such as pain redness, heat and swelling are joined by a fifth and less transient feature, namely, loss of function of involved organs. Therefore control of inflammation is sought to protect the body function (Denko, 1992; Parnham, 1991).

In the field of inflammation research, several experimental models have been used to evaluate the inflammation. The usual methods of determining whether compounds have anti-inflammatory activity are to test them against animal and biochemical models of inflammation. There is no experimental model of inflammation that covers all aspects of inflammation (Lewis, 1989).

The experimental models can be divided into two broad classes: (1) acute inflammatory models and (2) chronic inflammatory models. Acute models are designed to test drugs that modulate blood flow (erythema), changes in vascular permeability, leukocyte migration and chemotaxis, phagocytosis - PMNLs and other phagocytic cells, measurement of local pain, antipyretic activity, local analgesic action and rat paw edema. Chronic models are designed to find drugs that may modulate the disease process and these include sponge and pellet implants and granuloma pouches which deposit granulation tissue, adjuvant induced arthritis and rabbit monoarticular arthritis which have an immune etiology (Lewis, 1989). Experimental inflammation in whole animal is the usual starting point for anti-inflammatory testing. These experiments are varied and widely used, specially the rat paw edema test. It can be adapted in numerous ways using different inflammatory agents in attempt to mimic pathological inflammation and arthritis (Willianson, 1996).

It has been demonstrated numerous physiological changes that find a parallel in human disorders such as different forms of arthritis and acute inflammation. These responses to inflammation include variation in temperature, leukocyte counting, sedimentation rate.

Natural products have long been recognized as an important source of therapeutically effective medicines. Of the 520 new drugs approved between 1983 and 1994, 39% were natural products or derived from natural

products and 60–80% of antibacterial and anticancer drugs were also derived from natural products (Cragg et al., 1997). Plants offer a vast source of compounds that present different effects in human.

The alkaloids comprise the largest single class of secondary plant substances. They have a remarkable range of pharmacological activity. The term alkaloids generally include those basic substances that contain one or more nitrogen atoms, usually in combination as part of a cyclic system (Harborne, 1991). They are often toxic to man and many have dramatic physiological activities.

Different approaches used to analyze the anti-inflammatory potential of plant and plant-derived compounds have been developed in the past years (Mascolo, 1987; Alcaraz; Jiménez, 1988; Handa et al., 1992; Gorzalczany et al., 1996, Falcão et al., 2005). In this work we review specially the alkaloids isolated and identified from the plants, previously demonstrated to have an anti-inflammatory activity. These compounds have been selected, classified in appropriate subgroups and the data are reported based on their pharmacological activity in different experimental models.

MATERIAL AND METHODS

The keywords used for this review were anti-inflammatory activity plus alkaloids. The search was done using Chemical Abstracts, Biological Abstracts and in the data bank of University of Illinois in Chicago – NAPRALERT (Acronym for NATURAL PRoducts ALERT), updated until December 2000. The references found in the search were later consulted.

RESULTS AND DISCUSSION

Alkaloids are most common in flowering plants, and usually in the Papaveraceae (poppies), Papilionaceae (lupins), Ranunculaceae (aconites), and Solanaceae (tobacco and potatoes). They are also found in lower plants, insects, marine organisms, microorganisms and animals (Lewis, 1989).

The pharmacological studies in alkaloids have been largely concerned with the effect of alkaloids on physiological processes other than inflammation.

Only one alkaloid, colchicine is an established clinical agent for arthritic disease and leukocytoclastic vasculitis (Sais et al., 1995). The alkaloid is present in corns and seeds of crocuslike plants. Colchicine is best known for its preventive action against gout, but it also reduces pain and swelling in degenerative and immunological inflammatory disease (Malkinson, 1982).

Isoquinoline, indole and diterpene alkaloids were the most studied about their activities on inflammation. Aconitine and others alkaloids from *Aconitum* genus were screened for anti-inflammatory activity. They were effective on different assays including carrageenin-induced paw o edema, adjuvant-induced

arthritis and acetic acid induced vascular permeability tests (Benn; Jacyno, 1983; Luo et al., 1991; Zhang et al., 1982; Hikino et al., 1982; Saito et al., 1982). There are about 500 species of *Aconitum* and the species has been intensively investigated for the pharmacological activity of their alkaloids. Since anti-rheumatic properties have been associated with this plant, some attention has been made to the anti-inflammatory activity of alkaloids in *Aconitum* (Lewis, 1989).

Several isoquinoline alkaloids (berbamine, berberine, cepharanthine and tetrandine) were examined for anti-inflammatory activity. They showed to be active in different assays as reported by different authors (Wong et al., 1992; Yasukawa et al., 1993; Ono, 1994; Hikino et al., 1980). For instance, tetrandrine, a bisbenzylisoquinoline alkaloid extracted from the root of the creeper *Stephania tetrandra* S. Moore (Menispermaceae) has been shown to inhibit neutrophil and monocyte functions, including adherence, locomotion and superoxide generation (Seow et al., 1986; Seow et al., 1988) and the plant has been used for the treatment of rheumatic diseases, silicosis and other chronic inflammatory disease (Binggi et al., 1983). Several studies showed that the alkaloid suppress antigen and mitogen-induced lymphocyte proliferation, natural-Killer cell cytotoxicity, histamine release by mast cells, interleukin-1 (IL-1) secretion by human monocytes and the action of PAF on platelets (Seow et al., 1989). Teh et al. (1989 and 1990) showed that tetrandine and its natural analogue, berbamine inhibit prostaglandin and leukotriene generation by human monocytes and neutrophils in dose-dependent manner.

Berberine is a major compound present in *Phellodendri* cortex and *Coptidis* rhizoma and the plant has been used for the treatment of diarrhea and other gastrointestinal disease in Japan and some Eastern countries. Ivanovsk; Philipov (1996) and Yasukawa et al. (1991) showed berbamine had an inhibitory effect on the ear TPA-induced inflammation indicating that this alkaloid may have important activity in chronic inflammation.

The alkaloids tend to be rather toxic, although the toxicity appears to be well below the therapeutic levels. The alkaloids appear to offer the considerable promise for further investigation as anti-inflammatory compounds, and some appears to be remarkably active.

Of the 171 evaluated alkaloids, 137 presented anti-inflammatory activity, and among those, the isoquinoline type was the most studied. The Carrageenin-induced pedal edema was the most used model for evaluating the anti-inflammatory activity. In this review, 174 references were cited.

ACKNOWLEDGEMENTS

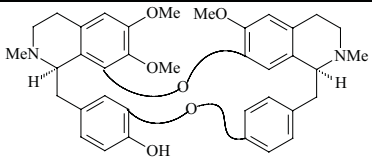
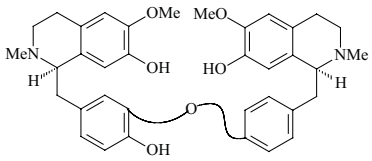
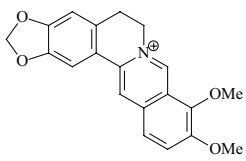
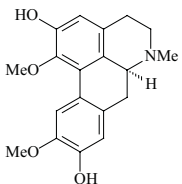
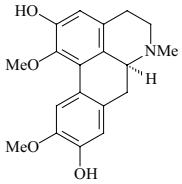
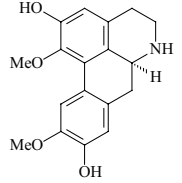
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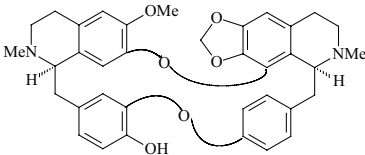
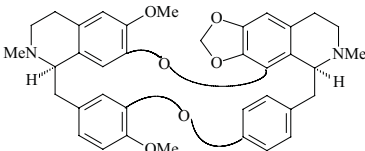
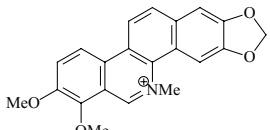
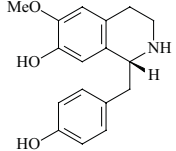
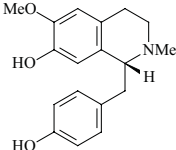
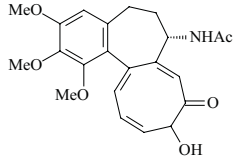
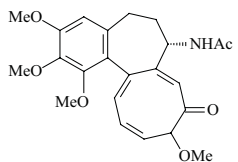
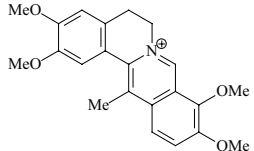
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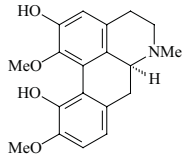
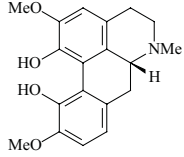
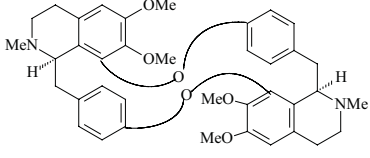
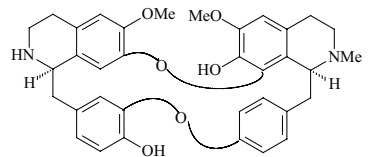
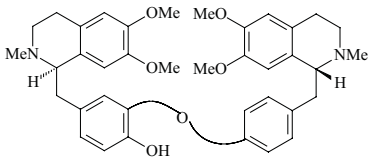
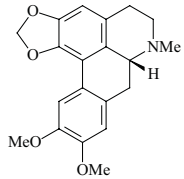
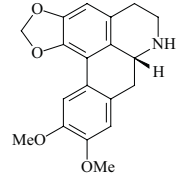
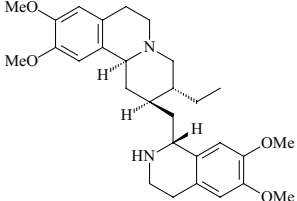
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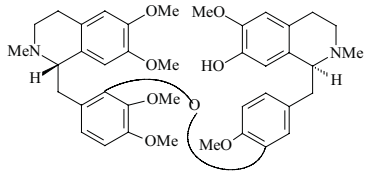
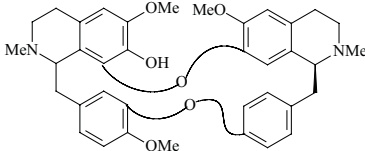
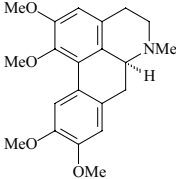
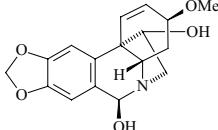
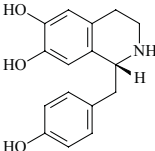
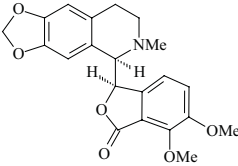
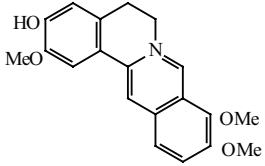
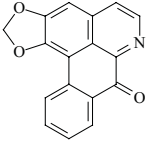
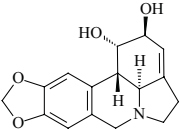
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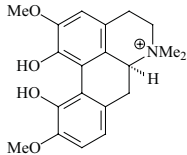
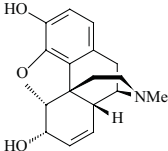
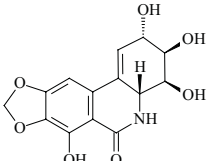
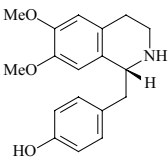
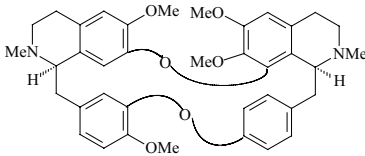
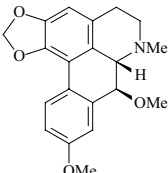
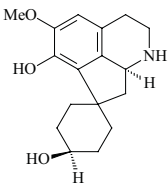
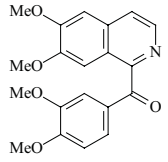
Table 1. Alkaloids isoquinoline summary showing anti-inflammatory activity

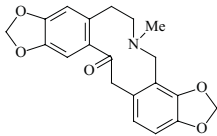
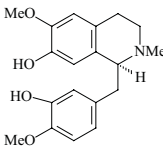
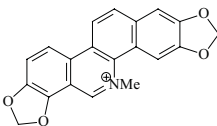
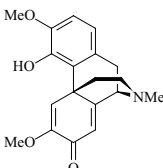
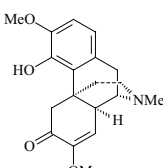
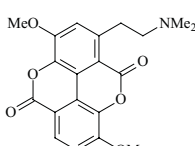
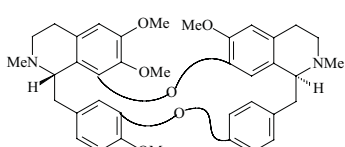
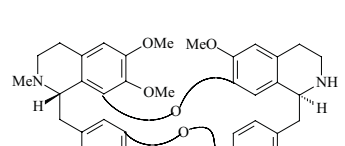
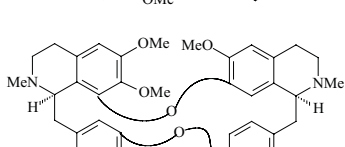
Isoquinoline Alkaloids	Structure	Effect	Assay	References
Berberine		Active	Air-pouch/carrageenin, IL-1, TNF or PAF-induced inflammation; Aracdonic acid induced inflammation; TPA induced inflammation; Adherence, locomotion and 3-Hdeoxyglucose uptake neutrophils were suppressed Sheep red blood cell; Trinitrochlorobenzeine and <i>Brucella abortus</i> induced delayed type hypersensitivity	Wong et al., 1992 Yasukawa et al., 1993 Ono, 1994 Li et al., 1989 Wong et al., 1991 Naidovich et al., 1976
Berberine		Inactive	Carrageenin-induced pedal edema	Sadritdinov, 1980
Berberine		Weak activity Inactive Active	Adjuvant-induced arthritis; Carrageenin-induced inflammation; Granuloma on chorio-allantoic membrane of fertilized eggs; Xilene-induced ear swelling Carrageenin-induced pedal edema; Cholera toxin or formalin induced inflammation Croton pellet granuloma pouch; Granulation tissue using fertile eggs; Cotton oil granuloma pouch; Granulation tissue on chick embryo chorio-allantoic membrane;	Ivanovska; Philipov, 1996 Akhter et al., 1977 Otsuka et al., 1981a Hikino et al., 1977 Zhang et al., 1990 Akhter et al., 1977 Endo et al., 1979 Otsuka et al., 1981a Hikino et al., 1980 Otsuka et al., 1982
Boldine		Active	Carrageenin-induced pedal edema	Backhouse et al., 1994
Boldine (+)		Inactive	Intracolonic acetic acid-induced colitis, edema, neutrophil, infiltration and myeloperoxidase activity were all decreased;	Gotteland et al., 1997 Grupta; Bhakuni, 1989 Lanhers et al., 1991
Boldine, nor		Inactive	In vivo, route not given Dose not stated	Grupta; Bhakuni, 1989

Cepharanoline		Active	Inflammation inhibitor	Ono, 1994
Cepharanthine		Active	Aracdonic acid induced inflammation; TPA induced inflammation Chronic inflammation and TNF- α production; Carrageenin-induced pedal edema; Croton-oil-induced edema Histamine induced edema TPA-inducer ear edema;	Yasukawa et al., 1993 Ono et al., 1994a Ono et al., 1994b Yasukawa et al., 1991
		Inactive	Granuloma formation induced with a sc implant of hcho-soaked filter paper	Fujiwara et al., 1980
Chelerythrine		Active	Carrageenin-induced pedal edema Carrageenin-induced pedal edema	Ulrichova et al., 1984 Lenfeld et al., 1981
Coclaurine		Inactive	Granuloma pouch	Kimura et al., 1985
Coclaurine, methyl		Inactive	Granuloma pouch Concanavalin-A induced inflammation; Antigen-antibody IG-E induced inflammation	Kimura et al., 1985
Colchicine		Active	In vivo, rat	Kiselev, 1977
Colchicine		Active	Mustard oil-induced edema; Pericarditis; Fibromatosis palmar; Chronic cutaneous leukocytoclastic vasculitis; Familiar mediterranean fever; Pustulosis palmaris;	Morita, 1926 Millaire; Ducloux, 1992 Pitts-JR, 1995 Plotnick et al., 1989 Kiselev, 1977 Takigawa et al., 1982
Corydaline, dehydro		Active	Edema formation; Acetic-acid-induced vascular permeability; Serotonin or bradykinin-induced edema; Histamine-induced edema; LTC4-induced edema	Matsuda et al., 1997

Corydine, iso		Inactive	In vivo	Gupta; Bhakuni, 1989
Corytuberine		Inactive	In vivo	Gupta; Bhakuni, 1989
Cycleanine		Active	In vivo	Berezhinskaya, 1972
Daphnoline		Active	Rat paw edema model; Dextran induced pedal edema; Carrageenin induced pedal edema	Yamahara et al., 1974a Salama et al., 1987 Rios et al., 1989
Dauricine		Active	In vivo	Yamahara et al., 1974b
Dicentrine		Inactive	In vivo	Gupta; Bhakuni, 1989
Dicentrine nor		Inactive	In vivo	Gupta; Bhakuni, 1989
Emetine		Active	Decrease of granulation tissue on chick embryo chorioallantoic membrane	Otsuka et al., 1981c

Fetidine		Active	Formalin-induced pedal edema	Sadritdinov, 1972
Fangchinoline		Active	Cytokine production inhibition; Yeast-induced inflammation of the paw	Onai et al., 1995 Choi et al., 2000 Hristova; Istatkova, 1999
Glaucine		Active Inactive	Granuloma pouch assay; Carrageenin-induced pedal edema	Nikolov, Peneva, 1978 Pinto et al., 1998
Haemanthidine		Active	Carrageenan-induced pedal edema	Citoglu et al., 1998
Higenamine		Active	Histamine induced paw edema; As measured by edema volume in hind paw	Zhang, 1985 Shin et al., 1996
Hydrastine		Inactive	Decrease of granulation tissue on chick embryo chorioallantoic membrane	Kisolov, 1978
Jatrorrhizine		Active	In vivo	Arens et al., 1985
Liriodenine		Inactive	Granuloma pouch	Kimura et al., 1985
Lycorine		Active	Formalin arthritis; Egg white induced pedal edema; Egg white induced pedal edema in adrenalectomized rats	Chen et al., 1965

Magnoflorine		Inactive	In vivo	Gupta, Bhakuni, 1989
Morphine		Active	Given prior to topical mustard oil	Morita, 1926
Narciclasine		Active	Adjuvant-induced arthritis	Mikami et al., 1999
Norarmepavine		Inactive	Edema in the Randall-Selitto antiinflammatory test	Kupchan et al., 1963
Obaberine		Active	Carrageenin-induced pedal edema	Sadritdinov, 1980
Oliverine		Active	Formalin-induced pedal edema	Sadritdinov; Sultanov, 1971
Oridine		Active	Carrageenin-induced pedal edema	Apoyan et al., 1984
Papaveraldine		Active	Carrageenin-induced pedal edema	Buzas et al., 1974

Protopine		Active	Dext.-induced pedal edema	Molokhova et al., 1973
Reticuline		Inactive	Granuloma Pouch	Kimura et al., 1985
Sanguinarine		Active	Carrageenin-induced pedal edema	Ulrichova et al., 1984 Hu et al., 1979 Cerna et al., 1984 Lenfeld et al., 1981
Sinoacutine		Active	Phlogistic response	Dekker et al., 1988
Sinomenine		Active	Mustard oil-induced edema	Morita, 1926
Taspine		Active	Carrageenin-induced pedal edema; Adjuvant-induced arthritis Cotton pellet granuloma Adjuvant poly arthritis	Persinos, 1972 Perdue et al., 1979
Tetrandrine		Active	Carrageenin-induced pedal edema; Aseptic or formalin induced inflammation; Carrageenin-induced inflammation; Interleukin induced inflammation	Yamahara, 1974a Choi et al., 2000 Sadritdinov, 1974 Wong et al., 1992 Naidovich et al., 1976
Tetrandrine, demethyl		Active	Aseptic or formalin-induced inflammation	Sadritdinov, 1974
Tetrandrine, iso		Active	Arachidonic acid induced inflammation; Phorbol ester induced inflammation; Cytokine production inhibition.	Yasukawa et al., 1993 Onai et al., 1995

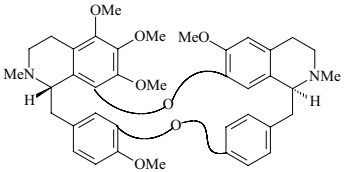
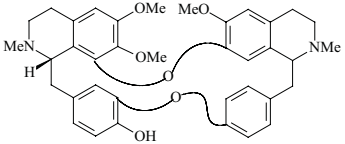
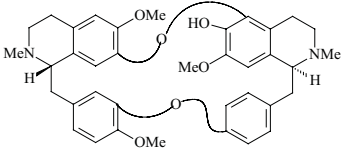
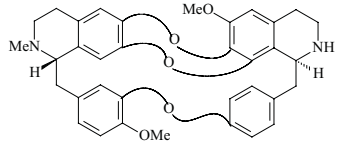
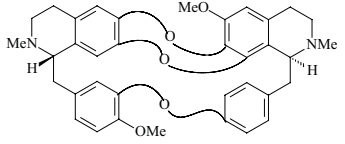
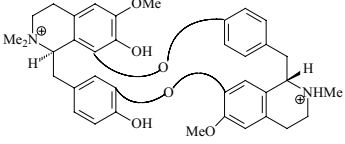
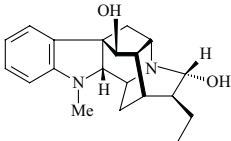
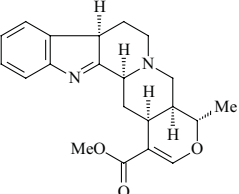
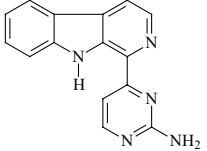
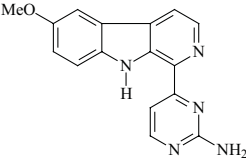
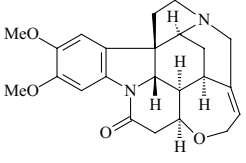
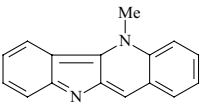
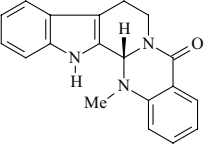
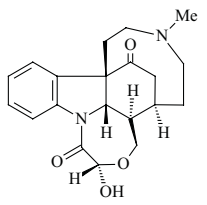
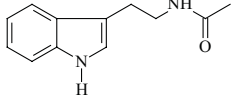
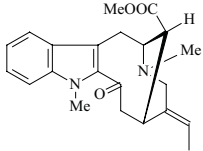
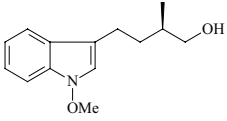
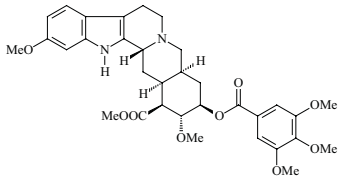
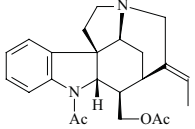
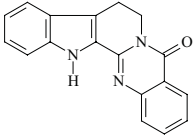
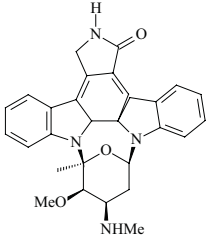
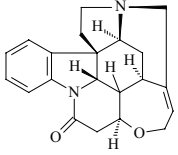
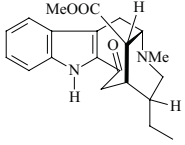
Thalicsimine		Active	Aseptic or formalin-induced inflammation	Sadritdinov; Sultanov, 1971
Thalieberine, <i>O</i> -methyl		Active	Mouse pedal edema assay	Sadritdinov; Sultanov, 1971
Thalmine		Active	Mouse pedal edema assay	Sadritdinov; Sultanov 1971
Trilobine		Active	In vivo	Yamahara et al., 1974b
Trilobine, iso		Active	In vivo	Yamahara et al., 1974b
Tubocurarine		Inactive	Decrease of granulation tissue on chick embryo chorioallantoic membrane	Otsuka et al., 1981a

Table 2. Alkaloids indole summary showing anti-inflammatory activity

Indole Alkaloids	Structure	Effect	Assay	References
Ajmaline		Active	Carrageenin-induced pedal edema	Saeed et al., 1993
Alstonine, tetrahydro		Weak activity	Carrageenan-induced pedal edema	Kocislski et al., 1972
Annomontine		Active	In vivo	Lebouef et al., 1982
Annomontine, methoxy		Active	In vivo	Lebouef et al., 1982
Brucine		Inactive	Carrageenin-induced pedal edema	Tits et al., 1991
Cryptolepine		Active	Carrageenin-induced pedal edema	Noamesi; Bamgbose, 1983 Bamgbose; Noamesi, 1981
Evodiamine		Active	Carrageenan-induced pedal edema; Serotonin induced edema; Bradykinin-induced edema; Arachidonic acid-induced ear swelling	Matsuda et al., 1998
Holstiine		Inactive	Carrageenin-induced pedal edema	Bamgbose; Noamesi, 1981 Tits et al., 1991
Melatonin		Active	Carrageenin-induced pedal edema	Mimura et al., 1982

Ochropamine		Active	In human, oral	Anonymous, 1974
Paniculidine B		Active	In vivo, IP, rat	Somei, 1987
Reserpine		Active	Egg albumin edema	Bertelli et al., 1956
Retuline, iso: O-acetyl		Inactive	Carrageenin-induced pedal edema;	Tits et al., 1991
		Active	Zymosan induced paw edema	
Rutaecarpine		Active	Carragenan-induced pedal edema;	Moon et al., 1999
		Active	Serotonin-induced edema;	Matsuda et al., 1998
		Inactive	Histamine-induced edema	
Staurosporine		Inactive	TPA-induced skin inflammation	Yamamoto et al., 1989
Strychnine		Inactive	Decrease of granulation tissue on chick embryo chorioallantoic membrane	Otsuka et al., 1981a
Tabernaemontanine		Active	In human, oral	Anonymous, 1974

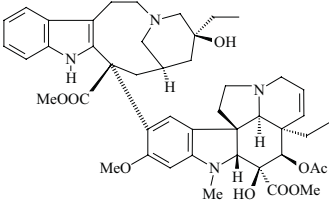
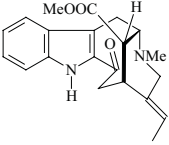
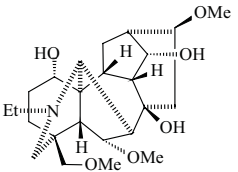
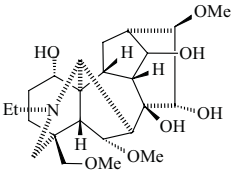
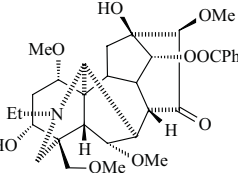
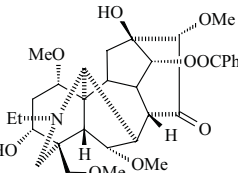
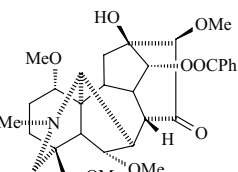
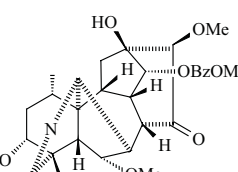
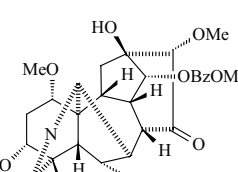
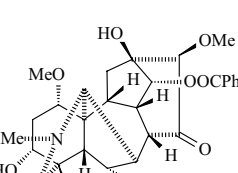
Vincalukoblastine		Active	Claimed useful in the treatment of rheumatoid arthritis	Anonymous, 1974
Vobasine		Active	In human, oral	Schinitsky, 1980

Table 3. Alkaloids diterpene summary showing anti-inflammatory activity

Diterpene Alkaloids	Structure	Effect	Assay	References
Aconine, 14 anisoyl		Active	Paw-swelling method	Murayama et al., 1991
Aconine benzoyl		Active	Carrageenin-induced pedal edema	Benn; Jacyno, 1983
Aconitine		Inactive Active	Topical mustard oil; UV light-induced erythema; Carrageenin-induced pedal edema; Adjuvant-induced arthritis Increase of vascular; Permeability induced by acetic acid.	Morita, 1926 Benn; Jacyno, 1983 Kitagawa et al., 1984 Luo et al., 1991 Benn; Jacyno, 1983
Aconitine, 3 acetyl		Active	Increased of vascular permeability induced by acetic acid; Cotton pellet granuloma	Tang et al., 1984
Delphinine Iso		Inactive	In vivo	Zhang et al., 1982
Hypaconitine		Active	Adjuvant-induced arthritis	Luo et al., 1991 Benn; Jacyno, 1983 Zhang et al., 1982
Ignavine		Active	Carrageenin-induced pedal edema	Saito et al., 1983 Saito et al., 1982
Mesaconitine		Active Inactive	Adjuvant induced pedal edema; Carrageenin-induced pedal edema; Histamine-induced pedal edema; 5-HT-induced pedal edema; PGE-1-induced pedal edema; Bradykinin-induced pedal edema.	Luo et al., 1991 Hikino, 1982

Neoline		Active	In vivo	Zhang et al., 1982
Neoline, 15-alpha-hydroxy		Active	In vivo	Zhang et al., 1982
Pyroaconitine		Active	Carrageenin-induced pedal edema	Murayama et al., 1991
Pyroaconitine, 16 epi		Active	Carrageenin-induced pedal edema	Murayama et al., 1991
Pyrohyaconitine		Active	Carrageenin-induced pedal edema	Murayama et al., 1991
Pyrojesaconitine		Active	Carrageenin-induced pedal edema	Murayama et al., 1991
Pyrojesaconitine, 16 epi		Active	Carrageenin-induced pedal edema	Murayama et al., 1991
Pyromesaconitine		Active	Carrageenin-induced pedal edema	Murayama et al., 1991

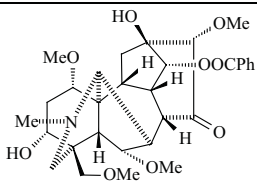
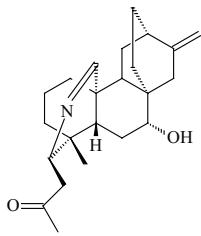
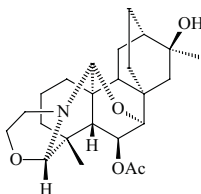
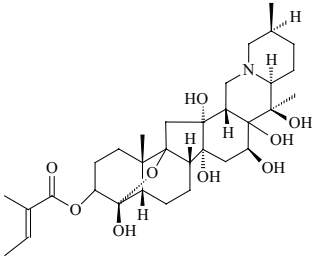
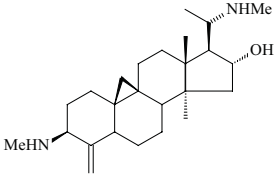
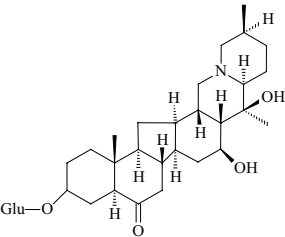
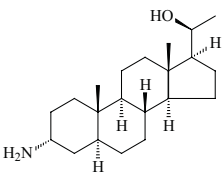
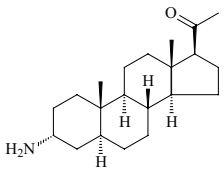
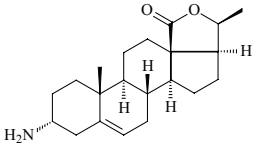
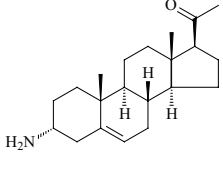
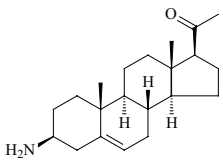
Pyromesaconitine, 16 epi		Active	Carrageenin-induced pedal edema	Murayama et al., 1991
Spiramine K		Active	In vivo	Fuji et al., 1991
Thalicsiline		Active	Carrageenin-induced pedal edema	Wu et al., 1988

Table 4. Alkaloids steroid summary showing anti-inflammatory activity

Steroid Alkaloids	Structure	Effect	Assay	References
Cevadine		Inactive	Topical mustard-oil Endotoxin induced posterior uveitis	Morita, 1926
Cyclobuxine D		Active	Formalin-induced arthritis Ovalbumin-induced arthritis	Saidkasymov, 1978
Edpetiline		Active	Kaolin-induced inflammation; Egg albumin induced inflammation	Saidkasymov et al., 1971
Funtumidine		Active	Edema in the rat's paw	Blanpin; Quevauviller, 1960
Funtumine		Active	Edema in the rat's paw	Blanpin; Quevauviller, 1960
Gitingensine		Inactive	Histamine-induced ventilation overflow	Estrada et al., 1966
Holamine		Active	Not specified	Oletta, 1964
Holaphyllamine		Active	Not specified	Oletta, 1964

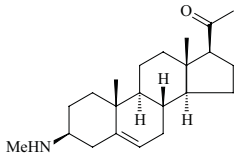
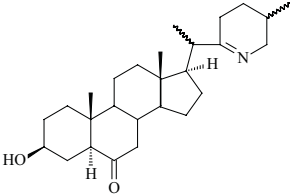
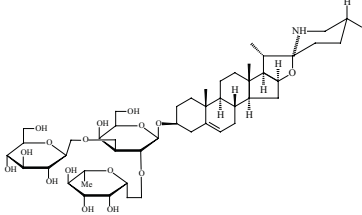
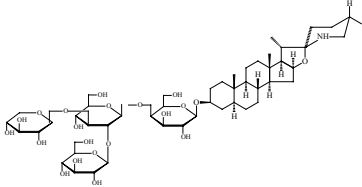
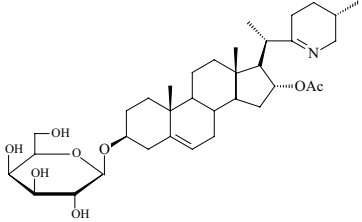
Holaphylline		Active	Not specified	Oletta, 1964
Petiline		Active	Egg albumin induced inflammation; Kaolin-induced inflammation	Saidkasimov et al., 1971
Solasonine		Active	Cotton pellet granuloma Carrageenin-induced pedal edema	Basu; Lahiri, 1977
Tomatine		Active	Carrageenan induced paw edema; Granulation tissue formation induced by the s.c. implantation of carrageenan impregnated cotton pellets; I.p. injection of acidified saline and i.v. pontamine sky blue	Filderman; Kovacs, 1969
Veralosine		Active	In vivo, rat	Saidkasimov, 1978

Table 5. Alkaloids amide summary showing anti-inflammatory activity

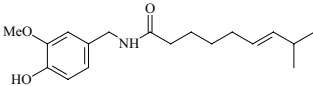
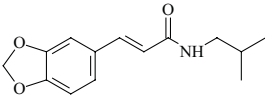
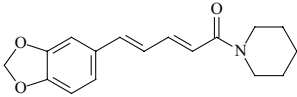
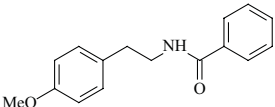
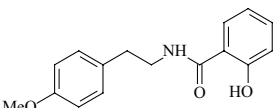
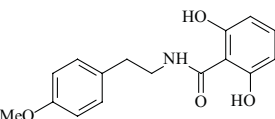
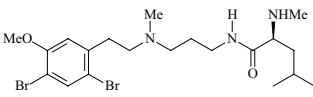
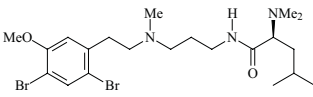
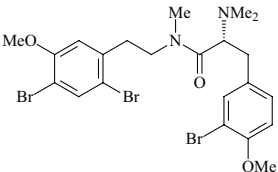
Amide Alkaloids	Structure	Effect	Assay	References
Capsaicin		Weak activity Active	Carrageenin-induced pedal edema; Non-allergic rhinitis; <i>Mycobacterium tuberculosis</i> -induced polyarthritis; Rheumatoid arthritis or osteoarthritis; Carrageenin-induced inflammation; Adjuvant-induced arthritis.	Reddy; Lokesh, 1994 De; Ghosh et al., 1988 Clarke, 1993 Cruwys et al., 1995 McCarthy et al., 1992 Raychaudhuri et al., 1991 Hara et al., 1984 Joe; Lokesh, 1997
Fagaramide		Active	Carrageenin-induced pedal edema	Oriowo, 1982
Piperine		Active	Carrageenin-induced pedal edema; Histamine-induced edema; Formalin-induced pedal edema; Cotton pellet granuloma Granuloma pouch	Reddy; Lokesh, 1994 Lee et al., 1984 Munjudar et al., 1990
Riparin I		Inactive	Carrageenan-induced pedal edema	Castelo-Branco et al., 2000
Riparin II		Inactive	Carrageenan-induced pedal edema	Castelo-Branco et al., 2000
Riparin III		Inactive	Carrageenan-induced pedal edema	Castelo-Branco et al., 2000
Volutamide B		Active	Phorbol ester induced ear inflammation	Montanari et al., 1996
Volutamide C		Active	Phorbol ester induced ear inflammation	Montanari et al., 1996
Volutamide D		Active	Phorbol ester induced ear inflammation	Montanari et al., 1996

Table 6. Alkaloids quinolizidine summary showing anti-inflammatory activity

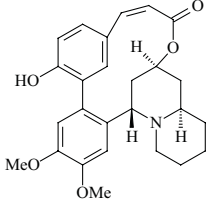
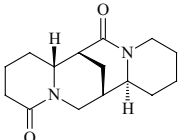
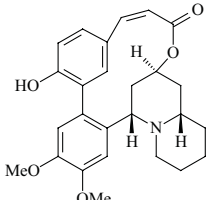
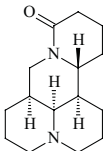
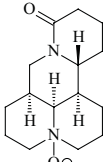
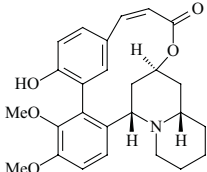
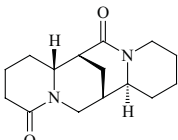
Quinolizidine Alkaloids	Structure	Effect	Assay	References
Cryogenine		Active	Carrageenan-induced pedal edema; Chronic anti-inflammatory evaluation; Adjuvant-induced arthritis	Kocialski et al., 1972 Kaplan et al., 1967 Omaye et al., 1972
Lupanine, 17 oxo		Active	Carrageenin-induced pedal edema	Murakoshi et al., 1992
Lythrine		Active	Carragenin-induced pedal edema	Byrne; Malone, 1981
Matrine		Active	Decrease ear inflammation	Tan; Zhang, 1985
Matrine, oxy		Active	In vivo, rat	Ma et al., 1991
Nesodine		Active	Active	Handa et al., 1992
Sparteine		Active	Croton-oil induced edema	Chang, Malone, 1971

Table 7. Alkaloids quinoline summary showing anti-inflammatory activity

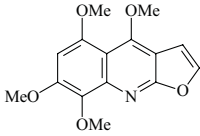
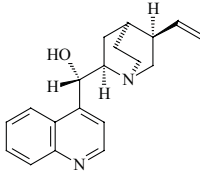
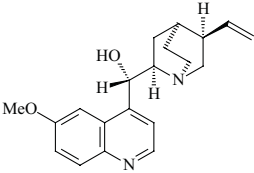
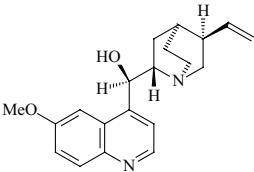
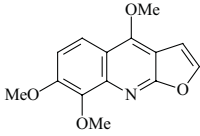
Quinoline Alkaloids	Structure	Effect	Assay	References
Acronycidine		Inactive	Erythema block	Svoboda; Kattau, 1967
Cinchonine		Active	Mustard oil-induced edema	Morita, 1926
Quinidine		Active	Mustard oil-induced edema	Morita, 1926
Quinine		Active	Mustard oil-induced edema; Decrease of granulation tissue on chick embryo chorioallantoic membrane; Carrageenan-induced pedal edema	Morita, 1926 Otsuka et al., 1981b Santos; Rao, 1998
Skimmianine		Active	TPA-induced inflammation	Garcia-Argaez et al., 2000

Table 10. Alkaloids monoterpene summary showing anti-inflammatory activity

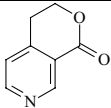
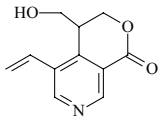
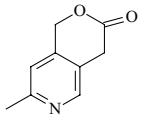
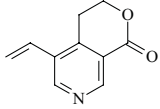
Monoterpene Alkaloids	Structure	Effect	Assay	References
Gentianadine		Active	In vivo, oral, rat	Sadritdinov, 1972
Gentianamine		Active	Formalin-induced pedal edema	Sadritdinov, 1971
Gentianidine		Weak activity	Formalin-induced pedal edema	Sadritdinov, 1971
Gentianine		Active	Mouse paw edema test; Formalin-induced-pedal edema; Egg white-induced pedal edema	Tulyaganov, 1971 Sung et al., 1958

Table 11. Alkaloids pyrrole summary showing anti-inflammatory activity

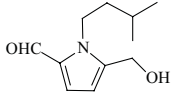
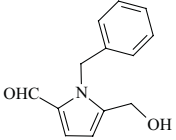
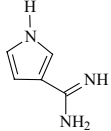
Pyrrole Alkaloids	Structure	Effect	Assay	References
Ganoderma A		Active	In vivo	Yang; Yu, 1990
Ganoderma B		Active	In vivo	Yang; Yu, 1990
Hopamidine		Active	Cobra venom. Induced edema	Birkner et al., 1986

Table 12. Alkaloids phenethylamine summary showing anti-inflammatory activity

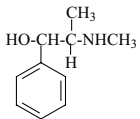
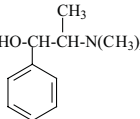
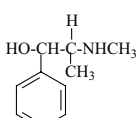
Phenethylamine Alkaloids	Structure	Effect	Assay	References
Ephedrine		Active	Dinitrofluorbenzene-induced swelling;	Hwang et al., 1990
			Carrageenin, PGE-1, histamine, serotonin and bradikinin-induced pedal edema;	Kasahara et al., 1985
		Active	Carrageenin-induced pedal edema;	Alkiewicz, 1983
		Inactive	Increased vascular permeability induced by acetic acid, resistance of heat-induced hemolysis of rat RBC, decrease of granulation tissue on chick embryo chorioallantoic membrane	Hikino et al., 1980
Ephedrine, <i>N</i> -methyl		Inactive	Carrageenin-induced pedal edema;	Hikino et al., 1980
		Weak activity	Resistance of heat-induced hemolysis of rat RBC; Effect on increased vascular permeability induced by acetic acid	
Ephedrine, pseudo		Active	Dinitrofluorbenzene-induced swelling;	Hwang et al., 1990
			Carrageenin-induced pedal edema;	Hikino et al., 1980
			Effect on increased vascular permeability induced by acetic acid;	
		Active	Carrageenin-induced pedal edema;	Hikino et al., 1980
			Effect on increased vascular Permeability induced by acetic acid;	
		Inactive	Resistance of heat-induced hemolysis of rat RBC;	
		Weak activity	Decrease of degranulation tissue on chick embryo chorioallantoic membrane;	
		Active	Croton oil-induced edema	Wang et al., 1996

Table 13. Alkaloids piperidine summary showing anti-inflammatory activity

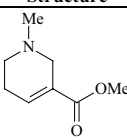
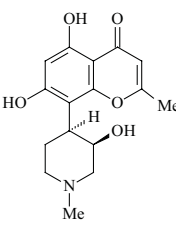
Piperidine Alkaloids	Structure	Effect	Assay	references
Arecoline		Inactive	Granulation tissue on chick embryo chorioallantoic membrane	Otsuka et al., 1981b
Rohitukine		Active	Carrageenin-induced pedal edema	Naik et al., 1988 Bhat et al., 1986 Lakdawala et al., 1988

Table 14. Alkaloids piridine summary showing anti-inflammatory activity

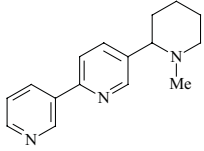
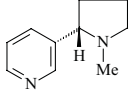
Piridine Alkaloids	Structure	Effect	Assay	references
Anabasamine		Active	Dextran, serotonin, histamine induced pedal edema	Mukhamedzhanova 1984
Nicotine		Inactive	Decrease of granulation tissue on chick embryo chorioallantoic membrane	Otsuka et al., 1981a

Table 15. Alkaloids indolizidine summary showing anti-inflammatory activity

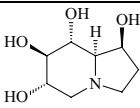
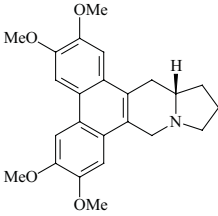
Indolizidine Alkaloids	Structure	Effect	Assay	References
Castanospermine		Active	Passively induced experimental allergic encephalomyelitis	Willenborg et al., 1990
Tylophorine		Active	Granuloma pouch assay; Cotton pellet granuloma	Gopalakrishnan et al., 1979

Table 16. Alkaloids tropane summary showing anti-inflammatory activity

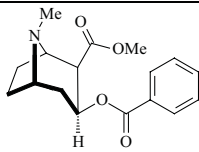
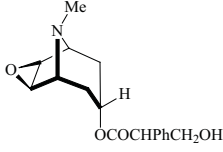
Tropane Alkaloid	Structure	Effect	Assay	References
Cocaine		Active	Mustard-oil-induced edema	Morita, 1926
Scopolamine		Inactive	Decrease of granuloma tissue on chick embryo chorioallantoic membrane	Otsuka et al., 1981a

Table 17. Alkaloids imidazolidine summary showing anti-inflammatory activity

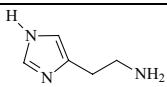
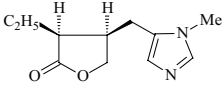
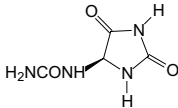
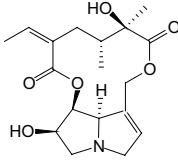
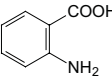
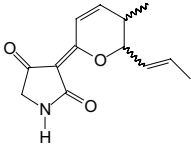
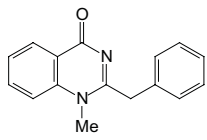
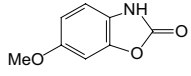
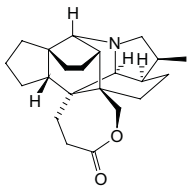
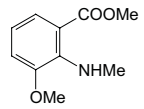
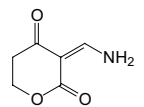
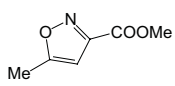
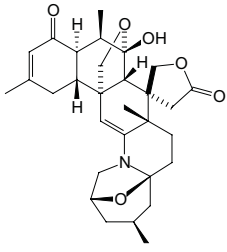
Imidazolidine Alkaloids	Structure	Effect	Assay	References
Histamine		Inactive	Decrease of granulation tissue on chick embryo chorioallantoic membrane	Otsuka et al., 1981a
Pilocarpine		Inactive	Decrease of granulation tissue on chick embryo chorioallantoic membrane	Otsuka et al., 1981a

Table 18. Alkaloids miscelane summary showing anti-inflammatory activity

Alkaloid-Miscelane	Structure	Effect	Assay	references
Allantoin		Active	Conjunctivitis due to irritation	Fukahori et al., 1990
Anacrotine		Active	Carrageenin, hyaluronidase, bradikinin or PG-induced pedal edema	Ghosh; Singh, 1974
Anthranilic acid		Active	In vivo, rat male	Yamasaki; Saeki, 1967
Apiodionen		Active	In vitro	Takahashi et al., 1992
Arborine		Inactive	Yeast-induced pedal edema	Svoboda; Kattau, 1967
Choline	$(\text{CH}_3)_3\text{N}^+\text{CH}_2\text{CH}_2\text{OH}$	Inactive	Fertile egg method	Otsuka et al., 1974
Coixol			Histamine release from rat Mast cells.	Otsuka et al., 1988
Cystine	$\text{HOOC}-\text{CH}(\text{NH}_2)-\text{CH}_2-\text{S}-\text{S}-\text{CH}_2-\text{CH}(\text{NH}_2)-\text{COOH}$	Inactive	Carrageenan-induced pedal edema	Madan; Al-Motrefi, 1986
Bukittinggine		Active	Carrageenin-induced pleurisy; Carrageenin induced pedal edema; Coton pellet granuloma; Adjuvant induced arthritis	Panthong et al., 1988
Damascenine		Active	Formaldehyde-induced edema of the rat	Bekemeier et al., 1968
Gentianaine		Active	Formalin-induced pedal edema	Sadritdinov, 1971
Premnazole		Active	Cotton pellet granuloma	Barik et al., 1992

Zoanthamine, 28-deoxy		Active	Phorbol ester induced inflammation	Rao et al., 1989 Sullivan et al., 1991
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