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1: Alkaloid - Wikipedia

Each volume provides, through its distinguished authors, up-to-date and detailed coverage of particular classes or sources of alkaloids. Over the years, this series has become the standard in natural product chemistry to which all other book series aspire.

Nasir Tajure Wabe, Email: This article has been cited by other articles in PMC. Abstract Catha edulis khat is a plant grown commonly in the horn of Africa. The leaves of khat are chewed by the people for its stimulant action. Its young buds and tender leaves are chewed to attain a state of euphoria and stimulation. Khat is an evergreen shrub, which is cultivated as a bush or small tree. The leaves have an aromatic odor. The taste is astringent and slightly sweet. The plant is seedless and hardy, growing in a variety of climates and soils. Many different compounds are found in khat including alkaloids, terpenoids, flavonoids, sterols, glycosides, tannins, amino acids, vitamins and minerals. The phenylalkylamines and the cathedulins are the major alkaloids which are structurally related to amphetamine. The major effects of khat include those on the gastro-intestinal system and on the nervous system. Constipation, urine retention and acute cardiovascular effects may be regarded as autonomic peripheral nervous system effects; increased alertness, dependence, tolerance and psychiatric symptoms as effects on the central nervous system. The main toxic effects include increased blood pressure, tachycardia, insomnia, anorexia, constipation, general malaise, irritability, migraine and impaired sexual potency in men. Databases such as Pubmed, Medline, Hinary, Google search, Cochrane and Embase were systematically searched for literature on the different aspects of khat to summarize chemistry, pharmacology, toxicology of khat Catha edulis Forsk. Khat can be grown in droughts where other crops have failed and also at high altitudes. Khat is harvested throughout the year. Planting is staggered to obtain a continuous supply. Reasons for chewing khat and behaviors associated with the ritual of khat chewing The vast majority of those ingesting khat do so by chewing. Only a small number ingest it by making a drink from dried leaves, or even more rarely, by smoking dried leaves. The chewer fills his or her mouth with leaves and stalks, and then chews slowly and intermittently to release the active components in the juice, which is then swallowed with saliva. The plant material is chewed into a ball, which is kept for a while in the cheek, causing a characteristic bulge. Only a minority frequently chew alone. A session may last for several hours. During this time chewers drink copious amounts of non-alcoholic fluids such as cola, tea and cold water. In a khat chewing session, initially there is an atmosphere of cheerfulness, optimism and a general sense of well-being. After about 2 hours, tension, emotional instability and irritability begin to appear, later leading to feelings of low mood and sluggishness. Chewers tend to leave the session feeling depleted. Chewing khat is both a social and a culture-based activity. It is said to enhance social interaction, playing a role in ceremonies such as weddings. In Yemen, Muslims are the most avid chewers. Some believe that chewing facilitates contact with Allah when praying. However, many Christians and Yemenite Jews in Israel also chew khat. Khat is a stimulant and it is used to improve performance, stay alert and to increase work capacity. Students have chewed khat in an attempt to improve mental performance before exams. Yemeni khat chewers believe that khat is beneficial for minor ailments such as headaches, colds, body pains, fevers, arthritis and also depression. In the Yemen Arab Republic, about 44 different types of khat exist originating from different geographic areas of the country. The cathedulins are based on a polyhydroxylated sesquiterpene skeleton and are basically polyesters of euonyminol. Recently, 62 different cathedulins from fresh khat leaves were characterized. These compounds are structurally related to amphetamine and noradrenaline. The plant contains the - -enantiomer of cathinone only. Cathinone is mainly found in the young leaves and shoots. These compounds seem to contribute less to the stimulant effects of khat.

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2: Chemistry, Pharmacology, and Toxicology of Khat (Catha Edulis Forsk): A Review

The Alkaloids: Chemistry and Pharmacology. Latest chapters. Chapter 4 Macrocyclic Peptide Alkaloids From Plants. Volume pp. iii-vii, () Volume

Biosynthesis[edit] Biogenetic precursor of all indole alkaloids is the amino acid tryptophan. For most of them, the first synthesis step is decarboxylation of tryptophan to form tryptamine. Psilocin is produced from dimethyltryptamine by oxidation and is then phosphorylated into psilocybin. Then, the aromaticity is restored via the loss of a proton at the C 2 atom. In the synthesis of monoterpenoid indole alkaloids, secologanin plays the role of the aldehyde. Pirroloindole alkaloids are synthesized in living organisms in a similar way. The resulting 4-dimethylallyl-L-tryptophan undergoes N-methylation. Further products of biosynthesis are chanoclavine-I and agroclavine â€" the latter is hydroxylated to elymoclavine, which in turn oxidizes into paspalic acid. In the process of allyl rearrangement, paspalic acid is converted to lysergic acid. Then, the biosynthesis of most alkaloids containing the unperturbed monoterpenoid part Corynanthe type proceeds through cyclization with the formation of cathenamine and subsequent reduction to ajmalicine in the presence of nicotinamide adenine dinucleotide phosphate NADPH. In the biosynthesis of other alkaloids, 4,dehydrogeissoschizine first converts into preakuammicine an alkaloid of subtype strychnos, type Corynanthe which gives rise to other alkaloids of subtype strychnos and of the types Iboga and Aspidosperma. Bisindole alkaloids vinblastine and vincristine are produced in the reaction involving catarantine alkaloid of type Iboga and vindolin type Aspidosperma. Besides, bisindole alkaloids vinblastine and vincristine show antineoplastic effect. Yohimbine was used for the treatment of erectile dysfunction in men until emergence of more efficient drugs. So, harmine and harmaline are reversible selective inhibitors of monoamine oxidase-A. Rauwolfia serpentina , which contains reserpine as the active substance, was used for over years in India to treat snake bites and insanity. Reserpine was the second after chlorpromazine antipsychotic drug; however, it showed relatively weak action and strong side effects, and is not used for this purpose any longer. Medical use of ibogaine is hindered by its legal status, as it is banned in many countries as a powerful psychedelic drug with dangerous implications of overdose. However, illegal network in Europe and United States provide ibogaine for treating drug addiction. The Aztecs used and the Mazatec people continue to use psilocybin mushrooms and the psychoactive seeds of morning glory species like Ipomoea tricolor. It is believed that the main function of the harmala alkaloids in ayahuasca is to prevent the metabolization of DMT in the digestive tract and liver , so it can cross the bloodâ€"brain barrier , whereas the direct effect of harmala alkaloids on the central nervous system is minimal.

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3: Chemistry and Pharmacology Academic Press

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Introduction The indolizidine and quinolizidine ring systems are found in bewildering profusion in nature. We have adopted the following policy in preparing the material for this chapter: If the azabicyclic nucleus is embedded within a fused polycyclic ring system, the alkaloid is no longer considered to be simple. This effectively ex- cludes a huge variety of compounds, ranging from a few tricyclic alkaloids to some highly complex structures like those of the Aspidosperma alkaloids and many steroidal alkaloids. Of course, many simple indolizidine and quinolizidine alkaloids bear additional rings as substituents, and these compounds fall within the ambit of this chapter. Several families of alkaloids include a few simple indolizidines and quinolizidines among their members. In most cases, these families have formed the subject of previous chapters in this treatise. The alkaloid families falling into this category include Elaeocarpus, Lythraceae, Nuphar, and lupine alkaloids, as well as compounds obtained from amphibians. In our endeavors to provide a comprehensive catalog of alkaloids containing isolated indolizidine and quinolizidine nuclei, we could not avoid duplicating material that may be found elsewhere in these volumes. For these compounds, we have done little more than list their structures and natural sources and have included biosynthetic and syn- thetic discussion only where such material updates that in the previous reviews. Our rigorously limited view of what constitutes a simple alkaloid inevitably entails artificial exclusion of certain compounds that have obvious structural and biogenetic relationships to those under discussion. The bicyclic compound por- antherilidine, for instance, should ideally be discussed alongside its tri- and tetracyclic relatives. On the other hand, an alkaloid like septicine, which is merely a seco version of the phenanthroindolizidine alkaloid tylophorine, was excluded on structural grounds from the recent chapter on phenanthroin- dolizidine alkaloids 2 but will find an appropriate home in this review. Those alkaloids that remain within the scope of this chapter nevertheless form a large group and comprise an impressive diversity of structural types. There are representatives from a cross section of natural sources, including fungi, higher plants, insects, amphibians, and mammals. In order to keep the volume of subject matter in this chapter to manageable proportions, we have dispensed with most of the detail on the isolation and separation of alkaloids from their source materials, and also much of the minutiae of structural proofs based on chemical degradations and interconversions, or on the interpretation of spectra. The great- er part of the literature on the systems of interest deals with their synthesis, and this is reflected in our review. Biosynthetic work, on the other hand, is sparse; and pharmacological or other biochemical studies, with the notable exception of the indolizidines slaframine, swainsonine, and castanospermine, are virtually nonexistent. We have endeavored to include all references up to the end of , and publications from the early literature have also received coverage. There are a few other fairly general reviews available, which survey facets of the chemistry of simple indolizidine and quinolizidine alkaloids. Foremost among these is the indispensable Royal Society series The Alkaloids 3 , an annual current awareness series, which highlights important developments in all aspects of alkaloid chemistry. This series has recently been absorbed into a bimonthly publication, sections of which have already been devoted to indo- lizidine and quinolizidine alkaloids 4 , 5. Other reviews on the alkaloids of interest are also available ; reviews on specific classes of these alkaloids are referenced in the appropriate sections of this chapter. There are several reviews 1 2 3. Finally, the important and complex subject of the ster- eochemistry and conformation of indolizidine- and quinolizidine-containing compounds has also been reviewed In the following chapter, we shall be using the Chemical Abstracts numbering system for indolizidines and quinolizidines as shown in 1 and 2. The most commonly seen variant of this system designates position 8a in I and 9a in 2 as 9 and 10, respectively. In fact, the only naturally occurring coniceine is y-coniceine 4 , a hemlock alkaloid isolated from Conium maculatum L. The origins of the misconceptions are obscure, but that it has persisted is surprising in view of the quite unambiguous statements in previous volumes of this treatise as to its origin. Many syntheses of the compound, some showing a high degree of originality, have been reported, and several of these have expressly been designed as models for the synthesis of more complex indolizidine alkaloids. It is therefore appropriate to

begin this review with a brief discussion of recent syn- thetic approaches to the unadorned indolizidine skeleton. Since the last coverage of the topic in this treatise extended only to , we have had to be selective in our choice of material, and some of the more routine approaches have received only passing mention. Supplementary information may be found in two old reviews and summaries 23,24 and among the material contained in a review When optically active coniine is used to prepare 5, the synthesis can be made to yield either enantiomer of 6-coniceine. This work provides the best values to date for the optical rotations of both antipodes of 3 and also establishes their absolute configurations. Incidentally, it is somewhat ironic that the only syntheses of optically active 6-coniceines should be by this relatively unsophisticated old procedure. The reaction is induced by silver [under both homogeneous and heterogeneous conditions. The authors find no evidence for the inter- mediacy of discrete nitrenium ions: Nitrenium ions, on the other hand, appear to be involved in the silver-induced rearrangement of N-chlorogranatinine 6 to? When the reaction is performed with silver tetrafluoroborate in benzene, it appears, on the basis of NMR evidence, that the iminium ion 7 is an intermediate Intramolecular Cyclo-N-alkylation and Cyclo-N- acylation of 2-Substituted Piperidines and Pyrrolidines The cyclization of 2- 3-hydroxypropyl piperidine 9 , generally obtained by reduction of the corresponding pyridine derivative, to 6-coniceine has been per- 3. In a similar vein,? Synthesis of 6-coniceine by Edwards and Meyers The synthesis of 6-coniceine in the latter case is only incidental; the main thrust of the report is on the use of tritylsulfenyl as a protecting group for amines. Of greater interest is the versatile formamidine methodology developed by Meyers Scheme l , which provides a neat and general route to l-azabicyc- lo[m. The N - t-butylformamidine derivatives of both pyrrolidine and piperidine undergo a-metalation with t-butyllithium. The lithiated species may be converted to the cuprates 11 and 12, which, on treatment with the appropriate a,w-chlo- roiodoalkanes, yield crude products, which cyclize directly to 1-azabicycles in the presence of base. Intra- molecular ureidomercuration of 13 with mercury I1 acetate gives a crude prod- uct formulated as The radical species resulting from the reduction of 14 with sodium trimethoxyborohydride can be trapped with methyl acrylate, giving the ester When the protecting group on nitrogen is removed by hydrogenolysis and the resulting product is warmed, bicyclic lactam 16 is formed in excellent yield. Synthesis of 6-coniceine by Danishefsky and co-workers The effect is ascribed to the ready formation of the species 18, containing a transannular bond The ease of transannular bond formation has been exploited by several groups in their syntheses of 6-coniceine; one example, the transannular Hofmann-Loffler-Freytag cyclization of N-chloroazacyclononane, has already been quoted Garst and Bonfiglio set up an azacyclononanone system by hydroborating the N-protected diene 19 with thexylborane Scheme 3 46, Hydrogenolysis of 21 over palladium catalyst corn- pletes this simple synthesis of? Synthesis of 6-coniceine by Garst and Bonfiglio The approach adopted by Wilson and Sawicki 48 depends on electrophilical- ly initiated transannular attack by nitrogen on to the double bond of an azacyclononene mixture, 22 and Reduction of 16 to? Intramolecular Cyclizations a to Nitrogen The generalized approach to alkaloid synthesis developed by R. Stevens has been tremendously successful in terms of the range of structures to which it permits access The main features of its application to? In the present case, the role of the SPh group is to stabilize the endocyclic enamine 27, a type of compound that is otherwise extremely susceptible to polymerization. The ring closure to the bicyclic system, 27 to 28, effectively completes a Mannich reaction. Synthesis of 6-coniceine by Stevens and co-workers Hart has developed a generalized approach to heterocyclic synthesis, which employs a-acylamino radical cyclizations. The method is related to the well-known cyclization of a-acyliminium ions, studied extensively both by Hart and by Speckamp The desired indolizidinone 30 makes up only about a quarter of the product mixture. In addition, since only the lactam 31 and the major pyrrolizidinone isomer can be separated from the product mixture, com- pletion of the synthesis by reduction with lithium aluminum hydride must be performed on a mixture of indolizidinone 30 and the minor pyrrolizidinone isomer. The reduced products can, however, be separated as their picrate salts. The same product ratio results when the S-methyl analog of 29 is used initially, although the reaction proceeds at a much slower rate Synthesis of 6-coniccine by Hart and Tsai Heterocyclic Synthesis by Cycloaddition An unusual 1,3-dipolar cycloaddition has been used by Pizzorno and Albonico in a general synthesis of 5,6,7,8-tetrahydroindolizines The reaction proceeds via the intermediacy of 34, effectively the equivalent of

the 1,3-dipole Synthesis of 6-coniceine by Pizzorno and Albonico The intramolecular imino Diels-Alder reaction has been developed to a fine art by Weinreb, who has used it in the synthesis of a wide variety of alkaloids Formation of the bicyclic lactam 37 is presumably by way of the transient intermediate Hydrogenation of 37 yields the known lactam 30, reduction of which with diborane completes the synthesis 56, Synthesis of 8-coniceine by Weinreb and co-workers Three of these, two simple indolizidines and a bisindolizidine, fall within the scope of this chapter. The alkaloid den- droprimine 39 , a 5,7-dimethylindolizidine, will be discussed here, while the remaining two compounds, which bear aromatic rings as substituents, will be treated in Section V,A. Dendroprimine 39 has been isolated from the species Dendrobium pri- mulinum Lindl. The gross structure of the compound was deduced from its NMR and mass spectra, and from its dehydrogenation with selenium to 2,4-dimethylpropyIpyridine. Synthesis of the four diastereomers of dendroprimine by Luning and Lundin These compounds were synthesized as shown in Scheme 8. Having the full set of diastereomers affords a rare opportunity for investigating substituent effects on the conformations of indolizidines in a co- herent fashion. The stereochemistry of ring fusion may be deduced from the presence or absence of Bohlmann bands 62 in the IR spectra. Both 40 and 42 have strong Bohlmann bands; this fact, taken in conjunction with the NMR data, suggests conformations 43 and 44, respectively, for these compounds. Compound 41 has weak Bohlmann bands; when this is interpreted along with the broadness of certain NMR signals and the doubling up of the signal for the C-5 methyl group, the existence of 41 as an equilibrium mixture of conformers 45a and 45b seems likely. Finally, the diastereomer 39, spectroscopically identical to natural dendroprimine, completely lacks Bohlmann bands, and conformation 46 is proposed. The stereochemistry of ring junction in this compound appears to be preserved on protonation and N-methylation, again as judged by NMR effects. Some years after the relative configuration of dendroprimine was deduced, its absolute configuration was established as 5R,7S,8aR 63 , as shown in This gives additional evi- dence for the R configuration at the pyrrolidine ring of the intermediate and hence at position 8a in dendroprimine The insect is a persistent nuisance primarily in heated buildings; since it is a carrier of pathogenic bacteria, it presents a health hazard, particularly in hospitals where it can enter sophisticated isolation units and even penetrate bandages and sterile packs. The nests tend to be well hidden, and the usual insecticidal measures fail. The possibility of controlling this pest by pheromone manipulations was initiated by Ritter and co-workers at the instigation of the Dutch Ministry of Public Health and Environmental Hygiene A wide variety of rather simple alkaloids are produced by members of the Arthropoda, an extremely populous animal phylum Among these animals, ants are well known as alkaloid producers, and a comprehensive listing of ant metabolites is contained in ref. The genus Monomorium is the source of various pyrrolidine alkaloids 67 , but simple indolizidines appear to be unique to the Pharaoh ant Several compounds have now been identified in the trail 3.

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4: Indole alkaloid - Wikipedia

The Alkaloids: Chemistry and Pharmacology Volume 31, Pages iii-ix, () Edited by Arnold Brossi. Volume 47 pp. iii-vii, () Entitled to full text.

In Thailand, the tree and leaf-preparations from it are called kratom. Traditionally, fresh or dried kratom leaves are chewed or made into tea; they are seldom smoked. At a low dose, kratom has stimulant effects and is used to combat fatigue during long working hours. At high dosages, however, it can have sedative-narcotic effects. It is also used in traditional medicine and as an opium substitute. The phytochemicals isolated from various parts of the tree include over 40 structurally related alkaloids as well as several flavonoids, terpenoid saponins, polyphenols, and various glycosides. The main psychoactive components in the leaves are mitragynine and 7-hydroxymitragynine, both found only in Mitragyna speciosa. It was first isolated in and its chemical structure was fully elucidated in Mitragynine is insoluble in water but soluble in conventional organic solvents, including acetone, acetic acid, alcohols, chloroform and diethyl ether providing fluorescent solutions. The chemical total syntheses reported for several kratom alkaloids are too complex to be used for economic production of any these compounds. However, mitragynine can serve as a chemical precursor to the more potent 7-hydroxymitragynine. The veins of the leaves are either greenish-white or red â€" the former is reputed to be more potent. The average weight of a fresh and a dried leaf is about 1. The yellow and globular flowers of the tree bear up to florets. The fruit is a capsule containing numerous small flat seeds. Kratom products are usually supplied as crushed or powdered dried leaves that are light to dark green in colour. Powdery, greenish or beige-brown kratom preparations fortified with extracts from other leaves are also available. Stable, paste-like extracts and dark brown kratom resin can be made by partially or fully boiling down the water from aqueous kratom leaf suspensions. Tinctures and capsules, filled with powdered kratom, are also available. Human clinical studies are scarce. In general, the effects of kratom in humans are dose-dependent: After taking a few grams of dried leaves, the invigorating effects and euphoria are felt within 10 minutes and last for one to one and a half hours. Kratom users report increased work capacity, alertness, sociability and sometimes heightened sexual desire. The pupils are usually normal or very slightly contracted; blushing may be noted. For regular kratom users, loss of weight, tiredness, constipation, and hyperpigmentation of the cheek may be notable side effects. The pharmacological mechanism responsible for stimulant activity is unclear. Kratom taken in large, sedating doses corresponding to 10â€"25 g of dried leaves may initially produce sweating, dizziness, nausea and dysphoria but these effects are shortly superseded with calmness, euphoria and a dreamlike state that last for up to six hours. Contracted pupils miosis are noted. The receptor agonist effect of kratom alkaloids is antagonised by the opioid receptor antagonist naloxone. In animal studies, the antinociceptive and cough-suppressant effects of mitragynine were comparable to those of codeine. In mice, 7-hydroxymitragynine was several times more potent analgesic than morphine even upon oral administration. Kratom is slightly toxic to animals. Mice chronically treated with 7-hydroxymitragynine developed tolerance, cross-tolerance to morphine and withdrawal signs that could be precipitated by naloxone administration. Regular kratom use may produce dependence. The withdrawal symptoms in humans are relatively mild and typically diminish within a week. Craving, weakness and lethargy, anxiety, restlessness, rhinorrhea , myalgia , nausea, sweating, muscle pain, jerky movements of the limbs, tremor as well as sleep disturbances and hallucination may occur. In a man who fatally overdosed propylhexedrine and kratom, the postmortem mitragynine concentrations ranged from 0. The consumption of kratom concomitantly with other drugs can provoke serious side effects. In fact, adverse drug interactions involving kratom tea taken with carisoprodol, modafinil, propylhexedrine or Datura stramonium have been reported. A fatal case in the United States involved a blend of kratom, fentanyl, diphenhydramine, caffeine and morphine sold as a herbal drug. When making tea, lemon juice is often added to facilitate the extraction of plant alkaloids ; before drinking, sugar or honey may be added to mask the bitter taste of the brew. The dried leaves are occasionally smoked. Only the masticated material is swallowed. Consumption is followed by drinking warm water or coffee, tea or palm sugar syrup. Regular and addicted users chew 3 to 10 times a day. When kratom is not available, the

leaves of Mitragyna javanica other name Mitragyna parvifolia are used as substitute. The cocktails are made from kratom leaves, a caffeine-containing soft drink, and codeine- or diphenhydramine-containing cough syrup as the three basic ingredients to which ice cubes, an anxiolytic, an antidepressant or an analgesic drug is added. Other names of the plant are krathom, kakuam, ithang or thom Thailand , biak-biak or ketum Malaysia , and mambog Philippines. Phylogenetic characterisation of kratom samples by specific DNA nucleotide sequences can complement the phytochemical analyses. Kratom alkaloids can be separated by thin layer chromatography on silica gel plates with detection by UV nm. The UV spectrum of the methanol solution of mitragynine shows a maximum at nm with shoulders at , and nm. The characteristic absorption bands in the IR spectrum of mitragynine are at 3 , 1 and 1 cm The UV spectrum of the ethanol solution of 7-hydroxymitragynine shows a maximum at nm with shoulders at and nm. The characteristic absorption bands in the IR spectrum of 7-hydroxymitragynine in CHCl3 are at 3 , 2 , 2 , 2 , 1 , 1 , 1 , 1 , 1 , 1 and 1 cm In a poisoning case, the blood serum concentration of mitragynine two weeks after cessation of regular oral ingestions of large doses 14â€”21 grams daily of dried kratom leaves was 0. No conventional immunological drug screening test is known that will detect kratom alkaloids. The total alkaloid concentration in dried leaves ranges from 0. About three such drinks a day are said to be sufficient to diminish opiate withdrawal symptoms. ODT is a bioactive metabolite of the synthetic opioid analgesic tramadol and was apparently added to the herbal preparations to mimic the sedative-narcotic effects of kratom. Other countries that control kratom under their narcotic law are Australia, Malaysia, Myanmar and Thailand. In Thailand, the National Household Surveys provide information on drug use prevalence in that country. The Survey 26 respondents aged 12â€”65 years indicated that the lifetime, past year and past 30 days prevalences for kratom were 2. These figures, with the exception of lifetime use, were significantly higher than those for cannabis making kratom the most widely used illicit drug in the country. Past year and past days prevalence use data followed similar trends. A recent roadside survey involving 1 motor vehicle drivers in Thailand revealed the use of kratom by 0. In South East Asia, kratom is used as an antidiarrheal, a cough suppressant, an antidiabetic, an intestinal deworming agent and wound poultice as well as to wean addicts off heroin. Outside Asia, anecdotal use of kratom preparations for the self-treatment of chronic pain and opioid withdrawal symptoms and as a replacement for opioid analgesics have been reported. There is, however, no approved use of kratom or its alkaloids in modern medicine. It has been suggested that the therapeutic potential of kratom or its purified ingredients for the treatment of pain, depression and drug withdrawal symptoms should be explored. Transactions, Volume , pp. Fitoterapia, Volume 78, pp.

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5: Geoffrey A. Cordell | Open Library

-chapter 1- plant biotechnology for the production of alkaloids: present status and prospects robert verpoorte and robert van der heijden biotechnology devt leiden projectgroup.*

Bioconversion of Available Precursors. Production by Genetically Engineered Plan E. Production of Novel Compounds.. Feeding of Precursors and Bioconversions. Differentiation and Culture Type Genetic Approaches and Genetic Modification. Production by Means of Plant Cell Cultures Strategies to Improve Product Yield: Cellular and Extracellular Aspects.. Murashige and Skoog medium; NAA: All rights of reproduction in any form reserved. Secondary Metabolites in Cell Cultures. Screening, Selection, and Stability C. Effects of Growth Conditions. Production of Tropane Alkaloids by Cell Cultures. Introduction Plants produce a variety of alkaloids. Table I presents some of the ma- jor classes and an estimation of the number of representatives N. About 30 alkaloids have great commercial interest, mostly because of their use as medicines, flavorings, or poisons, sometimes as important tools in pharmacological studies. In all cases the total amounts produced worldwide are rather limited. For exam- ple, by volume, possibly the largest production involves the alkaloids quinine and quinidine. For their isolation , metric tons of Cin- 1. Totals include alkaloids isolated from plant, animal, and marine sources. Farnsworth, per- sonal communication. The alkaloid ajmalicine, used as an antihypertensive, has a yearly market volume of about kg 2 , for which probably tons of roots of Catharanthus roseus is needed. Compared to laboratory-scale isolations, these seem impressive amounts, but compared to agricultural crops they are only very small volumes. Several compounds of interest are isolated from plants which need several years to develop. For example, Cinchona trees need years before they can be har- vested, and Coptis japonica rhizomes, a source of barberine, require years of growth before harvesting. In many cases little plant breeding has been done to improve yields of the alkaloids, and in some cases one simply relies on collection of plant material from the wild e. Alkaloids are consequently valuable chemicals. Table I1 gives prices per gram of some commonly used alkaloids. As no single source was available for bulk prices of these chemicals, we used the price list of a large supplier of fine chemicals. These prices are per gram, higher than the bulk prices, but they give at least some indication of the values of these alkaloids. Shikonin is not an alkaloid, but because it is the first product from a plant cell biotechnological production, it is cultures; RC, root cultures; HR, hairy root cultures; ShC, shoot cultures; DW, dry weight; FW, fresh weight. Strategies followed to obtain high production Section 11 and aspects of technology involved in the large-scale culture of plant cells and the economy of such processes Section are discussed briefly. Different classes of alkaloids are then discussed separately, with emphasis on production, be it by de nouo biosynthesis or bioconversion of added precursors by plant cells. Patents concerning the production of various alkaloids are also listed. We confine ourselves only to alkaloids derived from higher plants which are presently produced on an industrial scale by extraction of plant materials. Some classes of alkaloids for which production in cell cultures has been studied extensively are thus omitted, for example quinolizidine lupine alkaloids , pyrrolizidine Senecio and Symphytum alkaloids , and acridone alkaloids Ruta alkaloids. For these classes of alkaloids we refer to recent authora- tive reviews For some widely used alkaloids, such as pilocarpine, physostigmine, cocaine, strychnine, and tubocurarine, no studies have been published yet on the plant cell tissue and organ culture see Table Several possibilities can be con- sidered for applying biotechnology, namely, production of plant com- pounds by genetically engineered microorganisms; production by means of plant cell cultures; bioconversion of readily available precursors, by using genetically engineered microorganisms, plant cell cultures, or iso- lated plant enzymes; production by means of genetically engineered plants or plant cell cultures; and production of novel compounds. Besides the possibilities for production of known compounds, biotechnology can also be used to produce new compounds. We shall consider these possibilities in more detail. One can thus consider the possibilities of transferring the production of a plant secondary metabolite into a microorganism. To be able to do so one has to know the biosynthetic pathway of the compound concerned; one must identify the enzymes involved and the genes coding for the enzymes. As most plant secondary metabolites result from pathways involving a large number

of steps is quite normal , at least as many genes are involved. In fact, only a few secondary metabolite pathways are com- pletely known at the level of enzymes, for example, the flavonoid pathway and the biosynthesis of some isoquinoline alkaloids. Consequently only very few genes from secondary metabolism are known e. In the case of alkaloids only a few isolated steps from the biosynthetic pathways have been studied to the level of the genes, for example, strictosidine synthase, a key enzyme in indole alkaloid biosynthesis from RauuolJia see below 6,7 and trypto- phan decarboxylase, another regulated enzyme from indole alkaloid bio- synthesis 8,9. Even if all the genes were known, transferring a large number of genes to a microorganism is not feasible, particularly as the enzymes produced have to act in a concerted way. Furthermore, in plants secondary metabo- lism is often compartmentalized on the subcellular or even cellular level. This will be impossible to realize in microorganisms. Plant cells are totipotent, which means that each cell carries all the genetic 1. In theory it is thus possible to have in uitro cultured plant cells produce secondary metabolites. Below, in the review on the state of the art of plant cell biotechnology for the production of various commercially interesting alkaloids, it will become clear that this is only partly true. Table I1 summarizes the results for most of the alkaloids discussed here. Secondary metabolism is a form of differentiation, but cells grown in uitro are rapidly dividing, undifferentiated cells. Only at the end of the growth phase of batch-cultured cells may some form of differentiation occur, connected with the production of secondary metabolites. A plant produces a wide variety of secondary metabolites, all with different, mostly unknown functions. In in uitro cultured cells those compounds which defend the plant against microorganisms, namely, phytoalexins, are often easily formed. For example, Cinchona cell cultures produce large amounts of anthraquinones, but the alkaloids of interest, the quinolines, are produced in trace amounts only. Similarly Papauer cell cultures pro- duce sanguinarine and closely related alkaloids, but no morphinane al- kaloids. The various strategies followed to obtain high producing cell lines will be briefly discussed separately see Section The economics of a plant cell culture production process are discussed below see Section For cell lines that do not produce, it will be necessary to learn more about the regulation of secondary metabolism in order to eventually be able to use genetic engineering for improving production see below. This could, for example, be stereospecific reactions, like the reduction of quinidinone in quinine or quinidine and the epoxidation of atropine to scopolamine. For the bioconversion one can consider using plant cells [e. An interesting example of the latter is the S -tetrahydroprotoberberine oxi- dase STOX enzyme, which oxidizes S -reticuline but not its stereo- isomer This feature can be used in the production of R -reticuline from a racemic mixture see below. Immobilized strictosidine synthase has been successfully used to couple secologanin and tryptamine. The gene for this enzyme has been isolated from Rauuolfia 6 and cloned in Escherichia coli, in which it is expressed, resulting in the biosynthesis of active enzyme 7. The genetically engineered microor- ganism can thus be used for the large-scale production of this intermediate for indole alkaloid biosynthesis, using tryptamine and secologanin as pre- cursors. Strictosidine, with its two secondary nitrogens, two aldehyde groups, a double bond, and an ester group, is an ideal synthon for the bio synthesis of a variety of new compounds which could be studied for biological activity The first small steps have been made, but the field of bioconversion still contains numerous possibilities yet to be explored. Cloning of plant genes into microorganisms could be of interest, particularly in the case that cofactors are required. Bioconversions with plant enzymes seem to offer great potential for biotechnological applications. By unraveling the biosynthetic pathways and the regulation thereof on the level of enzymes and genes, it might become possible to identify genes which could be subject for genetic engineering. Various possibilities can be envisioned: The latter approach seems particularly interesting. One could consider transferring a pathway from a slowly growing plant into a plant which grows rapidly and is suitable for agriculture e. This would mean that the alkaloids could be produced in an annual crop, which is more easily tuned to the demand for the alkaloid. Recently we have been able to introduce the tryptophan decarboxylase gene from Catharanthus roseus into tobacco, resulting in plants producing significant amounts of tryptamine 9 , thus again proving that genetic engineering of secondary metabolism in plants and plant cells is feasible nowadays. For all applica- tions of genetic engineering, however, one has to know the mode of regulation of secondary metabolism at the level of a number of enzymes and genes. For the near future this will be a major challenge; at present knowledge is very

limited. However, plant biotechnology also offers possibilities for new com- pounds. A number of plants have been studied phytochemically, some- times in combination with assays for certain types of biological activity. This has resulted in discovery of numerous compounds with interesting biological activities. Many of the plants studied were collected in remote areas, and the large-scale production of the compounds isolated would be very difficult. Plant cell cultures do offer interesting perspectives, and they could be used to produce on a large scale compounds first found in the plant. Alternatively, one can screen cell cultures for new biologically active compounds. Such an approach has shown to be fruitful Z Among others two alkaloids, pericine and apparicine, with activity in the central nervous system CNS have been isolated from cell cultures of Picrulima nitida In connection, one might also think about the addi- tion of elicitors to cell cultures; this would lead to the production of antimicrobial compounds phytoalexins which could be of interest for futher development as antibiotics. This approach has, for example, been used to introduce new flower colors It could also be of interest in improving the resistance of plants against microorganisms or predators. However, more insight into the role of alkaloids in plant survival in native ecosystems is needed for this. Cellular and Extracellular Aspects The production of alkaloids in plant cell cultures is a result of an enor- mously complex set of interactions between cellular and extracellular compartments. The extracellular compartment should at least offer possi- bilities for survival of the cellular compartment, but often cell growth and cell differentiation are prerequisites. The changed environment of the cells will in turn affect the cellular compartment, and so on.

6: veratridine - Wiktionary

*Chemistry and Biology, Volume 53 (The Alkaloids) [Geoffrey A. Cordell] on www.enganchecubano.com *FREE* shipping on qualifying offers. Alkaloids are a major group of natural products derived from a wide variety of organisms, which are used as medicinal and biological agents.*

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