

Kratom and Other Mitragynines: The Chemistry and Pharmacology of Opioids from a Non-Opium Source

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Abstract

The biochemical machinery of plants generates a broad range of chemicals to aid survival in a competitive environment. For mankind, these natural products have been, from time immemorial, sources of bioactive substances used not only to heal or provide support in daily work but also to escape from life's harsh realities. The isolation of the alkaloid morphine from opium by Sertner (1805) laid the foundation of phytochemistry and modern pharmacy. Since then, research on opioids led to the discovery of endogenous opioid peptides and their receptors in the 1970s.

Keywords Opioids; Kratom; *Mitragyna speciosa*; Mitragynine; Analgesic; Opium substitute; Pharmacology; Toxicology; Addiction

Book Review

Plants produce a broad range of bioactive substances to aid their survival in a competitive environment. From time immemorial, mankind have used such natural products to heal or to provide support in daily work and also to escape from life's harsh realities. The isolation of morphine alkaloid from opium by Sertürner (1805) laid the foundation of phytochemistry and modern pharmacy. Research on opioids afforded many (semi-)synthetic analgesics, cough suppressants and antiarrhythmic agents and also led to the discovery of endogenous opioid peptides and their receptors in the 1970s. Opioids, however indispensable they are in medicine, are not without unwanted side effects and their misuse has also created health and social problems. Regrettably, the quest for the 'Holy grail', that is developing opioid-based pain medications devoid of adverse effects, dependence and abuse liability in particular, has appeared to be vain.

Twenty years ago few addiction specialists heard about kratom. Kratom (*Mitragyna speciosa*, Rubiaceae), called 'krathom' in Thailand and 'biak' or 'ketum' in Malaysia, is a tropical tree indigenous to Southeast Asia; it is also cultivated in the region. Kratom is also the name of various leaf preparations that are either chewed or made into tea for various purposes. Other *Mitragyna* species that grow in Africa and India are used in ethnomedicine as well as a source of wood. Kratom has been used in local medicine for centuries. The fresh or dried leaves of the tree have also been used as a stimulant (low doses) or opium substitute (high doses). In fact, kratom has become one of the most widely abused illicit substances in Malaysia and Thailand. Recently, kratom has become internationally popular as one of the so-called 'herbal highs' or 'legal highs': its dried and powdered leaves, often fortified with extracts from other leaves, are sold in special shops and over the Internet.

Initial scientific studies with kratom concentrated on the chemical characterization of its constituents. Mitragynine, which is the most abundant alkaloid in the leaves, was first isolated in 1921; its chemical structure was elucidated four decades later. By now, over 40

structurally related alkaloids have been described from various parts of the tree. Due to their novel structure and unique pharmacology, mitragynine and related compounds are considered to be a promising class of opioids. This book is therefore a much welcome summary of what is presently known about kratom and its constituents. Hitherto only one monograph dealt with this emerging psychoactive plant [Assanangkornchai S. and Siriwongse na Ayuthya A. (eds.). *Krathom in the Thai Society*. Bangkok: Office of the Narcotics Control Board. 2005. ISBN: 974-9867-19-X. pp. 179] but it was written in Thai language, had limited availability and is now out of print.

To provide a state-of-the-art overview on kratom the editor of the book reviewed here has assembled an expert group of authors from Japan, Malaysia, Philippines, Switzerland and the USA. The book features 20 chapters that cover different aspects related to kratom and its alkaloids. An additional chapter gives an overview on salvinorin A, a chemically unrelated botanical hallucinogen.

Chapter 1 is a short essay on the chemical ecological aspects of co-evolution of plants and their biological competitors, including humans. It also speculates on how humans discovered the psychoactive effects of plant preparations. Chapter 2 gives a general overview on mitragynine and related kratom alkaloids. It briefly surveys our current knowledge on the phytochemistry, the opioid and non-opioid pharmacology, including receptor studies, antinociceptive activity, tolerance and withdrawal phenomena related to mitragynine and the more potent 7-hydroxymitragynine. Studies on the toxicology and abuse potential of kratom alkaloids are also reviewed. These issues are elaborated in more detail in subsequent chapters. Complementing the first chapter, Chapter 3 presents examples of some psychoactive indole alkaloids from terrestrial plants focusing on the structurally complex ibogaine, reserpine, physostigmine and a geissoschizine derivative; other alkaloids and their principal pharmacology are also mentioned.

Chapter 4 on the chemistry, pharmacology and the changing legal status of salvinorin A and related compounds from *Salvia divinorum* appears to be a 'cuckoo's egg' in the tome: this non-alkaloidal neoclerodane terpenoid has no chemotaxonomic relationship with kratom. The only justification for the inclusion in the book of this

potent hallucinogen could be its mode of action, that is the activation of kappa-opioid receptors in the central nervous system.

Chapter 5 provides an excellent overview on the botany as well as the traditional and current uses of *M. speciosa* and related plants. The Internet availabilities of various genuine or fake kratom preparations, including the ominous 'Krypton' product dangerously adulterated with the synthetic opioid O-desmethyltramadol, are also discussed here. Chapter 6 is an outstanding overview on the phytochemicals identified so far from *M. speciosa*. In addition to the alkaloids isolated from kratom and taxonomically related plants, other constituents, such as flavonoids, polyphenols and triterpenoids are also listed.

Following a short introductory chapter on the (bio)chemistry of mitragynine-type alkaloids, Chapter 8 is a detailed chemical description of these alkaloids: the total syntheses of mitragynine and related compounds as well as the potent semisynthetic mitragynine pseudoindoxyl are discussed. Chapter 9 reviews the medicinal chemistry of the most important kratom alkaloids. The results of structure-activity relationship studies of the natural and synthetic mitragynine derivatives and their relative potencies to morphine, as determined in isolated tissues in guinea pig ileum or in mouse pain models, are tabulated.

Chapter 10 is essentially a 17-page long table listing the chemical structure of opioid receptor ligands acting either as agonist or antagonist. Obviously, such a table cannot be complete but the impressive enumeration of some 180 compounds demonstrates the importance of these substances both in research and the clinic. Chapter 11 surveys the forensic chemical methods used for the detection and quantification of mitragynine and its congeners in botanical and other biological matrices. The chapter draws attention to the analytical challenges posed by herbal blends sold for 'recreational' purposes and demonstrates the value of DNA analyses in such cases. Chapter 12 reviews studies on the pharmacokinetics of mitragynine and depicts its postulated human metabolic pathway.

Chapter 13 deals with the antinociceptive effects of kratom as demonstrated in a plethora of animal pain models by comparing the biological activity of mitragynine, 7-hydroxymitragynine, a large number of their synthetic derivatives and morphine. It is notable that, in contrast to morphine, the mitragynines are typically more effective upon oral administration than by injection. The involvement of mu-opioid receptor is evident. Unfortunately, human clinical studies are lacking. Being highly potent and devoid of adverse side effects, a synthetic derivative of mitragynine, MGM-9, acting as an agonist of both mu- and kappa receptors appears to be a promising analgesic. Chapter 14 surveys the non-analgesic effects of kratom preparations that include cough suppression, respiratory depression, and antidepressant and psychostimulant activities. Continuing on this theme, Chapter 15 summarizes other central and peripheral effects such as constipation and food and water intake.

Chapter 16 is somewhat unusual in a scholarly book: it presents 55 'experience reports' selected from several hundred narratives submitted to an Internet forum by anonymous kratom-users. Although suffer from methodological problems, these excerpted self-reports confirm historical records of the effects of traditional kratom use, correlate with the opioid-like effects and side-effects (e.g., stimulation and sedation, euphoria, the 'opium nod', miosis, pruritus,

nausea), attest dependence, delineate withdrawal symptoms, as well as provide information on the dosage and use-patterns for self-medication of pain and opioid withdrawal symptoms, or for 'recreation'. Since human clinical studies are scarce, data of such a 'global uncontrolled clinical trial' add to our understanding of kratom use and abuse.

The following three chapters describe the toxicology of selected alkaloids. Chapter 17 is a condensed description of the toxic effects of brucine, reserpine as well as harmala and vinca alkaloids. Chapter 18 is more pertinent to the topic of the book: it reviews the adverse effects induced by opioids in general and thus provides a background to Chapter 19, which is specifically devoted to what is currently known about the toxicology of mitragynine and its analogs. The acute and sub-chronic animal toxicity studies that are tabulated indicate toxic effects only at high doses of the alkaloid extract of kratom or of mitragynine. Also summarized here are the few studies on the adverse effects of kratom observed in humans and the few fatal poisoning cases which typically involved not only kratom but other drugs as well.

Chapter 20 reviews animal models commonly used to assess tolerance, dependence and abuse potential of opioids and briefly reiterates findings of studies with mitragynine already described in detail in previous chapters. Chapter 21 contains a very brief review of the few epidemiological studies reported from Southeast Asia, mostly from Thailand. It may be estimated that well over a million people in that region use kratom on a regular basis even though it is illegal there. Although other chapters touched upon it briefly, the international regulatory status, which gets more and more restrictive making the summary out-of-date by now, of kratom and mitragynine is discussed in detail.

In addition to the comprehensive and up-to-date (up to 2014) reference lists that follow each chapter a supplementary bibliography is also provided in a separate section. The book concludes with an adequate index. Obviously, for searching specific keywords the electronic version of the book is preferred.

In general, the chapters are well-written. Since different authors have contributed to the book there are several repetitions, which a more careful editing could have reduced; but this is perhaps unavoidable given the complex and intertwined, or one should say interdisciplinary nature of the subject. I could find only few errors or omissions. For example, on page 16, the general structure of mitragynines lacks the double bond of the indole moiety while from the extensive list of opioids (pages 136-152) tramadol and its recently launched congener, tapentadol, are conspicuously missing.

Kratom has garnered a lot of attention in recent years and further investigations, especially human clinical studies, are warranted. To some, kratom holds great potential for the development of safe medicines while to others it is an emerging psychoactive drug of concern. This book should be an indispensable single-volume information source for anyone working in the fields of opioid chemistry, pharmacology and toxicology. Some chapters would be of particular interest to phytochemists and medicinal chemists as well as specialists working in addiction treatment and drug regulation. The book would also be an excellent addition to any library collection specialized in natural products or drugs of abuse.