Review

Formulation and Delivery of Mitragynine: A Mini Review

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Received: 31 August 2025; Revised: 22 September 2025; Accepted: 22 September 2025; Published: 23 September 2025

Abstract: Mitragynine is the most abundant psychoactive indole alkaloid found in the leaves of *Mitragyna speciosa*, which is commonly known as "Kratom", and is distributed widely in Indonesia, Malaysia, Papua New Guinea, the Philippines, and Thailand. The leaves of *M. speciosa* are prepared for oral consumption and typically involve dried leaves that are brewed into tea or ground and placed into capsules. Additionally, *M. speciosa* is also used as a leaf poultice to treat fever, diarrhoea and for wound healing. In addition to peroral delivery, mitragynine could also be delivered through nasal and transdermal routes. The application of nanotechnology has been found to enhance the delivery of mitragynine and thus to enhance its therapeutic efficacy. This mini review, for the first time, presents a critical appraisal of the available literature on the formulation and delivery of mitragynine.

Keywords: delivery; formulation; kratom; mitragynine; nasal; oral; transdermal

1. Introduction

Mitragynine (molecular formula: $C_{23}H_{30}N_2O_4$; molecular weight: 398.503 g/mol; melting point 102–106 °C) (Figure 1), a well-known psychoactive indole alkaloid with opioid-like properties, was first isolated from *Mitragyna speciosa* (Korth.) Havil. (Figure 2) of the family Rubiaceae, which is a Southeast Asian medicinal plant commonly known as "Kratom", and distributed widely in Indonesia, Malaysia, Papua New Guinea, the Philippines, and Thailand [1,2]. Its chemical name is methyl (16*E*)-9,17-dimethoxy-16,17-didehydro-20β-corynan-16-carboxylate (Figure 1), and it is mainly used in pain management and the treatment of opioid withdrawal symptoms [2,3].

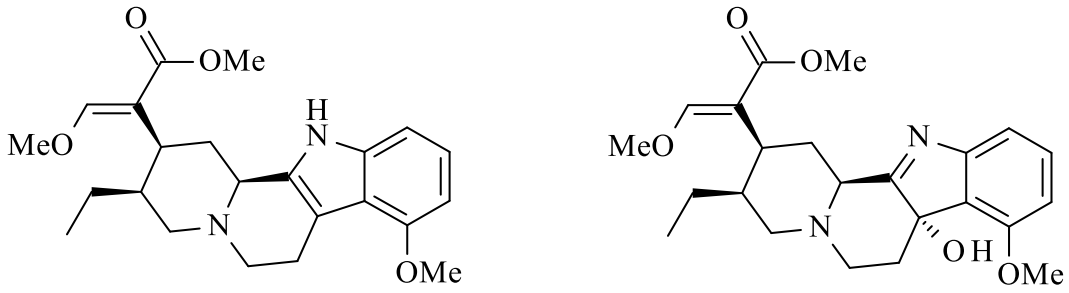

Figure 1. Chemical structures of mitragynine and 7-hydroxy-mitragynine.

There are well over a hundred published review articles available on mitragynine and *M. speciosa*, covering various aspects of this bioactive alkaloid [3–10]. However, no review article has been published on the formulation and delivery of this compound, which captures various formulations and delivery modes reported in the literature. Therefore, a literature search was conducted on the formulation and delivery of mitragynine using databases like Web of Science, Google Scholar and PubMed; mitragynine, delivery and formulation were used as the search keywords. This mini review, for the first time, critically appraises the available literature on the formulation and delivery of mitragynine.

Figure 2. *Mitragyna speciosa* (Korth.) Havil., the main source of mitragynine.

2. Distribution

Mitragynine is the most abundant bioactive indole alkaloid in the leaves of *M. speciosa*. However, the abundance varies significantly among *M. speciosa* plants growing in different geographical locations [11,12]. For example, the Thai varieties of this species have the highest level of mitragynine (up to 66% of total alkaloids), while 7-hydroxy-mitragynine (7-OH) (Figure 1) is a minor constituent (up to 2% of total alkaloid content) [13]. In Malaysian varieties, mitragynine is present at a lower concentration (12% of total alkaloids). In a recent study [14], it has been shown that the accumulation of mitragynine in *M. speciosa* is enhanced by herbivores as a defence mechanism against herbivory, indicating the influence of interaction with insect herbivory. Furthermore, a study about the effect of light intensity and polyethyleneglycol-induced water stress on the accumulation of mitragynine in *M. speciosa* demonstrated the physiological adaptability of this plant to variable environmental stresses and their influence on mitragynine accumulation [15].

A few other species of the genus *Mitragyna* Korth., including *M. diversifolia* (Wall. ex G.Don) Havil. (also known as *M. javanica* Koord. & Valeton), *M. hirsuta* Havil. and *M. rotundifolia* (Roxb.) Kuntze from Thailand, have been reported to produce mitragynine, together with other alkaloids like 7-hydroxy-mitragynine and mitraphylline [16].

3. Formulation and Delivery of Mitragynine

The leaves of *M. speciosa,* which contain mitragynine as the major bioactive substance, are prepared for oral consumption and typically involve dried leaves that are brewed into tea or ground and placed into capsules [17] (Figure 3). However, *M. speciosa* can also be employed, as a leaf poultice (Figure 3), to treat fever, diarrhoea and for wound healing. In the northern states of peninsular Malaysia bordering Thailand, the consumption of kratom as a decoction is popular and kratom is commercially available as a decoction for consumption by drug users to manage opiate withdrawal symptoms. *M. speciosa* is also formulated and sold as crude extracts, tablets, tinctures and beverages (shots and seltzers) (Figure 3).

Due to the low absorption and bioavailability of mitragynine, there is a need for improved formulations and delivery systems [18]. Various delivery modes for mitragynine have been studied to enhance absorption, bioavailability and overall therapeutic efficacy [18–27]. The following sections provide a summary of these delivery systems. Some of these studies involved purified mitragynine, while the others used the ground dried leaves of *M. speciosa* or its extracts. An increased level of the use of nanotechnology in the formulation and delivery of mitragynine has also been observed in recent years [18,19].

Figure 3. Different formulations of *Mitragyna speciosa* leaf containing mitragynine.

3.1. Nasal Delivery

Nasal delivery of drugs involves the administration via the nasal passage as a spray or drops, serving as both a local method for nasal conditions and a systemic route for rapid absorption or direct delivery to the brain [28]. This non-invasive and needle-free approach bypasses (like any other topical application) the gastrointestinal (GI) tract, avoiding first-pass metabolism in the liver, and is used for treatments like allergies, pain, hormones, and neurological disorders. Nasal delivery could address issues related to poor bioavailability, as in the case of mitragynine, slow absorption and drug degradation. The feasibility of nasal delivery of mitragynine was explored using an ex vivo porcine nasal mucosa (0.26–1.47 mm) model and employing the Phoenix™ DB-6 Diffusion Franz Cell system with a diffusion area of 1.0 cm^2 and a receptor chamber volume of 10 mL [20]. Mitragynine was found to possess high permeability through the nasal mucosa, albeit dependent on the thickness of the nasal mucosa. This study demonstrated that mitragynine formulations could be developed for nasal delivery.

3.2. Peroral Delivery

Oral route of administration of drugs is the most convenient, cheap, safe and acceptable route for administration; it usually involves intraoral, where the drug is absorbed through the oral cavity, and peroral, where the drug is absorbed mainly through the intestine. Peroral delivery is the administration of drugs through the mouth, typically involving dosage forms that require moderate solubility for effective absorption and therapeutic action [29]. Peroral delivery of purified mitragynine includes its formulation mainly as tablets and capsules. However, poor water solubility of mitragynine (45.4 mg/L at 25 °C) limits its absorption when taken orally. To address this limitation, peroral systems of the ethanolic extract of the leaves of *M. speciosa*, containing ca. 10% mitragynine, were studied [21], where the ability of various liquid vehicles to enhance the dissolution and intestinal permeation of this compound was investigated. Mitragynine was found to be sparingly soluble (12.2–15.6 mg/g) in ethanol and diethylene glycol monoethyl ether, and slightly soluble (2.3–5.9 mg/g) in the other investigated solvents and surfactant-type liquids. In vitro test, conducted using the basket apparatus Erweka dissolution tester (model: DT826, Germany), showed limited dissolution of mitragynine from *M.* speciosa with a dissolution efficiency DE_{120min} of 34.6. However, the presence of a liquid vehicle could enhance the dissolution rate of mitragynine as much as 4.8-fold and boost dissolution efficiency by up to 2.2-fold. The enhancement in the dissolution rate of a drug using a liquid vehicle can be achieved through enhanced wetting ability and apparent solubility in the dissolution media. The presence of liquid vehicles could increase the apparent solubility of mitragynine in the aqueous medium, and this could occur through a cosolvency process in which a nonpolar or semipolar solvents reduce the dielectric constant in the diffusion layer surrounding the liquid-mass particles [21]. In the case of nonionic surfactants, the enhancement of solubility can be achieved through a micellar mechanism, in which, the mitragynine molecules are trapped within the micelles. It can be noted that drug dissolution is an essential requirement for the absorption and efficacy of nearly every orally administered medication, and dissolution analysis is a crucial method for evaluating the release of peroral formulations. The improvement in the apparent permeability coefficient of mitragynine by 1.2-4.8-fold with the liquid vehicle was observed in the ex vivo

intestinal permeation study using isolated rat intestinal sacs. The highest level of dissolution and intestinal permeation improvement for mitragynine was observed with ethanol and diethylene glycol monoethyl ether. The capacity of drug molecules to pass through the intestinal mucosa is a crucial aspect in determining the availability and effectiveness of the molecules [21]. The efficiency of intestinal permeation enhancers, also known as absorption promoters, is determined by numerous factors such as the physicochemical and permeation pathway of the permeants, and the concentration or quantity of the enhancers at the site of permeant absorption. The solvent-type liquids and surfactant-type liquids have been reported to enhance the intestinal uptake of poorly bioavailable drugs like mitragynine.

Nanostructured lipid carriers are effective vehicles for enhancing the drug loading capacity, controlled release, and bioavailability of poorly water-soluble compounds like mitragynine and protecting them from degradation and metabolism [18]. It can be noted that nanostructured lipid carriers are a type of nanoparticle, consisting of a mixture of solid and liquid lipids; they represent a second-generation biocompatible lipid nanoparticle, building upon the foundation of solid lipid nanoparticles [30,31]. The major advantages of nanostructured lipid carriers usually include more loading capacity for some drugs, less water in dispersion, prevention or minimisation of drug expulsion during storage, controlled and targeted drug release, feasibilities for loading both lipophilic and hydrophilic drugs, utilisation of biodegradable and biocompatible lipids, avoidance of use of organic solvents, better physical stability, increase of skin hydration and elasticity, and enhanced stability of drugs [31]. Different types of excipients are used in formulating nanostructured lipoid carriers, for example, solid lipid (bees wax, caranauba wax 2442, stearic acid, cetyl palmitate, Apifil®, Cutina CP®, Dynasan® 116, Dynasan®118, Precifac ATO, Compritol®888 ATO, Elfacos® C 26, Imwitor 900®, Precirol® ATO 5, tristearin, cholesterol and palmitic acid), liquid lipids or oils (Cetiol V, Miglyol® 812, castor oil, oleic acid, davana oil, palm oil, olive oil, isodecyl oleate, paraffin oil, propylene glycol dicaprylocaprate, linoleic acid, decanoic acid, argan oil and coconut oil), emulsifying agents (Pluronic® F68, Pluronic® F127, Tween 20, Tween 40, Tween 80, polyvinyl alcohol, Solutol® HS15, trehalose, sodium deoxycholate, sodium glycocholate, sodium oleate, polyglycerol methyl glucose distearate, Tego®Care 450, Tween™80, Maquat® SC 18Maquat® BTMC-85%, egg lecithin, soya lecithin, phosphatidylcholines, phosphatidylethanolamines, Gelucire® 50/13 and Miranol ultra 32), and counter ions (sodium hexadecyl phosphate, monodecyl phosphate, mono hexadecyl phosphate, mono octyl phosphate, dextran sulphate sodium salt, hydrolysed and polymerised epoxidised soybean oil) [31]. The impact of preformulation factors on different liquid lipids and solid lipids with diverse chemical structures and hydrophilic-lipophilic balance for the critical quality attributes of *M. speciosa* leaf extract-based nanostructured lipid carriers suitable for a drug delivery system was investigated [18]. The maximum solubility of the leaf extract in oleic acid (liquid lipid) and compritol ATO 888 (solid lipid) was, respectively, 2.859% and 53.02%, at a ratio of 70:30. Tween 80 was used as the main surfactant because of its high emulsification efficiency (51.53%). The findings from this preformulation study offered valuable insights into the development of an efficient and cost-effective formulation of *M. speciosa* leaf extract and the delivery of mitragynine.

Chitosan-based microencapsulation of *M. speciosa* alkaloids, including mitragynine, was reported as a new approach for the effective delivery of *M. speciosa* alkaloids for the treatment of Alzheimer's disease, focusing on cholinesterase inhibition and antioxidant properties [22]. Encapsulation of *M. speciosa* was accomplished in chitosan microparticles using ionic gelation. The microencapsulated formulation demonstrated controlled release under simulated GI conditions while retaining anticholinesterase activity. The optimized formulation had improved stability and enhanced controlled release properties. Previously, the different levels of microencapsulated-*Mitragyna* leaves extract supplementation on nutrient degradability, rumen ecology, microbial dynamics, and methane production in vitro were studied [32]. It is noteworthy that microencapsulation is a technology that encloses tiny particles or droplets of a core substance within a protective, micrometric-sized shell or coating, creating microcapsules that are 1 μm to several 100 μm in diameter [23]. It is an effective technique for the therapeutic delivery of drugs, live mammalian and bacterial cells and other biopharmaceuticals [24].

3.3. Transdermal Delivery

Transdermal delivery is a topical drug delivery system that is widely used because of the advantages, including bypassing the GI tract, avoiding GI irritation and the hepatic first-pass effect, and precisely reaching the lesion to reduce unnecessary adverse reactions [23,25,26]. The development of nanoparticle-based topical gels from ethanolic extracts of four kratom (*M. speciosa*) varieties, including Kan Daeng, Hang Kang, Tai Bai-yao, and Kan Keaw, has been reported recently, where the nanoparticles of kratom were prepared using a solvent displacement method [19]. However, kratom nanoparticle formulations exhibited slightly reduced levels of mitragynine. Nanoparticle-based kratom gels showed superior enzyme inhibition against collagenase, elastase, and

hyaluronidase. The nanoparticle-loaded gels had acceptable physicochemical stability after heating/cooling cycle testing, with pH (7.27 to 7.88), viscosity (10.719 to 12.602 Pas), and favorable visual and textural properties. This study demonstrated that nanoparticle-loaded gels could be used as multifunctional cosmeceutical agents for protecting oxidative damage of the skin, skin rejuvenation and as an anti-ageing agent.

The transdermal delivery potential of the ethanolic extract of the leaves of *M. speciosa* was investigated [27]. Porcine ear skin, which shares similar structural and lipid composition characteristics with human skin, was used in this ex vivo investigation. Skin permeation of mitragynine from *M. speciosa* extract was restricted, with permeation flux ranging from 0.4 to 11.6 mg/cm^2/h and skin deposition at 24 h ranged from 8.7 to 60.5 mg/cm^2. Mitragynine permeation was found to be influenced by vehicle composition and lipophilicity. The mixture of hydrophilic chemical enhancers, propylene glycol and diethylene glycol monoethyl ether as *M. speciosa* extract vehicle, yielded the highest skin permeability coefficient of mitragynine. It can be noted that during the ex vivo permeation study, the sink condition must be maintained within the receptor compartment of static diffusion cells to ensure that the permeation rate is not limited by the ingredient concentration in the receptor medium [27].

The potential of mitragynine to be delivered through the skin was studied and a gradient HPLC-UV analytical method was developed and validated to determine mitragynine in the samples collected during in vitro skin permeation studies [33]. This method was used to evaluate the in vitro skin permeation of mitragynine (5% *w*/*v*) from simple solvent systems over 48 h. It was observed that a cumulative amount of mitragynine permeated at 11 mg/cm^2 for dimethyl sulfoxide and similar to 4 mg/cm^2 for propylene glycol. This was the first proof-of-concept report on skin permeation of mitragynine, highlighting the need for further work to overcome the current shortcomings, especially optimising the skin permeation parameters such as skin flux.

3.4. Miscellaneous

Like many other natural products, mitragynine is also available as a component in e-liquids for e-cigarettes for inhalation [34].

4. Future Outlook

Kratom (*M. speciosa*) is not an FDA-approved drug for medical use, and there are no official dosage guidelines, although dosage is a critical factor for its therapeutic efficacy and safety. Any future studies on its formulation and delivery must consider dosage requirements to optimise expected therapeutic efficacy and low toxicity. The kratom market offers opportunities for product innovation, especially around effective delivery methods and formulations, which may involve further work involving nanotechnology. The emerging market of kratom-infused beverages demands further work related to product quality, safety and consumer satisfaction. Formulations for transdermal applications also demand further research. Future innovation in delivery and formulation may also include combinations with other botanicals or developing targeted formulations for specific effects and applications.

5. Conclusions

The dried leaves of *M. speciosa* are typically consumed as decoctions and teas or as ground powders. For oral consumption, tablets and capsules of *M. speciosa* leaves are commercially available. Other emerging products include beverages produced from this plant. In addition to peroral delivery, mitragynine could also be delivered through nasal and transdermal delivery routes. The application of nanotechnology has been found to enhance the delivery of mitragynine and thus enhance its therapeutic efficacy.

Author Contributions: Both authors (S.D.S. and L.N.) contributed equally to the literature search, preparation of the manuscript and editing. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Acknowledgments: Lutfun Nahar gratefully acknowledges the support of the European Regional Development Fund—Project ENOCH (No. CZ.02.1.01/0.0/0.0/16_019/0000868), the Czech Agency Grants—Project 23-05474S and Project 23-05389S, and the PIFI Project 2025PVA0074 from the Chinese Academy of Sciences.

Conflicts of Interest: The authors declare no conflicts of interest.

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