Debilitating pain is a constant backdrop of daily life, resulting in personal suffering, substantial health costs, and an economic burden for society. Pain is not only a disabling symptom of many medical conditions but also a disease state in its own right. With its prevalence in 20–30% of the adult population, chronic pain affects more people than heart disease, cancer, and diabetes combined and will continue to grow as our population ages. Pain medicine represents one of the most rapidly developing medical specialties of today, with effective pain control being a therapeutic priority. Chronic pain is still poorly managed because of the lack of efficacious therapies and significant adverse side effects of currently available analgesic drugs. Now, the article of Kruegel et al. presents different pain therapeutics based on a natural product, Mitragyna speciosa, and new insights into its pharmacology and analgesic activity.3

Opioids are highly effective analgesics and the most widely prescribed class of medications in the US.4 Most opioid analgesics (e.g., morphine, fentanyl, and oxycodone) used in clinical practice target mu-opioid receptors.2 Medical use and misuse of opioids have strongly increased in the past decades. It has emerged as a major public health threat due to the dramatic rise in opioid-related overdose deaths (over 47,000 in 2017 or 67.8% of all drug overdose deaths) and diagnoses of opioid-use disorder (addiction) associated with prescription opioids (1.8 million in 2016). The cost of the opioid epidemic in the US is estimated to be $80 billion annually.5 6

Medicinal plants are tremendous sources of new drug candidates. Lately, there has been a renewed interest in natural product research due to the failure of alternative drug discovery methods to deliver many lead compounds in key therapeutic areas such as pain. Mitragyna speciosa, known as “kratom”, a plant native to Southeast Asia, has been used traditionally as a stimulant and analgesic and for the treatment of opioid addiction.6 During the past years, kratom use has become increasingly popular in the US, where the consumption of kratom leaves was reported as an efficacious treatment of pain, particularly in cases where other available treatments have either failed or caused intolerable side effects.7 A significant number of users have also reported use of kratom as a tool to stop or reduce the use of prescription or illicit opioids—a potential application that is nowadays gaining high attention given the ongoing opioid abuse epidemic in the US.

Given the unique and fascinating pharmacology surrounding mitragynine, the major alkaloid in kratom, Kruegel et al.3 present a systematic study on the metabolism-dependent mechanism for the analgesic effects of mitragynine. It offers a possible explanation for the apparently safer profile of mitragynine compared to classical opioids. In their report, the authors rationalized the importance of 7-hydroxymitragynine (7-OH) as an active metabolite of mitragynine and a key mediator of its analgesic activity, thus providing the essential in vivo link signifying the pharmacological relevance of 7-OH (Figure 1).

In a previous report, both mitragynine and 7-OH were found to display G protein-biased agonism at the mu-opioid receptor,8 a concept which gained significance in drug discovery over the recent years, where G protein-biased...
mu-opioid receptor agonists may deliver the desired analgesia without the unwanted side effects. In their latest work published in *ACS Central Science*, the authors have proven that, besides the conversion of mitragynine to 7-OH via chemical oxidation, mitragynine can also undergo biotransformation in vitro in both mouse and human liver preparations to 7-OH, with cytochrome P450 3A4 as the main metabolic pathway (Figure 1). In both microsome preparations, 7-OH was the major metabolite and was produced concomitant with the disappearance of mitragynine. The metabolic conversion was more efficient in human liver microsomes suggesting that an appreciation of interspecies differences is likely to be important for understanding the pharmacology of mitragynine. Mitragynine as well as 7-OH were highly stable in mouse plasma, indicating that plasma metabolism does not contribute significantly to the bio-transformation of these alkaloids. 7-OH was reported earlier as having much higher analgesic potency in mice after subcutaneous (s.c.) administration compared to mitragynine and morphine. Using genetic approaches, the authors demonstrated in vivo that mitragynine and 7-OH produce analgesic effects acting through a mu-opioid receptor-dependent mechanism. They have demonstrated that metabolic conversion of mitragynine to 7-OH occurred also in vivo, where both alkaloids were detected in the plasma and brain, confirming that 7-OH is formed as a metabolite of mitragynine and that it enters the brain. Further, the authors have proven in mice that 7-OH contributes to the analgesic activity of mitragynine as a metabolite when comparing the pain response of compounds given at equianalgesic s.c. doses and confirmed this by quantifying concentrations of 7-OH in the brain, thus being consistent with 7-OH as the primary mediator of central analgesic activity. At the same time, other groups independently described the formation of 7-OH as a metabolite of mitragynine in vitro and in vivo.

However, pharmacokinetic studies will be required to elucidate the importance of 7-OH as a mitragynine metabolite in man, where the interspecies differences in the metabolic processes must be carefully considered. Overall, this work provides knowledge that can be used for creating novel pain therapeutics based on kratom. The *Mitragyna* alkaloid scaffold represents an attractive framework for the development of functionally biased opioid modulators, which may exhibit improved therapeutic profiles as analgesic drugs. In particular, respiratory safety is of major importance to clinicians due to the risk for fatal outcomes and because respiratory suppression is the primary cause of opioid-related overdose mortality. The pharmacological profile of 7-OH as a partial G protein-biased agonist at the mu-opioid receptor would signify a desirable, wide analgesia-respiratory depression therapeutic window. Many challenges still lie ahead in the process of solving the current opioid epidemic.

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**Figure 1.** Metabolic transformations of mitragynine to 7-hydroxymitragynine (7-OH), with 7-OH as an active metabolite of mitragynine and a key mediator of its analgesic activity.
Dedication
This paper is dedicated in remembrance of Dr. Gavril W. Pasternak who passed away in February 2019.

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