MITRAdalis

Product Information

Mitradalis Formula is designed to attenuate inflammation and pain. Contains phytotherapeutic extracts of **Mitragyna speciosa, Corydalis yanhusuo, Salix alba, Curcuma longa, Berberis vulgaris, Coptis chenesis, Zingiber officinale and *Cinnamomum verum.*** This is a synergistic herbal formula known to alleviate analgesic pain.

Pain is described as a sensation that is felt because of a physically hurting stimulus. Pain can be divided into nociceptive, inflammatory, and neuropathic pain. Nociceptive pain is defined as a form of physical pain that is experienced during external Injury. Inflammatory pain is classified as tissue damage and infiltration of immune cells, while neuropathic pain is described as pain that is experienced through any damage to the nervous system. The transmission of pain sensation is relayed through affected neurons to the spinal cord, which then transfers the signal to the brain for processing. To date, antinociceptive and anti-inflammatory drugs are the gold standard to manage pain while anticonvulsants and antidepressants are used to treat neuropathic pain. For over 7000 years, various extracts of plants have served as analgesics. These plant extracts offer analgesic compounds that relieve pain.

Mitragyna speciosa, mitragynine (MG) is the main lipophilic alkaloid present in kratom. Its active metabolite 7-hydroxy-mitragynine (7-HMG) is widely studied in preclinical models for its analgesic properties.

Corydalis yanhusuo, has been shown to alleviate pain caused by blood stasis, improve blood circulation, promote movement, and alleviate stagnation-induced pain. Various studies have shown that YHS has pharmacological effects on the nervous, digestive, and cardiovascular systems, as well as therapeutic benefits in treating thrombosis,

Salix alba, is an inhibitor of COX-1 and COX-2, used to block inflammatory prostaglandins.

Curcuma longa, is an antioxidant, antiseptic, antifungal and anti-inflammatory.

Berberis vulgaris, berberine has been used as an antimicrobial, antiprotozoal, and antidiarrheal agent in Ayurvedic medicine and traditional Chinese medicine. Berberine effects markers of glycemic control, blood lipids, markers of liver function, and anthropometric parameters in people with metabolic disorders.

Coptis chenesis, has been proved to have anti-cancer, anti-inflammatory, and anti-bacterial properties and to help to improve cardiovascular conditions.

Zingiber officinalis, Gingerols (found in fresh extracted root) increases the uptake of calcium by the myocardium and enhance the force of contractions (cardiotonic). It is hepatoprotective, anti-inflammatory, antioxidant, antiseptic, and promote gastric secretions.

Cinnamomum verum, Cinnamon health benefits are attributed to its content of a few specific types of antioxidants, including polyphenols, phenolic acid and flavonoids.

Mitradalis is uniquely extracted from select organic herbs, organic cane alcohol and deep ocean mineral water, as the extraction solvent. Utilizing advanced all-glass apparatus **Mitradalis**'s ingredients undergo hours of reflux extraction that applies heat and hydro-alcohol to enhance the bioavailability of the resultant extraction.

- **Highly bio-available due to heat and hydro-alcohol reflux extraction**
- **Organic**, Non-GMO, Gluten free
- Extracted with **Maui-grown organic sugarcane alcohol** and deep ocean mineral water

molecules

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Review

The Analgesic Properties of *Corydalis yanhusuo*

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Abstract: *Corydalis yanhusuo* extract (YHS) has been used for centuries across Asia for pain relief. The extract is made up of more than 160 compounds and has been identified as alkaloids, organic acids, volatile oils, amino acids, alcohols, and sugars. However, the most crucial biological active constituents of YHS are alkaloids; more than 80 have been isolated and identified. This review paper aims to provide a comprehensive review of the phytochemical and pharmacological effects of these alkaloids that have significant ties to analgesia.

Keywords: *Corydalis yanhusuo*; alkaloids; analgesia; pain; inflammation

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1. Introduction

Pain is described as a sensation that is felt as a result of a physically-hurting stimulus [1]. Pain can be divided into nociceptive, inflammatory, and neuropathic pain [1]. Nociceptive pain is defined as a form of physical pain that is experienced during external injury [2]. Inflammatory pain is classified as tissue damage and infiltration of immune cells, while neuropathic pain is described as pain that is experienced through any damage to the nervous system [2]. The transmission of pain sensation is relayed through affected neurons to the spinal cord, which then transfers the signal to the brain for processing [2]. To date, antinociceptive and anti-inflammatory drugs are the gold standard to manage pain, while anticonvulsants and antidepressants are used to treat neuropathic pain [3].

The CDC recommends anti-inflammatory drugs (i.e., nonsteroidal anti-inflammatory drugs known as NSAIDS and COX-2 selective inhibitors) to treat low to moderate types of pain [4]. However, for more severe pain, opiate drugs are the gold standard [4]. Opiates are shown to be effective for 70–80% of patients, hence they are the go-to when it comes to analgesia. However, these potent opiates cause a wide array of adverse side effects, such as tolerance, dependence, respiratory depression at high doses, and reduction in GI motility [5].

Pain itself has caused a huge burden in our healthcare system, as many patients suffer from adverse pain sensations, which ultimately reduces their quality of life [6]. The CDC reports that pain affects more than 50 million adults in the U.S. and costs an estimated $635 billion annually [4]. Moreover, chronic pain prevalence is expected to increase in the coming years, due to an aging population, increase in cases of diabetes and cancer survival rates [7]. Therefore, the search for new analgesic compounds that present a therapeutic alternative is crucial.

2. Plant Extracts and Pain Management

For over 7000 years, various extracts of plants have served as analgesics [8]. Indeed, morphine (the gold standard in analgesic therapy) is a plant alkaloid [8]. These plant extracts offer an opportunity to identify new analgesic compounds that may contain analgesic

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Review

Chemistry and Pharmacology of Analgesic Indole Alkaloids from the Rubiaceous Plant, *Mitragyna speciosa*

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The leaves of a tropical plant, *Mitragyna speciosa* KORTH (Rubiaceae), have been traditionally used as a substitute for opium. Phytochemical studies of the constituents of the plant growing in Thailand and Malaysia have led to the isolation of several 9-methoxy-Corynanthe-type monoterpenoid indole alkaloids, including new natural products. The structures of the new compounds were elucidated by spectroscopic and/or synthetic methods. The potent opioid agonistic activities of mitragynine, the major constituent of this plant, and its analogues were found in *in vitro* and *in vivo* experiments and the mechanisms underlying the analgesic activity were clarified. The essential structural features of mitragynines, which differ from those of morphine and are responsible for the analgesic activity, were elucidated by pharmacological evaluation of the natural and synthetic derivatives. Among the mitragynine derivatives, 7-hydroxymitragynine, a minor constituent of *M. speciosa*, was found to exhibit potent antinociceptive activity in mice.

Key words *Mitragyna*; alkaloid; indole; analgesic; opioid; structure–activity relationship

1. Introduction

Mitragyna speciosa KORTH (Rubiaceae), endemic to tropical Southeast Asia, is a species of particular medicinal importance.[1)] Known as "Kratom" in Thailand and "Biak-Biak" in Malaysia, the leaves have been traditionally used by natives for their opium-like effect and coca-like stimulant ability to combat fatigue and enhance tolerance to hard work under the scorching sun. It has been used also as a substitute for opium and for weaning addicts off morphine. However, the use of this plant has been banned in those countries because of its narcotic effect. Due to its unique medicinal properties, a number of chemical and pharmacological studies have been carried out over the last forty years. Several indole alkaloids have been found[2)] and a preliminary study of the antinociceptive activity[3)] of the major constituent has been reported. However, the principle and the mechanisms underlying the biological activities have not been completely elucidated at the time when we embarked on the chemical and pharmacological investigation of *M. speciosa*. In this review, recent findings from our study of *Mitragyna* alkaloids are discussed.

2. Chemical Constituents in the Leaves of *Mitragyna speciosa*

2.1. Thai Plant In the 1960s, the Chelsea group in the U.K. reported the isolation of several indole alkaloids from the leaves of *M. speciosa* from Thailand.[4—6)] Almost ten years later, Shellard *et al.*, in their investigation of the alkaloidal constituents in various samples of *M. speciosa* from Thailand, isolated more than twenty kinds of Corynanthe-type alkaloids, including oxindole derivatives.[7—9)] They pointed out that the variation in the constituents among different batches of leaves may be an indication of the presence of geographical variants of the species within Thailand. For chemical re-investigation, we chose the plant growing on the campus of the Faculty of Pharmaceutical Sciences, Chulalongkorn University in Bangkok, in collaboration with Dr. Ponglux. From the young leaves of *M. speciosa*, mitragynine (**1**) was obtained as the major constituent (66.2% based on the crude base) together with its analogues, speciogynine (**2**, 6.6%), speciociliatine (**3**, 0.8%), and paynantheine (**4**, 8.6%). In addition, a new alkaloid, 7α-hydroxy-7*H*-mitragynine (**5**), was isolated as a minor constituent (2.0%), the structure of which was elucidated by spectroscopic analysis and chemical transformation from mitragynine (**1**) (Fig. 1).[10)] As is mentioned later, this new alkaloid was proven to be a key compound in this series of research.

2.2. Malaysian Plant The Chelsea group also started in the mid 60 s the chemical investigation of Malaysian *M. speciosa*,[11)] which resulted in the isolation of several mitragynine-related indole alkaloids. Houghton and Said reported the isolation of a new alkaloid (**6**),[2)] *i.e.*, a 3,4-dehydro derivative of mitragynine, from the fresh leaves of *M. speciosa* growing on the campus of Universiti Kebangsaan Malaysia. They also found new types of indole alkaloids, mitragynaline (**7**), corynantheidaline (**8**), mitragynalinic acid (**9**), and corynantheidalinic acid (**10**) (Fig. 2), in the very young leaves of the same plant.[12)] Those alkaloids have an unusual skeleton, namely, a carbon function at the C14 position, compared with hitherto known monoterpenoid indole alkaloids. However, the structures of **7** and **8** were revised as described later (Section 2.3).

In collaboration with Dr. Said of Universiti Kebangsaan Malaysia, we also re-investigated the constituents in

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REVIEW ARTICLE

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Advances in phytochemical and modern pharmacological research of *Rhizoma Corydalis*

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ABSRACT

Context: *Rhizoma Corydalis* (RC) is the dried tubers of *Corydalis yanhusuo* (Y. H. Chou and Chun C. Hsu) W. T. Wang ex Z. Y. Su and C. Y. Wu (Papaveraceae). Traditionally, RC is used to alleviate pain such as headache, abdominal pain, and epigastric pain. Modern medicine shows that it has analgesic, anti-arrhythmia, and other effects.

Objective: We provided an overview of the phytochemical and pharmacological properties of RC as a foundation for its clinical application and further research and development of new drugs.

Methods: We collected data of various phytochemical and pharmacological effects of RC from 1982 to 2019. To correlate with existing scientific evidence, we used Google Scholar and the journal databases Scopus, PubMed, and CNKI. '*Rhizoma Corydalis*', 'phytochemistry', and 'pharmacological effects' were used as key words.

Results: Currently, more than 100 chemical components have been isolated and identified from RC, among which alkaloid is the pimary active component of RC. Based on prior research, RC has antinociceptive, sedative, anti-epileptic, antidepressive and anti-anxiety, acetylcholinesterase inhibitory effect, drug abstinence, anti-arrhythmic, antimyocardial infarction, dilated coronary artery, cerebral ischaemia reperfusion (I/R) injury protection, antihypertensive, antithrombotic, antigastrointestinal ulcer, liver protection, antimicrobial, anti-inflammation, antiviral, and anticancer effects.

Conclusions: RC is reported to be effective in treating a variety of diseases. Current pharmacological studies on RC mainly focus on the nervous, circulatory, digestive, and endocrine systems, as well as drug withdrawal. Although experimental data support the beneficial effects of this drug, its physiological activity remains a concern. Nonetheless, this review provides a foundation for future research.

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KEYWORDS
Traditional Chinese medicine; bioactive components; phytochemistry; pharmacological effects

Introduction

Rhizoma Corydalis (RC), also known as *Corydalis yanhusuo*, *YuanHu*, *YanHu*, or *XuanHu* in China, is a well-known traditional Chinese medicine (TCM) prepared from the dried tubers of *Corydalis yanhusuo* (Y. H. Chou and Chun C. Hsu) W. T. Wang ex Z. Y. Su and C. Y. Wu (Papaveraceae). (Wang et al. 2016). RC has a long history of medicinal use and is mainly cultivated in the Zhejiang, Jiangxi, and Anhui provinces of China. RC was first recorded in Shennong Herbal Classic and was listed as a medium-grade drug. RC is pungent, bitter, and warm, and is transported to the spleen and the liver meridians. In TCM, RC is believed to have functions such as activating blood, reinforcing vital energy, and relieving pain (Chinese Pharmacopoeia Commission (CPC) 2015). In the clinical practice of Chinese medicine, RC often appears as a compound. Alkaloids are important biological active constituents of RC (Wu et al. 2012), including tertiary amines, quaternary alkaloids, and many non-alkaloids. Presently, more than 80 alkaloids have been isolated and identified from RC (Xiao et al. 2011; Zhou et al. 2012). Modern medical research has revealed that RC has significant analgesic, sedative, and hypnotic effects, and in a variety of diseases such as arrhythmia, gastric ulcer, and coronary heart disease, it displays a good clinical effect (CPC 2015; Wang et al. 2016). To date, however, there has been no comprehensive review on the phytochemical and the pharmacological effects of RC. Based on the high therapeutic value of RC, we sought to systematically summarize the latest findings regarding the phytochemical and pharmacological effects of RC and its bioactive components between 1982 and 2019 by using Google Scholar and the journal databases Scopus, PubMed, and CNKI, in an attempt to provide a foundational knowledge guide for its subsequent research and utilization.

Phytochemistry

To date, more than 100 compounds have been isolated and identified from RC (Wu et al. 2012). Alkaloids are important biological active constituents of RC, including tertiary amines and quaternary alkaloids. Besides alkaloids, there are additionally many non-alkaloid components, including organic acids, steroids, carbohydrates, and other chemical compounds (Liu et al. 2013). To better understand the physiological effects of different active ingredients of RC, the primary components of the compound are shown in Table 1.

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