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**Journal of Wellness, Complementary, and Traditional Medicine, 1 (1), 2025, p. 1-10**

# POTENTIAL OF MENISPERMACEAE FAMILY AS HERBAL TREATMENT FOR COVID-19: LITERATURE REVIEW

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**Abstract***:* Covid-19 pandemic is an infectious disease caused by SARS-CoV-2. Many natural products are known have antiviral activity, including Menispermaceae family. This plant were widely distributed in tropical forest, including in Indonesia. Existing studies are still limited regarding the benefits of this family in the treatment of Covid-19. This review aims to discuss and identify the use of plants from the Menispermaceae family in the treatment of Covid-19. We found that some components in the Menispermaceae family that have been utilized in the treatment of Covid-19 are still limited, although several studies have shown anti-infective effects against various bacterial, viral, and fungal pathogens. Cepharanthine (CEP) is the only bioactive component of Menispermaceae plants that has been clinically tested and used in the treatment of Covid-19. The effect of CEP has been trials effectively against other viral infections. Further identification of components in this family is needed for potential therapy against various infections in the future.

**Keywords**: ACE inhibitor, Bisbenzylisoquinoline, COVID-19, Menispermaceae.

## INTRODUCTION

Since its emergence in Wuhan, China in late 2019, coronavirus disease (COVID-19) infection has resulted in millions of deaths worldwide (Kumar et al., 2021). This infection is caused by new strain of the Severe Acute Respiratory Syndrome (SARS- CoV-2) group of the Beta-Coronavirus genus that can cause pneumonia (Kumar et al., 2021). Based on further research, bats act as the initial host and cause transmission to humans (zoonotic) (Mackenzie and Smith, 2020). Like previous coronavirus, SARS-CoV-2 virus can be transmitted through airborne droplets from coughing, sneezing, and hand-to-hand contact (Meyerowitz et al., 2021). In some cases, viruses have been found to mutate in the human body so that they have a very strong and infectious ability to spread (Korber et al., 2020; Meyerowitz et al., 2021). By the end of December 2020, more than 80 million Covid cases had been confirmed with a death toll of 1.7 million and a case fatality rate varying from country to country between 0 – 20% (average case fatality rate 2.2%) (Rahman et al., 2021).

Covid-19 has common symptoms such as dry cough, sore throat, fever, and shortness of breath with some uncommon symptoms such as abdominal pain and dizziness were associated with severe infection (Li et al., 2021). Some studies has showed that risk of Covid-19 infection in patients with comorbidities tends to show more severe symptoms and has higher mortality risk (Li et al., 2021). COVID infection can result in long-term effects (12-24 weeks) or persistent symptoms (more than 24 weeks) in the form of fatigue and myalgia, cough, dyspnea, and disturbances of olfactory and gustatory function (Fernández-de-las-Peñas et al., 2021; Healey et al., 2022). There are also several reports of reinfection cases where the symptoms that arise can be worse than those of the first infection, which is influenced by comorbid risk factors and current therapy from previous infection (Goldman et al., 2020; Mulder et al., 2020; Van Elslande et al., 2020). It is still unclear whether reinfection with COVID-19 can cause more severe symptoms (Yahav et al., 2020).

Herbal medicine has been widely studied for its various health benefits, one of which is its antiviral effects (Srivastava et al., 2025). In addition, herbal products have been shown to have immunomodulatory effects that can reduce the inflammatory effects associated with infections (Alarabei et al., 2023). The use of herbal supplements has become one of the treatment options for Covid-19 even

though there have been few clinical trials (Onyeaghala et al., 2023). However, along with the risk of reinfection and re-emergence in the future, it is necessary to explore the potential of herbal content as an alternative treatment that has been clinically tested (Onyeaghala et al., 2023). One of the most commonly used herbal plants is from the Menispermaceae family which commonly grows in tropical and subtropical areas and has been widely used in traditional medicine. This type of family has 65 genera, the majority of which are spread across tropical East and Southeast Asia (Shang et al., 2024) Several previous studies have shown the benefits of this family of plants in previous viruses such as MERS and SARS by preventing viral replication and developing worsening symptoms (Hu et al., 2021). However, its influence on symptoms and risk of Covid-19 infection has not been widely discussed. This review emphasizes the potential of natural compounds from the Menispermaceae family and their mechanisms of action as potential treatments for Covid-19 disease considering the limited studies related to herbal medicine from this family against SARS-CoV-2 infection.

## METHODS

The design of this study is a literature Review that critically examines or reviews knowledge, ideas, or findings contained in the literature with an academic orientation (academic-oriented literature) to provide theoretical and methodological contributions to a particular topic. The search for published articles was carried out on electronic database Google Scholar, PubMed, and ScienceDirect with broad keyword Covid-19, SARS-CoV-2, Menispermaceae, and other relevant keywords from included studies. In-vivo or in-vitro studies, clinical trials with randomized controlled trials, or reviews focusing on products of the Menispermaceae family were included in our inclusion criteria.

## RESULT AND DISCUSSION

A total of 53 articles were used in compiling this review. Three studies focused on the effects of Menispermaceae on Covid-19 infection according to our inclusion criteria with details of 2 in-vivo studies (Li et al., 2022; Rajan et al., 2023) and 1 clinical study in healthy populations to determine the side effects of Menispermaceae family products (Dar et al., 2022) which we will discuss in the next section.

### Characteristics of and Mechanism of Infection SARS-COV2 Virus

SARS-CoV-2 is a type of single-stranded RNA beta-coronavirus virus with genomic investigation studies proving that this virus has 79.5% and 51% similarity in protein coding genes to SARS-CoV and MERS-CoV type were commonly found in the Middle East and is transmitted by mammals such as camels. (Liu et al., 2021; Lotfi et al., 2020). The size of SARS-CoV-2 ranges from ~29.9 kB with a diameter of 50–200 nm (Triggle et al., 2021). The structure of this virus has a double-layered lipid envelope, including a spike (S) glycoprotein that has a receptor-binding domain (RBD) to interact with host cell receptors, envelope proteins, membrane glycoproteins, and nucleocapsid proteins (Triggle et al., 2021). Compared to its predecessor (SARS-CoV-1), there are genetic differences that are mostly clustered in the non-structural protein genes with 27 mutations found in the gene encoding the S spike protein virus which is responsible for receptor binding and cell entry (Jones et al., 2020).

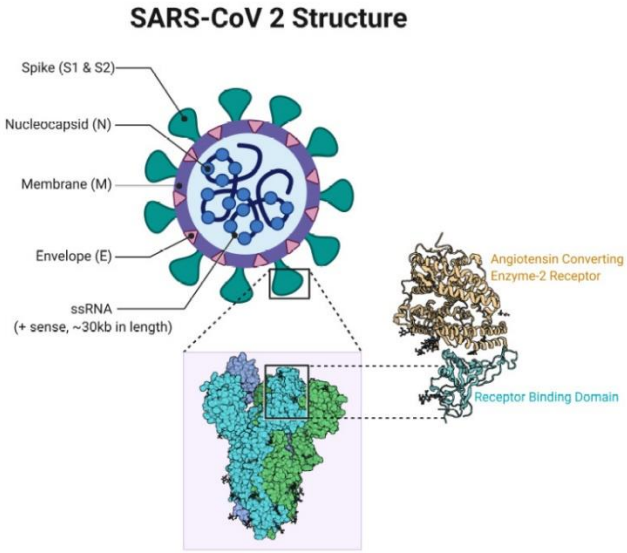


**Figure 1.** SARS-CoV-2 Structure.(Cascella et al., 2020)

SARS-CoV-2 infection in humans targets respiratory epithelial cells with the most likely targets being multiciliated cells in the nasopharynx or trachea or sustentacular cells in the nasal olfactory mucosa (Lamers and Haagmans, 2022). The virus then binds to the Angiotensin-converting enzyme 2 (ACE2) receptor and initiates the production of viral proteins, including the replicase protein that forms the replication factory of the endoplasmic reticulum membrane (Triggle et al., 2021). Unlike previous SARS-CoV viruses, this type of virus has the ability to further increase receptor binding and make the respiratory tract have a high viral load and facilitate transmission (Martines et al., 2020).

The detection mechanism of SARS-CoV-2 by host immune cells is triggered by pattern recognition receptors (PRRs) which then secrete pro-inflammatory cytokines including Interleukin-1 (IL-1) and IL-6, tumor necrosis factor alpha (TNF-a), and interferon type I/III (IFN) to induce antiviral activity in host cells, which then induces an adaptive immune response (Triggle et al., 2021). Under certain conditions, pro-inflammatory cytokines can develop excessively into a cytokine storm as a strong immune response that can quickly clear pathogens but can also cause extensive organ damage and compromise tissue function (Giasuddin et al., 2021). If the immune system is unable to eliminate pathogens, the virus can spread to the lower respiratory tract causing infection in the alveoli and and infect alveolar type 2 (AT2) cells which are progenitor cells of AT1 cells in the adult human lung (Lamers and Haagmans, 2022). Autopsy results in one study of Covid infection showed the damaging effects of alveoli due to the cytopathic effects of inflammation (Bradley et al., 2020). Furthermore, the process of damage to the lower respiratory tract causes epithelial necrosis and results in blockage of the alveoli due to the formation of scar tissue that damages normal lung tissue (Haick et al., 2014). Cytokine storm caused by systemic SARS-CoV-2 virus infection results in systemic sepsis which results in disruption of vital organs such as the heart, kidneys and brain and increases the risk of death in patients with cardiovascular disorders and other comorbid diseases (Qudus et al., 2023).

**Characteristic and Distribution Menispermaceae Family**

Menispermaceae is a family of dioecious lianas and an important component of ecosystems that form tropical low-wetlands (Wefferling et al., 2013). They are members of a shrubland (rarely herbs, erect shrubs, or small trees) consisting of 72 genera and about 520 species with the most specific genera including *Odontocarya Miers* (~37 species), *Stephania Lour.* (30–60 species), and *Tinospora Miers* (25–35 species) (Wefferling et al., 2013). The Menispermaceae family produces aggregate of 3 or 6 seeds, and species rarely produce more than 10 seeds (except in the species Tiliacora Colebr which produces up to 30 seeds) (Wefferling et al., 2013). The leaves in this family are usually simple, but compound leaves are seen in the Malagasy species Burasaia Thouars and in Disciphania cubijensis (R. Knuth) Sandwith in South America. Leaf venation is usually palmate, but some genera have pinnate venation (Ortiz et al., 2007). Although the family has wide variation with some differences among morphological characters, the main feature historically used to define the family is the curved seeds found in many genera, hence the popular name "moonseeds" (Ortiz et al., 2007).

The origin of Menispermaceae has been estimated to date back to more than 100 million years ago in the Indo-Malayan region with the spread and then spread to tropical regions in Africa, Australia and America and associated with the simultaneous emergence of modern neotropical and paleotropical forests worldwide after the mass extinction at the Cretaceous-Paleogene boundary (Wang et al., 2012). This family has a specific distribution in rainforests spread across the southern hemisphere in tropical climates (Lian et al., 2023). Although Menispermaceae are predominantly climbing woody plant, they also play a major role in many aspects of tropical forests and their importance may increase with global climate change due to their contribution to overall species diversity (Ortiz et al., 2007). Some members of Menispermaceae can also be found extending into the northern temperate zone (Hina et al., 2020). For example, *Menispermum dauricum* DC grows in central to northeastern China, southern Siberia, Korea, and Japan, while *Menispermum canadense* L. is found in temperate eastern North America and grows abundantly in deciduous forests and shrublands (Song et al., 2023). In the humid forests of tropical America, *Curarea Barneby* & Krukoff from the Menispermaceae plant family is widely distributed, mostly in the lowlands from eastern Brazil to Costa Rica in Central America (Ortiz, 2018).

Some species of this plant are known by various names in local languages such as Broom creeper (English), Huyer (Bengali), or Farid buti, Jamti ki bel (Hindi) (Logesh et al., 2020). In Indonesia, one of the Menispermaceae family is *Cyclea barbata* or popularly known as cincau and and *Tinospora crispa L.* which is more commonly known as brotowali which is known for its bitter taste.(Ikrar Musyaffa et al., 2024; Kusriani et al., 2023). In Kalimantan, one type of this family is sengkubak (Albertisia papuana Becc) which is commonly used by the Dayak people as a cooking spice (Bastian et al., 2024). Table 1 show several popular Menispermaceae and their distribution in Indonesia.

**Table 1.** Popular Menispermaceae and Their Distribution in Indonesia (Budiarti et al., 2020; Hasan et al., 2018; Kristiana et al., 2022; Kusumo et al., 2023).

| **Species** | Popular name in Indonesia | Most place |
|---|---|---|
| *Cyclea barbata* | Daun cincau | Java, Sumatra, and Sulawesi |
| *Tinospora crispa* | Brotowali, Tali Pahit | Sumatra, Kalimantan, Papua |
| *Albertisia papuana Becc* | Sengkubak | Kalimantan |
| *Fibraurea Tinctoria* | Akar kuning | Kalimantan, Papua |
| *Stephania japonica* | Umbi akar kepleng | Nusa Tenggara, Sulawesi |
| *Arcangelisia flava* | Kayu kuning | Kalimantan, Sulawesia, Papua |
| *Pericamphylus glaucus* | Akar gamet | Jawa, Sumatra, Kalimantan |

**Helath Benefits Compound From Menispermaceae Family**

Several studies have shown that the components of Menispermaceae, namely alkaloids in various forms (Bisbenzylisoquinoline, apomorphine, morphine, proberberberine, and berberine) and other components such as polysaccharides, tannins, saponnins, and quinones (Zhai et al., 2023). However, each species has a different percentage of chemical components. For example, *Cocculus hirsutus* (L.) which is commonly found in India and Africa has alkaloid components jasminitine, hirsutine, and cohirsitine (Logesh et al., 2020). While in *Menispermi Rhizoma* which is commonly used in traditional Chinese medicine has alkaloid content bibenzylisoquinolines, apomorphins, and oxidized isoapomorphins (Zhai et al., 2023). In *Tinospora crispa*, the most common alkaloids found are aporphine, furonoquinolone, and protoberberine (Ahmad et al., 2016). The many studies on the bioactive content of Menispermaceae plants play an important role in researching the therapeutic potential of this family (Chambhare, 2025).

Plant species from the Menispermaceae family are widely used in traditional medicine in several countries (Logesh et al., 2020). Various uses of plants are based on the area where the plants are cultivated (Logesh et al., 2020). In some Southeast Asia region, this plant is useful for gynecological disorders such as dysmenorrhea and menstrual disorders (de Boer and Cotingting, 2014). In Thailand, escpecially among minority ethnic such as Karen, Menispermaceae is a type of herbal medicine

commonly used for bacterial infections, helminths, and other causes of infection (Phumthum and Balslev, 2020). One study showed the antimicrobial effects of methanol and chloroform extracts of *Cocculus hirsutus* leaves, a member of the Menispemaceae family, working by binding to the bacterial cell wall protein and significant bactericidal activity against several common infectious pathogens such as Klebsiella pneumoniae and Pseudomonas (Kumdini et al., 2018). Components of the Menispermaceae family also have antifungal effects that inhibit the growth of the pathogenic fungi *Fusarium solani*, *Rhizopus arrhizus*, and *Sclerotium rolfsii* (Devi et al., 2017). Several species from the Menispermaceae family that are not common such as *Tinospora crispa*, *Fibraurea tinctoria*, *Tinospora sinensis*, and *Arcangelisia flava* are known used as natural antimalarials on Papua Island (Budiarti et al., 2020).

Apart from being an anti-infective, the components of the Menispermaceae family have been studied for their anti-inflammatory and antioxidant effects that are useful for preventing chronic diseases such as tumors and Alzheimer's disease (Lin et al., 2013; Song et al., 2024; Thavamani et al., 2013; Zhai et al., 2023). *Tinospora crispa*, another type of Menispermaceae plant, has been studied for its anti-inflammatory effects through the mechanism of inhibiting the production of pro-inflammatory cytokines such as interleukin (IL)-6 and IL-8 which prevent inflammation-related tissue necrosis (Abood et al., 2014; Merici et al., 2020). Several types of plants such as *Triclisia sacleuxii* and *Stephania venosa* also have acetylcholinesterase inhibitory activity which plays an important role in the progression of Alzheimer's disease (Ahmed et al., 2021). Studies on *Pericampylus glaucus* show anticancer effects of root, leaf and stem extracts by preventing protein denaturation and inhibiting red blood cell damage, although toxic effects need to be monitored (Shipton et al., 2017). Further trials of the compound would not only modernize traditional medicine but could potentially develop clinically proven drugs.

**Table 2.** Health Benefit from Popular Menispermaceae.

| Mechanism | Species |
|---|---|
| Antibacterial agent | *Cocculus hirsutus* |
| | *Arcangelisia flava* |
| | *Albertisia villosa* |
| | *Coscinium fenestratum* |
| | *Fibraurea tinctora* |
| Antiviral agent | *Tinospora crispa* |
| | *Cocculus hirsutus* |
| | *Cissampelos sympodialis* |
| Antifungal agent | *Fusarium solani* |
| | *Rhizopus arrhizus* |
| | *Sclerotium rolfsii* |
| Anticancer agent | *Pericampylus glaucus* |
| | *Cocculus hirsutus* |
| | *Cissampelos pareira* |
| Spasmolytic agent | *Albertisia papuana Becc* |
| | *Cissampelos sympodialis* |

**Antiviral Menispermaceae Compound For SARS-CoV-2 Infection**

The Covid-19 pandemic has shown the potential of herbal medicine based on the bioactive activity of plant components, one of which is from the Menispermaceae family (Al-kuraishy et al., 2022). Bisbenzylisoquinoline alkaloids (BBIQ) are one of the most studied components among other Menispermaceae compounds (Wei et al., 2021). This alkaloid contains two benzyl isoquinoline units which have diverse structures because they are composed of direct carbon-carbon bonds or indirectly through ether or methyleneox bonds (Alamzeb et al., 2021; Zhang et al., 2021). One type of BBIQ is cepharanthine (CEP), which is the only component of BBIQ that has been approved for use in humans since 1950 after being first discovered in 1934 and has long been used in the treatment of acute and chronic diseases (Bailly, 2019; Liang et al., 2022). Previously, several studies have shown that cefarantine has strong antiviral activity against various viruses such as SARS-CoV, MERS-CoV, and HIV-1 (Liang et al., 2022). The effectiveness of CEP against SARS-CoV-2 infection is influenced by previous studies on coronoviruses where CEP not only binds to the same receptor target as the virus,

namely ACE, but also binds to the outer structure of the virus spike protein and main protease of SARS-CoV-2, NPC1 and TPC2 (Fan et al., 2022; Ohashi et al., 2021; Zhou et al., 2020).

One study found antiviral effect from CEP to threat SARS-CoV-2 infection where CEP inhibits the proliferation of viral cells to replicate in host cells.(Hijikata et al., 2022). Another study also found that combination CEP and nelfinavir (a protease inhibitor drug) had a synergistic effect in inhibiting SARS-CoV-2 infection, and the combination of the two drugs could reduce viral RNA levels to 0.068% of untreated controls, thereby improving SARS-CoV-2 clearance time compared to nelfinavir (Ohashi et al., 2021). This mechanism, in addition to being associated with the inhibition of viral cell binding to host receptors, is also associated with the ability of CEP to be transported to lysosomes after entering cells by interacting with NPC1 protein and inhibiting NPC1 protein, resulting in the accumulation of lysosomal cholesterol and an increase in intralysosomal pH which results in disruption of cellular/lysosomal lipid homeostasis (Liu et al., 2023). In addition to having antiviral effects, inhaled administration of CEP has improvement effect on pulmonary tissue after damage from inflammatory-induced Covid-19 responses (Li et al., 2022). Several clinical trials currently demonstrate the potential of CEP in various preparations ranging from injection, inhalation, to nanoparticles with reported side effects that are not harmful to humans (Liang et al., 2022).

Apart from CEP, some Menispermaceae plants also have antiviral effects against SARS-CoV-2, although the effects on humans are still limited. A study by Rajan et al on *Cocculus hirsutus* extraction showed that the phytochemical components in the plant, namely betulin, coclaurine, and quinic acid, have the ability to bind to the SARS-CoV-2 virus and interact with viral amino acids (Rajan et al., 2023). While clinical trials of aqueous extract of Cocculus hirsutus (AQCH), in healthy humans showed minimal side effects including increased transaminase, no harmful effects were reported at doses up to 800 mg for 10 days of intervention (Dar et al., 2022). The limited studies may be related to the lack of identification of bioactive components in the Menispermaceae family that can be effective in treating Covid-19. Future research is needed for identification and clinical testing of future infections.

## CONCLUSION

The Menispermaceae family is one of the plants that are widely found in tropical areas. Although plants from this family are widely used in traditional medicine, the therapeutic effect on Covid-19 infection is still limited. Future research is needed on the use of bioactive components from this family for the development of future therapies.

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