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A Meta-Analysis of Traditional Medicine Systems in the Management of COVID-19: Roles of Siddha, Ayurveda, Homeopathy, and Traditional Chinese Medicine

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ABSTRACT

Background: Throughout the COVID-19 crisis, traditional and alternative medicine systems were heavily promoted and used in different environments, often alongside conventional treatments. However, the evidence supporting these methods is varied and often based on small studies with inconsistent outcome definitions. This review compiles clinical data on four widely recognized systems—Traditional Chinese Medicine (TCM), Ayurveda, Siddha, and homeopathy—focusing on their effectiveness and safety in treating COVID-19.

Methods:We conducted a comprehensive search across PubMed/MEDLINE, Scopus, the Cochrane Library, the AYUSH Research Portal, CNKI, and Google Scholar for peer-reviewed research released between December 2019 and June 2024. Eligible studies included randomized controlled trials (RCTs), controlled clinical trials, and prospective cohort studies involving patients with lab-confirmed COVID-19, comparing traditional medicine interventions—either on their own or combined with standard treatments—against placebos, no treatment, or usual care. We evaluated study bias using RoB 2 for RCTs and the Newcastle-Ottawa Scale for observational research. When data allowed, we conducted a random-effects meta-analysis using relevant effect measures (risk ratio/odds ratio for binary outcomes; mean difference/standardized mean difference for continuous ones).

Results:We included 78 studies (48 on TCM, 22 on Ayurveda, 3 on Siddha, and 5 on homeopathy). Most studies focused on patients with mild-to-moderate COVID-19. TCM was linked to slight improvements in symptom duration (SMD -0.32, 95% CI -0.50 to -0.14) and shorter hospital stays (MD -1.62 days, 95% CI -2.30 to -0.94). Ayurvedic treatments—such as AYUSH-64 and Ashwagandha-based plans—were often reported to help clear the virus faster and ease symptoms, although results varied significantly. Evidence on Siddha remedies (e.g., Kabasura Kudineer) was limited to small studies that suggested potential symptom relief. Homeopathy trials didn't show any significant advantages over placebos or standard treatments. Reported side effects were mostly minor, but safety reporting across studies was inconsistent.

Conclusions: Findings indicate that specific TCM and Ayurvedic treatments may offer modest additional benefits for easing symptoms in mild-to-moderate COVID-19 cases. However, variations in study design, inconsistent safety reporting, and scarce data on severe cases weaken confidence in these results. Siddha treatments need more thorough investigation, and homeopathy lacks solid evidence of effectiveness. Future research should emphasize standardized formulations, clear outcome definitions, preregistered protocols, and thorough monitoring of side effects to support evidence-based inclusion of traditional methods where appropriate.

Keywords: *COVID-19; SARS-CoV-2; Traditional Chinese Medicine; Ayurveda; Siddha medicine; homeopathy; complementary and integrative medicine; herbal medicine; systematic review; meta-analysis; randomized controlled trials; safety..*

1. INTRODUCTION

Stem cell therapy is a cornerstone of regenerative medicine due to stem cells' unique abilities to self-renew and differentiate into specialized cell types . They hold promise for treating neurodegenerative diseases, heart failure, diabetes, and tissue injuries (Trounson & McDonald, 2015). However, challenges like immune rejection and ensuring long-term safety remain (Morrison *et al.*, 2017). Siddha medicine, an ancient healing system from South India, offers a holistic approach using herbal formulations, diet, and lifestyle modifications to restore health (Kumar *et al.*, 2019). Interestingly, evidence suggests certain herbs used in Siddha can influence stem cell behavior – enhancing proliferation, guiding differentiation, and improving survival . This opens an emerging integrative approach: using **Siddha phytotherapy to augment stem cell-based regenerative medicine**. Researchers are now examining how bioactive compounds in Siddha herbs (which often show antioxidant, anti-inflammatory, and immunomodulatory properties) might synergize with stem cells to promote tissue repair (Subramanian *et al.*, 2020; Ramesh & Prasad, 2018). This comprehensive overview summarizes stem cell biology, key Siddha medicinal plants and their pharmacological effects, molecular mechanisms of herb-stem cell interactions, current evidence, and the therapeutic potential as well as challenges of combining these two disciplines.

Stem Cells Overview:

Types of Stem Cells: Stem cells are broadly classified by their developmental potency and source : (1) **Embryonic Stem Cells (ESCs)** are pluripotent cells derived from blastocyst inner cell mass, capable of forming virtually any cell type (Thomson *et al.*, 1998). While they have high differentiation potential, ethical issues and risk of immune rejection or teratoma formation complicate their use . (2) **Adult Stem Cells (ASCs)** are tissue-specific multipotent cells (such as hematopoietic stem cells in bone marrow or mesenchymal stem cells in bone marrow and fat) responsible for maintenance and repair of particular tissues (Pittenger *et al.*, 1999). These are widely used clinically (e.g. HSC transplants for blood disorders) due to fewer ethical concerns, though their differentiation range is limited to certain lineages . (3) **Induced Pluripotent Stem Cells (iPSCs)** are adult somatic cells reprogrammed back to a pluripotent, embryonic-like state by introducing key transcription factors (like **Oct4**, **Sox2**, **Klf4**, **c-Myc**) (Takahashi & Yamanaka, 2006). iPSCs can generate patient-specific stem cells, avoiding immune rejection and ethical issues, but they require careful screening for genetic/epigenetic abnormalities or tumorigenicity . Additionally, **perinatal stem cells** (from umbilical cord blood, placenta, or amniotic fluid) are multipotent with low immunogenicity, offering another promising source for therapy.

Properties and Signaling: All stem cells share two defining features : **self-renewal** (the ability to proliferate and produce more stem cells, maintaining an undifferentiated state) and **differentiation** (the capacity to mature into specialized cell types under the right cues). These processes are governed by intrinsic factors and the extracellular **stem cell niche** – a specialized microenvironment providing signals (growth factors, extracellular matrix, cell–cell contacts) that regulate stem cell fate . Key signaling pathways influence stem cell behavior, many of which can be targets of herbal compounds: for instance, the **Wnt/β-catenin pathway** stimulates stem cell proliferation and maintenance of "stemness," the **Notch pathway** mediates cell fate decisions (especially in neural and hematopoietic stem cells), and **BMP (Bone Morphogenetic Protein)** signaling promotes differentiation like bone or cartilage formation . Survival and migration often involve pathways such as **PI3K/Akt** and **MAPK**, and developmental pathways like **Hedgehog** contribute to tissue patterning and regeneration . The concept of the niche is crucial – even potent stem cells need a supportive environment. Interestingly, some Siddha herbs may modulate the niche by providing antioxidant protection or by altering cytokine/growth factor levels, thereby indirectly enhancing stem cell function (Scadden, 2006).

Therapeutic Applications: Clinically, stem cell therapies are being explored or applied for various conditions: **hematopoietic stem cell transplantation** for leukemias and lymphomas is well-established; **mesenchymal stem cells** are in trials for cartilage repair, inflammatory disorders, and myocardial infarction repair ; neural stem cells and iPSC-derived neurons are being investigated for treating **Parkinson's, spinal cord injury, and stroke**, while pancreatic progenitors or iPSC-derived β-cells aim to treat **diabetes**. In these contexts, integrating Siddha herbal medicine could be advantageous – if certain herbs enhance stem cell survival, promote differentiation into needed cell types, or reduce adverse immunological reactions, they could improve outcomes of stem cell therapy. For example, **antioxidant-rich herbs** might protect transplanted cells from oxidative stress in injured or inflamed tissues, and **anti-inflammatory herbs** could create a more favorable milieu for engraftment and regeneration . Such synergy is an exciting premise of integrative regenerative medicine.

Siddha Medicine Overview:

Philosophy and Principles: Siddha medicine is an ancient Tamil system of medicine thought to be over 2000 years old (Kumar *et al.*, 2019). It is holistic, seeking to balance the body's vital energies to maintain health. Core to Siddha philosophy is the concept of **tridosha** – the three fundamental humors or energies: *Vatham* (air + ether), *Pitham* (fire), and *Kapham* (water + earth) . Health is seen as a state of equilibrium among these doshas, while disease arises from their imbalance (acing to the Ayurvedic dosha theory) . Siddha practitioners aim to restore balance using a combination of **dietary guidance, lifestyle changes, detoxification techniques, and especially herbal formulations**. The system also emphasizes concepts of **ojas** (vital energy, akin to vitality/immune strength) and **kaya kalpa** (rejuvenation therapy) to promote longevity and rejuvenation of the body at a cellular level. This rejuvenation concept interestingly aligns with modern ideas of slowing cellular aging and promoting tissue regeneration.

Herbal Pharmacology in Siddha: Siddha medicine's materia medica includes **hundreds of medicinal plants**, often combined into polyherbal formulas. Many of these herbs have known **pharmacological effects** beneficial for regeneration: they are rich in **antioxidants** (which combat oxidative stress and may protect cells, including stem cells, from damage), have **anti-inflammatory** action (reducing chronic inflammation that can impair regeneration), and exhibit **immunomodulatory** effects (balancing immune responses to facilitate healing) . For example, Siddha herbs like *Phyllanthus emblica* (Amla) are loaded with vitamin C and polyphenols that scavenge free radicals, and *Curcuma longa* (Turmeric) contains curcumin, a potent anti-inflammatory and antioxidant agent . Additionally, some herbs are noted for **neuroprotective** and **anti-aging** properties (e.g., *Bacopa monnieri* or Brahmi improves cognition and may encourage neural cell growth; *Withania somnifera* or Ashwagandha is traditionally a "rasayana" or rejuvenator that boosts strength and vitality) (Ramesh & Prasad, 2018; Subramanian *et al*., 2020). Siddha pharmacology classifies certain remedies as *Muppu* (universal salts) and *Rasayana* (rejuvenators) that purportedly renew tissues and enhance life force – conceptually resonating with stimulating the body's own stem cells or regenerative capacity. Modern phytochemical analysis shows Siddha plants contain bioactive compounds like **alkaloids** (which can interact with cellular signal pathways), **flavonoids** (often antioxidant and anti-inflammatory), **triterpenoids** (which may modulate apoptosis and cell proliferation), and other **polyphenols**. These compounds can influence cell signaling and gene expression and are thus prime candidates for affecting stem cell biology.

Importantly, Siddha remedies often use **polyherbal formulations** – combinations of multiple plants (and sometimes minerals) prepared as decoctions, powders, or pills. The synergy among different herbs is believed to enhance efficacy and reduce toxicity. In an integrative context, these complex formulations could provide a broad-spectrum support to the body's regenerative processes: for instance, one herb might supply antioxidants to protect cells, another might encourage blood flow and nutrient delivery to injured tissue, while a third might directly stimulate cell proliferation. However, this complexity also poses challenges for modern science in pinpointing mechanisms and standardizing doses.

Siddha Herbs with Stem-Cell-Modulating Potential:

Researchers have started identifying specific Siddha herbs that have demonstrated effects on stem cells in lab or animal studies (Ramesh & Prasad, 2018). Below are some notable examples, along with their active constituents and observed effects:

Withania somnifera (*Ashwagandha*): A renowned adaptogenic herb in Siddha and Ayurveda, considered a tonic for longevity. Key active compounds are **withanolides** (steroidal lactones). *Ashwagandha* extracts have been shown to promote **neurogenesis** and neuronal differentiation, partly by upregulating neurotrophic factors like BDNF (Brain-Derived Neurotrophic Factor) and NGF (Nerve Growth Factor) in the brain. In rodent models of neural injury, Ashwagandha improved recovery, which correlated with increased proliferation of endogenous neural stem/progenitor cells and better neuron survival (Ashraf *et al.*, 2017). It also exhibits antioxidant effects that protect brain tissue from oxidative stress. Clinically, Ashwagandha has shown benefits in cognitive and neurodegenerative conditions (e.g., mild cognitive impairment), hinting at its potential to support neural regeneration in humans (Choudhary *et al.*, 2017).

Tinospora cordifolia (*Guduchi* or *Amritha*): An immunomodulatory climbing shrub. Active constituents include **diterpenoid lactones** (e.g., giloin, tinocordifolin) and alkaloids. Guduchi is traditionally used to boost the immune system and vitality. Preclinical studies indicate it can protect and stimulate the **hematopoietic stem cell (HSC) compartment** in bone marrow – mice given *T. cordifolia* extracts recovered faster from chemically induced bone marrow suppression, suggesting enhanced HSC proliferation or protection (Choudhary *et al.*, 2019). It also supports mesenchymal stem cell growth, likely by its anti-inflammatory and antioxidant milieu. Clinically, cancer patients taking *T. cordifolia* during chemotherapy showed improved blood counts and immune recovery, consistent with better bone marrow stem cell function (Upadhyay *et al.*, 2010).

Centella asiatica (*Vallarai* or *Gotu Kola*): A creeping herb known for wound healing and cognitive enhancement. Major compounds are **triterpenoids** like asiaticoside and madecassoside. *Centella* promotes collagen synthesis, angiogenesis, and nerve regeneration. In wound-healing models, it accelerated closure of wounds, partly by recruiting **endothelial progenitor cells** for new blood vessel formation and stimulating fibroblast activity (Gray *et al.*, 2018; Dhanasekaran *et al.*, 2016). In the brain, *Centella* is shown to enhance memory and has been linked to increased neuronal branching and possibly neurogenesis. It likely influences pathways like **VEGF** (vascular endothelial growth factor) for angiogenesis and **Wnt/Notch** for neural growth.

Curcuma longa (*Turmeric*): A cornerstone of South Asian medicine. The active polyphenol **curcumin** has well-documented anti-inflammatory and antioxidant effects. Curcumin can modulate multiple signaling pathways; for example, it can activate **Wnt/β-catenin** and **BMP pathways**, which are important for tissue regeneration and stem cell differentiation (Aggarwal & Harikumar, 2009). In vitro, curcumin has been found to enhance the osteogenic differentiation of mesenchymal stem cells (promoting bone formation) and chondrogenic differentiation for cartilage, making it potentially useful in orthopedic regenerative therapy. It also protects stem cells from inflammatory cytokines and oxidative damage. Patients with osteoarthritis taking curcumin have shown reduced symptoms and possibly improved cartilage matrix, suggesting it might support the body's intrinsic repair mechanisms (Daily *et al.*, 2016).

Bacopa monnieri (*Brahmi*): A brain tonic herb with **bacosides** as key compounds. *Bacopa* has neuroprotective and anxiolytic effects. Research indicates it can stimulate **neurogenesis** in the hippocampus – the brain's memory center – where it increased the survival of new neurons and enhanced synaptic plasticity in animal studies (Stough *et al.*, 2013). This suggests that *Bacopa* may aid neural stem cells in forming new functional neurons, aligning with its traditional use for improving memory and cognitive function.

Phyllanthus emblica (*Amla* or Indian Gooseberry): A vitamin C-rich fruit widely used in Siddha and Ayurveda as a rejuvenator. It has strong **antioxidant** properties due to high ascorbic acid and polyphenol content. By reducing reactive oxygen species, *Amla* can protect stem cells from DNA damage and telomere shortening (i.e., anti-aging effects on cells). In a mouse study, *Amla* supplementation improved the maintenance of hematopoietic stem cells and reduced markers of cellular senescence in the bone marrow (Sasikumar *et al.*, 2018). This fruit also modulates immune responses, which could create a more supportive environment for stem cell therapy in conditions like immune-mediated tissue damage.

These examples illustrate how Siddha medicinal plants contain bioactives that can impact stem cell behavior: **enhancing proliferation**, guiding **differentiation** into needed cell types (e.g., osteoblasts from MSCs, neurons from neural stem cells), **protecting stem cells** from harmful stressors, and **modulating the niche** (e.g., via angiogenesis or immune modulation) to favor regeneration.

Molecular Mechanisms of Herb-Stem Cell Interaction:

Siddha herbs appear to exert their beneficial effects on stem cells through several interrelated mechanisms:

Antioxidant Effects: Many Siddha herbs are rich in antioxidants (vitamins, flavonoids, tannins) that reduce oxidative stress. This is critical because excessive reactive oxygen species (ROS) in injured or inflamed tissues can kill transplanted cells or resident stem cells and impair their function. By **scavenging ROS and upregulating endogenous antioxidant enzymes**, herbs like turmeric, amla, and ashwagandha protect stem cells' DNA and mitochondria, enhancing cell survival and maintaining their "youthful" functioning. For instance, curcumin and withanolides have been shown to lower lipid peroxidation and restore glutathione levels in cells under stress (Aggarwal & Harikumar, 2009; Ashraf *et al.*, 2017). This protective effect likely helps stem cells in hostile environments (e.g. ischemic tissue post-heart attack) survive longer and work better.

Anti-Inflammatory and Immunomodulatory Actions: Chronic inflammation can create a hostile environment for stem cell engraftment and can skew stem cell differentiation undesirably. Siddha herbs like *Guduchi* and *Turmeric* are noted anti-inflammatories: they inhibit inflammatory cytokines (like TNF-α, IL-1β, IL-6) and COX-2 and promote a balanced immune response. *Guduchi*, for example, modulates cytokine profiles and enhances macrophage and lymphocyte function in a way that supports healing (Choudhary *et al.*, 2019). This could translate to a more receptive niche for stem cells. Additionally, some herbs might suppress excessive scar formation (fibrosis) by modulating TGF-β signaling, thereby aiding regenerative healing over non-functional scarring.

Activation of Regenerative Signaling Pathways: Bioactive compounds can directly influence pathways that govern stem cell fate:

Wnt/β-Catenin: Certain herbal compounds (maybe asiaticoside or withanolides) have been reported to activate Wnt signaling. Wnt activation can maintain stem cell proliferation and "stemness," which is useful to expand stem cells in culture or stimulate resident progenitors in tissues (Liu *et al.*, 2019).

Notch: While context-dependent, Notch signaling is essential for proper differentiation. Antioxidant herbs might prevent oxidative stress-induced disruptions of Notch signaling in stem cells, ensuring proper cell fate decisions.

PI3K/Akt: Many herbal compounds (curcumin, bacosides) activate Akt, a pro-survival kinase. Akt activation leads to **improved stem cell survival** and resistance to apoptosis under harsh conditions (e.g., ischemia reperfusion injury) . This is beneficial for keeping transplanted cells alive.

BMP and TGF-β: For musculoskeletal regeneration, herbs that enhance BMP signaling (like curcumin) can promote bone and cartilage formation from MSCs. Conversely, controlling TGF-β can prevent pathological fibrosis while still aiding normal repair.

Hedgehog: Some evidence suggests indirect herbal effects on Hedgehog, which is involved in tissue patterning and stimulating progenitor cells in the brain and elsewhere. This remains an area for more research.

Epigenetic Modulation: Emerging research indicates phytochemicals can influence epigenetic markers. For instance, polyphenols can alter DNA methylation or histone acetylation states of certain genes (including those regulating stemness or differentiation). Withaferin A (from Ashwagandha) and curcumin have been noted to influence histone modifications, potentially reactivating silenced genes that promote regeneration or silencing genes that impede it. This epigenetic tuning could partially explain improved cognitive function or tissue repair seen with long-term use of some herbs.

Enhancing the Stem Cell Niche: By promoting **angiogenesis** (new blood vessel formation) with agents like *Centella asiatica* (which increases VEGF) and improving **blood circulation**, Siddha herbs ensure that injured tissues (and any transplanted cells there) receive better oxygen and nutrients supply, crucial for regeneration . Also, by modulating immune cells (macrophages, T-cells) towards a healing phenotype (e.g., M2 macrophages), herbs can create a more regenerative microenvironment.

These mechanisms often act in concert. For example, in a spinal cord injury model, Ashwagandha likely reduced inflammation (less glial scar formation), provided antioxidant neuroprotection, and directly stimulated neural stem cells through growth factor induction – collectively leading to improved neuronal regeneration (Ashraf *et al.*, 2017). A key point is that **herbal compounds are multitargeted**, unlike single synthetic drugs – they exert broad but generally gentle influences on multiple pathways, which might be ideal for the complex process of tissue regeneration that requires coordination of proliferation, differentiation, and remodeling phases.

Evidence and Potential of Integration:

Preclinical Studies: A growing number of in vitro and animal studies support the idea that combining Siddha herbs with stem cells could yield better outcomes:

Bone Marrow and Blood Recovery: Mice treated with *Tinospora cordifolia* after bone marrow suppression had faster recovery of white cell and platelet counts, indicative of stimulated hematopoietic stem cells (Choudhary *et al.*, 2019). Similarly, *Emblica officinalis* (Amla) given to mice enhanced the functional capacity of hematopoietic stem/progenitor cells in bone marrow and spleen (faster recovery in bone marrow transplant models) . These findings suggest patients undergoing **chemotherapy or bone marrow transplantation** might benefit from adjunct herbal therapy to improve marrow stem cell resilience and engraftment. In one small clinical study, cancer patients using *Guduchi* during chemotherapy had higher hemoglobin and leukocyte counts than controls (Upadhyay *et al.*, 2010), aligning with these preclinical results.

Neural Regeneration: In rodent models of **neurodegenerative disease** or brain injury, herbs like *Ashwagandha* and *Bacopa* improved outcomes. Ashwagandha-fed rats after spinal cord injury showed greater locomotor recovery and increased markers of new neuron growth compared to controls (Ashraf *et al.*, 2017). In a rat Alzheimer's model, *Bacopa monnieri* extract enhanced the generation of new neurons in the hippocampus and improved memory performance (Stough *et al.*, 2013). *Centella asiatica* also demonstrated neurogenic effects in aged rats, increasing neural stem cell proliferation in parts of the brain and benefiting cognitive function (Dhanasekaran *et al.*, 2016). These suggest a potential to combine such neuroprotective herbs with cell therapies for stroke, Parkinson's, or spinal injuries: the herbs might create a brain environment that is more conducive for transplanted neural stem cells or even stimulate the patient's own dormant neural progenitors for repair.

Musculoskeletal Repair: Curcuma longa is extensively studied for joint diseases. Lab studies have found that **curcumin** not only suppresses inflammation in osteoarthritis models but also promotes **chondrogenesis** (cartilage formation) from mesenchymal stem cells. In tissue-engineering experiments, adding curcumin to MSC cultures increased deposition of collagen and proteoglycans (Aggarwal & Harikumar, 2009). When combined with biomaterial scaffolds, curcumin improved bone defect healing in animals, implying that a **MSC + herbal compound** approach could be synergistic for bone regeneration. Clinical trials in osteoarthritis patients show curcumin provides significant pain relief and some cartilage-protective effect (Daily *et al.*, 2016), supporting its use alongside stem-cell based cartilage repair.

Wound Healing: Chronic wounds could benefit from integrative therapy. For instance, *Centella asiatica*-based creams have long been used for wound care. Experimental data confirm *Centella* speeds wound closure by recruiting progenitor cells and inducing growth factors (Gray *et al.*, 2018). If one were to apply *Centella* or its active compound asiaticoside along with stem cell therapy (such as applying skin progenitor cells to burn wounds), the herb might enhance vascularization and matrix formation, improving graft success.

The table below (from the compiled literature) summarizes a few representative findings:

Herb	**Model & Outcome**	**Stem Cell-Related Effect**	**Reference**
Withania somnifera (Ashwagandha)	Rat spinal cord injury – improved motor function	↑ Neural stem cell proliferation, ↑ neurotrophic factors (BDNF)	Ashraf *et al.*, 2017
Tinospora cordifolia (Guduchi)	Chemotherapy-treated mice – faster marrow recovery	↑ HSC and MSC proliferation, immune modulation	Choudhary *et al.*, 2019
Centella asiatica (Gotu Kola)	Rat wound healing – faster closure & nerve regrowth	↑ Angiogenesis (endothelial progenitors), ↑ neural regeneration	Dhanasekaran *et al.*, 2016
Curcuma longa (Turmeric)	MSC culture – enhanced osteogenesis	↑ Differentiation into bone (via BMP/Wnt), ↑ proliferation	Aggarwal & Harikumar, 2009
Bacopa monnieri (Brahmi)	Aged rat brains – improved memory	↑ Hippocampal neurogenesis, ↑ synaptic plasticity	Stough *et al.*, 2013
Phyllanthus emblica (Amla)	Mouse bone marrow transplant – better engraftment	↑ Stem cell viability, ↓ oxidative stress, ↓ senescence markers	Sasikumar *et al.*, 2018

These preclinical outcomes demonstrate that Siddha herbs can indeed positively influence stem cell-mediated regeneration. They often work by **multi-pronged mechanisms**: for example, Ashwagandha both boosts intrinsic regenerative signals and protects cells, whereas Amla provides a biochemical environment for stem cells to thrive by reducing oxidative/inflammatory burden.

Emerging Clinical Insights: Direct clinical trials combining herbal medicine and stem cells are still scarce. However, some clinical evidence indirectly supports their combined use:

In mild cognitive impairment or early Alzheimer's disease, trials with Ashwagandha reported improved cognitive function and functional recovery (Choudhary *et al.*, 2017). This could suggest that Ashwagandha's neuroregenerative effect in humans, possibly via encouraging brain plasticity and new neuron formation, complement approaches like stem cell transplantation or cognitive training.

Patients undergoing chemotherapy who took *Tinospora cordifolia* had a trend towards faster immune recovery (higher white cell counts) (Upadhyay *et al.*, 2010). While not a stem cell transplant trial per se, it hints that Guduchi supports bone marrow stem cell function in humans, which could be harnessed to improve outcomes of bone marrow or cord blood transplants.

A clinical study on chronic wounds found that a topical formulation containing *Centella asiatica* expedited wound healing (Gray *et al.*, 2018). This aligns with the idea that *Centella* could be an adjunct to cell-based skin grafts or to mobilize a patient's own skin stem cells for repair.

Meta-analyses of curcumin in joint arthritis show reduced joint pain and possibly improved joint function (Daily *et al.*, 2016). If curcumin helps maintain cartilage, it might improve the milieu for stem cell injections aiming to regenerate cartilage in osteoarthritic patients. Some regenerative clinics already advise antioxidant or anti-inflammatory supplements alongside cell therapies on an empirical basis.

Though these clinical findings are not yet definitive or directly measuring stem cell activity, they underscore the **safety and potential benefits of Siddha herbs in relevant patient populations**. The data encourages more formal trials, such as testing whether adding a Siddha herbal extract to a standard stem cell treatment yields better functional outcomes than stem cell treatment alone.

Integration Strategies and Future Perspective:

Combining Siddha medicine with stem cell science can be envisioned in a few ways:

Adjunct Herbal Therapy: Patients receiving stem cell transplants or infusions could concurrently take standardized Siddha herbal extracts to enhance engraftment and efficacy. For example, after an MSC injection for knee osteoarthritis, the patient might take *Curcuma longa* and *Withania somnifera* supplements to reduce inflammation and promote cartilage regeneration.

Careful clinical trials would be needed to optimize dosages and timing.

Herb-Primed Stem Cells: In the lab, one could **pre-treat stem cells with herbal derivatives** before transplantation. Some studies hint that culturing MSCs with curcumin or Ashwagandha increases expression of homing receptors and survival genes, potentially yielding a more robust cell product for therapy. This "priming" could make cells more resilient once in the body.

Bioactive Compound Discovery: Research into Siddha herbs might identify novel small molecules that modulate stem cell pathways. These could be developed into drugs that mimic the herb's effect in a controlled manner. For instance, withaferin A (from Ashwagandha) or asiaticoside (from Centella) could be isolated and optimized as pharmaceuticals to promote neurogenesis or angiogenesis, respectively.

Patient's Own Stem Cell Mobilization: Certain Siddha remedies might mobilize endogenous stem cells. G-CSF injections are used clinically to mobilize bone marrow stem cells into blood for collection; perhaps herbal formulations could have a gentler but sustained mobilizing effect for tissue repair. This is speculative but worth investigating, given some herbs (like *Guduchi* and *Amla*) COVID-19, caused by the SARS-CoV-2 virus, led to a significant global crisis marked by high illness and death rates, while also highlighting the limitations of healthcare systems during surges. Alongside efforts to develop vaccines and assess antiviral and anti-inflammatory treatments, there was a resurgence of interest in traditional and complementary medicine systems for symptom relief, recovery support, and risk reduction. The most discussed systems in this regard include Traditional Chinese Medicine (TCM), Ayurveda, Siddha medicine, and homeopathy, each rooted in unique philosophies and treatment practices [1–4]. Initially, COVID-19 care focused on supportive measures and the rapid testing of existing drugs, with breakthroughs like corticosteroid use in severe cases coming after extensive trials and data analysis [5,6]. However, during the uncertain early phase of the pandemic and with limited access to conventional care, traditional remedies gained popularity. Nationally, China officially included TCM in its COVID-19 treatment protocols, while India's Ministry of AYUSH released recommendations highlighting Ayurveda, Siddha, and homeopathy for preventive care and managing mild symptoms [7–11]. Proponents of traditional medicine often highlight their use of complex formulations and focus on boosting the body's immune responses and controlling inflammation, rather than directly attacking the virus [12,13]. This approach aligns with the nature of COVID-19, where the body's own overreaction can worsen the illness, helping sustain research interest in these therapies. Despite this, the supporting clinical evidence varies significantly across the different systems and treatments, with frequent issues such as small sample sizes, inconsistent outcomes, lack of blinding, and biased reporting [9,14].

This study was conducted to systematically review and combine existing clinical research on Siddha, Ayurveda, homeopathy, and TCM in the context of COVID-19 treatment. The goals were to (i) outline the scope and quality of current clinical studies, (ii) calculate combined effect estimates where possible, and (iii) assess the trade-offs between potential benefits and risks, especially considering common biases that may affect results in urgent health situations.

2. Methods

2.1 Design and reporting standards

This systematic review and meta-analysis followed PRISMA guidelines, including the 2020 update [15,16]. Due to the variety in traditional medicine types and how studies were designed, we planned separate analyses for each system (TCM, Ayurveda, Siddha, and homeopathy) and grouped outcomes by category, such as symptom improvement, viral clearance, disease progression, mortality, biomarkers, and side effects.

2.2 Data sources and search strategy

We searched six databases—PubMed/MEDLINE, Scopus, the Cochrane Library, the AYUSH Research Portal, CNKI, and Google Scholar—for peer-reviewed papers published between December 2019 and June 2024. The search combined COVID-19–related terms with names of traditional treatments (e.g., "Traditional Chinese Medicine," "Ayurveda," "Siddha," "homeopathy") and specific formulas. To minimize missed studies, we also checked references in relevant reviews and included variations in product names or spellings.

2.3 Eligibility criteria

We included studies that met all of the following: (i) they were randomized trials, controlled clinical trials, or prospective cohort studies; (ii) enrolled patients had lab-confirmed COVID-19 (RT-PCR or similar); (iii) the treatment clearly belonged to one of the four traditional systems and was used either alone or with standard care; (iv) the comparison group received either a placebo, no additional treatment, or only standard care; and (v) there was at least one measurable clinical result (such as symptom duration, viral clearance, or side effects). We excluded lab or animal studies, editorials, commentary articles, and preprints without peer review. Studies in non-English languages were excluded unless they could be reliably translated.

2.4 Study selection and data extraction

Two reviewers independently evaluated the titles, abstracts, and full texts. Any disagreements were discussed and, if necessary, a third reviewer helped make the final decision. We used a standardized form to collect data on study type, location, number of participants, patient profiles, COVID-19 severity, treatment details (type, dosage, duration, and if used with standard care), details of the control group, definitions of outcomes, and how side effects were reported.

2.5 Risk of bias assessment

For randomized studies, we assessed bias using the Cochrane RoB 2 tool, which evaluates aspects like randomization, deviations from the intended treatment, missing data, how outcomes were measured, and selective reporting [18]. For observational studies, we used the Newcastle-Ottawa Scale [19]. These tools helped us identify study weaknesses that might exaggerate or hide the real treatment effects—such as poor randomization, lack of blinding, or missing outcome data.

2.6 Data synthesis and statistical analysis

We summarized all studies descriptively and statistically combined data where study designs and results were similar enough. For binary outcomes (like progression or death), we calculated risk ratios (RRs) or odds ratios (ORs) with 95% confidence intervals (CIs). For continuous outcomes (like hospital stay or lab markers), we used mean differences (MDs) or standardized mean differences (SMDs), also with 95% CIs [20]. We used the I^2 statistic to measure variability across studies and applied random-effects models to account for differences in study methods and patient populations [20]. We looked for publication bias using funnel plots and Egger's test if 10 or more studies were available for a specific outcome [21]. Planned sensitivity checks included breaking results down by COVID-19 severity and, when possible, by type of treatment and dosage.

3. Results

3.1 Study selection

Out of all the search results reviewed against the set eligibility criteria, 78 studies were ultimately included in this analysis. The volume of evidence was uneven across the traditional systems: 48 studies investigated TCM, 22 looked at Ayurvedic treatments, 3 focused on Siddha medicine, and 5 evaluated homeopathy.

3.2 Study characteristicsMost of the studies involved patients with mild to moderate COVID-19 and explored traditional therapies as additions to standard medical care rather than replacements. Sample sizes varied greatly, from small trials at a single site with fewer than 50 participants to larger studies spanning multiple centers with over 500 participants. Commonly tracked outcomes included how quickly symptoms were resolved, the time it took for RT-PCR tests to turn negative, hospital stay duration, and changes in inflammation-related lab markers. Critical outcomes like mortality were reported less often, especially in studies not involving TCM.

3.3 Risk of bias and reporting quality

The overall quality of the studies differed widely. In randomized trials, details about how participants were assigned to treatment groups and whether the assignment was concealed were often missing. Because of the complexity of multi-herbal remedies, blinding was frequently not done or was not possible. Around 70% of the studies gave enough information to evaluate their randomization processes, and only about 60% clearly reported how they tracked side effects. This raises concerns about biased outcome or safety reporting. Observational studies generally scored moderately on the Newcastle-Ottawa Scale, but many were at risk of bias due to confounding, especially when traditional treatments were used along with evolving standard COVID-19 care.

3.4 Effects by traditional medicine system

3.4.1 Traditional Chinese Medicine

Out of the 48 TCM studies reviewed, the most investigated remedies were multi-herb formulations like *Lianhua Qingwen* and *Shufeng Jiedu*. In cases of mild-to-moderate COVID-19, pooled results showed a small but noticeable decrease in how long symptoms lasted (SMD -0.32, 95% CI -0.50 to -0.14) and a shorter stay in the hospital (MD -1.62 days, 95% CI -2.30 to -0.94). However, evidence was unclear or inconsistent regarding whether TCM helped prevent progression to more severe illness or reduced the risk of death. When side effects were reported, they were usually mild, with gastrointestinal issues being the most common.

3.4.2 Ayurveda

The 22 studies on Ayurveda covered a variety of treatments, including *AYUSH-64*, Ashwagandha-based remedies, *Guduchi*-infused formulas, and other multi-herb mixtures. Several of these trials found that Ayurvedic treatments helped speed up viral clearance (quicker RT-PCR negativity) and reduced symptoms such as coughing and fatigue. However, the strength of these effects varied depending on the study's design, how severe patients' symptoms were at the start, and what other treatments they were receiving. Where safety was assessed, Ayurvedic treatments were generally well tolerated, with most reported side effects being minor digestive complaints.

3.4.3 Siddha MedicineOnly three studies focused on Siddha treatments, typically involving *Kabasura Kudineer* or similar formulas. These trials suggested some relief from symptoms like fever, cough, and nasal congestion. However, the studies were small, and information was limited, especially concerning patients with severe illness or longer-term outcomes. Mild side effects were occasionally noted, but the limited data makes it hard to draw firm conclusions about safety or effectiveness.

3.4.4 Homeopathy

Five studies investigated the use of homeopathy for COVID-19. In controlled trials, homeopathic treatments did not show any meaningful improvement in major outcomes like recovery time, viral clearance, or mortality when compared to placebos or usual care. A few studies mentioned that patients with mild illness felt better subjectively, but the small number of trials and inconsistent study quality made these findings difficult to interpret reliably.

4. Discussion

4.1 Principal findings

This review shows that the most extensive body of clinical evidence exists for TCM, followed by Ayurveda. In mild-to-moderate COVID-19 cases, selected TCM treatments were linked to slight improvements in how long symptoms lasted and how long patients stayed in the hospital. Ayurvedic studies often reported benefits like symptom relief and quicker viral clearance, though the findings varied and weren't always easy to combine statistically. On the other hand, data for Siddha medicine is still very limited, and the available controlled trials on homeopathy do not provide strong support for its effectiveness.

4.2 Interpretation and clinical relevance

Understanding how meaningful these results are in real-world settings requires caution. Effect sizes like an SMD of -0.32 for symptom duration indicate only minor differences, which may not be noticeable or significant for individual patients—especially when outcomes are subjective and studies lack blinding. Since most studies used traditional therapies alongside standard treatments, it's difficult to determine whether improvements were due to the traditional remedy, other treatments, or the overall context. Claims that traditional and modern medicines work together synergistically remain theoretical unless tested in well-designed controlled trials.

4.3 Safety considerations

There are limitations in drawing conclusions about safety because many studies didn't report adverse events consistently. While the side effects that were reported were usually mild, such as digestive issues, small sample sizes, brief follow-up periods, and lack of standardized definitions could have led to underreporting. Herbal mixtures also pose unique safety concerns, like differences in how they're made, potential contamination, and possible interactions with other drugs. Future studies need to follow structured systems for tracking side effects, set clear harm-related outcomes in advance, and report findings according to recognized standards like CONSORT.

4.4 Limitations

There are several issues that make it hard to draw firm conclusions from the current data. First, there's a lot of variation in the types of treatments, doses, patient populations, comparison groups, and how outcomes are measured, making it hard to combine or compare studies. Second, many trials were conducted in countries where traditional medicine is part of the health system, which may introduce bias in treatment delivery or reporting. Third, because most studies involved patients with only mild or moderate symptoms, we don't know if the results apply to more severe cases. Lastly, for Siddha and homeopathy, the small number of studies makes it impossible to draw strong conclusions. In particular, the lack of positive outcomes in homeopathy trials, combined with low biological plausibility, raises questions about whether further studies on it are worth pursuing.

4.5 Implications for research and policy

Future research should focus on conducting large, well-registered randomized controlled trials with clearly defined and important outcomes for patients. It's also critical to establish standardized production and quality control for herbal products. Mechanistic research should be tied to meaningful clinical outcomes rather than explained after the fact. Finally, safety monitoring should be rigorous and transparent. As standard COVID-19 care—including vaccines and antivirals—continues to evolve, future trials must clearly describe what background treatments were used and adjust for patient risk factors and virus variants when possible.

5. Conclusion

This systematic review and meta-analysis, covering 78 clinical studies published between December 2019 and June 2024, found that TCM and Ayurveda had the strongest evidence bases. Both were linked to modest additional benefits for symptom relief in patients with mild to moderate COVID-19. However, differences in treatments, how outcomes were measured, varying risks of bias, and inconsistent reporting on safety make it difficult to fully trust or generalize the findings. Siddha medicine is still lacking in strong research, and the current body of controlled studies does not support the clinical effectiveness of homeopathy in treating COVID-19. For traditional medicine systems to be used responsibly in future pandemic responses, upcoming studies must focus on standardized formulations, solid trial design, pre-registered protocols, and thorough monitoring of potential harms

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