“Folklore medicine *Artemisia*”-a treasure trove of new drug

Shivani Dogra*1(0000-0002-0656-2560), Hem Raj Vashist2 (0000-0003-4575-8636) and Joginder Singh1 (0000-0001-6968-4912)

1Department of Microbiology, School of Bioengineering and Biosciences, Lovely Professional University, Phagwara, Punjab 144001, shvndogra241995@gmail.com, joginder.15005@lpu.co.in
2CMJ University, Pharmacy Meghalaya, IN 793003, shimla_pharmacy@rediffmail.com

**Corresponding author**

Shivani Dogra

Department of Microbiology, School of Bioengineering and Biosciences, Lovely Professional University, Phagwara, Punjab 144001, shvndogra241995@gmail.com

**Abstract:** India is currently facing a number of waves of Covid-19 infection, a rapid global pandemic that posed a threat to human health, the social health system, the global economy and even the global governance. The impact of COVID-19 infection has far exceeded the initial estimation. *Artemisia* can be the promising anti-Covid remedy; suitable attention should be given to the treatment of Covid-19. *Artemisia* ubiquitous pharmacological activity, since long used as folklore medicine from ancient time as an antibacterial, antispasmodic, hepatoprotective, antiarthritic, anthelminthic agent, neuroprotective, cardioprotective, antiepileptic, antiasthmatic and bronchodilator, antiulcer, diuretic, antidepressant, larvicidal, wound healing and for the treatment of cancer, inflammation, malaria, menstrual-related disorders and in hepatitis. Several bioactive ingredients participate in its broad spectrum bioactive activities through various modes of action. The inverse correlation between the antiviral activity of artemisinin contents and total flavonoid contents is reported beside artemisinin or the combination of other components acting synergistically to block the post-entry viral infection. Essential oil and extract of the pre and post-flowering stage of *Artemisia* reported antifungal activity against *Aspergillus, Penicillium, Candida, Fusarium* sp. and can be suspected to be an effective novel drug against Mucormycosis, i.e. Black fungus. To achieve the best outcomes, scientific corroboration can support this concept and current knowledge based on the synergistic effects of the plant. This review encompasses traditional uses, pharmacological activities, and keeping in view today’s scenario, medicinal plants anticipated
as pinch-hit with synergistic plant–drug interactions that provide surplus benefit to patients with less adverse effects.

**Keywords:** Folklore medicine, Covid, Mucormycosis, *Artemisia*, Bioactive compounds, Pharmacological activities

1. **Introduction**

About 500 species, occurring throughout the world of the genus *Artemisia*. The well-known anti-malarial drug, i.e. artemisinin, has been discovered from this genus. *Artemisia annua* Chinese herb contain, notably artemisinin which has been isolated from this herb. So the research has been focussed from various species of *Artemisia* species on the secondary metabolites basically volatile on the basis of chemical composition. One of the most popular local herbal medicine which is the species of this genus *Artemisia* used to treat various ailments ranging from coughs, diabetes, cold, malaria. So, one of the most popular herbal medicine which is commonly used is *Artemisia vestita* in upper region of Himachal as folklore medicine for wound healing.

Scientific name: *Artemisia*
Family: Asteraceae
Kingdom: Plantae
Order: Asterales
Higher classification: Anthemideae
Rank: Genus

2. **Artemisia**

It belongs to the daisy family Asteraceae with a large, diverse genus of plants. Many species in the genus have their common names namely wormwood, mugwort and sagebrush. These are hardy herbaceous shrubs, powerful chemical constituents contained in their essential oils. They usually grow in dry habitats or semi-arid habitat. Most species of plant leaves are covered with white hairs. Notable species include *A. vulgaris* (common mugwort), *A. tridentata* (big sagebrush), *A. annua* (sagewort), *A. absinthium* (wormwood), *A. dracunculus* (tarragon), and *A. Abrotanum* (southernwood). White hair covered leaves found in most of the species. Many species have a very strong aromas and bitter tastes which come from terpenoids and sesquiterpene lactones, which discourage herbivory, and may have had a selective advantage. The small flowers are wind-pollinated. *Artemisia* species mainly used as food plants by the larvae of a number of Lepidoptera species. Some botanists split the genus into several genera, but DNA analysis does not support the maintenance of the genera *Crossostephium*, *Filifolium*, *Neopallasia*, *Seriphidium*, and *Sphaeromeria*; three other segregate genera *Stilnolepis*,

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Elachanthemum, and Kaschgaria, are maintained by this evidence. Occasionally, some of the species are called sages, causing confusion with the Salvia sages in the family Lamiaceae. The name "Artemisia" derived from the Greek goddess Artemis (Roman Diana), the namesake of Greek Queens Artemisia I and II. A more specific reference may be to Artemisia II of Caria, a botanist and medical researcher who died in 350 BC.

3. Cultivation and uses
Some species have very aromatic leaves which are used for flavouring. Many species have an extremely bitter taste. A. dracunculus (tarragon) is widely used as a culinary herb, specially used in French cuisine. Artemisia vulgaris (mugwort) was used to repel midges (mug > midge), moths and fleas, intestinal worms, and also in brewing (mugwort beer, mugwort wine) as a remedy against nightmares and hangovers. Artemisia absinthium is used to make a highly potent spirits absinthe. Malor also contains wormwood. The aperitif vermouth (derived from the German word Wermut, "wormwood") is a wine flavored with aromatic herbs, but originally with wormwood. Artemisia pontica (Roman wormwood), Artemisia arborescen (tree wormwood, or sheeba in Arabic) is a Middle eastern indigenous aromatic herb used in tea, usually with mint. Some of the species are grown as ornamental plants, the fine-textured ones mainly used for clipped bordering. All of them grow best in unfertilized free-draining sandy soil, and in full sun. The largest collection of living Artemisia species, subspecies and cultivars is held in the National Collection of Artemisia in Sidmouth, Devon, UK, which holds about 400 taxa. The National Collection scheme is administered in the British Isles by Plant Heritage (formerly National Council for Conservation of Plants and Gardens, NCCPG).

4. Medicinal purpose
Artemisinin (from Artemisia annua) and derivatives are used to treat malaria which is a group of compounds with the most rapid action of all current agents. Treatments with artemisinin derivative (artemisinin-combination therapies) are now in standard treatment protocol worldwide for malaria caused by Plasmodium falciparum. Artemisia cina and other Old World species are the source of the antihelminthic drug, santonin. Traditional Chinese medicine use Chinese mugwort, Artemisia argyi in many treatments. Artemisia species live on every continent. Except Antarctica, as a result, they are the part of many ecosystems all over the world. About 80% of the world's populations rely on non-conventional medicines, especially herbal sources, in their primary healthcare reported in the survey conducted by World Health Organisation. Medicinal herbs are the local heritage with global importance. Our world is gifted with a rich wealth of medicinal herbs. Owing to the global trend of health towards improved “quality of life”, there is considerable evidence of an increase in demand for medicinal plants.
Use of plants and herbs for treating various ailments of both humans and animal is a practice as old as human life itself. India is richly endowed with a wide variety of plants having medicinal value where Great Himalayan range possess many rare plants and species of great medicinal value. These plants are widely used by all sections of society for betterment of health and also in medicinal perspective, whether directly as folk remedies or indirectly as pharmaceutical preparations of modern medicine. In this current scenario, focus is on the plant research has increased all over the world and a large body of evidence has collected to show the immense potential within medicinal plants used in various traditional systems of medicine. Medicinal plants are a major source of biodynamic compounds which are of great therapeutic value, but the different variety of plants with different therapeutic properties is quite astonishing and needs to be explored. It is a heterogeneous genus, consisting over 500 diverse species distributed mainly in the Asia, North America and temperate zones of Europe. These species are perennial, biennial and annual herbs or small shrubs.

5. General morphology

General morphological features of the genus *Artemisia* is described as leaves alternate, usually racemose, paniculate or capitulates capitula small, inflorescence, rarely solitary; involucral bracts in few rows, receptacle flat to hemispherical, without scales and sometimes hirsute; florets all tubular, achenes obovoid, pappus absent or sometimes a small scarious ring. The increasing popularity and acceptability of herbal medicine is the belief in general public that all-natural products are safe, cheaper, and commonly available. However, there are also some concerns that are associated with herbal medicine and conventional drugs regarding pharmacognosy and standardization of herbal medicine. From the past two-decade research efforts have been intensified both in developed and developing countries to scientifically prove, evaluate and validate the herbal drugs using clinical trials.

6. Synergistic action of *Artemisia*:

Synergistic action of *Artemisia absinthium* extract on healing in patient with Crohn’s disease by reducing tumour necrosis factor alpha (TNF-α) has been reported which indicates its immunomodulatory activity. The hydroalcoholic extract of *Artemisia absinthium* on tropical application of infection showed remarkable antibacterial activity against *S. aureus*. The antimicrobial activity so obtained was documented because of synergistic activity the minor components like α and β pinene and the major components like caryophyllene, camphor, p-cymene. The active compounds present in the *A. absinthium* reported for synergistically increase in the antifungal activity of Ag NPs. It has been reported that the application of *A. absinthium* in combination with diminazine aceturate atovaquone found to show synergistic
activity against Babesia and theileria parasite in in vivo and in vitro activity. Similarly the combination therapy of artemisinin with quinin and artemisin with curcumin also reported to show synergistic activity [1].

Anti-mycobacterium activity of Artemisia annua leaf extract was tested against E.coli, Pseudomonas aeruginosa, S. aureus, methicillin-resistant S.aureus, M.smegmatis strains using its isolated components to assess their synergistic activity. The antimicrobial activity was tested for crude extract, isolated compounds and the control artemisinin (Table 1)

Table. 1: Antimicrobial activity of Artemisia leaf extract, isolated compounds and pure Artemisinin.

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<tr>
<th>Sr.No.</th>
<th>Compounds/Combination</th>
<th>Active against</th>
<th>Activity</th>
<th>MIC</th>
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<tr>
<td>1.</td>
<td>Deoxyartemisinin</td>
<td>S. aureus</td>
<td>Active</td>
<td>1000 µg/L</td>
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<tr>
<td>2.</td>
<td>Artemisinic acid</td>
<td>S. aureus</td>
<td>Active</td>
<td>2000 µg/L</td>
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<th>Sr.No.</th>
<th>Combination</th>
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<th>Activity</th>
<th>FIC/ MIC</th>
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<tr>
<td>1.</td>
<td>Deoxyartemisinin+ Artemisinic acid</td>
<td>M. smegmatis</td>
<td>Synergistically active (reduced MIC)</td>
<td>0.5/4-125 µg/L</td>
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Accept for S. aureus, Deoxyartemisinin and Artemisinic acid proved less effective. The reason for this variation was given for less ability of both the components to cross their cell wall and membrane [2]. Synergistic activity of petroleum ether and methanolic extract of A. annua have been evaluated against fungal and bacterial pathogens. The minimum inhibitory concentration and synergistic activity was performed in broth dilution method. The mixture of both the extract were reported to show synergistic potential from 4 to 264-fold decrease in MIC against candida strains and against bacteria (E. coli and S. aureus). Isolation of subtraction of methanolic and petroleum ether extract was isolated by TLC using silica for isolation. This isolated subtraction was reported to show 10-fold more antimicrobial activity in comparison to crude extract. The GC-MS analysis of subtraction of A. annua was added to show the presence of 13 major compounds out of which 2- propenoic acid and ridecyl ester (25.88%) were found the major component [3]. This study demonstrate that these two components had played vital role in increasing the activity which may be due to synergism between these two components. Effective antioxidant activity of the essential oils of the A absinthium before flowering stage than the essential oil at flowering stage and after flowering stage. This was said to happen due to the presence of active components such as α- phellandrene, sabinene, β- pinene, ρ- cymene
and chamazulene which were reported as 58.36%, 48.98 % and 53.99 at before, at and after flowering stage respectively. This was reported due to the synergistic activity between these components. Volatile oil of A. ordosica possessed less toxicity against T. castaneum adults than its chemical constituent capillene, capillinol, capillin, cis-dihydrometricaria ester. Researchers reported 100% repellence for capillin among the compound tested and the essential oil. From this result they concluded that the toxic effect of essential oil could be due to synergistic effects different minor and major components [4].

Synergistic effects of Artemisia vulgaris, Ocimum tenuiflorum, Castonopsis indica, Azadirachta indica, have been reported against Methicillin-resistant Staphylococcus aureus (MRSA). Antibacterial activity was performed by dissolving 100g powder of leaves in 70% of methanol to make 1000ml solution. The evaporated methanolic extract had tested for antibacterial activity using agar diffusion method. The four plants giving six synergistic combinations have been studied and the results have been reported for each combination. Here the methanolic extract of all the four selected plants were tested against five MRSA isolates against five different concentrations. The zone of inhibition observed at the concentration of 100µl. Significant zone of inhibition at the p>0.05 was reported for O.tenuiflorum + C. indica, O. tenuiflorum + A. vulgaris, C.indica+ A. vulgaris, and O. tenuiflorum + A. indica. All plant extracts were found to show resistance in some MRSA isolates at 1µl and complete resistance at 100µl. For Artemisia we may conclude from this research article that the antimicrobial and antifungal activity of this plant in combination with other antimicrobial plants tested here increased, which can be due to the synergism between the secondary metabolites present in their extracts. The synergistic activity between different plant extract and antimicrobial drug and antibiotics have been reported. The methanolic extracts are better reported than methanolic extract for the antimicrobial activity. Strongest effect against P. areuginosa have been reported when extract of N.oleander, Artemisia herba-alba and Withania somnifera were mixed with Amikacin. The best synergistic activity was reported when the aqueous extract of Artemisia herba-alba and each of Iopermide Hcl and paracetamol were tested against S. aureus. Antipseudomonal activity of essential oil from Artemisia quettensis podlech and its synergistic activity with imipenem has been reported. The major components of essential oil extracted by hydrodistillation of the areal parts of A. quettensis identified using GC and GC-MS were reported as homoadmantane, eugenol and Camphor in the concentration of 9.38%, 10.46% and 7.91% respectively. The antibacterial activity with the synergistic activity with imipenem has tested using disc diffusion assay for Pseudomonas aeruginosa. The synergistic effect of oil and antibiotic was reported as 0.2µl/ ml and 4µg/ml for MIC and for MBC it was added as 2µl/ml
and 8µl/ml. The result concluded for the formulation in combination of these components from *A. quettensis* essential oil with imipenem.

7. **Antimicrobial activity**

Essential oil extracted by hydrodistillation from three species like *Artemisia absinthium*, *A. sieberi* and *A. scoparia* had tested against different fungal and bacterial strains. Four common compounds i.e., limonene, camphor, terpene-4-ol and ethyl 2- methylbutyrate were analyzed by combining gas chromatography-flame ionization detector with the gas chromatography-mas spectroscopy technique. The antimicrobial activity of essential oil from all species were evaluated by broth microdilution method. Researchers reported the growth inhibiting potential of essential oil extracted from all three species of Artemisia [5]. The nephroprotective and hepatoprotective activities of *A. absinthium* methanol and ethylacetate extract had reported against diclofenac induced toxicity. From the histopathological study researchers observed that *A. absinthium* exhibits the potential to decrease hepatic and renal necrosis induced by diclofenac [6]. The water extract of *Artemisia annua* have been reported to exhibit effective treatment against non-alcoholic fatty liver disease. The inhibition of accumulation of lipids in HepG2 cells and protection of cells from oxidative stress mediated damage through the activation of antioxidant enzymes and its own scavenging activity [7].

Antihelmintic activity of aqueous extract from *Artemisia absinthium* L and *Malva sylvestris* L was reported against *Haemonchus contortus* in sheep. In the result researchers added insufficient intensity in the reduction of parasitic infection because of the low varieties and lack in the synergy of plant polyphenols and combination of bioactive compounds from both the plants. From the results they concluded that the study add new knowledge on the antihelmintic effects of dry medicinal plant as dietary supplement [8]. Antimalarial activity of green silver nanoparticles prepared from two artemisia species *A. Arbotanum* and *A. arborescens* had been reported for antimalarial activity against *Plasmodium falciparum*. Both the silver nanoparticle for *A. arbotanum* and *A. arborescens* had were designated as A. AgNPs (1) and A. AgNPs (2) in their work. Researchers reported A. AgNMPs effective to stop the growth of parasite in ring stage [9]. High therapeutic efficacy of *Artemisia annua* and *Artemisia afra* reported for the treatment of diabetes by collecting data from five case reports. This result had been reported first time for these Artemisia species teas in humans. They reported that blood sugar could be lowered to standard level and added it as polytherapy where various constituents from plants participated for synergistic work with no toxicity and side effect [10].

8. **Antifungal activity of Artemisia**
The in vitro antifungal activity of *Artemisia annua* 39 endophytes after fermentation and its ferment broth had reported for its antifungal activity against six different crop threatening fungi. Researchers, found that out of 39 endophytes only 21 can produce invitro substance that were reported to be active against almost to all type or few of the phytopathogens whereas others were reported inactive. Further, they added that the most active broth endophyte which they designated as IV403 was extracted with n-butanol and EtOAc. Among these two extracts the EtOAc extraction components played the major role for *Artemisia annua* antifungal activity. *Artemisia absinthium, Artemisia vulgaris* and *Artemisia abrotanum* were reported for their antimicrobial and antifungal after extracting with 40%, 70% and 90% of ethyl alcohol [11]. The essential oil fraction of *Artemisia persica* Bioss had tested for the antifungal activity against *Aspergillus ochraceus* and *Aspergillus parasiticus*. After the hydrodistillation of aerial parts of the plant 31 components were identified by GC-MS analysis astranspinocarveol (10.2%), α-pinene (5.8%), Laciniata furanone (17.1 %), pinocarvone (8.5), atedouglasia oxide C (13.2%). The minimum fungicidal concentration (MFC) of 1.25µl/ml v/v been reported against both the fungal strain. Strong fungicidal effect was also reported at MFC value of 2.5 µl/ml against *A. flavus* and *A. nidulans*.Researchers demonstrated the role of *Artemisia persica* essential oil as antifungal agent for crop protection [12].The essential oil from *Artemisia argyi* levl.et Vant inflorescence have been reported against *Botrytis cinerea* and *Alternaria alternate* the common storage pathogens of fruits and vegetables. The essential oil of *Artemisia persica* with dilution 1 and ½ had reported for its significant antifungal role against *Aspergillus niger* in comparison to fluconazole. The role of borneol and 1,8-cineole have been demonstrated in this study. The essential oil after extraction by supercritical CO₂ extraction and hydrodistillation were characterized by GC-MS analysis. The oil was identified as terpeniol (10.18%), camazulene (2.05%), 1,8-cineole (4.46%) borneol(3.58%) spathulenol (10.03%), camphor (3.49%) and juniper camphor. They reported 93.3 and 84.7% inhibition of both the fungi *Botrytis cinerea* and *Alternaria alternate* respectively by the volatile oil obtained from hydrodistillation and 70.8 %, 60.5% inhibition were reported for essential oil extracted by supercritical CO₂.

9. Artemisia as promising AntiCovid remedy

Effective components present in *A. annua* against bovine viral diarrhoea virus epstein- Barr virus and hepatitis virus. *A. annua* virus have been proved for its significant activity against SARS-CoV-2 in the year 2002.Here the researchers added that a suitable attention should be given for *A.annua* for the treatment of Covid-19 [13]. Different extracts of *Artemisia annua* the rich source of artemisinin is under clinical trial examination for the Covid-19 treatment.
since 2020 in Madagascar. *Artemisia annua* extracts due to its remarkable effect on COVID-19 are being utilized for the treatment and prevention of COVID-19. Recently scientists have examined the efficacy of Artemisia afra and Artemisia annua extracts and Covid-Organics in the in vitro examination for the prevention of SARS-CoV-2 infection by using various experimental animals. They particularly checked the efficacy of these extracts for the inhibition of replication of feline coronavirus and SARS-CoV-2 [14,15]. COVID-19 protease (MPro) activities of a sesquiterpenoids lactone and flavonoids have reported for areal part ethanolic extract from *Artemisia sublessingiana*, six flavonoids and a sesquiterpenoid was isolated from the extract. After elucidation the structures of these isolated components by EI-MS, ID and 2D NMR spectroscopic methods the specified their name as 1) 3’,4’-dimethoxyluteolin 2) hispidulin 3) eupatilin, 4) 5,7,3’- trihydroxy-6,4’,5’trimethoxyflavone 5) apigenin 6) velutin and 7) sesquiterpene lactone as 8α, 14- dihydroxy-11, 13-dihydromelampolide. For the isolated compounds researchers followed *in silico* examination against the COVID-19 main protease enzyme. In the result compound 1-6 were reported to exhibit promising binding modes showing free energies ranging from -6.39 to -6.81 (kcal/mol). Compound 2 was found to exhibit best binding energy [16]. Dry water extract of seven cultivars of *Artemisia annua* sourced from four continent have tested for its activity against SARS-CoV-2. Artemisinin, total flavonoids or dry leaf extract have been reported to show antiviral activity with minimum inhibitory concentration of 0.1- 8.7 µM, 0.01-0.14 µg, and 23.4-57.4 µg respectively. Rather than the effective result observed for all the hot extracts researchers observed 100-fold variation in the artemisinin and flavonoids concentration. Also, the inversely correlation for antiviral activity of artemisinin contents and total flavonoids contents were reported. In the conclusion of this work researchers specified that beside artemisinin or the combination of other components acting synergistically to block the post-entry viral infection [17]. *In silico* examination for the efficacy of artemisinin to bind with and to inhibit the SARS-CoV2 spike proteins had performed taking chloroquine and hesperidin as positive control. The activity of Artemisinin binding to SARS-CoV2 spike glycoprotein, SARS-CoV2 main protease and SARS-CoV-2 papain like protease. The highest binding capacity has been reported for hesperidin (-5.8, -10.0 and -8.1 kcal/mol) after this for artemisinin (-4.8, -8.3 and -6.0 kcal/mol) in the end for chloroquine (-4.1, -8.2, and -4.8 Kcal/mol) which was reported as lowest binding capacity. Artemisinin, chloroquine and hesperidin were observed to have similar positioning towards the targeted spike proteins [18]. WHO has proposed Artemisia annua as as possible treatment for COVID-19. Also, the components from this plant were demonstrated to play an important role in preventing the severity of inflammation which occurs.
due to the Covid-19 [19,20]. Madagascar protocol involves the use of Artemisia annua and ivermectin in combination in the treatment of COVID-19. This is due to the role of artemisinin in targeting ferritin, its immunomodulatory action and anti-inflammatory activity [21]

10. Mucormycosis

Mucormycosis is an angioinvasive fungal infection, due to fungi of the order Mucorales. Its incidence cannot be measured exactly, since there are few population-based studies, but multiple studies have shown that it is increasing. The prevalence of mucormycosis in India is about 80 times the prevalence in developed countries, being approximately 0.14 cases per 1000 population. Diabetes mellitus is the main underlying disease globally, especially in low and middle-income countries. In developed countries the most common underlying diseases are hematological malignancies and transplantation. The epidemiology of mucormycosis is evolving as new immunomodulating agents are used in the treatment of cancer and autoimmune diseases, and as the modern diagnostic tools lead to the identification of previously uncommon genera/species such as Apophysomyces or Saksenaea complex. In addition, new risk factors are reported from Asia, including post-pulmonary tuberculosis and chronic kidney disease. New emerging species include Rhizopus homothallicus, Thamnostylum lucknowense, Mucor irregularis and Saksenaea erythrospora. Diagnosis of mucormycosis remains challenging. Clinical approach to diagnosis has a low sensitivity and specificity, it helps however in raising suspicion and prompting the initiation of laboratory testing. Histopathology, direct examination and culture remain essential tools, although the molecular methods are improving. The internal transcribed spacer (ITS) region is the most widely sequenced DNA region for fungi and it is recommended as a first-line method for species identification of Mucorales. New molecular platforms are being investigated and new fungal genetic targets are being explored. Molecular-based methods have gained acceptance for confirmation of the infection when applied on tissues. Methods on the detection of Mucorales DNA in blood have shown promising results for earlier and rapid diagnosis and could be used as screening tests in high-risk patients, but have to be validated in clinical studies. More, much needed, rapid methods that do not require invasive procedures, such as serology-based point-of-care, or metabolomics-based breath tests, are being developed and hopefully will be evaluated in the near future [22]. Coronavirus disease 2019 (COVID-19) infections may be associated with a wide range of bacterial and fungal co-infections. We report the case of a patient with COVID-19 infection, which, during the course of the treatment, developed rhino-orbital mucormycosis. A 60-year-old male patient, a longstanding diabetic, with a positive reverse-transcriptase polymerase chain reaction
(RT-PCR) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was admitted for treatment. He received parenteral meropenem and oral oseltamivir with parenteral methylprednisolone. Over the course of the admission, he developed signs of orbital cellulitis. Magnetic resonance imaging (MRI) of the brain, orbits, and paranasal sinuses, revealed soft tissue swelling in the right preseptal, malar, premaxillary and retrobulbar regions with paranasal sinusitis. A nasal biopsy revealed broad aseptate filamentous fungal hyphae suggestive of mucormycosis, which was confirmed on culture. Extensive use of steroids/monoclonal antibodies/broad-spectrum antibiotics may lead to the development/exacerbation of a preexisting fungal disease. Physicians should be aware of the possibility of secondary invasive fungal infections in patients with COVID-19 infection. COVID-19 is associated with a significant incidence of secondary infections, both bacterial and fungal probably due to immune dysregulation. Additionally, the widespread use of steroids/monoclonal antibodies/broad-spectrum antibiotics as part of the armamentarium against COVID-19 may lead to the development/exacerbation of preexisting fungal diseases. Physicians should be aware of the possibility of invasive secondary fungal infections in patients with COVID-19 infection especially in patients with preexisting risk factors and should enable early diagnosis and treatment with the subsequent reduction of mortality and morbidity. The use of therapeutic agents should be monitored to achieve a therapeutic effect at the lowest dose and shortest durations. The use of broad-spectrum antibiotics, especially in the absence of infection, should be re-evaluated [23]. In summary, physicians caring for critically ill COVID-19 patients must be aware of serious infections that can complicate the course of COVID-19. A high degree of clinical suspicion is required to diagnose pulmonary mucormycosis. Early diagnosis and timely management are necessary to improve outcomes in pulmonary mucormycosis [24]. The exact prevalence of mucormycosis in India is unknown, though the estimated prevalence is much higher than that in developed countries. The possible reason for the high prevalence is the abundant presence of Mucorales in the community and hospital environment, large number of susceptible hosts especially diabetics, and the neglect for regular health checkups of Indian population. A considerable number of patients are ignorant of diabetes status till they acquire mucormycosis. Though uncontrolled diabetes is a common risk factor in all types of mucormycosis, it is significantly associated with ROCM type. Other emerging risk factors of mucormycosis are pulmonary tuberculosis, chronic kidney disease, and critically ill patients. Isolated renal mucormycosis in an immunocompetent host is a unique clinical entity and requires more studies on pathogenesis. Like in the global data, *Rhizopus arrhizus* is the most common causative agent isolated in all clinical forms of mucormycosis.
However, the spectrum of agents causing the disease is considerably large in India. *Apophysomyces* and *Saksenaea* species are common agents causing cutaneous mucormycosis. Newer species like *Rhizopus homothallicus*, *Rhizopus microsporus*, *Mucor irregularis*, *Thamnostylum lucknowense*, and *Saksenaea erythrospora* are emerging in India and require expertise in laboratory identification. The broad spectrum of agents emphasises the need to improve routine clinical laboratory facilities to identify rare Mucorales associated with mucormycosis. Mortality associated with mucormycosis in India is considerably high due to delays in seeking medical attention and diagnosing the disease, and challenges in managing the advanced stage of infection. It is necessary to conduct population-based studies in India to determine the exact prevalence of mucormycosis in diverse at-risk populations, which would help draw stakeholder attention to the early diagnosis and managing the disease. Though AmB is routinely used in the treatment of mucormycosis, it is important to study the role of newer antifungal agents such as isavuconazole in the treatment of mucormycosis in the Indian population [25].

11. Future prospects of herbal medicine

In the phase of the increasing use and fast-growing market of herbal medicines and other herbal healthcare products, in both developing and developed countries of the world, policy-makers, health professionals and the public are increasingly expressing concerns about the safety, efficacy, quality, availability, preservation, and further development problems of these herbal products. Public demand has also grown for evidence on the safety, efficacy and quality of herbal products and TM/CAM practices. In order to these concerns and to meet public demands, extensive research on herbal medicines is needed to be undertaken not only for their great healthcare value but also for the commercial benefits. The traditional medicine is increasingly solicited through the traditional practitioners and herbalists in the treatment of infectious diseases. Medicinal plants play a vital role for the development of new drugs. The bioactive extract should be standardized on the basis of active compound [26]. The bioactive extract should undergo limited safety studies. Ongoing globalization driven by neo-liberalism increases medical plurality through intercultural knowledge and information exchange. Since sound scientific data for many commercialized health products is still lacking, this calls for a much more rigorous multidisciplinary science-driven approach to local and traditional medicines, which also empowers the local keepers of this knowledge and their users.

12. Conclusion

Synergism of artemisia indicates that its several activities of separated components with its own extract get increased several folds. Also, the increase of antimicrobial activity of artemisia
increases in combination with other antimicrobial plants. This synergistic activity also indicates towards the combined use of cinchona and artemisia alkaloids in the effective treatment of malaria. As hydroxychloroquine the synthetic antimalarial and anti-rheumatic had been used in 2020 and up to the time when no vaccine was available against pandemic Covid-19. Artemisinin the antimalarial sesquiterpenes have been proved against COVID-2 several time. This fact about both artemisinin and synthetic hydroxychloroquine strongly indicates for the research about their combined use against COVID-19 and with respect to antifungal properties by modifying or with advancement Artemisia can prove effective novel drug for mucormysosis as well.

Conflicts of Interest
The authors declare no conflict of interest.

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