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MERS- Middle East Respiratory Syndrome

Madhavi Pillalamarri*[1], K. Nitya Sai Sree[1], P. Deepika[1], Subhas Sahoo[2], Mogili Komali[1]

[1]*Department of Pharmacology, Pulla Reddy Institute of Pharmacy, Hyderabad, Telangana, India*
[2]*Department of Pharmaceutical chemistry, Pulla Reddy Institute of Pharmacy, Hyderabad, Telangana, India*

ABSTRACT

Middle East Respiratory Syndrome (MERS) is a lethal zoonotic respiratory illness caused by MERS- COV, a positive-sense RNA beta-coronavirus first identified in 2012 in Saudi Arabia. Dromedary camels are the primary reservoir host, with transmission to humans via direct/indirect contact or consumption of raw camel products; human-to-human spread occurs through respiratory droplets. MERS-COV binds to the host cell receptor Dipeptidyl Peptidase-4 (DPP4/CD26), initiating infection on lungs, liver, kidney, and immune cells. Common symptoms include fever, cough, and dyspnoea, with severe cases progressing to pneumonia and multiorgan failure. As of December 2019, WHO reported 2,499 cases with 34.3% mortality. No specific antiviral exists, though lopinavir, acyclovir, ribavirin, and chloroquine have been used. The review also examines medicinal plants like Artemisia Judaica, Azadirachta indica, Echinacea, and Glycyrrhiza uralensis for antiviral and anti-inflammatory properties, but clinical validation is needed.

Keywords: Middle East Respiratory Syndrome, Coronavirus, MERS, Epidemiology, Transmission, Diagnostic tests, Herbal remedies.

INTRODUCTION

Middle East Respiratory Syndrome is a (lethal zoonotic pathogen) viral respiratory illness caused by a novel single stranded, positive sense RNA C-Beta Coronavirus [**14**]. Which was first identified in the year 2012 in Jeddah, Saudi Arabia. Later as of May 31, 2015-1180 laboratory confirmed cases (483 deaths; 40% mortality) have been reported to WHO. Between April 2012 and December 2019 around, 2499 laboratory confirmed cases of MERS-Cov infection including 858 deaths (34.4% mortality) were reported from 27 countries to WHO, the majority of which were reported by Saudi Arabia (2106 cases, 780 deaths) [**15**].

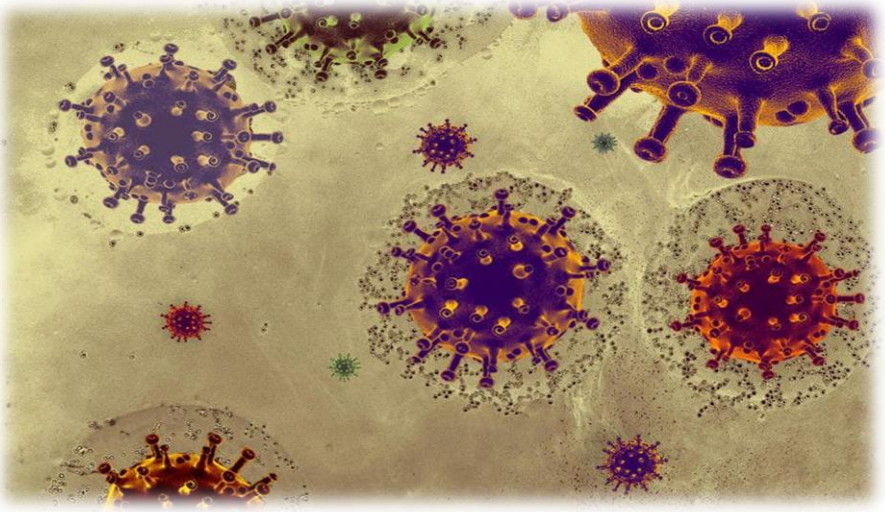


Fig., 1. Structure of MERS-CoV (Middle East Respiratory Syndrome Coronavirus)

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Scientist believe that Dromedary Camels are primary reservoir host and the main animal source of MERS infection in humans. This virus can be transmitted from animal to human via direct or indirect contact such as touching, grooming, consuming raw camel products like milk, urine, meat etc… It can also be transmitted from human to human in the form of wheezing or coughing, where the droplets stay alive for about 24hrs in air after expelling from humans. Common symptoms of MERS include fever, cough, shortness of breath & pneumonia in severe cases. Some cases may also witness Gastrointestinal symptoms similar as diarrhoea. People with weakened vulnerable system, Diabetes, order complaint, or habitual lung complaint are at high threat of severe illness. No specific medicine treatment exists for MERS and infection forestallment and control measures are pivotal to help spread in health-care installations. MERS-COV had continued to be an aboriginal, low position public health trouble.[**15**] The current knowledge and perspectives on MERS epidemiology, virology, mode of transmission, pathogenesis, opinion, clinical features, operations, infection control, development of new rectifiers, vaccines and highlights were unanswered questions. The medicinal operation of natural factory remedies is well established. An ethno-botanical study of medicinal shops used for the operation of respiratory tract disorders in Northern corridor of Palestine. In Palestine, cases with respiratory complaint or disease calculate heavily on the use of herbal medicinal remedies [**16**]. But there was no significant association with the source of information about medicinal plants and the position. For treating viral infections some of the anti-virals have been used. The rapid-fire emergence of viral conditions has accelerated the development of synthetic antiviral medicines, offering potent and targeted remedial options. These medicines are designed to inhibit viral replication, boost host immunity, and reduce complaint inflexibility. The specifies used are lopinavir, acyclovir, ribavirin, chloroquine.

PATHOGENESIS

The main cause for MERS-COV is attachment or infusion of Mers-COV to the host cells. The main component which initiates the infection is DPP4 (Dipeptidyl Peptidase) which is also known as CD26. This DPP4 was identified in the host cell receptor for MERS-COV. DPP4 is observed in only certain species of animals that is responsible for restriction of species tropism of MERS-COV [**3**].

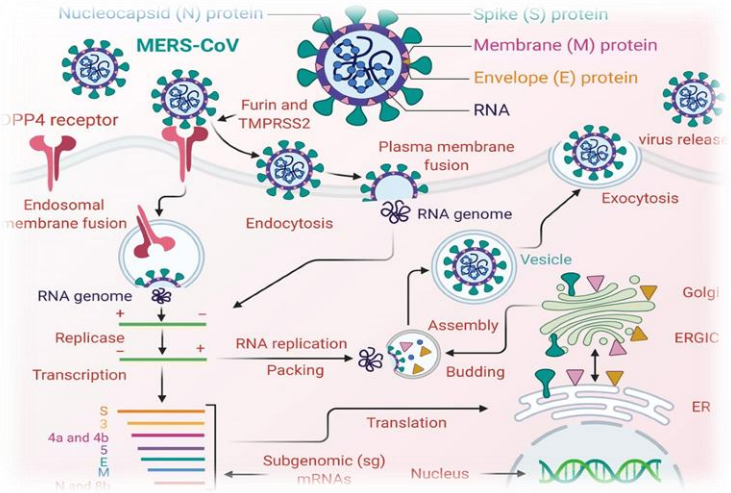


Fig.,2 Pathogenesis of MERS-CoV, focusing on how it enters and replicates with in the host cell.

DPP4 is mainly seen in human parenchyma cells of liver, intestine and kidney tissues. It is also seen in T and B-cells. After performing animal studies, it has been proved that hCD-26/ DPP4 effected with MERS-COV leads to respiratory injury and extra pulmonary organ damage. MERS antigens are found in type-1, type-2 pneumocytes, ciliated bronchial epithelium, unciliated terminal bronchioles and alveolar macrophages, where DPP4 receptors are localised. In addition, spike glycoprotein, a crown like peplomer found on the surface of corona virus particle functions

as an entry protein which binds to receptor of DPP4 and host cell.[**15**]

DPP4 [DIPEPTIDYL PEPTIDASES]:

These are class of oral medications used for type-2 diabetes. This enzyme that breaks down incretin hormones like GLP-1, which regulate blood sugar.

TYPES OF DPP4:

- Sitagliptin [Januvia]- These are used for type-2 diabetes.
- Linagliptin [Tradjenta]-These medications are used as dose adjustment for renal failure.
- Saxagliptin [Onglyza]-these are used as combination therapies.
- Alogliptin [Nesina]- Non-peptidomimetic agents.
- Vildagliptin [Galvus]- These are used outside the United States [US], not approved by FDA.

EMERGENCY DRUGS:

- Teneligliptin-These are used for type-2 diabetes mellitus.
- Omarigliptin- These are used for type-2 diabetes and renal insufficiency.

LOCATION OF DPP4:

DPP4 is located on the surface of cell types with high concentrations in kidneys, intestine, liver, pancreas, lungs, activated immune cells. It exits as a transmembrane protein, soluble, soluble form in plasma.

- Main Role: Metabolic regulation and immune response.
- Kidneys: These shows action on renal tissues.
- Liver: These act on liver tissue, specifically biliary tract.
- Pancreas: These act on islet alpha-cells.
- Immune Cells: These act on T-cells, B-cells, natural killer CNK cells, macrophages.
- Other Tissues: These act on lung parenchyma, endothelial layer of arteries, skeletal muscle and spleen.

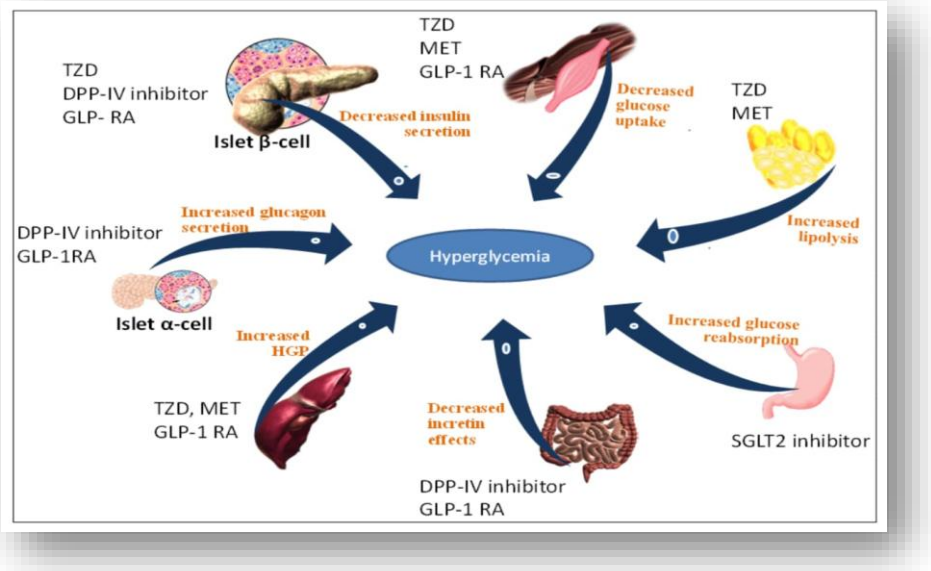


Fig.,3 'Ominous Octet' , which describes the eight core pathophysiological mechanisms contributing to hyperglycemia in Type-2 Diabetes Mellitus, along with pharmacological classes that target them.

- Plasma: Soluble DPP4 circulates in blood, originating from various tissues.

INFECTIONS:

1. **RESPIRATORY AND COMMON:**

- **UPPER RESPIRATORY TRACT INFECTIONS:** Slightly Increased Reporting Of Urti's Such As Nasopharyngitis, Pharyngitis, Sinusitis, Mainly With Sitagliptin.

- **OTHER INFECTIONS:** Other Infections Include Incidence Of Herpes Zoster(Shingles).

2. **DERMATOLOGICAL REACTIONS[SKIN/IMMUNE]:**

- **BULLOUS PEMPHIGOID [BP]:** Association observed between use of DPP4 & development of bullous pemphigoid, an autoimmune blistering skin disease, effects mainly elder patients, mainly effected with vildagliptin and linagliptin.

- **OTHERS:** Others may include cases of pruritic (itching), angioedema (swelling), urticaria(hives).

- **RARELY STEVENS-** Johnsons Syndrome.

3. **GIT [GASTRO INTESTINAL TRACT] REACTIONS:**

- **INFLAMMATORY BOWEL DISEASE-RISK OF IBD:**

ACUTE PANCREATITIS: This is not an infection but patients with severe, persistent abdominal pain.

EPIDEMOLOGY:

The causative agent of MERS is the virus that belongs to the corona virus family (which includes other viruses that cause respiratory disease in humans and other animals). The MERS is caused by a novel single stranded positive-sense RNA C-beta corona virus; that belongs to the **family**: Coronaviridae, Genome-Enveloped RNA virus with spike projections on its surface. MERS-COV virus contains protein structures like spike protein(S), Envelope(E), membrane(M), nucleoside(N).

RESERVOIR AND SOURCE OF INFECTION [2]:

- Primary Reservoir: Dromedary camels.

- Bats are suspected to be the Original natural reservoir.

- Humans usually get infected through direct or indirect contact with infected camels.

TRANSMISSION [15]:

- Animal to Human: Animal to human transmission through direct or indirect contact with infected dromedary camels via touching, grooming (or) consuming raw camel products such as milk, meat or urine.

- Human to Human: Human to human transmission happens by a close contact with an infected person.

This virus was first isolated from the patient who died from severe respiratory illness in June, 2012, in Jeddah, Saudi Arabia. As of May 31, 2015, 1180 laboratory-confirmed cases (483 deaths; 40% mortality) have been reported to WHO. Although most of the cases were from Saudi Arabia and United Arab Emirates; cases have been reported in Europe, the USA, and Asia in the people who travelled from the Middle East or their contacts [**18**]. Intermittent sporadic cases, community clusters, and nosocomial outbreaks of Mers continued. Between April 2012 and December 2019, 2499 laboratory-confirmed cases of MERS-COV infection, including858 deaths (34.3% mortality) were reported from 27 countries to WHO, the majority of which were reported by Saudi Arabia (2106 cases, 780 deaths).

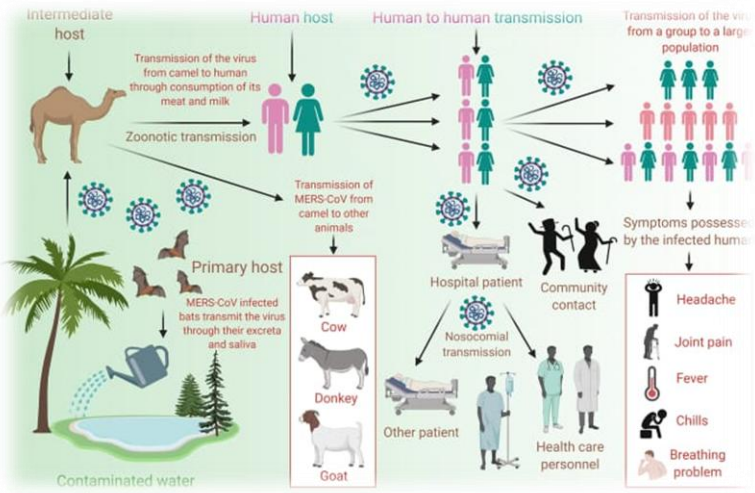


Fig.,4 Overview of the MERS-CoV virus, detailing its transmission, symptoms, and impact.

Large outbreaks of human-human transmissions have been highly reported in Riyadh and Jeddah in 2014 and in South Korea in 2015 (around 186 cases). The mortality internationally is 36% and guidance for clinical management has yet to be developed. Incubation period is usually 2-14 days (average about 5-6 days). People with chronic diseases (diabetes, kidney disease, lung disease), elderly individuals, healthcare workers, people with frequent camel exposure are high prone to this disease. Clinical features of MERS range from asymptomatic or mild disease to acute respiratory distress syndrome and multiorgan failure resulting in death. No specific drug with treatment exits for MERS and prevention and control measures such as avoiding close contact with camels in affected regions, proper infection control in hospitals, hand hygiene and respiratory protection are crucial to prevent the spread in health care facilities. MERS-COV continues to be endemic, low-level public health threat [**18**].

SYMPTOMS:

COMMON SYMPTOMS:

- Fever (was a common symptom in 95.2%individuals).
- Cough.
- Shortness of breath.
- Sore throat.
- Myalgia (Muscle pain).
- Headache.
- Fatigue.
- Arthralgia (Joint pain).
- Skin irritation or reactions.

SEVERE RESPIRATORY SYMPTOMS: people with weak immune system, the infection may progress.

- Severe Pneumonia-was detected in 68.3% of patients at admission.
- Difficulty in breathing.
- Acute Respiratory distress.

GASTROINTESTINAL SYMPTOMS:

- Diarrhoea.
- Nausea.
- Vomiting.
- Abdominal pain.

High Risk in Patients with diabetes, chronic lung disease, kidney disease, weakened immune system. At admission, leukopenia (42.6%), thrombocytopenia (46.6%), and elevation of aspartate aminotransferase (42.7%) were observed in patients. Pneumonia was detected in 68.3% patients and was developed in 80.8%during the disease course [**2**].

DIAGNOSTIC TESTS:

Diagnostic tests are used in detection of MERS are given below:

RT-PCR:

Reverse transcriptase- polymerase chain reaction is considered as the **Gold Standard test.** Main confirmatory test for detecting Middle East Respiratory Syndrome Coronavirus RNA.

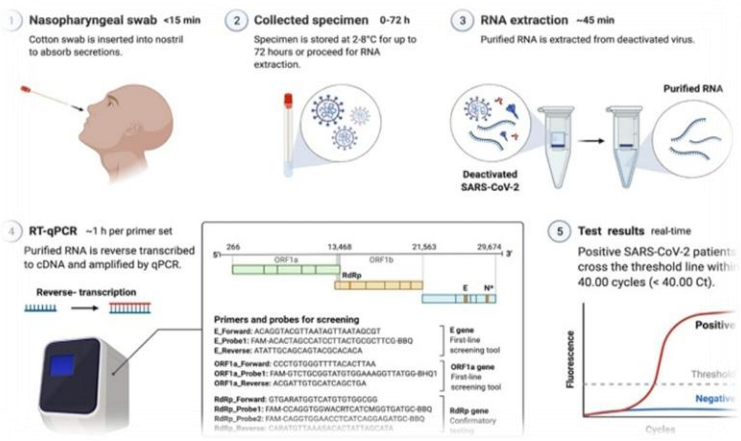


Fig.,5 Diagnostic process for Middle East Respiratory Syndrome (MERS)

- Performed on respiratory samples such as:

➢ Nasopharyngeal swab.
➢ Sputum.
➢ Bronchoalveolar lavage.

SEROLOGICAL TESTS:

Serological tests are used to detect antibodies against the virus and helps in confirming past infection. Examples include:

➢ ELISA-Enzyme-linked immunosorbent Assay.
➢ Immunofluorescence assay.
➢ Neutralization tests.

CHEST IMAGING:

➢ Chest X-ray or CT scan may show pneumonia or lung infiltrates.
➢ Helps assess disease severity, but noy confirms the infection.

TREATMENT:

Basic treatment are given for the patients who are severely facing viral infections to stabilize the patient and provide nutritional support, antibodies to the patient.

❖ **SUPPORTIVE MEDICAL CARE** – Oxygen Therapy, I.V fluids, Fever, pain medication, Monitor BP & oxygen levels.

❖ **ANTI-VIRAL MEDICATIONS –** Ribavarin, Interferon

❖ **TREATMENT FOR SEVERE CASES** – ICU, Mechanical Ventilation, Treats pneumonia / Kidney Problems**.[16]**

SYNTHETIC DRUGS FOR MERS:

The drugs which are used for treating MERS-COV virus are Liponavir, Ribavirin, Acyclovir, Chloroquine. Each drug has different action at different location.

1.ACYCLOVIR:

Acyclovir is an antiviral medication classified as a nucleotide analogue. It is commonly used to treat infections caused by herpes viruses, including herpetic keratitis, varicella-zoster infections, viral labialis, and herpes labialis. Because of the first-line treatment. In pediatric cases, especially for children under six years of age, specific dosage forms and treatment recommendations are provided to ensure safe and effective therapy.[**1**]

MECHANISM OF ACTION:

Acyclovir is first converted into acyclovir monophosphate by the viral enzyme thymidine kinase. The host cellular enzymes such as guanylate kinase further phosphorylate it to acyclovir diphosphate and finally to the active form acyclovir

triphosphate. This active metabolite has a high affinity for viral DNA polymerase, much greater than for cellular DNA polymerase. Acyclovir triphosphate competes with natural nucleotides and gets incorporated into the growing viral DNA chain. Once incorporated, it terminates DNA chain elongation because no further nucleotides can attach. As a result, viral DNA synthesis stops and viral replication is inhibited.

USES:

It is an antiviral medication used to treat various viral infections. It is commonly prescribed for herpes simplex infections affecting the lips and mouth, skin, and mucous membranes.

2. CHLOROQUINE:

On June 15, 2020, the U.S. Food and Drug Administration (FDA) revoked the Emergency Use Authorization (EUA) that had previously allowed the use of chloroquine and hydroxychloroquine for the treatment of COVID-19, stating that the available scientific evidence no longer supported their effectiveness and raised concerns about potential safety risks.[**1**]

MECHANISM OF ACTION:

Chloroquine acts against malaria by inhibiting the conversion of heme to hemozoin in malarial trophozoites through the inhibition of the heme polymerase enzyme. This results in the accumulation of toxic heme within plasmodium parasites, ultimately leading to their destruction. In addition, chloroquine can diffuse across cellular membranes and accumulate in organelles such as endosomes, lysosomes, and Golgi vesicles, where it increases the internal pH. This rise in pH interferes with viral fusion and entry into host cells. Although chloroquine does not alter the ACE2 receptor expression on the cell surface, it inhibits the terminal glycosylation of ACE2, which may reduce the ability of certain viruses to bind and enter the host cell.

HERBAL MEDICINES USED IN MERS TREATMENT:

The medical application of natural plant remedies is well established. An ethno-botanical study of medicinal plants used for the management of respiratory tract disorders in northern parts of Palestine. Which mainly focused on medicinal plants used to treat respiratory. A questionarie was distributed to 120 respondents for the final analysis that included plants used, part of plant used, & for which disease the products were applied. The highest % of herbal use was reported for flu 85.8% (103 participants) followed by cough 83.3%. While the lowest % of herbal use was reported for bronchitis i.e with 54.1%. The above studies showed that around 31 plant species of 19 families were used for respiratory disorder treatment.

- ✓ Where 6 species were from lamiaceae family.
- ✓ Where 3 species were from Apiaceae family.
- ✓ Where 2 species were from Amaryllidaceae, fabaceae, mrytaceae, rutaceae, zingiberaceae family.
- ✓ 1 plant species from other families.

Decotion was the method of preparation and was taken as a hot drink. In Palestine, patients with respiratory diseases rely heavily on the use of herbal medicinal remedies. Leaves and fruits are most commonly used. Age & marriage are significantly associated with use of botanical remedies. But there was no significant association with the source of information about medicinal plants & their location (were to purchase/ growth). It is vital to conduct comprehensive clinical investigation & pharmacological assessments of these remedies in order to identify their efficacy, safety& toxicity levels.**[18]**

ARTEMISIA JUDAICA:

One of the largest families of flowering plants.

FAMILY- Asteracea

Commonly called the daisy, sunflower, or composite family.

KINGDOM: Plantae

GENUS: Artemisia

SPECIES: Artemisia Jaudaica

DIVISION: Angiosperms

CLASS: Dicotyledons

ORDER: Asterales

SYNONYM: Desert warm wood, Judea warm wood, Arabic regious often called "shih". Aerial plant parts like leaves, tender stem, flowering tops are mostly used. Plant type- stems, woody at base; branched & covered with fine hairs.

- Leaves – small, grey-green, finely divided, strong aromatic smell.
- Flowers – small yellow flower heads arranged in clusters.
- Fruit – small dry fruit- achene

CHEMICAL CONSTITUENTS:

Aerial parts contain several compounds that researchers think may affect viruses such as MERS-Cov that causes MERS. The main constituents are essential oils [camphor, cineole,thujone], flavonoids[sesquiterpene lactones], terpenoids[phenolic compounds].

USES:

Artemisia Judaica is used for treating respiratory problems, digestive disorders, fever, anti-microbial and anti-parasitic.

ROLES OF ARTEMISIA JUDAICA IN MERS: Laboratory studies suggest several potential mechanisms.

1. Anti-viral activity (may inhibit viral replication in laboratory cell studies)
2. Anti-inflammatory – may reduce long inflammation, which is a major problem in severe respiratory infection.
3. Anti-oxidant – to reduce oxidative stress, caused by viral infection.
4. Immune Modulation – certain plant compound may help regulate immune response.

LIMITATION: Research in mostly laboratory or regulate thereotically. There are no clinical trials proving Artemisia Judaica treats MERS. Medical care remains the main treatment recommended by WHO.**[23]**

AZADIRACTA INDICA:

Azadiracta Indica is commonly known as neem. It belongs to meliaceae family and it is rich in anti-oxidant. Earlier confirms that the constituents of neem play role in scavenging of free radical generation and prevention of disease. By modulationg various molecular pathways like p53, pTEN, NF-KB, P13/Akt, Bcl-2, VEGF these shows anti-cancer activity.

CHEMICAL CONSTITUENTS:

Quercetin and beta-sitosterol are the first polyphenolic flavonoids purified from leaves. Other than Quercetin and sitosterol it contains many constituents those are nimbin, nimbidin, nimbolide, limonoide, azadirachtin. Herbal oils are used for treating MERS virus. These oils show their effectiveness based on 2 basic terms

Antiviral- which inhibits the multiplication of viruses.

Virucidal – which destroys the viruses or kills the viruses.

Herbal extracts of Cibotium Barometz, Gentiana Scabra, Dioscorea Batatas, Cassia Tora, Taxillus Chinese which also inhibits SARS.

ECHINACEA:

It is also known as Echinacea purpurea, E.pallida, E. angustifolia show anti-viral activity against cold and influenza. Glycyrrhiza Uralensis [liquorice root] inhibits the RNA replication and blocks assembly. Aglaia foveolata [fruits & twings] Silvestrol, a flavagline compound prevent protein translations. Griffithsia species [Red algae] a protein which exhibits antibody dependent neutralisation of MERS-Cov. Resveratrol found in cranberry, grape and

huzhang which blocks nucleocapsid(N), protein expression of MERS virus.**[20]**

SOPHORA TOMENTOSA:

It is also known as Yellow Necklacepod, shows antiviral activity against MERS-Cov viruses. The plant parts like leaves, seeds have bioactive compounds which are flavonoids, isoflavanoids, alkaloids used for antiviral activity.

KEY POINTS:

- Flavanoids – luteolin, apigenins and quercetin are the potential inhibitors.
- Matrine – It exhibit anti-inflammatory and analgesic properties.
- Cystisine – This combine/interact with nicotinic acetylcholine receptors which shows mild bronchodilation & mood uplift.
- Leaves – it contains higher antioxidant & phenolic compounds can be used for daily purpose.
- Seeds – it contains anti-bacterial activity, which have compounds like 9-octadecenoic acid, Hexadecanoic acid.
- Bark – it contains high matrine content but leaves are most preferable**. [6]**

CONCLUSION:

In summary, the reviewed studies consistently shows that dromedary camels play a significant role in MERS virus which is a novel single stranded, the sense RNA C-Beta coronavirus with high mortality and no specific treatment was available. Prevention of infection and control measures such as diagnosis and public awareness were remained essential. While few synthetic drugs such as anti-viral drugs (Acyclovir, Chloroquine) & herbal remedies like Artemisia Judaica, Azadiracta Indica, Sophora Tomentosa shows potential activity but, further research is needed to confirm the effectiveness of the herbal remedies. Continuous research & strong healthcare measures are essential to control its spread.

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