



Potential bioactive molecules from natural products to combat against coronavirus

Yengkhom Disco Singh¹ · Barsarani Jena² · Rina Ningthoujam³ · Sneha Panda² · Pratigyan Priyadarsini² · Sabita Pattanayak² · Manasa Kumar Panda⁴ · Mayanglambam Chandrakumar Singh⁵ · Kunja Bihari Satapathy²

Received: 7 July 2020 / Accepted: 20 August 2020 / Published online: 15 September 2020
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Abstract

Covid-19 is terribly spreading around the globes and there is no stoppage. It is causing mass destruction in mankind allowing them to lock inside home to contain the disease. At present, there are no remedial medicines, drugs, or vaccines available in the market. Researchers are trying their best level to produce drugs to fight against the disease. Various efforts are being considered by using different directions of scientific knowledge and technologies on treating the disease. The existing antiviral drugs such as lopinavir/ritonavir, pitavastatin, nelfinavir, perampanel, and praziquantel are being administered as remedies of covid-19 patients. Unfortunately, none of these drugs works absolutely against the current pandemic. Therefore, bioactive molecules from plants, animals, and microorganisms could be a better option to treat against the covid-19 and its family. Plants can treat many diseases due to the presence of bioactive molecules and their antiviral properties. Presence of secondary metabolites such as flavonoids, alkaloids, terpenoids, polyphenols, curcumin, kaempferol, catechin, naringenin, quercetin, apigenin-7-glucoside, luteolin-7-glucoside, demethoxycurcumin, oleuropein, and epigallocatechin can fight against the coronavirus including covid-19. The listed plants such as litchi seeds, *Houttuynia cordata*, Chinese Rhubarb extracts, beta-sitosterol from *Isatis indigotica* root extract have capacity to obstruct the enzymatic activity of SARS. In this article, we have highlighted the bioactive molecules from different plants, animals, and microorganism and their potential activity against the coronavirus. It is a need of the hour to come together to explore more on such bioactive compounds of plants, animals and other microorganism to fight against the covid-19.

Keywords Covid-19 · Bioactive molecules · Pandemic · Plant extracts · Coronavirus

Introduction

The scariest and terrifying problem hammering over our head is covid-19. In the current century for human race covid-19 is a problem that seems to be with zero solution by looking at the present situation. We cannot imagine how fast it can be growing, developing, and transmitting. The rate of

Yengkhom Disco Singh, Barsarani Jena, Rina Ningthoujam, Sneha Panda, Pratigyan Priyadarsini, Sabita Pattanayak, Manasa Kumar Panda, Mayanglambam Chandrakumar Singh and Kunja Bihari Satapathy have contributed equally and carry same weightage.

✉ Yengkhom Disco Singh
disco.iitg@gmail.com

✉ Kunja Bihari Satapathy
kbs_bot@rediffmail.com

¹ Department of Post Harvest Technology, College of Horticulture and Forestry, Central Agricultural University, Pasighat, Arunachal Pradesh 791102, India

² Department of Botany, School of Applied Sciences, Centurion University of Technology and Management, Bhubaneswar, Odisha 752050, India

³ Department of Vegetable Science, College of Horticulture and Forestry, Central Agricultural University, Pasighat 791102, Arunachal Pradesh, India

⁴ Environment and Sustainability Department, CSIR- Institute of Minerals and Materials Technology, Bhubaneswar 751013, India

⁵ Department of Basic Sciences and Humanities, College of Horticulture and Forestry, Central Agricultural University, Pasighat, Arunachal Pradesh 791102, India

transmission is like wildfire that spread fast within few periods. The infected people do not show any symptoms at the very beginning stage but capable of spreading successfully when they are with us and fights against shadow. It is not bad to mention that the overexploitation of our nature and natural resources brings back ill effects on the human being. Human is digging its own graveyard by digging nature's heart.

It spread its arm all over the world. More than 206 countries have been already suffering from covid-19 pandemic. On December 31st, 2019, the first patient with covid-19 was reported from Wuhan, Hubei province, China. In the year of 2020, 7th January, a new virus was confirmed and named it as novel coronavirus-2019 (Covid-19) and comes to know it was related to SARS-CoV-2 (Burki 2020). SARS-CoV-2 is belonging to same family of virus with MERS-CoV (Middle East Respiratory Syndrome) and SARS-CoV (Severe acute respiratory syndrome) which was reported in 2012 and 2002 from Middle East countries and China. The patient infected in covid-19 showed respiratory problems along with cough, fever, and diarrhea. By February 20, 2020, nearly seventy thousand (70,000) cases were reported and eighteen hundred (1,800) people were dead (Sun et al. 2020). The growth curve of covid-19 is generally increasing due to the rapid transmission through human to human contact. On March 11, 2020, the World Health Organization (WHO) declared covid-19 as a pandemic disease. The causative organism for covid-19 is a virus with having a single stranded positive RNA and the virus type is beta-coronavirus (Chen et al. 2020). From the genomic study, it was confirmed that SARS-CoV-2 has the 79.5% similarities with SARS-CoV (Severe Acute Respiratory Syndrome) (Zhou et al. 2020).

Family of coronavirus

Corona viruses are belonging to family coronaviridae in order Nidovirales and the sub-family Orthocoronaviridae (Shereen et al. 2020). Coronaviridae is a large family of virus which causes mild common cold, fever to Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). Torovirinae and Coronavirinae are two sub-families of Coronaviridae and corona virus belong to Coronaviridae subfamily and coronaviridae causes' illness in mammals and birds (James 2017). Based on genomic structure Deltacoronavirus, Gammacoronavirus, Alphacoronavirus, and Betacoronavirus are four genera of Orthocoronaviridae sub-family. Mammals got infected by betacoronaviruses and alphacoronaviruses. Humans, respiratory illness is caused by Betacoronavirus. Birds and some selective mammals are got infected by deltacoronaviruses and gammacoronaviruses (Woo et al. 2012). Human corona virus (HCoV) such as HCoV-NL63, SARS-CoV, MERS-CoV, and HCoV-OC43 are some viruses which are

responsible for respiratory problem in human (Cui et al. 2019). Scientists confirmed that the disease like SARS-CoV, HCoV-229E, MERS-CoV, and HCoV-NL63 are transmitted through human to human interaction and they have animal as origin for transmitting such as bats. The genus Coronaviridae family is bounded with the largest, positive RNA virus. Transmission of genome occur via spikes of the virus cell body; spikes attach on cell surface of host cell and release virus genome through plasma membrane and replication takes place in cytoplasm (Fig. 1).

Covid-19 pandemic

Covid-19 shows various symptoms like pneumonia, fever, breathing difficulty, and many more due to lung infections. These symptoms are similar to the corona virus (CoV) occurred in 2003 as severe acute respiratory syndrome (SARS). On February 11, 2020, the World Health Organization (WHO) named it as SARS-CoV-2 and the disease as CoV Disease-19 (COVID-19) (Velavan and Meyer 2020). SARS-CoV-2 is transmitted rapidly from human to human contact than SARS-CoV. More than 70,000 cases of SARS-CoV-2 infection were reported in 25 countries in February 2020 and the infected patient has pneumonia and severe lung damage (Jiang et al. 2020).

At very beginning, it was reported that many of the patients with unknown causes were suffered from pneumonia linked to local Huanan South China seafood market in Wuhan, Hubai province of China in December, 2019 (Zhu et al. 2020). A rapid response team was sent by Chinese Center for Disease Control and Prevention to help the health authorities of Hubai province and Wuhan city to investigate epidemiology and etiology due to outbreak of this disease, but the World Health Organization (WHO) confirmed that there was no specific animals that were responsible for the outbreak of epidemic coronavirus in Huanan South China sea food market place. Later on, the outbreak turns out to be epidemic and then slowly pandemic affecting the entire globe. The outbreak becomes more vigorous during Chinese New Year when the mobility of the Chinese people was high, and later virus spread rapidly throughout the China. The first genome of covid-19 was published by the researcher team led by Prof. Young-Zhen Zhang, 10 January, 2020 (Zheng 2020). During Chinese New Year when the mobility of the Chinese people was high, virus spread rapidly throughout the China. A similar pattern of symptoms was identified with the early outbreak of Severe Acute Respiratory Syndrome (SARS) and Middle East respiratory syndrome (MERS) corona virus. It was also confirmed that susceptibility of corona virus depends on the age, biological sex and other health conditions (Ferh et al. 2017). Later on, WHO declared covid-19 as Public Health Emergence

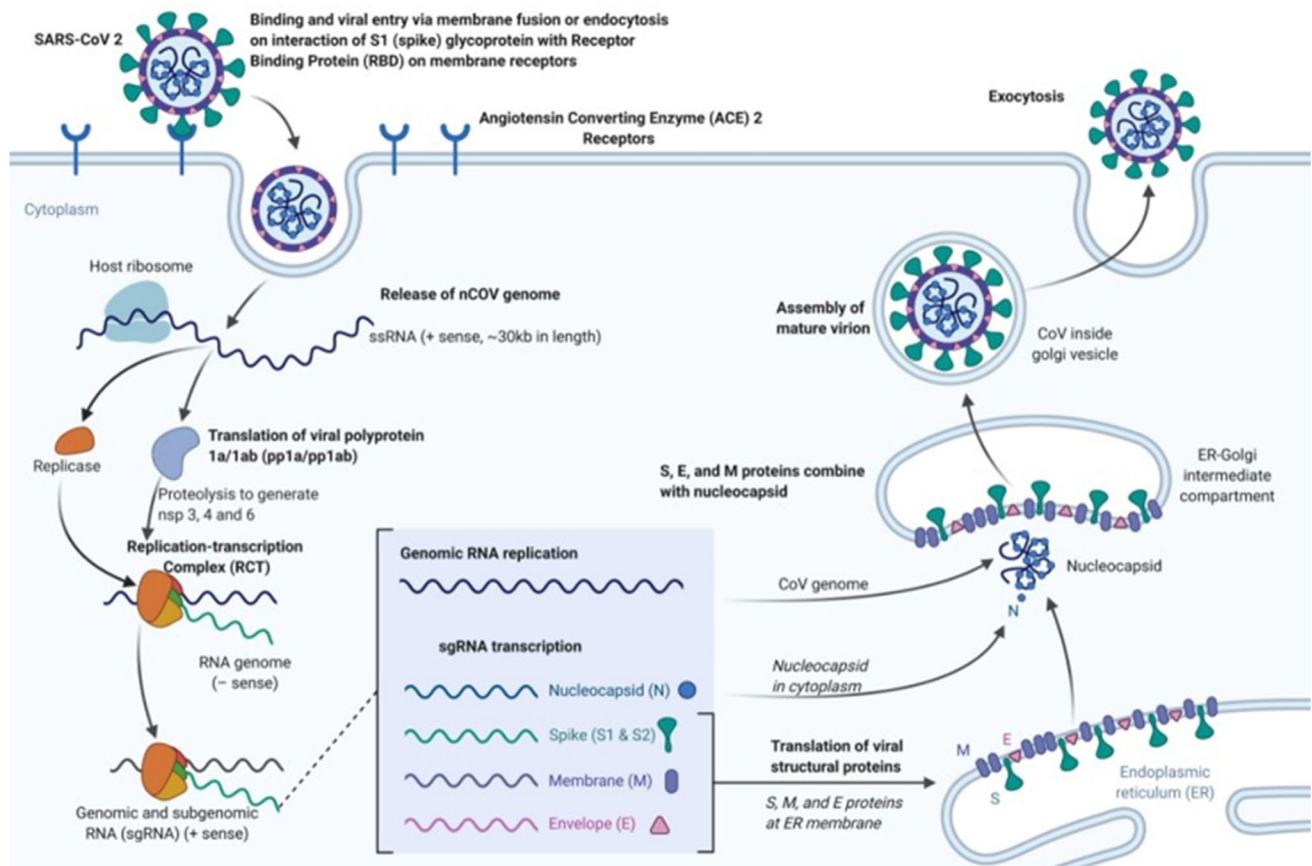


Fig. 1 Representing the steps of viral infection and mode of action of anti-bodies (adapted and reproduced from Cascella et al. 2020 under the terms of the Creative Commons Attribution 4.0 International License (<https://creativecommons.org/licenses/by/4.0/>))

of International Concern. This pandemic spread quickly throughout the entire country. For the control of SARS-CoV-2, all the approaches such as vaccines, monoclonal antibodies, oligonucleotides, peptides, interferon, and small molecule drugs are under pipelines (Li and Clercq 2020). As per the WHO recommendation, to slow down the rapid transmission among humans, social distancing strategy should be adapted widely (Ferguson et al. 2020).

Transmission of covid-19

The SARS-CoV-2 spread rapidly and causes covid-19 in China, US, Italy, Iran, Spain, and many other countries. Several studies suggested that bat may be the cause of SARS-CoV-19 (Giovanetti et al. 2020; Paraskevis et al. 2020) but there is no evidence that bat is the potential reservoir of SARS-CoV-2 (Hampton 2005; Banerjee et al. 2019; Li et al. 2005a, b). In case of human, CoVs have been considered as nonlethal pathogens which causing only common colds (de et al. 2016). SARS-CoV and MERS-CoV are highly pathogenic to human and outbreak occurred in 2003 at China and

in 2012 at Saudi Arabia (Paules et al. 2020). The third CoV that is covid-19 causing serious health pose around the globe and will be recorded in the history of mankind. The first fetal case was reported on January 15, 2020 from Wuhan (Wang et al. 2020a, b, c). The epidemic spread quickly and later change to pandemic causing worldwide in health emergency conditions. The transmission of corona virus from human to human contact was seen (Guan et al. 2020). There are three main routes for the covid-19 transmission recommended from Chinese health authorities such as droplets transmission, contact transmission and aerosol transmission. The droplets transmission occurs when an infected person coughs or sneezes, it respiratory droplets are inhaled by individuals who are closer to that person whereas the contact transmission occurs when a person touches their nose, mouth or eyes after touching of the virus contaminant surface or objects and aerosol transmission occurs when the infection causing respiratory droplets mix into the air, forming aerosol, and the high dose of aerosols ingested or inhaled into the lungs from the environment close to it (Jin et al. 2020). The human digestive system is a favorable route for covid-19 spreading out inside the body by showing symptoms like abdominal

discomfort and diarrhea. In regards to this, four datasets of single cell transcriptomes related to digestive system was analyzed and found that angiotensin-converting enzyme 2 gene (ACE2) was highly expressed in absorptive enterocytes from ileum and colon region (Zhang et al. 2020a, b).

Cold, fever, myalgia or fatigue, pneumonia, and complicated dyspnea are the most common symptoms reported whereas headache, diarrhea, hemoptysis, runny nose and phlegm producing cough are fewer common symptoms (Huang et al. 2020). The mild symptom patients are recovered after one week whereas the severe patients may lead to fatal due to alveolar damage and subsequently respiratory failure (Li et al. 2020). Generally, death cases are found to be surged in the old aged patient suffered from pre-existing diseases like tumor, surgery, cirrhosis, hypertension, coronary heart disease, diabetes, and Parkinson's disease (Li et al. 2020). In India rate of infection is less than other countries which is approximately 1.9%. The number of patients infected is increasing day by day in India and the scenario of corona virus infection is in stage II. On 25 march 2020, the government of India's lockdown was considered all over the country (Arti et al. 2020).

Possible drugs and vaccine for treatment of covid-19

Due to the outbreak of unknown viral pneumonia in Wuhan city of China on December 2019, many researchers from various countries are analyzing different treatments methods to fight against covid-19. But, till now explicit drugs or vaccine against this mysterious disease has not found. Within few months from the outbreak, it has spread uncontrollably in many other countries. War against covid-19 is on and it makes a challenge for scientists and health workers. Since there is no specific drug or vaccine for treatment of this deadly disease, different drugs available previously are used in process of medical care. Targeting the endocytic pathway and autophagy process in treating of covid-19 could lead development of treatment (Yang et al. 2020). In the series of infection inside the body, SARS-CoV-2 now term as covid-19 first attempt to infect our lungs. Other body system like gastrointestinal and kidney might also get infected to some extent. But according to the observation, major cause of death is due to the failure of respiratory system. Therefore, providing immediate intensive care unit support for the patient is necessary. Use of oxygen therapy, non-invasive ventilation, invasive mechanical ventilation and extra corporeal membrane oxygenation (ECMO) are very much required for the infected patients. Wang et al. (2020a, b, c) experiment the use of drugs like ribavirin, penciclovir, nitazoxanide, nafamostat, chloroquine, remdesivir, and favipiravir against this lethal

disease on Vero E6 cells in vitro (Table 1). Chloroquine and remdesivir observed to be most effective as anti-viral treatment with low cytotoxicity. It is also reported that incorporating hydroxychloroquine with antibiotic azithromycin shows some positive outcomes by reducing the number of virus in particular part of body. Chloroquine is a drug used to prevent or treat malaria and remdesivir is a novel anti-viral drug in under investigation process for the treatment of Ebola virus infection. Drugs like baricitinb, interferon- α , lopinavir, and ribavirin may be proposed for treatment with acute respiratory system but combine therapy with lopinavir can cause side effects like diarrhea, nausea, and liver damage (Hirsch et al. 2013). Use of steroids as immunosuppressant in the treatment shows some positive effect by reducing the severity of inflammatory damage but in high doses it may shows negative impacts. So, low doses and short course is recommended (Booth et al. 2003; Clark and Baillie 2020; Griffith et al. 2005). Another method of therapy which is currently under observation for the ill patients of covid-19 is generation of anti-body by collecting blood from recovered patients. Anti-bodies are derived from B lymphocytes to fight against foreign pathogens. Application of this method shows result of reducing inflammation, number of virus, and saturation of oxygen in blood. Nevertheless, more findings are needed as it may cause disadvantages in transferring plasma. The emerging of this highly infectious and transmittable disease cause death to almost all the country and it is increasing day by day. Any possible treatment to prevent or to recover from covid-19 is practicing in different part of countries and in China. Treatment with traditional Chinese medicine (TCM) of many other diseases has been practicing from olden times. TMC therapy has become another choice of treatment for covid-19 patients of very early stages and for those who have regain from severe stages. It is revealed that Shu Feng Jie Du capsules and Lian Hua Qing Wen capsules give good response in treatment of this new disease (Lu 2020). A study from Chinese academician Zhang Boli, check the effectiveness of treatment between western medicine alone and combination of western medicine with traditional Chinese medicine. After the experiment they concluded that treatment in combination takes less time for body temperature recovery and reduce symptomatic worsening from early to severe stage. Also, the mortality rate was lower in combine treatment than lone treatment of western medicine. Scientists are working day and night reluctantly on preparation of effective vaccine against covid-19. But release of a vaccine will take time as for now. Because it needs to be tested again and again before approval in order to check their side effects. Vaccination is important to break the chain of transmission and to prevent from this lethal disease. Scientists are struggling to develop effective vaccines to protect immunity

Table 1 List of some drugs and vaccines undergoing clinical trials for treatment of covid-19

Drugs	Type of medicine	Mechanism of action	Past records
Favipiravir	Anti viral drug	Inhibits viral RNA dependent polymerase	Typically used against influenza, inhibits polymerase of in vitro virus (ebola, norovirus, filovirus, arenavirus and bunyavirus)
Triazavirin	Non- nucleoside anti viral drug	Blockade of viral RNA synthesis	Effective against tick borne encephalitis virus and forest spring encephalitis virus
Umifenovir	Fusion inhibitor anti viral drug	Inhibits fusion between viral and cellular membrane	Membrane haemagglutinin fusion inhibitor in influenza virus and reduce risk of bacterial pneumonia
ASC09	Anti viral and antiretroviral drug	Protease inhibitor	Inhibits protease of HIV and use in combination with ritonavir
Azvdudine	Azidocytidine nucleoside analogue	HIV reverse transcriptase inhibitor	Antiviral activity against HIV, hepatitis B, hepatitis C
Danoprevir	Anti viral and antiretroviral drug	Protease inhibitor	Hepatitis C virus NS3 protease inhibitor use in combination with ritonavir
Darunavir	Anti viral and antiretroviral drug	Protease inhibitor	Inhibits protease of HIV and use in combination with cobcistat
Lopinavir/ritonavir	Transcriptase inhibitors	Blocks viral cellular entry	Inhibit HIV reverse transcriptase, enhance inhibition of CYP3A4 in vitro and have effective against SARS-CoV-2
Remdesivir	Adenosine nucleotide analogues	Inhibit viral activity	Drug for Ebola and Marburg virus, effective against SARS-CoV-1 in vitro and MERS
Baloxivir marboxil	Viral endonuclease inhibitor	Inhibits viral influenza	Inhibitor of influenza virus cap dependent endonuclease and combine with favipiravir or lopinavir
Chloroquine	Anti malarial drugs	Prevent viral entry and transport by inhibiting glycosylation of viral ACE-2 or quinine reductase 2	Effective against SARS-CoV-2 in vitro, approved for malaria treatments and have some efficacy in HIV-AIDS
Hydroxychloroquine	Anti malarial drugs	Prevent viral entry and transport by inhibiting glycosylation of viral ACE-2 or quinine reductase 2	Effective against SARS-CoV-2 in vitro, approved for malaria treatments and auto immune disease
Carriomycin	Anti biotic drug	Polyether anti biotic	Effective against gram positive bacteria, fungi and yeasts
Ribavirin + interferon	Anti viral drug	Inhibitor of viral replication	Effective to some extent in MERS
Camostat Mesilate	Protease inhibitor	Blocks viral cellular entry and maturation	Effective results against SARS-CoV-2 in vitro lungs cell
Aerosolized interferon α	Cytokines	Increase innate antiviral activity	Benefits to some extent in case of MERS
SARS-CoV-2 specific antibodies	Antibody	Binds to virus, infected cell and reduce infection	Blockade SARS-CoV-2 entry in cell in vitro

from covid-19. The plan of vaccination was developed for Middle East respiratory syndrome (MERS) by using nanoparticles, viral vectors, DNA plasmids, virus like particles, and recombinant protein sub units. It is reported that first US covid-19 vaccine trials in human was performed on March 16. It is the first vaccine tried in humans of mRNA vaccine. The vaccine dubbed mRNA-1273 which contain genetic material from the spike protein in SARS-CoV-2

and encapsulated with a lipid nanomaterial. However, the study of proper secure vaccine is currently under evaluation and results are yet to be out.

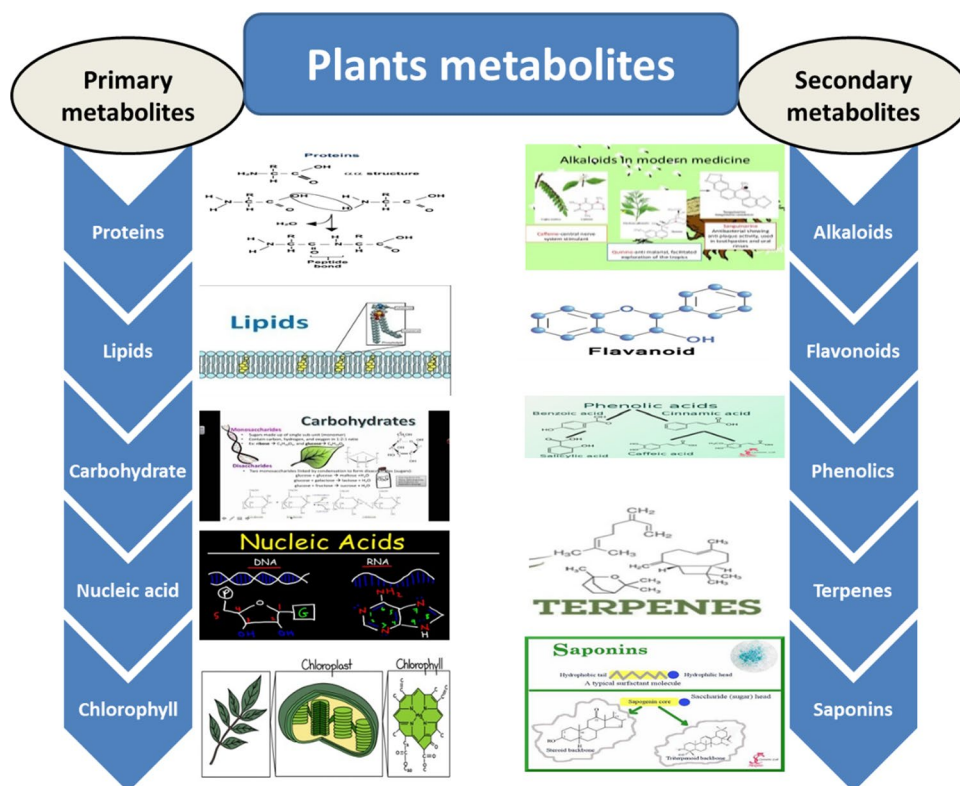
Bioactive molecule

The modern science is focusing on exploration of new materials obtained from natural products like plants, animals and other microorganism for treating different ailments. The natural products obtained from plants, animals and other microorganism which possess significant potential of therapeutic applications can be exploited for treating various diseases (Dash et al. 2020). This natural product mainly includes bioactive molecules as an important agents and they possess divers' applications and unique properties that can be useful for the pharmaceutical companies (Kang et al. 2013). Even from ancient times; natural remedies are playing a vital role in overcoming various diseases. Ancient traditional medicine practitioners were well equipped with the knowledge of plants as remedial ingredients against many ailments with or without knowing bioactive molecules of the plants but now a day's researchers are paying special attention to plants with more bioactive molecules in combating dreaded diseases on the note that natural products may produce fewer side effects on human beings. The extraordinary relationship between nature and human beings can be taken as a remedial point (Segneanu et al. 2017). Medicinal plants can cure many diseases and this ability of the plant is known as therapeutic capacity. This ability in the plants is all

because of their chemical composition mainly bioactive compounds, minerals and vitamins etc. (Sandberg and Corrigan 2001, Singh et al. 2020a, b).

Medicinal plants contain huge amount of minerals and vitamins which can be easily assimilated by human body. According to many scientific studies, the vitamins, and minerals obtained through chemical synthesis can't give the same benefits compared to natural products. Natural products have more bioactive molecules because it may have a synergistic and complementary action between vitamins, enzymes and minerals. Synthetic drugs have more side effects and it's interaction with other substances in the body may lead to more harmful effects to human. It has more disadvantages as compared to natural medicine sources (Taylor 2005). Botanic products are important for humanity since they possess phytochemicals which are active ingredients used in therapeutic applications. The natural compounds obtained from plants are classified in two major categories (Dias et al. 2012). Primary metabolites like protein, fats, sugar, etc. are common to all biological system whereas secondary metabolites are specific for different species and shows the direct result to the evolution process of a particular phylogenetic group (Fig. 2). In secondary metabolites bioactive molecules are included and exhibit therapeutic, toxicological and immune stimulating activity.

Fig. 2 Different types of plant metabolites



Plants metabolites

The different groups of compounds under primary and secondary metabolites are briefly discussed (Fig. 2). But continuous efforts in improving analysis techniques can give major information about highly bioactive molecules that are isolated from natural compounds. Improving Analysis techniques and choosing the right medicinal source may lead to overcoming many dreaded diseases without any specific treatment like Covid- 19.

Primary metabolites

Proteins, lipids, carbohydrate, nucleic acid, etc. are the major compounds found in all the living systems and they are grouped under primary metabolites.

Secondary metabolites

There are another group of compounds that are specific to different species. This group of compounds plays a vital role during adaptability and survival processes of the plant. Alkaloids, terpenes, saponins, flavonoids, phenol acid, tannins, volatile oils, etc. are the group of compounds which are termed as secondary metabolites (Dias et al. 2012, Azmir et al. 2013, Woolley 2001, Panda et al. 2020).

Bioactive molecules against coronavirus

Covid-19 is a major problem for whole world and till now there is no solution to tackle this pandemic. All the vaccines are under trial basis. It is reported that lopinavir/ritonavir drugs generally used for the treatment of human immunodeficiency virus HIV and can be administered as remedies of covid-19 patients (Wang et al. 2020a, b, c). Moreover, other drugs including pitavastatin, nelfinavir, perampanel, and praziquantel have therapeutic capacity against covid-19 (Xu et al. 2020). However, none of these drugs works absolutely against the current pandemic covid-19. Therefore, many other medical options are in targeted. Bioactive molecules obtained from natural products including plants, animals and other microbes as a source of antiviral against the covid-19 can be discussed and these natural compounds might be a solution for present ongoing amidst of covid-19 (Table 2).

Secondary metabolites are released from plants in order to overcome the unfavorable conditions developed due to some environmental factors. These metabolites can be used for the development of drugs and medicines. Now, at this uncontrol amidst of pandemic covid-19, all attentions go

to the plant and their derivative molecules as antiviral to develop medicine as they presence large number of secondary metabolites (Yang et al. 2018). Flavonoids, alkaloids, terpenoids and polyphenols are some compounds having antiviral activities reported from medicinal plants.

Different studies showed medicinal plants have the phenolic compound. Medicinal plants released compounds such as Curcumin, kaempferol, catechin, naringenin, quercetin, apigenin-7-glucoside, luteolin-7-glucoside, demethoxycurcumin, oleuropein and epigallocatechin which have potential role fighting against covid-19 and this study was conducted by molecular docking (Khaerunnisa et al. 2020). From the in-silico analysis, it is known that these compounds have pharmacophore similarities with nelfinavir. It was also found that, more than 24 compounds are available as bioactive molecules that can be more effective than nelfinavir for the treatment of covid-19. The study conducted by molecular docking and bioactive compounds like rutin, diacetyl curcumin, diosmin, beta, beta`-(4-Methoxy-1,3-phenylene) bis(2`-hydroxy-4`,6`-dimethoxyacrylophenone), (E)-1-(2-Hydroxy-4-methoxyphenyl)-3 [3-[(E)-3-(2-hydroxy-4-methoxyphenyl)-3-oxoprop-1-enyl] phenyl] prop-2-en-1-one and apiin released from medicinal plants have therapeutic properties against covid-19 (Adem et al. 2020). Lignoids, sesquiterpenes, R-cadinol, curcumin, lupane-type triterpenes, abietane-type and labdane-type diterpenes are some newly identified bioactive compounds which have antiviral properties against covid-19 and lignoids and diterpenoids have active SARS-CoV effect (Wen et al. 2007). From SARS-CoV and MERS-CoV it is confirmed that nature has a significant role for producing natural antiviral products, so, it is believed that nature also provide medication for covid-19 pandemic (Fig. 3).

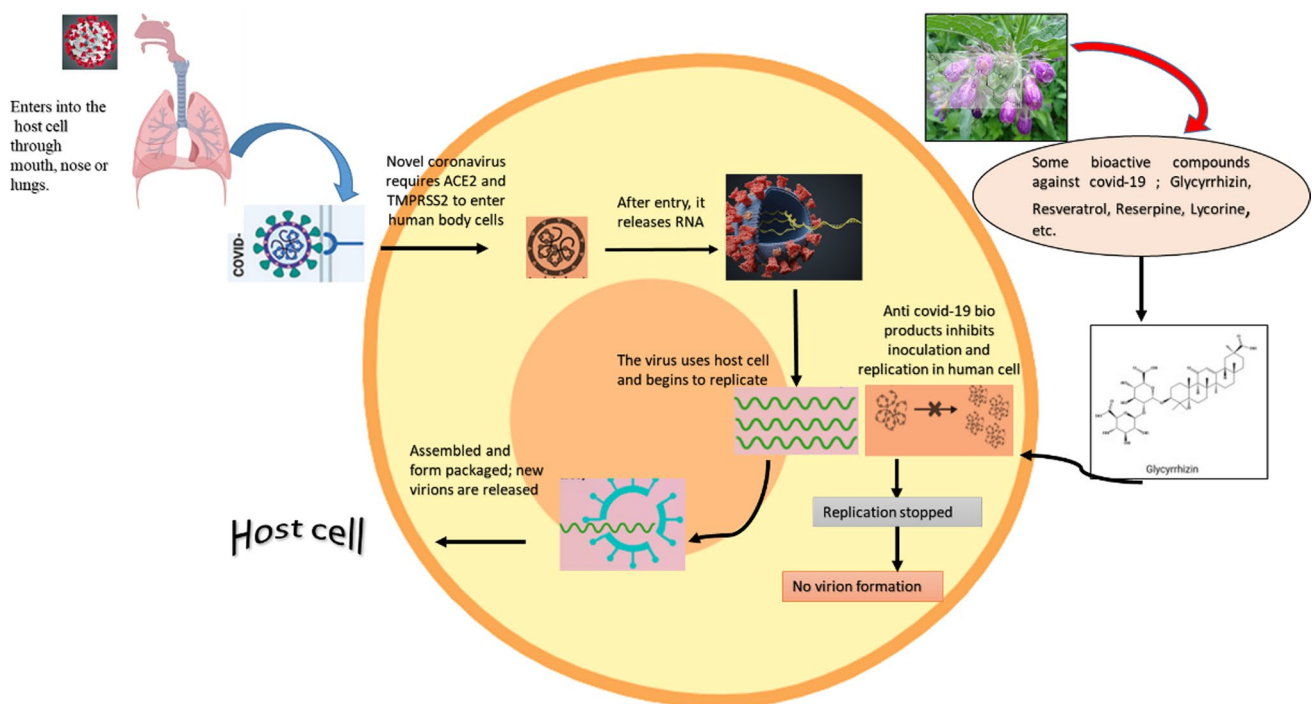
In history, 3-chymotrypsin-like protease have therapeutic capacity against SARS-CoV, so by using such compounds, human corona virus including SARS-CoV-2 can be treated (Yang et al. 2020). Scientists have identified some traditional Chinese herbs in the past decade, which can be treated against SARS-CoV. Herbal extracts such as, flavonoid extracted from litchi seeds, *Houttuynia cordata* water extract, Chinese Rhubarb extracts and beta-sitosterol from *Isatis indigotica* root extract have the capacity to obstruct the enzymatic activity of SARS (Gong et al. 2008). Aloemodin, quercetin, hesperetin, sinigrin, rhoifolin, epigallocatechin gallate, rhoifolin, herbacetin, pectolinarin and galocatechin gallate are some naturally occurring compounds having antiviral effect against SARS 3CLpro (Nguyen et al. 2012). 3 β -Friedelanol from *Euphorbia nerifolia* (Chang et al. 2012), Blancoxanthone from the roots of *Calophyllum blancoi* (Shen et al. 2005) *Artemisia annua*, *Lycoris radiata*, *Lindera aggregate* and *Pyrrosia lingua* (Li et al. 2005a, b) have anti-corona viral activity. From molecular docking analysis, it was known that an impressive medicine,

Table 2 Promising natural bioactive molecules against coronavirus

Sl. No	Name of plants	Bioactive molecule	Mode of action	References
1	<i>Rheum palmatum</i>	Emodin	Inhibit interaction of SARS-CoV spike protein	Ho et al. (2007)
2	<i>Scutellaria baicalensis</i>	Kaempferol	Prevent the early stage of HCoV-22E9 infection, including viral attachment and penetration	Deng et al. (2012)
3	<i>Allium sativum</i>	Allicin	–	Shang et al. (2019)
4	<i>Glycyrrhiza uralensis</i>	Flavonoids, glycyrrhetic acid (GA)	Inhibit SARS-3CLpro activity	Yang et al. (2019)
5	<i>Phaseolus vulgaris</i>	3,5,7,3',4',5'hexahydroxy flavanone-3-O-beta-D-glucopyranoside	Inhibit 3CLpro interacting through His41, Cys145, Thr24, Thr25, Thr26, Gln189 H-bonding	ul Qamar et al. (2020)
6	<i>Glycyrrhiza radix</i>	b-sitosterol	Inhibit viral adsorption and penetration	Cinatl et al. (2003)
7	<i>Olea europaea</i>	Oleuropein	–	Nicoli et al. (2019)
8	<i>Tonna sinensis</i>	Quercetin	Inhibit the cellular entry of SARS-CoV	Chen et al. (2008)
9	<i>Isatis indigotica</i>	5-hydroxyoxyindole, isaindigo-tone, indole-3-carboxaldehyde	Inhibit the cleavage activity of SARS-3CLpro enzyme	Lin et al. (2005)
10	<i>Astragalus membranaceus</i>	Flavonoids, lectin, isoflavones	Inhibit SARS-3CLpro activity	Yang et al. (2019)
11	<i>Lycium chinense</i>	Polyphenols, flavonoids, carotenoids	Inhibit the viral SAES-3CL pro activity	Miean et al. (2001)
12	<i>Houttuynia cordata</i>	Flavonoids, polysaccharides	Inhibit the viral SARS-3CLpro activity and Block viral RNA-dependent RNA polymerase activity (RdRp) Immunomodulation	Lin et al. (2005)
13	<i>Phyllanthus emblica</i>	(2S)Eriodictyol 7O-(6''-Ogalloyl)-beta D glucopyranoside	Inhibit 3CLpro interacting through Thr24, Thr25, Gly143, Met49, Cys145, His41, Thr26 H-bonding	ul Qamar et al. (2020)
14	<i>Fraxinus sieboldiana</i>	Calceolarioside B	Inhibit 3CLpro interacting through His41, Gly143, Cys145, Glu166, Thr24, Thr25 H-bonding	ul Qamar et al. (2020)
15	<i>Spinacia oleracea</i>	Kaempferol	–	Dabeek et al. (2019)
16	<i>Galla chinensis</i>	Luteolin and tetra-O-gallol-beta-D glucose gall	Avidly binds with surface spike protein of SARS-CoV	Yi et al. (2004)
17	<i>Myrica cerifera</i>	Myricitrin	Inhibit 3CLpro interacting through Gly143, Cys145, His41, Thr24, Thr25, Thr26 H-bonding	ul Qamar et al. (2020)
18	<i>Capsicum annum</i>	Quercetin, Luteolin-7-glucoside	–	Miean et al. (2001)
19	<i>Psoralea argyrea</i>	5,7,3',4'Tetrahydroxy2'-(3,3dimethylallyl) isoflavones	Inhibit 3CLpro interacting through His41, Cys145, Thr24, Thr25, Thr26, H-bonding	ul Qamar et al. (2020)
20	<i>Hyptis atrorubens Poit</i>	Methyl rosmarinatate	Inhibit 3CLpro interacting through Cys145, His41, Thr24, Thr25, Thr26, H-bonding	ul Qamar et al. (2020)
21	<i>Citrus sinensis</i>	Naringenin	–	Salehi et al. (2019)
22	<i>Amaranthus tricolor</i>	Amaranthin	Inhibit 3CLpro interacting through Thr26, Glu166, Cys145, His41, Thr24 H-bonding	ul Qamar et al. (2020)
23	<i>Glycyrrhiza uralensis</i>	Licoleafol	Inhibit 3CLpro interacting through Cys145, His41, Thr24, Thr25, Thr26 H-bonding	ul Qamar et al. (2020)
24	<i>Nigella sativa</i>	Thymoquinones, sterols and saponins	–	Yimer et al. (2019)
25	<i>Dioscorea rhizoma</i>	Saponins	–	Wen et al. (2011)

Table 2 (continued)

Sl. No	Name of plants	Bioactive molecule	Mode of action	References
26	<i>Dryopteris crassirhizoma</i>	Sutchuenoside A	Play significant role in regulation of inflammatory process	Cheng et al. (2016)
27	<i>Ephedra sinica</i>	(3R)-3-O- β -D-glucopyranosyl-3-phenyl propanoic acid		Zhang et al. (2020a, b)
28	<i>Flos lonicerae</i>	Chlorogenic acid		Chen et al. (2004)
29	<i>Galla chinensis</i>	Galla tannin	Binds with surface spike protein of corona virus	Yi et al. (2004)
30	<i>Glycyrrhizae uralensis</i>	Glycyrrhizin		Chen et al. (2004)
31	<i>Houttuynia cordata</i>	Quercetin	Block viral RNA- dependent RNA polymerase activity	Lau et al. (2008)
32	<i>Lonicera japonica</i>	Iridoids	Inhibits corona virus replication at non-toxic concentration	Xiong et al. (2013)
33	<i>Lycoris radiata</i>	Lycorine	Posses anticorona virus	Chen et al. (2004)
34	<i>Phragmitis australis</i>	lectins	Inhibits corona virus by interfering with two targets in the viral replication cycle	Keyaerts et al. (2007)
35	<i>Glycyrrhizae radix</i>	Liquiritin	Inhibits viral adsorption and penetration	Cinatl et al. (2003); Pilcher (2003)
36	<i>Rheum palmatum</i>	Rhein		Cheng et al. (2016)
37	<i>Saposhnikovia radix</i>	Cimifugin	Inhibitory effect against corona virus	Zheng et al. (2011)
38	<i>Scutellariae radix</i>	Baicalin		Islam et al. (2012)
39	<i>Toona sinensis</i>	Gallic acid	Inhibits the cellular entry of corona virus	Chen et al. (2008)
40	<i>Veronica linariifolia</i>	Iridoid	Binds with surface spike protein of corona virus	Yi et al. (2004)

**Fig.3** Schematic representation of bioactive molecules interfering viral replication

Nilavembu kudineer have antiviral properties against covid-19. *Nilavembu kudineer* binds to Angiotensin-Converting Enzyme (ACE2) enzyme receptor which is the entry of pathogen as a result pathogen cannot enters into host body (Walter et al. 2020).

Conclusion

The current situation of covid-19 is a big issue for the human population. As of now, there is no drug/vaccine available in the market that can cure the covid-19 patient. All the drugs and vaccines are at primarily stage and under clinical trials. As a preventive measure to fight against the covid-19, some strategies like social distancing, stay home stay safe, self-quarantine, maintaining hygiene, wear masks and use hand sanitizer can be mentioned. The only one-way hope for the present situation is to rely on bioactive molecules from natural products as they have antiviral properties against the covid-19. These could be our one hope to fight against the pandemic covid-19. Several plants, animals and microbes can be explored to produce bioactive compounds that have potent for antiviral properties against the covid-19. Plant derivative natural bioactive compounds have effective against the SARS and MERS, so, for the covid-19 medication, it must look forward to those plants, animals and microbes having antiviral properties and rigorous research should be carried forward. To contain this pandemic bioactive compound based therapeutic measures should be fostered and it is high time to explore on such natural products.

Acknowledgements The corresponding author (YDS) is very much thankful to Vice-Chancellor, Central Agricultural University, Imphal, Manipur, India, for providing the facilities and moral support while conducting this research.

Author contributions All authors contributed to the manuscript. Conceptualization, Y.D.S; validation investigation, resources, data curation, writing—all authors; review and editing, M.K.S, Y.D.S, B.J, R.N, S.P, P.P, S.P, K.B.S, and M.C.S. All the authors read and approved the final manuscript.

Funding There was no funding agency for this experiment.

Compliance with ethical standards

Ethical statement This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest Yengkhom Disco Singh has no conflict of interest. Barsarani Jena has no conflict of interest. Rina Ningthoujam has no conflict of interest. Sneha Panda has no conflict of interest. Pratigyan Priyadarsini has no conflict of interest. Sabita Pattanayak has no conflict of interest. Manasa Kumar Panda has no conflict of interest. Mayanglambam Chandrakumar Singh has no conflict of interest. Kunja Bihari Satapathy has no conflict of interest.

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