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PLANTS SECONDARY METABOLITES (PSMS), AS AN INVESTIGATIONAL SOURCE AGAINST COVID-19 FROM FLORA OF PAKISTAN

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Abstract

Plant Secondary Metabolites (PSMs) are naturally occurring organic compounds inside the plant produced in response to any internal or external environmental stress. These organic chemicals are in different forms (Terpenoids, polyphenols, alkaloids, etc.). PSMs are an active source of medicines against many types of viral as well as microbial diseases. Pakistani flora is also a rich source of medicinal plants, and their therapeutic range has great importance. These plants are already in use against various types of microbial diseases. The primary aim to write this paper is to highlight PSMs of medicinal plants of Pakistani flora, which can be effective against COVID-19.

Key words: Antimicrobial, Antiviral, Secondary metabolites, COVID-19.

Introduction

The SARS Cov-2 or COVID-19 is almost 80% identical to Beta coronaviruses responsible for severe acute respiratory syndrome (Chen *et al*., 2020). There is an intense requirement of an earnest therapeutic inquiry as there is no potential vaccine or medicine effective against this virus. Some computational techniques like molecular docking have provided large-scale screening of natural molecular compounds, which have the potential to inhibit specific proteins. These natural compounds are the plant's secondary metabolites that can intercalate with the lipid layers of the virus, protein, or intercalate with its DNA/RNA (Gyebi *et al*., 2020). Many PSMs can be an active source of a drug against COVID-19 because they have interacting capabilities with the lipid bilayer, spike protein, and DNA / RNA of the virus. Due to their interactions, PSMs are also very famous as intercalating compounds. These compounds are generally known as alkaloids, polyphenols, phenolics, flavonoids, terpenoids, well known for their practical medicinal activities, including antimicrobial, antifungal, antibacterial, anti-tumor, anthelmintic, antiviral. Many Pakistani medicinal plants contain various alkaloids, phenolic contents, flavonoids, terpenoids, etc. These PSMs are previously defending humankind in different types of pathogenic and lethal diseases. Now it is recommended that these PSMs, primarily discussed plants from Pakistani flora, should be investigated pharmacologically as a possible source of medicine against viruses especially COVID-19, in many ways. For example, Lipophilic terpenoids and their derivatives (essential oils) can disturb lipid layers of the outer envelope of the COVID-19 (Ben-Shabat *et al*., 2020; Wink, 2020).

Moreover, studies revealed that polyphenols and phenols (Tannins, Rosmarinic acid, Flavonoids, etc.) could attack and destroy the viral proteins present inside the virus or in the cell membrane. In this regard, phenols and polyphenols are also beneficial active PSMs that can be investigated to produce potential drugs against COVID-19. Other fascinating PSMs (sanguinarine, berberine, Tetraderine, piperidine, β-carboline, quinoline, etc.) or DNA intercalators that can inhibit the replication and development of the virus in the cell are alkaloids. Studies revealed that alkaloids showed positive defense against SARS –COV-1 and other viruses. Due to this reason, it should be investigated against COVID-19 (Mukhtar *et al*., 2008; Lin *et al*., 2014; Akram *et al*., 2018; Dhama *et al*., 2018; Reichling, 2018; Ben-Shabat *et al*., 2020; Wink, 2020).

Mode of action of plant's secondary metabolites (PSMs): Plant's secondary metabolites (PSMs) are intermediary compounds produced in response to stress and help the host interact and cope with environmental stresses. These compounds have fascinating antifungal, antimicrobial and antiviral properties (Korkina *et al*., 2018). There are 04 major PSMs categories: terpenoids or terpenes, polyphenols, and phenolics, glycosides, and alkaloids. Recent studies reveal that PSMs can defend against viral activities in humans, especially terpenoids, polyphenols & phenolic contents, and alkaloids (Mukhtar *et al*., 2008).

Studies reveal that these PSMs can attack the virus in various ways according to their specificity (Fig. 1). Some of them attack the free-living viruses, whereas inactive for those inside the cell. Some PSMs attack the membranous protein of the virus, whereas others intercalate with the virus's DNA or RNA and destroy their structure. For example, lipophilic terpenoids are PSMs that can interrupt the viruses' lipid envelope and inhibit their virulent activities. This characteristic of interruption is unique and needs evaluation against coronaviruses. As per the information, coronavirus can create different genetic makeup, which is very lethal viral activity and can defeat the immunization developed by vaccination. In this regard, lipophilic terpenoids and their derivatives can be evaluated for their fascinating ability to interrupt the virus's outer envelope (membrane) and destroy the functionality of attachment to the host's cellular membrane Mukhtar *et al*., 2008; Lin *et al*., 2014; Akram *et al*., 2018; Dhama *et al*., 2018).

Similarly, flavonoids, rosemerenic acids, and tannins are important PSMs that can attack the membranous proteins of the virus and destroy their structure. Phenols and polyphenols can be investigated for their phytochemical and pharmacological importance against COVID-19 because PSMs can destroy the proteins structuring the body of COVID-19. There is another group of PSMs, including β-carboline and quinoline alkaloids, which attack the DNA or RNA of the virus and destroy it. These DNA RNA intercalators can be effective against COVID-19 also as they have already shown the potential defense against SARS and MARS coronaviruses. Moreover, different studies demonstrate that coronaviruses can modify their genetic makeup, producing new strains, and vaccinations against modified strains become inactive. At the same time, alkaloids are PSMs that can intercalate with the DNA/RNA and demolish the corona virus's functionality. So, the pharmacological investigation against coronaviruses can indeed be a potential source of the drug (Mukhtar *et al*., 2008; Lin *et al*., 2014; Akram *et al*., 2018; Dhama *et al*., 2018; Reichling, 2018; Ben-Shabat *et al*., 2020; Wink, 2020).

In Pakistan, there are about 6000 to 7000 plant species, out of which about 700 species are actively participating in the medicinal field. In this review, we will explain the multifunctional PSMs present in the Pakistani Medicinal Flora, which can help produce a possible drug against the COVID-19 (a novel species of coronaviruses) (Shinwari, 2010).

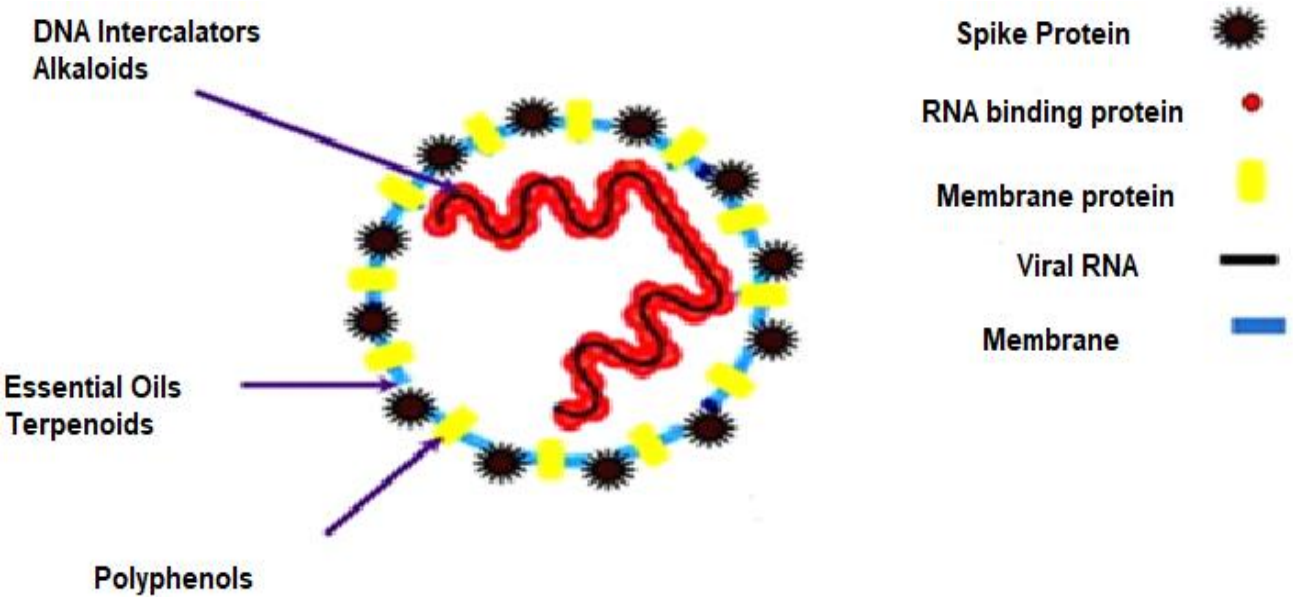

Fig. 1. Reaction sites of PSMs (Terpenoids, polyphenols, and alkaloids) with COVID-19.

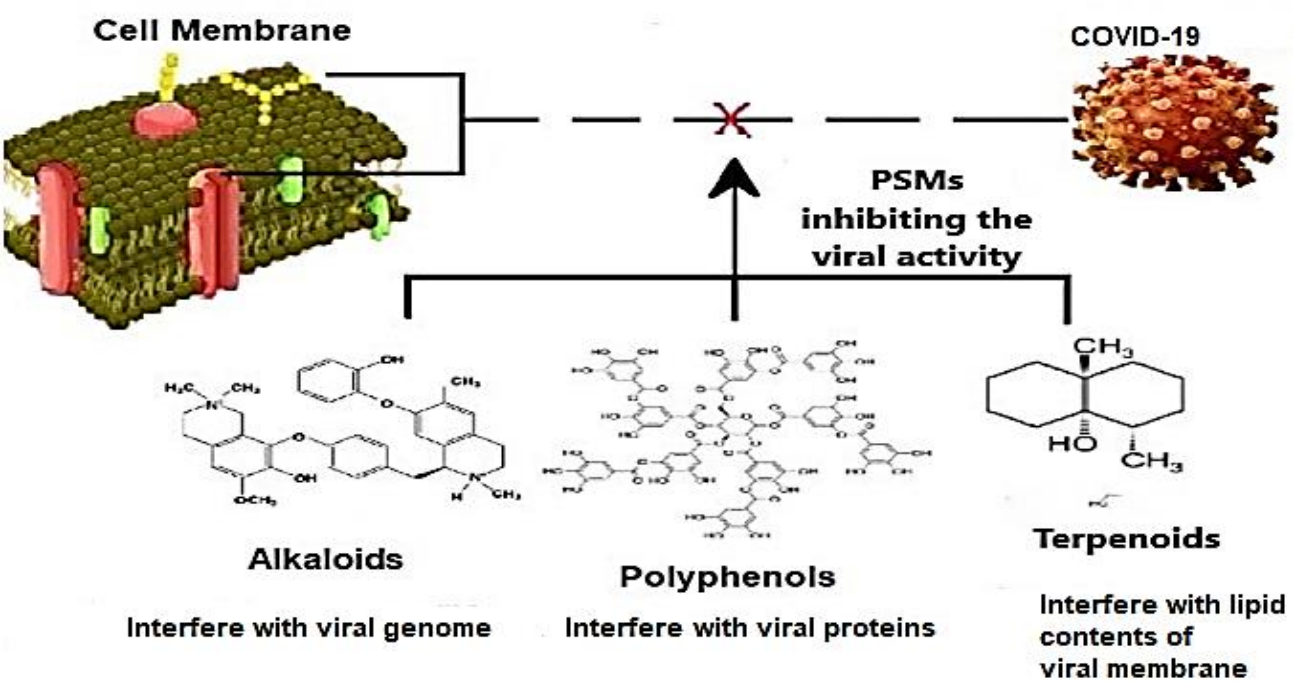

Fig. 2. The structures of PSMS and their interference with COVID-19.

Table 1. Summary of medicinal plants from Pakistani flora with their PSMS & medicinal uses.

S No.	Scientific name of plant	Family	Local name in Pak	Local name	PSMs	Medicinal uses	Ref
1.	*Caesalpinia crista* L.	Caesalpiniaceae	Karanjava	Crested fever nut	Phenolic acids such as caffeic acid, chlorogenic acid, p-coumaric acid, ferulic acid, and gallic acid, terpenoids, flavonoids	antioxidant, antibacterial, antiviral, antimalarial, anti-tumor, anticancer, antidiabetic, anti-inflammatory, analgesic, hepatoprotective, cardioprotective, anti-amyloidogenic, nootropic, wound healing, anthelmintic, insecticidal, antipyretic and antiulcer activities	(Chan *et al*., 2018)
2.	*Capparis decidua* (Forssk.) Edgew.	Capparaceae	Kair, Karri, Delha	Caperberry	Stachydrine, β-carotene, Rutin, Isothiocyanate, Glucosides, Hydrocarbons (Fatty acids), and Isocodonocarpine.	Antiviral, asthma, arthritis, anti-inflammatory, anti-fever, antimalaria, anti-rheumatism, anti-swelling, hepatoprotective, laxative, vermifuge properties	(Alamri *et al*., 2020; Upadhyay, 2020)
3.	*Carica papaya* (Linn)	Carecaceae	Papeeta	Papaya	Papain, a-tocopherol, flavonoids, cyanogenic glucosides, chymopapain, cystatin, glucosinolates.	antimicrobial, anti-respiratory diseases, anticancer, antiplasmodial, antihelmintic, antiamoebic, active inhibitory	(Seigler *et al*., 2002; Airaodion *et al*., 2020)
4.	*Cassia fistula* L.	Leguminosae	Amaltas	Golden shower	Terpenoids, steroids, tannins, flabotannins, saponins, flavonoids, anthraquinone	Antioxidant, anti-inflammatory, anticancer, antimicrobial, antiviral	(Kumar Ramanujam *et al*., 2014; Ravi, 2020)
5.	*Citrullus colocynthis* (L.) Schrad.	Cucurbitaceae	Korhtumma	Bitter apple	Polyphenolic flavonoids isosapnarin, Isovitexin and Isorientin 3-O-Methyl ether, Cucurbitacin B, Cucurbitacin E	antidiabetic, jaundice, asthma, leprosy, anti-respiratory diseases, anticancer, antibacterial, anti-inflammatory, antirheumatic, antioxidant antihelmintic,	(Qureshi *et al*., 2010; Hussain *et al*., 2014)
6.	*Ephedra* species (*Ephedra intermedia* Schrenk & C.A.Mey., *Ephedra procera* C.A.Mey., *Ephedra foliate* Boiss. ex C.A. Mey.)	Ephedraceae	Asmania, humma	Joint-pine	alkaloids, ephedrine, flavonoids, polyphenolics, lignins, proanthocyanidins, volatile organic compounds, quinoline,	chest problem, cough, asthma, antimicrobial, cold, flu, chilled fever, headache, nasal congestion, anti-inflammatory, antiviral,	(Wang *et al*., 2006; Wang *et al*., 2009; Lee *et al*., 2010; Ibragic & Sofić 2015; Elhadef *et al*., 2020)
7.	*Ferula assa-foetida* L.	Apiaceae	Hing	Asafetida	auraptene, umbelliprenin, galbanic acid, daucane esters, ferutinin, ferulenol, ferprenin, sinkiangenorin C and E, farnesiferols A and B.	Antimicrobial, insecticidal, antiviral anti-inflammatory, antitumor, anticancer, anti ulcerative, antiprotozoal	(Salehi *et al*., 2019)
8.	*Mentha species (Mentha longifolia* (L.) L., *Mentha x piperita* L., *Mentha spicata* L.)	Lamiaceae	Podina	Mint	Menthol, menthone, isomenthone , 1,8-cineole, methyl acetate , methofuran, limonene, pinenes, germacrene, and pulegone, rosemirinic acid, p&m-coumaric acid, neochlorogenic acid, caftaric acid, chlorogenic acid, o-coumaric acid	Reduces cough, sinusitis, and throat respiratory diseases. Antioxidant, antityrosinase, anticancer, antifungal anti-inflammation, antibacterial,	(Fatiha *et al*., 2015; Elansary *et al*., 2020; Upadhyay, 2020)
9.	*Nigella sativa* L.	Ranunculaceae	Kalwanji	Black cumin	Terpenoids, alkaloids, phenols, phytosterols, saponins, sterols, tannins	Immunity disorders, Lung complains, anti-inflammatory, anti-microbial, antiviral	(Sheriff *et al*., 2015; Mirzaie *et al*., 2020)
10.	*Peganum harmala* L.	Nitrariaceae	Harmal booti	Wild rue	β carboline & quinoline alkaloids	Antimicrobial, hypothermic hellucenogenic, anticancer	(Lamchouri *et al*., 2000)
11.	*Trachyspermum ammi* L. Sprague.	Apiaceae	Ajwain	Bishop's weed	Thymol, gamma-terpinene, pcymene, β-pinene. Cymene	Cough, congestion, antioxidants, strong fungicide, germicide, anti-arthritis, relief from muscular-joint pain, antiviral	(Roy *et al*., 2015; Upadhyay, 2020)
12.	*Trigonella foenum-graecum* L.	Leguminosae	Methi	Fenugreek	terpenoids, alkaloids, saponins, tannins, steroids, flavonoids	Antimicrobial, Antifungal, Antibacterial,	(ElNour *et al*., 2015)

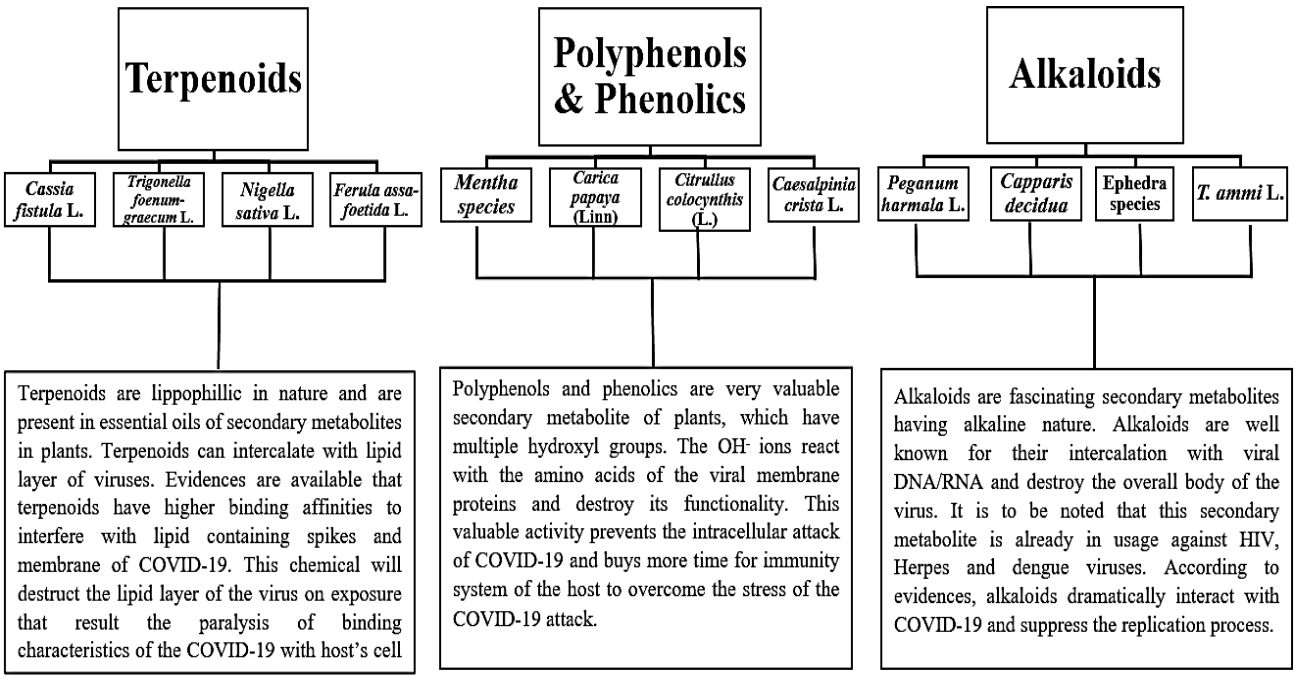

Fig. 3. Overview of PSMs.

Evidence of antiviral activity of PSMs: In many cases, the extraction from medicinal plants and their secondary metabolites showed intense antiviral activities. *In vitro* studies revealed that the incubation of PSMs and viruses has shown direct interference (Table 1). It led to the destruction of viral protein, its lipid layers, and the lysis of the cell. But the cell culture in which the virus already infects cells needs to be absorbed the PSMs so that they can assault the virus body (Akram *et al*., 2018; Wink, 2020).

Many PSMs are polar in their chemical nature (phenols and polyphenols). They have low absorption because they cannot pass through the channels of infected cells' semi-permeable membrane. Many studies revealed that the PSMs are the active source to attack against free viral particles but are less active against infected cells (Fig. 2). For example, Tannins have many hydroxyl groups and show high aggressive binding capability against membranous proteins of free viruses. Moreover, the antiviral activity of PSMs has been evaluated *In vitro*, which showed positive results. The effects of PSMs on infected cells showed low antiviral activity because of less absorption of PSMs through bio-membranes (Akram *et al*., 2018; Wink, 2020). In this regard, discussed PSMs are recommended to evaluate against coronaviruses and COVID-19 as a treating agent at the initial level of infection and as a preventive measure against this deadly pandemic.

Terpenoids (essential oils): Terpenoids are a very diverse and large group of naturally occurring organic compounds. Terpenes include a broad class of chemical compounds in plants, and they also have a strong odor that protects plants from different pathogens. They are lipophilic and present in many plants' essential oils (PSMs) (Van Wyk & Wink, 2018).

Recently terpenoids have gained particular importance due to their antimicrobial and antiviral activities. Terpenoids can interpolate with the lipid bi-layer of the virus and disturb the configuration of its structure. By this activity, terpenoids are specific as active inhibitory compounds against viruses (Fig. 3). Some terpenoids such as betulinic acid, celasdine-B, and ursolic acid have shown vigorous antiviral activities (IC50: 1–20 g/mL), recorded using a sensitive cell culture system (Reichling, 2018). Moreover, the study reveals that terpenoids have shown higher binding affinities and vigorous inhibition with all types of coronaviruses and can be very effective against COVID-19. The outer spiky lipid layer of COVID-19 is particular for its binding characteristics with the host's cellular membrane. Whereas terpenoids are specific for attacking the lipid layer of viruses, they can destruct the lipid layer of COVID-19 and paralyze the binding characteristics (Gyebi *et al*., 2020).

Due to these fascinating defensive characteristics, pharmacological investigation on terpenoids for drug production against COVID-19 can be rewarding.

The undermentioned Pakistani medicinal plant's secondary metabolites are already known as active agents of antimicrobial and antiviral activities. Studies revealed the availability of sufficient terpenoids and other PSMs in medicinal plants. Their therapeutic investigation can be effective against viruses, especially COVID-19 (Ramanujam *et al*., 2014; ElNour *et al*., 2015; Neamah, 2018).

1. *Cassia fistula* L. is a medicinal plant that belongs to the Leguminosae family (local name Amaltas), having antibacterial and antifungal characteristics. But the study reveals a sufficient amount of terpenoids in PSMs of *Cassia fistula* L. (Ramanujam *et al*., 2014). These terpenoids can be extracted out via ethanol or hexane solvents from the plant's fresh and dried leaves and flowers (Ramanujam *et al*., 2014). Moreover, this plant's PSMs (especially terpenoids) are involved in the antiviral activity as a protein inhibitor in COVID-19. It can

dissolve the lipid layer of coronaviruses and disturb the virus's ability to attach to the host cell membrane (Ravi, 2020). In this regard, it is recommended that *Cassia fistula* L. should be investigated for its phytochemical and pharmacological characteristics against coronaviruses. Especially terpenoids of the *Cassia fistula* L. should necessarily be examined for their pharmacological characteristics against the lipid layer of COVID-19. This investigation can lead to an active source of a drug against coronavirus and its strains.

2. *Trigonella foenum-graecum* L. is another well-known and one of the oldest medicinal plants of Pakistan which have effective antiviral and antimicrobial characteristics (Acharya *et al*., 2006). It is an annual legume plant used as a spice in many parts of the world (Sulieman *et al*., 2008). Studies revealed that the seeds of the *Trigonella foenum-graecum* L. herb possess a variety of toxic oils, volatile oils, and alkaloids as its secondary metabolites. These compounds are highly toxic to bacteria, parasites, and fungi and produce an active defense (Gottfried, 2007). Phytochemical analysis of this plant reveals that it also contains a sufficient amount of steroids and terpenoids which (Ramanujam *et al*., 2014) can be studied for inhibition against viruses (ElNour *et al*., 2015).

3. *Nigella sativa* L. Another Pakistani native medicinal plant is *Nigella sativa* L. (local name Kalwanji) belongs to the family of Ranunculaceae, which is well known for its therapeutic, antiviral, and antimicrobial importance. This plant can quickly grow in almost all parts of Pakistan. A study of PSMs of this plant shows that essential oils of the seeds of *Nigella sativa* L. contain a sufficient amount of steroids, saponins, terpenoids, and tannins (Neamah, 2018), which can be an active source of medicine against viral activities, especially COVID-19 and strains of viruses. Moreover, tannins have already been under observation for their antiviral characteristics. So, the tannins produced by Nigella sativa L. can be helpful to qualify the investigation for a drug against coronaviruses (Wink, 2020). Due to these valuable characteristics, we recommended that *Nigella sativa* L. be investigated again for its pharmacological importance to develop an effective medicinal cure against COVID-19.

4. *Ferula assa-foetida* L. Another essential medicinal plant of Pakistan belongs to the Apiaceae family and is well known for its antibacterial, antifungal, and antiviral activities. It has lipophilic essential oils containing terpenoids and steroids, which can react against viral activity (Salehi, Naghavi *et al*., 2019). *Ferula assa-foetida* L. can be studied for the treatment of COVID-19 due to its fascinating secondary metabolites with a sufficient amount of terpenoids and steroids. These terpenoids and steroids have been investigated against different viral species and showed a very effective response. So, it is recommended that the PSMs of this medicinal plant should also be reinvestigated for their validity against coronaviruses.

Phenolics and polyphenols: PSMs with aromatic rings and one or more hydroxyl groups named phenolics and polyphenols are very valuable in the medical field. These are also known as polyhydroxy phenols because of the presence of large multiples of phenol structural units. Phenols show fascinating chemistry by disassociating their hydroxyl group under physiological conditions and producing negatively charged phenolate ions. Polyphenols are the larger group of phenols that contain multiple phenolic OH groups. Polyphenols contain flavonoids, tannins, and rosemerinic acids (PSMs). The OH group of polyphenols can react with positively charged amino groups of the proteins that create inhibition by destroying the 3-dimensional structure of the protein (Wink, 2015). Due to their unique ligation with proteins, polyphenols are in medicines against microbes and viruses. The study reveals that on incubating polyphenols and viruses together, they showed active inhibitory effects against viruses by intercalating with membranous proteins.

Moreover, polyphenolic contents can intercalate with the virus's protein and DNA/RNA and can cause cell death. Thus many phenols are antiviral and can be used against all viruses (Reichling, 2018). In the light of their antiviral, anti-inflammatory, anti-carcinogenic, and antimicrobial importance, polyphenols from Pakistani medicinal flora can also be a precious source of investigation against viruses (Fatiha *et al*., 2015), especially COVID-19. Many medicinal plants of Pakistan contain many polyphenols that should be investigated for their phytochemical characteristics to produce a suitable preventive and curing drug against the world pandemic of COVID-19.

1. *Mentha species: Mentha* genus belongs to the Lamiaceae family. There is a very complex taxonomy of Mentha species all over the world due to their high hybridization. In Pakistan, the three species of mentha tribe are *Mentha longifolia* (L.) L., *Mentha×piperita* L., and *Mentha spicata* L., which are essential medicinal herbs of Pakistan. Studies reveal that Mentha species contain many secondary metabolites, including rosemarinic acid, menthol, carvone, menthone, polyphenols, and flavonoids. These compounds, especially polyphenols and flavonoids, can be studied against viral activities and can be helpful against different disease-causing viruses, especially corona family (COVID-19) (Abonyi *et al*., 2009; Adem *et al*., 2020; Shah *et al*., 2020) Study revealed that different mentha species used as a home remedy against COVID-19 patients which produced positive healing effects. This evidence discovered that secondary metabolites of Mentha species should be reinvestigated for their phytochemical and pharmacological characteristics against COVID-19 (Wannes & Tounsi, 2020).

2. *Carica papaya (Linn)*: It is a well-known medicinal plant that belongs to the Carecaceae family locally known as Papeeta (Nugroho *et al*., 2017). This plant is traditionally famous to treat asthma, colic, fever, beriberi, malaria cancer, and dengue fever in Pakistan, Srilanka, and Malaysia (Nguyen *et al*., 2016). Many *In*

vitro and *In vivo* experimental studies reveal that PSMs of *Carica papaya* (Linn), especially phenolics and polyphenols and their derivatives, are active in antibacterial, anti-dengue, anti-plasmodia, anti-inflammatory, antifungal, and antioxidant activities (Ahmad *et al*., 2011; Baskaran *et al*., 2012; Julianti *et al*., 2014). As discussed above, phenolics and polyphenols can react with the protein contents present in the outer membrane of the viruses. Due to its highly fascinating profile of phenolic contents, *Carica papaya* (Linn) can be studied against COVID-19 as an antiviral and immunity booster agent. So it is highly recommended that the PSMs of this particular plant be investigated pharmacologically against coronaviruses which can lead to the discovery of potential drugs against this pandemic.

3. *Citrullus colocynthis* (L.) Schrad: is an attractive medicinal plant of Pakistan that belongs to the Cucurbitaceae family, locally known as Korhtumma. It contains a sufficient amount of Polyphenolics, flavonoids, isosapnarin, Isovitexin, and Isorientin, which are best known PSMs for their antiviral activity, antioxidant activity, anti-cancerous activity, and against many heart diseases (Delazar *et al*., 2006). PSMs of this plant have stunning medicinal characteristics, due to which it involves in antiviral activities. This plant extract polyphenols and flavonoids should be studied against the recent breakthrough of COVID-19 because these secondary metabolites react with membrane proteins of the virus and create high resistance against viral growth and attachment. Due to its fascinating intercalation with viral membranous protein, these SMs are highly recommended to investigate against corona species (Gbadamosi, 2020).

4. *Caesalpinia crista* L. belongs to the Caesalpiniaceae family and is known as a vital medicinal plant worldwide. The PSMs of this plant are widely participating in anti-inflammatory, antimalarial, anthelmintic, and antipyretic drugs (Ramesh *et al*., 2010). Studies reveal that *Caesalpinia crista* L., contains a sufficient amount of polyphenolic contents, flavonoids, and other compounds, which shows complete inhibition against bacteria (gram-positive & gram-negative) and viruses (paramyxovirus & orthomyxovirus) (Usha & Sharma, 2012). Moreover, PSMs of this plant also showed antioxidant, cytotoxic, antihelmintic, cardioprotective, antipyretic, and anti-tumor activity (Upadhyay *et al*., 2019). Due to its pharmacological importance, PSMs of this plant should be further studied against COVID-19 (a novel coronavirus) for the preparation of possible drugs.

Alkaloids: Alkaloids are synthesized in plants as their secondary metabolites from amino acid predecessors and are specifically characterized by the versatility of their heterocyclic rings, such as pyrrolidine, piperidine, pyridine, indole, quinoline, isoquinoline, and tropane (Boone *et al*., 2020). Studies reveal that alkaloids are valuable PSMs that can intercalate with viral DNA or RNA and destroy its structure. Tetrandrine is a well-known alkaloid with anti-inflammatory and antiviral activity (HIV, Herpes simplex virus, dengue, and ebolavirus) (Sakurai *et al*., 2015; Bhagya & Chandrashekar, 2016). Another study reveals that alkaloids are very important PSMs that can be used against coronaviruses. This study investigated the antiviral effects of the alkaloids (tetrandrine, fangchinoline, cepharanthine) against human coronaviruses OC43 infected MRC-5 cells (medical research council cell strain 5, human cells cultured from lungs tissues), which resembles SARS and MERS coronaviruses. These compounds showed complete inhibition without any toxicity and dramatically suppressed the replication of coronavirus (Kim *et al*., 2019). This study reveals that alkaloids can be reinvestigated phytochemically and pharmacologically to discover an active drug against COVID- 19 and its strains. Many medicinal plants from Pakistani flora are a potential source of alkaloids in their secondary metabolites, and their PSMs can be investigated for their antiviral characteristics. Some plants from Pakistani medicinal flora which are rich in alkaloids are discussed below:-

1. *Peganum harmala* L. (commonly known as Hermal Booti) is an herbal plant, belongs to the Nitrariaceae family. It is a perennial, glabrous plant that grows spontaneously in the Middle East and a well-known medicinal plant of Pakistani flora that grows in almost all parts of Pakistan. All parts of the plant (root, seed, fruit, and bark) have been used as folk medicine from ancient times to treat respiratory disorders, diabetes, asthma, hypertension, and rheumatism (Zhao *et al*,. 2011; Moloudizargari *et al*,. 2013; Niroumand *et al*,. 2015). The study reveals that *P. harmala* contains a variety of PSMs, including alkaloids, flavonoids, polysaccharides, and anthraquinones (Moradi *et al*., 2017). Literature survey revealed that alkaloids of *P. harmala* have fascinating antiviral (Kiani *et al*., 2007; Asgarpanah & Ramezanloo, 2012), antifungal and antibacterial, characteristics (Nenaah, 2010). Due to its highly dominant PSMs, especially alkaloids, *P. harmala* can be studied as an active drug against COVID-19 because this plant is already used as a medicine against respiratory and inflammatory diseases. It has very valuable PSMs which can intercalate with the viral genome and can destroy its configuration (Mirzaie *et al*,. 2020)

2. **Ephedra species:** Study reveals that ephedra species (*Ephedra intermedia* Schrenk & C.A.Mey., *Ephedra procera* C.A.Mey., *Ephedra foliate* Boiss. ex C.A.Mey.) are important medicinal plants of Pakistan that belong to the Ephedraceae family. These ephedra species are widely used as a medicine against chest problems, cough, and asthma. Phytochemical study of ephedra species revealss the availability of unique alkaloids, which can be further studied against antiviral diseases. People use these species in Pakistan (Baluchistan's province Mastung) for different medicinal purposes. Based on their ethnobotanical importance, PSMs of ephedra species, especially alkaloids (ephedrine), can be further investigated for an active source of drugs against lethal pathogens,

especially COVID-19 (Bibi *et al*., 2014; Sriwijitalai & Wiwanitkit, 2020). In light of the characteristics mentioned above, it is highly recommended that Ephedra species be reinvestigated for their phytochemical characteristics to overcome the drugless virus-based pandemics, especially COVID-19.

3. ***Trachyspermum ammi* L. Sprague.:** It is a well-known plant of Pakistani medicinal flora (common name Ajowain) that belongs to the Apiaceae family, having a bitter and pungent taste. It grows in almost all part of Pakistan and people uses both leaves and seeds as a flavoring agent. Phytochemical studies of *T. ammi* has shown vital PSMs (alkaloids, flavonoids, resins, steroids, tannins), which Recent study reveals that PSMs of T. *ammi* can be used in combating with coronaviruses and should be further studied for its phytochemical and pharmacological characteristics because it has very important alkaloids and flavonoids that can destroy the genomic structure of corona species (Maurya *et al*., 2020). So, it is highly recommended that this plant be again considered for its viral defensive mechanism due to its valuable secondary metabolites.

4. *Capparis decidua* (Forssk.) Edgew. It belongs to the Capparaceae family, a well-known folk medicinal plant of Pakistani flora widely available in Asia, Africa, and Saudi Arabia (local name Kari, Kair, Delha) (Nazar *et al*., 2020). This plant has many attractive pharmacological characteristics such as anti-inflammatory, anti-tumor, antibacterial, analgesic, antifungal, and antioxidant activity. The Kari plant is a folk medicinal plant whose bark, leaves, roots, and fruit are anti-inflammatory agents. Recent studies reveal that this plant contains many important medicinal secondary metabolites, especially a diverse set of alkaloids in its stem, root, bark and fruit. Moreover, it has been reported that PSMs of *C. decidua* also participate in antiviral activities (Rathee *et al*., 2010; Mohammed *et al*., 2012). Studies reveal that the bark and root extracts of *C. decidua* contain alkaloids (carbicine, codonocarpine, isocodonocarpine & capparidisinine) (Forster *et al*., 2016a, 2017b). There is no reported search on *Capparis decidua* (Forssk.) Edgew PSMs for their antiviral activity against COVID-19 whereas, fascinating alkaloids of this plant can be investigated pharmacologically and phytochemically against coronaviruses.

Conclusion and Recommendations

There are many types of plant secondary metabolites that have very effective antimicrobial and antiviral activities. There is a wide variety in PSMs of different plants from Pakistani Flora, which show their reactive behavior against various pathogens differently. The primary reason behind this review article is to recommend medicinal plants from Pakistani flora for their fascinating PSMs, which can be a precious source of the antiviral drug, especially against corona species and COVID-19. Above mentioned plants are well-known medicinal plants of Pakistani flora, and these are participating in antimicrobial, antiviral, antibacterial anti-cancerous, and antifungal activities already. Due to their high potential and fascinating PSMs, medicinal plants from Pakistani flora (mainly discussed species) should be considered for investigation against COVID-19. The discussed species and their PSMs can help scientists and biologists to investigate the right plant against coronaviruses. So, it is highly recommended that above mentioned medicinal plants should be reinvestigated pharmacologically against coronavirus species. This investigation can bring valuable results in the discovery of drugs against the recent pandemic.

In this regard, the clinical trials and research of discussed species should be explored again. These clinical trials can help to discover a potential drug against this deadly virus. There are the evidences that nature has created many pandemics, and their solution is also available in the nature. The only need is to find that solution with struggle and trials. In light of the above, the discussed medicinal plants' secondary metabolites can cope with this situation. The only need is the economic support of the government and researchers to investigate these plants again against COVID-19. This research leads to a potential drug against this deadly virus and will explore new horizons of advancement in Pakistan economically.

In summary, the suggested research on Pakistani medicinal plants can contribute to the development of Pakistan economically and medically. So, the government of Pakistan should support the researchers to reinvestigate the plants mentioned above against the world pandemic of COVID-19. This research will lead to a precise medicine that will indeed contribute to the world's medical field and explore new horizons of the economic development of Pakistan.

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