



# Effects of *Boswellia* species on viral infections with particular attention to SARS-CoV-2

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## Abstract

The emergence of pathogenic viruses is a worldwide frequent cause of diseases and, therefore, the design of treatments for viral infections stands as a significant research topic. Despite many efforts, the production of vaccines is faced with many obstacles and the high rate of viral resistance caused a severe reduction in the efficacy of antiviral drugs. However, the attempt of developing novel natural drugs, as well as the exertion of medicinal plants, may be an applicable solution for the treatment of viral diseases. *Boswellia* species exhibited a wide range of pharmacological activities in various conditions such as bronchial asthma, rheumatism, and Crohn's illness. Additionally, pharmacological studies reported the observance of practical antiviral activities from different parts of this substance, especially the oleo-gum-resin. Therefore, this work provided an overview on the antiviral properties of *Boswellia* species and their potential therapeutic effects in the field of COVID-19 pandemic.

**Keywords** *Boswellia* species · Antiviral effect · SARS-CoV-2 · Natural therapies · Herbal medicine

## Introduction

Viral diseases are one of the most common worldwide health obstacles (Meganck and Baric 2021). Viruses are classified into two species including DNA virus and RNA virus, which are generally consisted of double-strand or single-strand. Single-stranded RNA viruses contain positive-sense-single-stranded RNA or negative-sense-single-stranded RNA (Durmuş and Ülgen 2017; Hughes

and Hughes 2007). Accordingly, human diseases caused by RNA viruses involve SARS, common cold, influenza, and hepatitis C or E, as well as Coronavirus disease (COVID-19) that is induced by the SARS-CoV-2 virus. The treatment of viral infections are typically a difficult challenge mainly due to the virus mutations, drug resistance, side effects, and high cost of antiviral medicines (Cosar et al. 2021; Caligiuri et al. 2016; Behravan et al. 2011). The attention of many scientists was focused on

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bioactive compounds, secondary metabolites, and the phytochemicals of medicinal plants for the design and development of legal drugs against viral diseases, which would lack or at least contain the most negligible rate of side effects (Jansi et al. 2021; Jassim and Naji 2003). As a genus of the Burseraceae family, *Boswellia* species were traditionally exerted for the treatment of numerous diseases such as chronic inflammatory illnesses, arthritis, blood disorders, cardiovascular diseases, diarrhea, ringworm, vaginal discharges, jaundice, fevers, mouth sores, dire throat, bronchitis, asthma, coughing, hair loss, hemorrhoids, syphilitic diseases, diaphoretic, astringent, and diuretic (Rashan et al. 2019; Upaganlawar and Ghule 2009). Different parts of *Boswellia* species such as roots, barks, leaves and oleo-gum-resin, can be used as safe therapeutic agents with potent antioxidant, antimicrobial, anti-inflammatory, anticancer, anticoagulant, antidepressant, and antifungal activities (Prakash et al. 2014; Marefati et al. 2022; Bhushan et al. 2013; Pan et al. 2015; Adake et al. 2013).

Nowadays, a wide range of brand formulations composed of *Boswellia* species, including 5-Loxin<sup>®</sup>, Aflapin<sup>®</sup>, and Sallaki<sup>®</sup>, are exerted for different purposes such as hepatoprotective, antiarthritic, antihyperlipidemic, anti-inflammatory, antiatherosclerotic, and analgesic activities (Sengupta et al. 2010; Knaus and Wagner 1996; Sharma et al. 2016). This review presented a summary on the antiviral effects of *Boswellia* species with a focus on its potent beneficial abilities against COVID-19 for the development of an alternative therapy in near future.

## Search strategy

The relevant articles were retrieved through the application of scientific databases such as “Google Scholar,” “Scopus,” “PubMed,” “Science Direct,” and “Wiley Online Library” using the keywords “*Boswellia*” or “*frankincense*” and “virus” or “viral.” We also gathered information from related local and foreign books.

## Botany and phytochemistry

Bursereae, Canarieae, and Protieae are the three subtribes of Burseraceae family, which include 19 genera, as well as approximately 700 species that are all shrubby and small to medium trees (2–8 m in height). Next to the exfoliated outer bark, the smaller leaves are glabrous with 7–9 tiny toothy leaflets. The flowers are composed of five lobes with disk-shaped internal stamens. The genus *Boswellia* is approximately consisted of 21 species that are native to Africa, southern Arabia, and India (Fig. 1). *Boswellia* species is bisexual with self-pollinate properties and grows in regions with hot and dry climate (Siddiqui 2011; Sultana et al. 2016). The diversity of various active phytochemicals that exist in this genus are caused by variable weather and climate (Rashan et al. 2019; Kadam et al. 2021; Pikhwal and Dhaneshwar 2019). Oleo-gum-resin is exuded from scratching the surface of *Boswellia* tree, which is an aromatic resin with a clear, sweet-smelling, and golden yellow appearance. The prominent producers of Oleo-gum-resin are comprised of four species including *B. carteri*, *B. frereana*, *B. sacra*,



**Fig. 1** The images of some species from *Boswellia*. **A** *B. carteri*, **B** *B. serrata*

and *B. serrata* (Greve et al. 2017; DeCarlo et al. 2018; Johnson et al. 2021). This material is consisted of essential oil, gum, and resin. The essential oil of *Boswellia* species contains various components such as monoterpene, diterpene, sesquiterpene, ether derivatives of alcohol, and ester derivatives that are capable of displaying different activities including antioxidant, acetyl-cholinesterase-inhibition, antimicrobial, anticancer, and antibiofilm effects (Satpathy 2020; Sharma et al. 2007; Gupta et al. 2011; Aldahlawi et al. 2020). Moreover, the gum is composed of different sugars including arabinose, xylose, and galactose (Sharma et al. 2007).

In addition to oleo-gum-resin, the other parts of this plant such as the leaves, roots, and bark can be exerted for the treatment of various diseases and disorders. A study reported the achievement of varying chemical compositions from different extracts of *B. dalzielii* leaves, which included phenolics, flavonoids, tannins, anthocyanins, and sugar. The highest and lowest yields were recorded in the cases of methanol (16.08%) and ethyl acetate (0.03%) extracts, respectively, while the product was 1.12% of the mass of dry leaves in the case of essential oil. Apparently, dissimilar pharmacological impacts were observed from different types of extracts. For instance, the inhibition percentage of cyclohexane extract in IGROV-1 cell lines was 92.60%, whereas the dichloromethane extract caused 65.10% of inhibition in OVCAR-3 cell lines. However, there were no signs of any toxic effects from methanolic extract (Kohoude et al. 2017). *Boswellia* resin is a mixture of more than 200 diverse ingredients such as b-boswellic acid, acetyl-b-boswellic acid, 11-keto-b-boswellic acid, acetyl-11-keto-b-boswellic acid, 3a-hydroxy-urs-9, 12-diene-24-oic acid, 3a-Hydroxy-lup-20(29)-en-24-oic

acid, 3 hydroxyl urs-9, and 11-keto- $\alpha$ -boswellic acid. In addition, this resin is capable of displaying different activities similar to antiinflammatory, antiarthritic, antiulcer, and analgesic effects.

## Safety and toxicity of *Boswellia* species

Certain investigations were performed on the Safety and toxic properties of *Boswellia* species in different animal models. Singh et al. reported the oral administration of *B. serrata* in rat models for 90 days at three different doses, i.e. 100, 500, and 1000 mg/kg body weight (B. wt.) /day. Their results confirmed the safety of *B. serrata* in dosages up to 500 mg/kg B.wt. without the inducement of any side effects (Singh et al. 2012). According to recent studies, different cytogenetic test results approved the ability of boswellic acids in facilitating a high rate of safety in Wistar rats, while lacking any signs of toxicity up to 1000 mg/kg when compared to positive controls (Sharma et al. 2009).

## Antiviral activities

Next to being exerted for vaccine formulations, *Boswellia* species can produce a variety of bioactive constituents with the potential of inhibiting different types of DNA or RNA viruses similar to Influenza, Hepatitis C, Chikungunya, Vesicular stomatitis, Epstein–Barr, Herpes Simplex, Newcastle disease, and Avian Infectious bronchitis viruses (Fig. 2).



Fig. 2 Antiviral activities of *Boswellia* species

## Hepatitis C virus (HCV)

Hepatitis C virus (HCV) is a universal health concern due to standing as the main cause of liver inflammation and injury. The envelopment of this virus implicates positive polarity and single-stranded RNA virus that belongs to the Flaviviridae family (Vega and Barbancho 2020). There are currently no competent vaccines or efficient antiviral medicines available against hepatitis C. However, the exerted combination therapies include pegylated interferon alpha (PegIFN- $\alpha$ ) injections and antiviral nucleoside analogue ribavirin (RBV) that cause many side effects such as hyperglycemia, pancreatitis, hypertension, and peptic ulcer, as well as fever, flu, anemia, and depression (Schaefer et al. 2007). Hussein et al. performed an assessment on the inhibitory impacts of 76 plants, which are commonly used in Sudanese for the treatment of hepatitis C virus (HCV) protease (PR). Apparently, eight samples displayed notable antiviral inhibitory activity including *Acacia nilotica*, *Piper cubeba*, *Embelia schimperi*, *Quercus infectoria*, *Trachyspermum ammi*, *Q. infectoria*, *Syzygium aromaticum*, and *B. carteri*. It is stated that the root of *B. carteri*, which was extracted by Methanol and H<sub>2</sub>O, exhibited great inhibitory properties against HCV ( $\geq 90\%$  inhibition at 100  $\mu\text{g}/\text{mL}$ ) (Table 1) (Hussein et al. 2000).

## Chikungunya virus (CHIKV)

Being the alphavirus of Togaviridae family, Chikungunya virus (CHIKV) is a single-stranded RNA virus with positive polarity that is transferred to humans through mosquito bites (Caglioti et al. 2013). The common symptoms of this infection include headache, fever, rash, joint swelling, muscle pain, fatigue, and nausea. Currently, there are no vaccines or special antiviral drugs available for CHIKV infection, while experts have been trying different approaches to reduce the symptoms (Simon et al. 2011). Von Rhein et al. investigated the antiviral effects of acetyl-11-keto- $\beta$ -boswellic acid or curcumin against CHIKV, which is one of the most important bioactive compounds of *B. serrata* gum resin. Their results confirmed the ability of acetyl-11-keto- $\beta$ -boswellic acid and curcumin in inhibiting the viral infection and proved their efficient blockage against the gene transfer of CHIKV Env or VSV-G-pseudotyped lentiviral vectors into HEK 293T cells (Table 1) (Rhein et al. 2016).

## Herpes simplex virus (HSV)

Herpes simplex virus (HSV) is a member of herpesviridae family that is enveloped with double-stranded DNA and cause infections and diseases in animals and humans (Corey and Spear 1986). Herpes simplex virus (HSV) types 1 and 2 (HSV-1 and HSV-2, respectively) are the two serotypes

of Herpesviridae family. The infection of HSV-1 is mainly oral and involves the lips, gums, or throat. It mostly infects the genital mucosa and stands as a risk factor for sexually transmitted diseases such as HIV infection (Buxbaum et al. 2003). There are some antiviral medicines available for the treatment of HSV infection including acyclovir, famciclovir, penciclovir, and valacyclovir, however, the clinical process is often disturbed by drug resistance (Pasternak and Hviid 2010). The work of Goswami et al. indicated the ability of *B. serrata* oleo-gum-resin, as well as one of its major constituent known as  $\beta$ -boswellic acid, to effectively inhibit Herpes Simplex virus 1 (HSV) infection (effective concentration (EC<sub>50</sub>): 5.2–6.2 and 12.1–14.63  $\mu\text{g}/\text{ml}$ , respectively) through the modulation of NF- $\kappa$ B that is essential for virus replication and p38MAPK pathway. In addition, their observations mentioned the considerable down-regulation of NF- $\kappa$ B, and p38 MAP-kinase activation along with the reduced expression of tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), Interleukin 1 $\beta$  (IL-1 $\beta$ ), and interleukin-6 (IL-6) (that are involved in the scheming process of NF- $\kappa$ B signaling (Goswami et al. 2018). In another study, Mothana et al. evaluated the antiviral activity of 25 different plant species extracts, used in traditional Yemeni medicine, against influenza virus type A and herpes simplex virus type 1. Among their samples, the methanol extract of *B. elongata* was one of the most effective drugs against herpes simplex. In addition, they proved the strong anti-bacterial effects of aqueous and methanol extracts of *B. elongata* as well (Mothana et al. 2006). In another work, Badria et al. investigated the anti-herpes activity of oleo-gum-resin of frankincense (*B. carteri* Bird wood). In comparison to the nine isolated compounds from oleo-gum-resin, their results confirmed the inducement of strongest impact by the total extract against the herpes simplex type I virus (Table 1) (Badria et al. 2016).

## Epstein–Barr virus (EBV)

Epstein–Barr virus (EBV) is an enveloped virus that contains a DNA core with a 184-kbp long member of herpes virus family. This infection frequently occurs in adolescents with the symptoms of inflamed throat, sore throat, enlarged spleen, swollen liver, fatigue, fever, and rash. Generally, EBV spreads through body fluids, blood transfusion, and sexual intercourse. There are no vaccines or any specific treatments available for the treatment of infection (Dunmire et al. 2018; Feng et al. 2004). Akihisa et al. extracted different compounds from the resin of *B. carteri* to study their antiviral activity against Epstein–Barr virus. Some of these compounds caused strong cytotoxic effects with the IC<sub>50</sub> value of 4.1–82.4  $\mu\text{M}$  against human neuroblastoma cells and displayed potent inhibitory impacts on EBV-EA induction. Their work proposed the potential benefits of using the triterpene acid ingredients of methanolic extract of *B. carteri*

**Table 1** Antiviral activities reported from *Boswellia* species

<i>Boswellia</i> species	Virus	Part used	Bioactive compound	Study design(in vitro/in vivo)	Scientific evidence	Ref
<i>B. serrata</i>	Epstein–Barr virus(EBV)	Resin (methanolic extract, n-Hexane, EtOAc, n-BuOH and H <sub>2</sub> O-soluble fraction/ 1, 10, 100 mg/ml	Acetyl b-boswellic acid, Lupeolic acid, Acetyl lupeolic acid, Elemonic acid, 3a-Hydroxytirucalla-7,24-dien-21-oiic acid, 3a-Acetoxytirucalla-7,24-dien-21-oiic acid, 3b-Hydroxytirucalla-8,24-dien-21-oiic acid	IMR-32, NB-39, and SK-N-SH and Raji cells lines	Inhibitory effects on EBV-EA, inhibit chemical carcinogenesis and cytotoxic activity on neuroblastoma cell lines	Akihisa et al. (2006)
	Chikungunya virus	Acetyl-11-keto-b-boswellic acid (AKBA)(1–25 µM)	Acetyl-11-keto-β-boswellic acid (AKBA)	HEK 293T cells, CHIKV-E2/E1 or VSV-G pseudotyped vector	Affect the eicosanoid biosynthetic pathway and anti-inflammatory properties	Rhein et al. (2016)
	Vesicular stomatitis virus (VSV)	Acetyl-11-keto-b-boswellic acid (AKBA)(1–25 µM)	Acetyl-11-keto-β-boswellic acid (AKBA)	HEK 293T cells, CHIKV-E2/E1 or VSV-G pseudotyped vector	Affect the eicosanoid biosynthetic pathway and anti-inflammatory properties	Rhein et al. (2016)
	Herpes simplex virus (HSV)	Methanol extract of <i>B. serrata</i> oleo-gum-resin (BSE) and β-boswellic acid (BA) (0–1000 µg/ml)	β-boswellic acid, 11-Keto-β-boswellic acid, 3-O-Acetyl-11-keto-β-boswellic acid	Vero cells (African green monkey kidney cells), and BALB/c mice	Inhibits HSV-1 through the modulation of NF-κB and p38 MAP kinase	Goswami et al. (2018)
	Avian infectious bronchitis virus (AIBV)	Essential oil (natural oil blend 2.5, 1.25, 0.625, 0.3125, 0.156, 0.08, 0.04, 0.01, 0.005, 0.0025 and 0.00125 ml)	–	Embryonated chicken eggs	Deactivate the AIBV in vitro medium	Keri Lestari et al. (2021)

Table 1 (continued)

<i>Boswellia</i> species	Virus	Part used	Bioactive compound	Study design(in vitro/in vivo)	Scientific evidence	Ref
<i>B. carteri</i>	Herpes simplex virus (HSV)	Oleo-gum-resin (total acid fraction 20 and 40 µg/ml)	Total acid extract (acetyl-11-keto-β-Boswellic acid, β-Boswellic, acetyl-b-Boswellic, 11-keto-β-Boswellic, 3-hydroxytirucallic acid, 3-oxo-tirucallic acid, acetyl-α-boswellic acid)	Vero cells (African green monkey kidney cells)	Reduced the number of plaques virus	Badria et al. (2016)
	Influenza virus	Gum	Largely of polysaccharides	Rat	Making the pH of blood alkaline and preventing viral infection	Ali and Hashim (2020)
	Peste des petits ruminants virus (PPRV)	Gum	Largely of polysaccharides	Goats and sheep	(vaccine delivery) Delayed release time and enhanced immune response	Mumin et al. (2020)
	Newcastle disease virus (NDV)	Gum	largely of polysaccharides	Nigerian local birds	(vaccine delivery) Delayed release time and enhanced immune response	Ola et al. (2021)
	Hepatitis C virus (HCV)	Root (aqueous and methanolic extract)	–	HCV-PR	Inhibitory effects on the HCV-PR activity	Hussein et al. (2000)
<i>B. elongate</i>	Herpes simplex virus (HSV)	Bark (aqueous and methanolic extract/100, 50, 25, 12.5, 6.25, 3.1, 1.5 and 0.7 µg/mL)	Triterpenoids and phytosterols	MDCK (Madin–Darby canine kidney and Vero cells (African green monkey kidney cells)	Anti-HSV-1 activity with 50% inhibition concentrations 0.35 µg/mL	Mothana et al. (2006)
	Influenza virus A	Bark (aqueous and methanolic extract/100, 50, 25, 12.5, 6.25, 3.1, 1.5, and 0.7 µg/mL)	Triterpenoids and phytosterols	MDCK (Madin–Darby canine kidney and Vero cells (African green monkey kidney cells)	Anti-influenza virus type A activity with 50% inhibition concentrations 3.1 µg/mL	Mothana et al. (2006)
<i>B. ameero</i>	Herpes simplex virus (HSV)	Bark (aqueous and methanolic extract /100, 50, 25, 12.5, 6.25, 3.1, 1.5 and 0.7 µg/mL)	Triterpenoids and phytosterols	MDCK (Madin–Darby canine kidney and Vero cells (African green monkey kidney cells)	Anti-HSV-1 activity with 50% inhibition concentrations 1.5 µg/mL	Mothana et al. (2006)
	Influenza virus A	Bark (aqueous and methanolic extract /100, 50, 25, 12.5, 6.25, 3.1, 1.5 and 0.7 µg/mL)	Triterpenoids and phytosterols	MDCK (Madin–Darby canine kidney and Vero cells (African green monkey kidney cells)	Anti-influenza virus type A activity with 50% inhibition concentrations 12.5 µg/ml	Mothana et al. (2006)

Table 1 (continued)

<i>Boswellia</i> species	Virus	Part used	Bioactive compound	Study design(in vitro/in vivo)	Scientific evidence	Ref
<i>B. dalzielii</i>	Newcastle disease virus (NDV)	Stem bark (methanol extract and the three fractions (ethyl acetate, n-butanol and aqueous/ 200, 100, 50, 25, 12.5, 6.25 and 3.125 mg/ml)	Tannins, saponin, flavonoids, terpenoids and steroids	Embryonated chicken eggs	Methanol stem bark extract of <i>B. dalzielii</i> have the most anti-NDV activity than the fractions	Ohemu et al. (2020)
		Stem bark (methanol extract, 250, 200, 150, 100, 50, 25, and 12.5 mg/ml)	Carbohydrates, steroids, triterpenes, cardiac glycosides, tannins and flavonoids and absence of alkaloid	Embryonated chicken egg	Alive of the embryo and complete clearance of the virus from the allantoic fluid	Ohemu et al. (2018)

resin for preventing the inducement of chemical carcinogenesis (Table 1) (Akihisa et al. 2006).

### Influenza virus

Influenza virus belongs to the Orthomyxoviridae family and contains single-stranded and negative-sense RNA. Since ACE2 functions as a receptor for cellular entry in this virus, it seems that its inhibition may be effective in blocking its entrance (Cotter et al. 2001; Chang et al. 2021). In conformity to previous reports, Mothana et al., studied the antiviral effects of different plant extracts used in traditional Yemeni medicine. Their outcomes indicated that the aqueous extracts of *B. ameero*, and *B. elongate* and methanol extract of *B. elongate* caused the strongest impacts against influenza virus A. In addition, they observed a decrease in the nucleic acid synthesis of influenza virus upon their exposure to the extracts of *B. ameero* (Table 1) (Mothana et al. 2006). Another study assessed the outcomes of diet therapy for inhibiting viral infections through the oral and inhalation usage of essential oils, *Saccharomyces cerevisiae*, *B. Carteri*, and Zinc. This treatment was able to prevent influenza infection and increase the number of leukocytes in the blood samples of animals through an appropriate diet. *B. Carteri* is capable of effectively strengthening the immune system, producing the alkaline pH of blood, and preventing viral infections (Table 1) (Ali and Hashim 2020).

### Vesicular stomatitis virus (VSV)

As a member of Rhabdoviridae family, Vesicular stomatitis virus (VSV) is a negative-strand RNA virus that causes infections in humans and animals. Human infections are commonly associated with exposure to infected animals. Insect bites commonly induce VSV infection in animals such as cattle, swine, and horses, which can be diagnosed by the symptoms of foot and mouth disorders (Garbutt et al. 2004; Brown 1987). According to the study of von Rhein et al., VSV vector particles and the viral infections of 293T cells were considerably inhibited by the exertion of *B. serrata* gum-resin extract and curcumin. According to related experiments, the main mechanism of viral inhibition by Acetyl-11-keto-b-boswellic acid implicates the blockage of virus entry into the target cells (Table 1) (Rhein et al. 2016).

### Newcastle disease virus (NDV)

Newcastle disease virus (NDV) belongs to the Paramyxoviridae family that has proved its importance in poultry industry by causing infections in domestic poultry. NDV is a single strand of negative-sense RNA virus that is extremely transmissible and has remained as the main poultry disease (Ganar et al. 2014; Munir et al. 2012).

In the work of Ohemu et al., the stem bark of *B. dalzielii* and *Enantia chlorantha* methanol extracts were used to study their impact on the virus of Newcastle disease (ND) through an *in ovo* assay on embryonated eggs. Preliminary phytochemical screening recorded the presence of carbohydrates, steroids, triterpenes, cardiac glycosides, tannins, and flavonoids in the stem bark extract of *B. dalzielii*. Interestingly, *this product* exhibited remarkable antiviral effects against NDV while the embryos were observed to survive throughout every studied concentration (Ohemu et al. 2018). In another report, Ohemu et al. investigated the impact of using fractions and extracts of *B. dalzielii* on NDV through the application of chicken embryonated eggs. The performance of solvent–solvent fractionation for the methanol extract of *B. dalzielii* required the application of solvents with various polarity, while four fractions were generated that included hexane, ethyl acetate, n-butanol, and aqueous. Tannins, flavonoids, saponin, terpenoids, and steroids were detected in the extract of stem bark and fractions of *B. dalzielii*. In comparison to the results of other fractions, the methanol stem bark extract of *B. dalzielii* displayed a considerably stronger anti-NDV activity (Ohemu et al. 2020).

### Avian infectious bronchitis virus (AIBV)

As a member of Coronaviridae family, Avian infectious bronchitis virus (AIBV) was observed to cause diseases only in chickens, while containing many antigenic types that differ in various regions. As a positive-sense single-stranded RNA virus, AIBV implicates the inducement of nephropathogenic infection and respiratory disorders. In addition, depression, ruffled feathers, wet droppings, greater water intake, and death are included among the other reported symptoms. Although wide vaccination was attempted as a solution to control the prevalence of AIBV, however, this procedure was faced with the challenging obstacle of resistance. So far, science has been incapable of developing any effective drugs or vaccines against this virus due to its highly mutable nature (Ignjatović and Sapats 2000; Bande et al. 2015). Lestari et al. exerted an allantoic fluid medium to investigate the effects of natural oil blend of *B. serrata*, *Gardenia jasminoides*, *Commiphora myrrha*, *Daucus carota*, and *Foeniculum vulgare* on Avian Infectious Bronchitis Virus H120 strain (AIBV H120). To counteract the lethal dosage of virus, various concentrations of natural oil blend (NOB) were inoculated into the allantoic fluid. Although the embryos of positive control group were annihilated, yet they reported the survival of treated samples with natural oil blend and revealed the capability of essential oil Blend in performing the

*in vitro* inhibition of AIBV H120 (Table 1) (Keri Lestari et al. 2021).

### Use *Boswellia* species in vaccine formulations

Natural gums and mucilage can be used in the designs of nasal drug or vaccine delivery due to their mucoadhesive properties. Next to the ability of mucosa in covering the nasal cavity, the applied drug/vaccine can be directly transferred to the systemic blood circulation without facing the hepatic first pass effect and intestinal metabolism. However, oral vaccines can provide certain advantages such as simple usage, low cost, and mucosal immune responses (Smart et al. 1984; Peppas and Sahlin 1996; Emikpe et al. 2016; Yonesi and Kamrani 2019). In addition, natural gums proved to be an appropriate choice for delaying the drug release, which has led to the growing interest in the application of these polymers in sustained drug and vaccine delivery (Bhosale et al. 2014; Manjula et al. 2014; Cox et al. 1999). In this section, a discussion is presented on the role of *Boswellia* gum in the preparation and formulation of various antiviral vaccines.

### Vaccine against Newcastle disease virus (NDV)

As described in Section 5.7., NDV is a significant avian virus with the ability to cause fatal infection in many species of birds. However, the applications of NDV vaccines were effective in reducing the cases of this disease (Sinkovics and Horvath 2000). Ola et al. reported an evaluation on the role of microbeads throughout the vaccine delivery of Newcastle Disease (ND) in chickens. Vaccine-containing beads were produced by the ionotropic-gelation technique that implicates the application of aluminum sulfate, sodium alginate, and *B. carteri* gum. This study involved 60 local birds of 8-weeks-old, which were divided into four groups (15 birds per group). The vaccination was orally administered into the samples as they reached 65 days old. Accordingly, group A was treated with vaccine-loaded bead (VLB), group B received the treatment of vaccine alone (VA), group C was treated with unloaded bead (UB), and group D did not receive any beads or vaccines (NBNV/negative control). The application of microbeaded-vaccine (group A) resulted in increasing the time of vaccine release and prolonged the systemic immune responses of birds (Table 1) (Ola et al. 2021).



## Vaccine against Peste des petits ruminants virus (PPRV)

Peste des petits ruminants virus (PPRV) is a fatal viral disease of domestic and wild small ruminants that can be diagnosed by the common symptoms of fever, pneumonia, cough, diarrhea, respiratory inflammation, ocular discharges, oral necrosis, and digestive tracts (Kumar et al. 2014; Kwiatek et al. 2007). Mumin et al. reported the preparation of gums from *B. frereana*, *B. carteri*, and *Commiphora myrrha*, as well as their investigation results on their mucoadhesive feature and immunomodulatory effects on intranasal vaccination against PPR. This study involved the participation of forty-eight animal samples (24 goats and 24 sheep) that were divided into eight groups (3 goats and 3 sheep in each group). Then, they prepared two ratios (1:1, 1:2) of gum-vaccine combinations and performed nasal vaccination. On the days 14, 28, 42, and 56 post vaccination, the existing antibody against PPRV was measured by the utilization of H-based PPR bELISA. The best inhibition was observed from the case of *B. carteri*-vaccine combination group at a ratio of 1:1, which displayed a similar antibody titer to that of a subcutaneous route. Therefore, this method can be suggested as a safe and noninvasive alternative for PPR vaccination (Table 1) (Mumin et al. 2020).

## SARS-CoV-2

### Overview of SARS-CoV-2

Coronavirus disease (COVID-19) is a novel viral illness generated from the SARS-CoV-2 virus and has caused the death of millions of people worldwide since the start of its pandemic that was around two years ago. Despite the presence of available antiviral drugs, there is a continuous worldwide effort to control and limit this disease (Organization 2020; Rothan and Byrareddy 2020). The major transmission routes of COVID-19 include the composed droplets and aerosol particles upon coughing and speaking, as well as making direct contact with an infected patient. Dry cough, loss of taste or smell, running nose, tiredness, high fever, and body ache are the common symptoms of this illness (Pullen et al. 2020). Coronaviruses (CoVs) are a very diverse family of enveloped positive-sense single-stranded RNA viruses. Alpha-coronavirus, Beta-coronavirus, Gamma-coronavirus, and Delta-coronavirus are the subfamilies of Orthocoronavirinae (Pal et al. 2020). The cytokine storm process of COVID-19 is a crucial factor that begins with the cellular entry of SARS-CoV-2 by cellular ACE2 receptor and proceeds with the provoking of immune response through the production of interferon (IFN), granulocyte-macrophage colony-stimulating factor (GM-CSF) and TNF- $\alpha$ ,

and interleukin-6 (IL-6), as well as the infiltration of macrophages and neutrophils into the lung tissue (Zhou et al. 2020). Other studies reported the observance of a larger amount of IL-2, IL-6, IL-7, IL-10, IP-10, MCP-1, TNF- $\alpha$  in patients with severe COVID-19 infection, while facing the exceeding counts of neutrophil, which is in contrast to that of the mild patients (Hu et al. 2021).

### Evaluating the efficiency of *Boswellia* species against SARS-CoV-2 by molecular docking

Computational methods were broadly exerted for discovering novel drugs throughout the last decade. During the course of SARS-CoV-2 infection, in silico analysis and molecular docking studies were immensely contributed to the topics of drug evolution action and potential inhibitors against this illness. Virtual screening were developed for the wide database of active compounds or known drugs through the performance of docking procedures against SARS-CoV-2. The candidate drugs were able to cause a great inhibitory effect on SARS-CoV-2 and also reduce the burden of in vitro and clinical experiments (Heiat et al. 2021). The in silico study of Kadhim et al. involved an evaluation on the inhibitory effects of boswellic acid and beta-boswellic acid against SARS-CoV-2 virus (Kadhim et al. 2021; Caliebe et al. 2021). Considering how the reproduction of this virus depends on the binding of its spikes to the cell receptors, the docking studies of this survey were conducted using Molecular Graphic Laboratory (MGL) tools and AutoDock Vina application to gather data on the interaction of virus spikes and alpha-Boswellic acid or beta-Boswellic acid, which resulted in indicating the existing of a high affinity among them and also confirmed the safety of using large doses of these compounds in humans due to their LC50 values (Kadhim et al. 2021). In another study, molecular docking and molecular dynamics simulations were used to screen a medicinal plant library for detecting potential compounds against COVID-19. As a result, Qamar et al., introduced nine phytochemical ingredients with potential inhibitory effects on COVID-19 (ul Qamar MT et al. 2020). Furthermore, Heiat et al. reviewed the available articles on various aspects of COVID-19, including the prevention, diagnosis, and treatment areas, while mentioning the studies that used computational methods and computer modeling approaches such as molecular dynamics (MD) simulation technique. Their conclusion emphasized the necessity of applying both traditional and modern sciences for designing combating approaches towards COVID-19 (Heiat et al. 2021). In another study, Roy et al. also evaluated the potential of existing bioactive compounds in *B. serrata* against the Mpro enzyme of SARS-CoV-2 through the application of computational techniques. Five compounds,

including Euphane, Ursane,  $\alpha$ -Amyrin, Phytosterol, and 2,3-Dihydroxyurs-12-en-28-oic, exhibited maximum binding affinities with the binding energies of  $-10.47$  kcal/mol,  $-10.41$  kcal/mol,  $-9.99$  kcal/mol,  $-9.94$  kcal/mol, and  $-9.72$  kcal/mol, respectively (Roy and Menon 2021).

### Anti-inflammatory and anti-bacterial effects of *Boswellia* species

The anti-inflammatory and anti-bacterial properties of *Boswellia* species could be considered as a treatment capacity against the symptoms of SARS-CoV-2. Chib et al. evaluated the anti-inflammatory potential of isolated compounds from *B. ovalifoliolata*. Two compounds (3a-hydroxy-tirucall-8,24-dien-21-oic acid and one type of triterpenoid) were taken from the ethanolic extract of oleo-gum-resin of *B. ovalifoliolata*, which were able to remarkably prevent the TNF- $\alpha$  expression in murine neutrophils and cause a decrease in the production of interleukin IL-6, IL-8, and nitric oxide. Furthermore, there are reports on the inhibition of 5-lipoxygenase enzyme and leukotriene by acetyl-11-keto- $\beta$ -boswellic acid that is a pentacyclic triterpene in the Gum resin extracts of *B. serrata* (Chib et al. 2014). According to other studies, *B. serrata* can enhance the clinical results of ischaemic stroke and conventional therapies due to the anti-inflammatory effect of Boswellic acids. This substance can inhibit certain pro-inflammatory cytokines such as TNF- $\alpha$ , interleukin-1 $\beta$  (IL-1 $\beta$ ), interferon-gamma (IFN- $\gamma$ ), and 5-lipoxygenase (5-LOX), which would lead to the blockage of inflammatory mediators such as leukotrienes. Another study displayed the superior enrichment of Aflapin® by the acetyl-11-keto- $\beta$ -boswellic acid extract of *B. serrata* when compared to that of 5-Loxin®, which is capable of providing a better protection from the induced proteolytic degradation by inflammatory and facilitating the recovery of articular cartilage damage (Sengupta et al. 2010). The antimicrobial activity of resin *B. serrata* was evaluated and compared with Ciprofloxacin in the concentrations of 25, 50, 75, and 100 mg/ml against eight Gram positive and negative bacteria (Ismail et al. 2014).

### Clinical trials of *Boswellia* species

A lot of clinical trials have been performed on *Boswellia* species (Kimmatkar et al. 2003). *Boswellia* extracts displayed some promise for the treatment of rheumatoid arthritis, asthma, knee osteoarthritis, collagenous colitis, and Crohn's disease (Karimifar et al. 2017). Kulkarni et al. presented a report on the clinical trials of herbomineral formulation for rheumatoid arthritis treatment, which included rhizomes of *Curcuma longa*, roots of *Withania somnifera*, the stem of *B. serrata*, and a zinc complex (Kulkarni et al. 1991). Another study showed

that oral supplementation of *B. serrata* extract containing 3-acetyl-11-keto- $\beta$ -boswellic acid and  $\beta$ -boswellic acid remarkably raised physical function by decreasing pain and stiffness compared with placebo. Additionally, radiographic assessment displayed that *B. serrata* extract remarkably increased between the knee joints and decreased osteophytes formation compared with the placebo. More importantly, *B. serrata* extract treatment comprising 30% 3-acetyl-11-keto- $\beta$ -boswellic acid and  $\beta$ -boswellic acid significantly decreased high-sensitive C-reactive protein values compared with the placebo group (Majeed et al. 2019). Barzin Tond et al. examined the effects of Infawell® syrup, a *Boswellia* extract formulation enriched for boswellic acids, (10 ml of Infawell® syrup thrice daily (30 ml/day for 14 days) in patients with moderate COVID-19. Their outcomes indicated the inducement of a reduction in the percentage of neutrophils, neutrophil-to-lymphocyte ratio levels, CRP, LDH, IL-6, and TNF- $\alpha$  levels, while heightening the percentage of lymphocytes and improving the clinical symptoms such as dyspnea, cough, myalgia, headache, and gustatory dysfunction and olfactory (Barzin Tond et al. 2022). In another study, forty female survivors of COVID-19, who were experiencing low energy levels after recovery, were treated by aromatherapy with Longevity™ (twice daily for 14 days) essential oils that were extracted from *Thymus vulgaris*, *Citrus sinensis*, *Eugenia caryophyllus*, and *B. carteri*. In conformity to the results, aromatherapy blend can notably enhance the energy levels of women who were experiencing fatigue after recovering from COVID-19 (Hawkins et al. 2022).

### Conclusion

In this review, we discussed the antiviral actions of *Boswellia* species that may be capable of displaying potential therapeutic activity against COVID-19, considering how different parts of this plant, especially oleo-gum-resin, is exerted in the treatment of several viral diseases. Besides, next to being implicated in the intranasal vaccine of animal viral diseases, gum-resin can increase the time of release. According to common knowledge, *Boswellia* species can display anti-inflammatory, antimicrobial, anti-asthmatic, antioxidant, antifibrotic, and anti-platelet activities, which consequently confirms its stance as a potential candidate for the treatment of COVID-19 symptoms. However, a vast range of clinical studies is required to estimate the accurate potential of antiviral *Boswellia* species to act as a leading approach towards the discovery and design of appropriate drugs.

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## Declarations

**Conflict of interest** The authors declare that they have no conflict of interest.

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