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# A NOVEL COMBINATION THERAPEUTIC APPROACH FOR COVID-19: CAN FRANKINCENSE BOSWELLIC ACID COMPLIMENT ANTIVIRAL THERAPY?

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## ABSTRACT

Healthcare systems are extremely undergoing pressure due to the increasing Covid-19 infection rate. There are several ongoing clinical trials to manage Covid-19, and Pharmaceutical companies claimed that a vaccine would be made available as early as Jan-March, 2021. The lack of an effective treatment and rapidly increasing cases, led many countries to focus on herbal medicines as a potential remedy to fight Covid-19. Natural compounds extracted from different plants have gained attention in the recent years for prevention and treatment for a variety of chronic conditions due to their multi-targeted characteristics. Frankincense gum resin is one among the many traditional natural medicines used in treating cancers, inflammation, respiratory and other chronic diseases. This article reviews the potential effects of Boswellia species gum resin, their extracts, and essential oils against several ailments, with a special focus on the Omani frankincense species B. sacra, which is reported to be anti-cancer, anti-inflammatory, anti- asthmatic, analgesic, immune-modulatory, and antiviral. The manuscript also summaried the reports on the effcts of boswellic acid extracts when taken as a supplement on immune system and potential antiviral properties.

**KEYWORDS:** Covid-19, Boswellic acid, anti-viral, anti-asthma, immunomodulatory, anti-**inflammatory.**

## INTRODUCTION

Antiviral agents are drugs approved by the Food and Drug Administration (FDA) for the treatment or control of viral infections. The current antiviral agents mainly target various stages in the viral life cycle[1], whereas, immune-modulators are substances that stimulate or suppress the immune system and may help the body fight cancer, infection, and other chronic diseases. However, specific immune-modulating agents, such as monoclonal antibodies, cytokines, and vaccines, affect specific parts of the immune system, while the Immune-modulatory drugs modify the response of the immune system by increasing (immunostimulatory) or decreasing (immunosuppressive) the production of serum antibodies.[1]

Coronavirus (CoVs), a family of enveloped positive-sense, single stranded RNA viruses, characterized by club-like spikes that project from their surface, unusually bearing large RNA genome, and unique replication capability. CoVs are known to cause potential lethal human respiratory infectious diseases,

such as severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and the recent pandemic coronavirus disease 2019 (Covid-19).

With the rapid expansion of this dreadful Covid-19 infection, the number of Covid-19 patients and contacts have taken a huge leap globally. Currently, numerous studies on drug development and vaccine production at experimental and clinical levels are being conducted worldwide against CoVs., Unfortunately, neither the drug nor the vaccine has been approved till date which could either prevent or treat this disease caused by the virus. In connection to this, medicinal plants, extracts and pure natural molecules isolated from plants that have been reported to exhibit anti-inflammatory and antiviral activity could be used against SARS-CoVs and other types of coronaviruses.

Phytomedicine has been in practice since ancient times, which relies up on the usage of plant and plant-derived products for medicinal purposes for treating various diseases, prepared in numerous forms, including capsules, tinctures, infusions, macerations, and decoctions. Till date, about 10,000 phytochemicals comprising of tannins, flavones, triterpenoids, steroids, saponins, and alkaloids have been identified and many more are yet to be discovered.[13-20] Natural medicine on the other hand is widely used in traditional Chinese medicine (TCM), Ayurvedic and traditional Arab. According to WHO, nearly 80% of the world's population depend upon phytomedicine for the management of various ailments.[2-11] In a developing nation like India, around 65% of the country's population gets benefited by using phytomedicines that play an essential role in health management system. In developed countries like the USA, the sale of phytomedicine has registered a sharp incline in recent years.[12] For generations, numerous natural compounds extracted from different plants with potential pharmacological properties, are being used to treat various chronic diseases.

Frankincense (also known as olibanum, al-libān in Arabic, an aromatic resin used in incense and perfumes), is obtained from trees of the genus Boswellia, family Burseraceae.[23] Reports indicate that there are about twenty-five different Boswellia species, however, a possibility for redundancy or error in counting can't be ruled out.[17,18] Although, frankincense is being traded in the Arabian Peninsula for more than 6,000 years[24,25], its usage was predominant during the religious rites throughout Mesopotamia and the Eastern Mediterranean from the earliest antiquity. Frankincense was reintroduced to Europe by Frankish Crusaders. However, the Greek historian Herodotus had prior knowledge regarding frankincense and was aware of its harvest from trees in Southern Arabia.[15] Zhao Rugua, a Chinese writer and customs inspector, has written on the origin of frankincense, and about its trade to China during the 13th century.[16] The main representative species grown in Oman is Boswellia sacra Flueck, a tree (Fig.1) belonging to the genus Boswellia Roxb.ex Colebr, family Burseraceae, nurtured in the south western areas of Oman and is widespread in the northeastern limited area of Hasik. It is reported that B. sacra gum resin (Figs.2 & 3) holds more than 30% boswellic acid and lupeolic acids, pentacyclic triterpenic acids (PTA), 10-14% essential oils, along with polysaccharide fraction as well as some polymeric substances to an extent (Tables 1 & 2).[26]

PTA is believed to be the active principle of frankincense boswellic (BAs) and lupeolic (LA) acids and has shown to modulate pathogenic inflammatory pathways and cancer treatment.[27-35] They also are reported to inhibit the gene expression of pro-inflammatory cytokines through interaction with IKB kinases.[33,34] Similarly, they inhibit 5-lipoxygenase (5-LOX) and cytokines and leukotrienes biosynthesis.[30,31] A study found that other BAs such as □-boswellic acids reported to play an important role, targeting the microsomal prostaglandin E2 synthases-1 as well as cathepsin G.[36] Several preclinical and clinical studies have revealed that it also exhibits potential activity in the management of inflammatory diseases such as asthma, arthritis, cerebral edema, chronic bowel diseases, cancer, pain syndrome, etc.[37,38] Badria et al.[39] demonstrated that the total acid mixture of oleo gum resin showed significant activity against Herpes simplex type 1 virus. It reduces the number of plaques by 100% with a minimum concentration of 20 µg/ml whereas, acetyl-11-keto- □-boswellic acid showed 75% inhibition at 20 µg/ml. The total alcoholic extract showed inhibition of 50% at 40µg/ml, acetyl-□-boswellic acids, and 11-keto- □-boswellic acids determined 75% inhibition at 80µg/ml, whereas, 3-hydroxy-triucallic acid, 3-oxo-tirucallic acid, acetyl-α-boswellic acid, and total volatile oil showed 50% at 80 µg/ml. Acid and total volatile oil showed 50% at 80 µg/ml, while, gum, palmitic acid and lupeol reduced the number of plaques only by 25% at the same concentration On the other hand, *B. sacra* essential oils component exhibited potential activity as immune-modulator, antimicrobial, and anticancerous.

When inhaled, the essential oils displayed an immune-modulating effect in TH1/TH2 mediated asthma in mouse model[40] suggesting its potential role for the treatment in allergic airway inflammation.[40] *Boswellia* EO (BEO) of different *Boswellia* spp. including *B. sacra* exhibited significant antimicrobial activity against Gram-positive and Gram-negative bacteria.[41-45] Also, the antifungal activity of various species of *Boswellia* including *B. sacra* showed its effect significantly on various fungal strains such as *Malassezia* spp (*Candida albicans* and *Trichophyton* species.[46,47,48] Besides, al-Harrasi *et al*., reported that shaebi essential oils (EO) possess potential analgesic activity in *in vivo* experiment.[49] BEO obtained from different *Boswellia* spp. has shown to be an effective anti-proliferative agent for breast cancer (MD-AMB-

231) and MCF-cells.[50] Suhail *et al.* demonstrated that *B. sacra* EO suppressed protein kinase B and extracellular signal regulated kinase (ERK1/2) expression in human breast cancer cell lines.[45,50] Michaeli *et al*. reported a strong immune stimulant activity in *B. carterii* EO (90%) and lymphocyte transformation in proliferation assay.[51] Hakkim *et al* demonstrated the anti-melanoma and hepatoprotective activities of *B. sacra* essential oil (FEO) in both *in vitro* and *in vivo* models.[52]

Further, they have also demonstrated that FEO (10 µg/ml) treatment down-regulated MCL1 in a time-dependent manner in human melanoma FM94 cells. *In vivo* toxicity analysis revealed that a weekly single dose of FEO (1200 mg/kg body weight) did not elicit detrimental effect on body weight during the four weeks of experimental period. Additionally, a few preclinical and clinical studies have reported its anti-inflammatory activity in managing inflammatory diseases like asthma, arthritis, cerebral edema, chronic bowel diseases, cancer, pain syndrome, etc.[37,38]

In line with the above-summarized work, based on the pharmacological properties of different components of *Boswellia* species both at preclinical and clinical studies, our group is consistently working on demonstrating its therapeutic benefits as anti-inflammatory and anticancerous agents.

Preliminary *in vitro* antiviral results revealed that BAs showed zero to moderate activity against representatives of ss RNA positive and ss RNA negative (Human Immunodeficiency Virus type- 1, Yellow Fever virus, and human respiratory syncytial virus) viruses. However, our group is further working on the other non-enveloped and enveloped viruses including coronavirus, of α and β strains.

On the other hand, the oral acute toxicity of the *B. sacra* standardized extract when studied in rats, there were no mortality and clinical signs of toxicity observed during the experimental period (14 days). Body weight gain (%), food consumption, and gross pathology were normal. In conclusion, boswellic acid standardized extract is classified under 'Category 5 or unclassified' and the LD50 is >2000 mg/kg. The oral administration with the standardized extract, did not result in any related mortality or show any abnormal clinical signs, in body weight gain, food consumption, detailed clinical examination, neurological observations, hematology, clinical chemistry, bone marrow examination, urine analysis, organ weights and gross pathology in all the test item administered groups when compared to the vehicle control group. In conclusion, the standardized extract did not result in systemic toxicity when administered to rats (Wistar) up to 1000 mg/kg by oral route for a period of 90 days.[36]

The aim of this article is to focus on the pharmaco-therapeutic potential of some of the novel standardized *B. sacra* extract and its possible effect when taken alongside with other pharmaceuticals as a complementary medication which might help in dealing with some of the lethal symptoms triggered as an after effect of Covid-19 and other Coronaviruses contraction, either by reducing the side effects due to the treatment and/or by boosting the immune system.

It is well known that traditional Arab medicine (TAM), traditional Chinese medicine (TCM) and Ayurvedic medicines (AM) have the characteristics of a multi-targeted approach in the treatment of various chronic diseases. Based on the above preclinical and clinical data, we believe that frankincense BA standardized extract might be the right natural substance that fit our proposed hypothesis **(Fig.4)**. However, further studies are warranted that leads to clinical studies according to WHO protocols.

**Chemical Analysis of BAs of *B.sacra* Oleo Gum Resin**

Several non-polar and polar solvents (ethanol, methanol, ethyl acetate, chloroform, acetone, acetonitrile and distilled water) were used for the extraction of boswellic and lupeolic acids at room temperature from both the oleo gum resin and other product residues of Omani *B. sacra*.

Further, the methods used resulted in several BAs and the yield in some of these extracts were over 70% higher when compared with other conventional methods. The color of these extracts varied from off white to white and were obtained in a crystalline form.[53]

For chemical characterization, eight PTA, α -boswellic acid (α -BA), acetyl- α -boswellic acid (α -ABA), β -boswellic acid (β -BA), acetyl- β -boswellic acid (β -ABA),11-keto- β -boswellic acid (KBA), acetyl-11-keto- β -boswellic acid (AKBA), lupeolic acid (LA) and acetyl-lupeolic acid (ALA) were quantified by HPLC-MS-MS analysis.[49,50] In addition, to enable sensitive quantification with limits of detection between 0.4-1.6 ng/mg, detection by Tandom mass spectrometry in multiple reaction monitoring mode (MRM) was followed.[26] The results of this analysis showed that the total percentages of PTA in most of these extracts was more than 30%.

In addition, the oleo gum resins were characterized by a high proportion of acetylated PTA, α-ABA, β -ABA, AKBA, and ALA. Furthermore, a standardized BAs extract was identified and characterized **(Fig) (Fig).** already in the text). The extract components were also characterized using HPLC/MS/MS analysis and showed that it contains "3.22 µg/mg of 11-keto- β -boswellic acid (KBA); 50.40 µg/mg of acetyl-11-keto- β -boswellic acid (AKBA); 8.66 µg/mg of lupeolic acid; 14.85 µg/mg of α-boswellic acid; 40.25 µg/mg of β -boswellic acid; 42.55 µg/mg of acetyl lupeolic acid; 49.9µg/mg of α-acetyl-boswellic acid and 86.20

µg/mg of acetyl –β –boswellic acid. Finally, the total phenolic and total flavonoid content of the standardized extract was found to be 8.9 mg/g in each when analyzed using both HPLC and spectrophotometer.[36]

**Pharmaco-therapeutic Properties of Bas**

**Effect on Asthma**

The anti-inflammatory properties of most of the BAs obtained from *B. sacra* especially the ethanolic and methanolic extracts demonstrated potential anti-inflammatory activity both *in vitro* and *in vivo*.[54] Also, it has shown to be potentially reducing the airway inflammation and hyperresponsiveness with asthma in guinea pigs (Ref needs to be added). In addition, it was tested on the lavage enzymatic activity of eosinophil selective peroxidase (EPO) and neutrophil selective peroxidase (NPO) inhibition. These studies suggest that this extract could be suitable for the treatment and prevention of respiratory related diseases including asthma[54] as several studies have demonstrated and reported the anti-inflammatory activity of the extract. To back this up, another study conducted by Gokaraju *et al*. showed that the extract selectively enriched in 3-O-acetyl-11-keto-β - boswellic acid (AKBA), derived from *B. serrata* non-acidic resin contents prevented and alleviated the inflammation and related diseases including asthma.[55]

Liu *et al*. investigated the effect of boswellic acid from *B.serrata* on airway hyperresponsiveness, inflammatory cell infiltration, T-helper cytokine secretion (Th2), cytokine, and ovalbumin-specific (OVA-specific) IgE production in a mouse model of asthma.[56] Gupta *et al*. conducted a double-blind placebo-controlled study on forty patients, 23 males and 17 females in the age group of 18 - 75 years having a mean duration of illness, bronchial asthma, of 9.58 ± 6.07 years[57], were treated with a preparation of *B. serrata* gum resin of 300 mg thrice a day for 6 weeks.

70% of the subjects showed improvement as evidenced by the disappearance of physical symptoms and signs such as dyspnea, number of attacks, increase in forced expiratory volume (FEV), forced vital capacity (FVC) and peak expiratory flow rate (PEFR) as well as decrease in eosinophilic count and erythrocyte sedimentation rate (ESR). The data showed a definite role of the gum resin of *B. serrata* in the treatment of bronchial asthma.[57] Yugandher *et al*. conducted a 56 days placebo-controlled and randomized double-blind study of a composition containing the extracts of *B.serrata* gum resin and *Aegle marmelos* on 36 patients with mild to moderate asthma. The patients received either 200 mg/day or a similar dosage of placebo and after 14 days, they had significant improvement in the clinical parameters (emotional function, asthma symptoms), when compared with placebo.[58]

**Anti-inflammatory and Analgesic Effect**

The anti-inflammatory and analgesic effects of *B. sacra* gum resin and the standardized BA extract were studied *in vivo* using several murine and human cell lines such as human primary monocytes, human dermal fibroblast, COX-2 in primary rat microglia and raw mouse macrophages. Both showed potential anti-inflammatory activity against many of the cells used in present research especially human cells.[54] The activity of the extract was investigated in rats by the inhibition of ascites and the Freund's adjuvant test. The results clearly showed that the standardized BA extract was potentially active as anti-inflammatory when compared with animals treated with Brufen and the untreated control animals.[54] In addition, two other reports in rats revealed the analgesic activity of both the oleo gum resin and the standardized BA extract.

The activity was tested using the hot plate and writhing induced by chemicals, resulting in a promising analgesic activity, which was almost similar or superior to the activity shown by the standard drug paracetamol.[54]

On the other hand, previously conducted studies indicated the potential anti-inflammatory effects of different *Boswellia* Spp. gum resin and boswellic acid extracts. Also, numerous studies showed that boswellic acids inhibited the gene expression of pro-inflammatory cytokines through interaction with IkB kinases.[59,60] Similarly, they have shown to inhibit 5-LOX and leukotrienes biosynthesis.[61,62] Furthermore, it has been reported that β-BA and KBA could inhibit the human protease cathepsin.[24] Bishnoi *et al*. clarified that boswellic acid is a non-reducing inhibitor of 5-LOX activity and boswellic acid either inhibits by directly reacting with 5-LOX or by blocking its translocation.[63] Boswellic acid lowers the synthesis of 5-LOX related to anti-inflammation, thereby helps in achieving the low production of leukotriene.[36] AKBA was recognized as a straight inhibitor of COX-1, while COX-2 showed very little inhibition and was only inhibited by boswellic acids.[36] Fan *et al.* reported that an acetone extract of gum resin of *B. carterii* decreased arthritic scores, reduced paw edema, and significantly suppressed local tissue TNF-α- and IL-1β in rats.[64] Kimmatkara *et al*. carried out studies involving a group of 30 patients with osteoarthritis of the knee. All patients who received *Boswellia* treatment reported a reduction in knee pain, improved knee flexion, and walking distance along with reduction in the incidence of knee joint inflammation.[65] The study concluded that *Boswellia* resin extract could be recommended in osteoarthritis condition of the knee with possible relaxing use in other arthritis cases. Juarranz *et al.*[66] found an association between bone homeostasis and in-flammation in rheumatoid arthritis related to cytokines like TNF-α, IFN-α-, IL-1β and IL-6, expressed in patients with retinoid acid and in the arthritic joints of rats with collagen-stimulated arthritis,

while both IL-4 and IL- 10 suppressed cartilage and bone pathology in retinoid acid. In this context, the results obtained by Borrelli *et al.*[66] confirmed that, at a dose of 200 mg/kg, *B. serrata* extracts shift the balance of cytokines towards a bone-protecting pattern, by reducing the levels of TNF-α-, IL-1β and IFN-α as well as raise the levels of IL-10.

**Cytotoxic Effect**

Extracts of the oleo gum resin of *B. sacra* exhibited cytotoxicity against the human, treatment-resistant metastatic breast cancer cell line MDA-MB-231. These extracts were most potent with an average $IC_{50}$ of 8.3 0.6 µg/ml when compared with 41 oleo gum resins of the species *B. dalzielli*, *B. papyrifera*, *B. serrata*, *B. carterii*, *B. neglecta*, *B. rivae*, *B. frereana* and *B. occulata*.[26] Further, an anti-proliferative study was carried out in a panel of 10 selected human tumor cell lines using a propidium iodide based monolayer assay. Cell lines used for the study were derived from eight different tumour histocytes, that includes bladder, colorectal, gastric, head and neck, lung, mammary, pancreas and renal cancer.[36] The BAs and essential oils showed variation in their responses ($IC_{50}$ = 0.008-31.31 µg/ml), however, the standardized BA extract showed significant activity against many of the above cell lines.[36]

On the other hand, extracts from different *Boswellia* species gum have reported anti-cancer activities, based on the data obtained from experiments to find out their pro-apoptotic and anti-proliferative activities in rat astrocytoma cell lines[67], human leukemia cell lines[68], including chemically induced mouse skin cancer models.[69] Clinically, gum extract of *B. serrate* decreases the peritumoral edema in glioblastoma patients[67] and reverses several brain metastases in breast cancer patients.[71] Boswellic acids and alcohol soluble ingredients of *Boswellia* species showed an apoptotic and cytostatic effect in multiple cancer cell lines of human like fibrosarcoma, malignance, meningioma, leukemia and colon cancer.[72]. Boswellic acid inhibited numerous signaling fragments such as 5-LOX, COX- 1, leukocyte elastase, and nuclear factor *κB (NF-κB)*.[56] AKBA active components of *B. serrata* resin potentiated apoptosis and suppress angiogenesis in neoplastic cells.[73]

Kirste *et al*. conducted a potential, placebo-controlled, pilot trial to examine the effect of *B. serrata* on forty-four patients with primary or secondary malignant cerebral tumors. Patients randomly treated with radiotherapy and either BS 4200 mg/day or placebo, showed significant reduction in Cerebral edema in 60% of patients and in 26% of patients treated with placebo (P =0.023).[74] Further, Xia *et al.* observed that hydro-distillation of gum resin of *B. sacra* have shown chemo preventive activity against invasive urothelial cell carcinoma.[75] Pasta *et al.* conducted a pilot study in combination with boswellic acid, betaine, and myo-inositol that could treat breast pain, confirm benign breast mass and reduce breast density, which are the crucial threats for the breast cancer development.[76] Berthold *et al.* recognized lupeolic acid in gum resins of *Boswellia* species that was able to inhibit cytosolic phospholipase $A_2\alpha$ responsible for inflammatory response.[78] Buchele *et al*. observed that extract of *B. sacra* repressed the growth of prostate cancer cells of chemotherapy-resistant human PC-3 *in vitro* and provoked apoptosis as shown by activation of caspase 3 and the induction of DNA fragmentation.[77] BA, especially AKBA, β-boswellic acid, and acetyl-β-boswellic acid, have shown to exert marked cytotoxicity on malignant glioma cells even at lower micromolar concentrations, primarily through apoptosis induction, that is independent of free radical formation. A variety of purified triterpenoids from frankincense oleo gum resin have proven pre-clinically to be apoptosis- inducing, antitumor agents, for example in treatment-resistant prostate cancer.[77-82]

**Antiviral Effect**

There are very limited *in vitro* results available on the effect of oleo gum resin, essential oils and BAs extracts against viruses. However, BA from *Boswellia serrata* showed inhibitory effect against Herpes Simplex Virus (HSV-1), by inhibiting the early stage of viral replication.[83] The methanolic extracts of *Boswellia carterii* have been described to inhibit HCV protease activity *in vitro*.[84]

Badria et al in 2003 demonstrated that the total acid mixture of oleo gum resin has the highest activity among all other compounds against Herpes simplex type 1 virus.[39] This mixture has shown to reduce the number of plaques by 100% with a minimum concentration of 20 µg/ml whereas, acetyl-11-keto-β-boswellic acid showed 75% inhibition at 20 µg/ml followed by the total alcoholic extract with 50% inhibition at 40 µg/ml, acetyl- β-boswellic acid and 11-keto-β boswellic acids by 75% showed inhibition at 80 µg/ml, whereas, 3-hydroxy-triucallic acid, 3-oxo-tirucallic acid, acetyl- α-boswellic acid, and total volatile oil showed 50% at 80 µg/ml. Gum, palmitic acid, and lupeol failed to show significant plaque reduction.

Research showed that the pharmacologically active compound of *Boswellia serrata* gum resin extract, acetyl-11-keto-β-boswellic acid (AKBA) inhibits Chikungunya (CHIKV) and vesicular stomatitis (VSV) viral infection.[85] Even though, our preliminary results have shown no significant activity of both oleo gum resin and some BAs against HIV-1, YFV and RSV (Unpublished data), the other extracts or isolated compounds could be explored for its potential antiviral activities against a wide panel of other RNA and DNA viruses including the pandemic Coronavirus.

**Current Treatment of Covid-19**

**Conventional**

Various new chemical entities or drug repurposing are undergoing clinical trials to assess the safety and/ efficacy for potential treatment of Covid-19 infection as an immune-modulator drug, antiviral, convalescent plasma, hyperimmune γ-globulin, and polyclonal antibody products.

Monoclonal antibodies gain more attention and are being developed by several pharma majors and academic investigators. Early-phase clinical trials sponsored by Eli Lilly (Ly-CoV555) and Regeneron (REGN-COV2) have yielded promising results suggesting that monoclonal antibodies may be effective in decreasing viremia and improving clinical outcomes in patients with early COVID-19.[86,87] From drug discovery to rigorous clinical trials, these challenges demand a significant level of commitment and effort from all parties involved including pharmaceutical companies, scientists, clinical trialists, and study volunteers.

**Non-conventional**

The efficacy of some selected natural compounds was investigated recently to characterize their antiviral effects, that may act as a guide for the development of a novel drug that can combat the Covid-19 infection. The effects of *Nigella sativa*, *Anthemis hyaline*, citrussinensis, Myrrh, on the replication of coronavirus and minimizing Covid-19 fatalities and morbidity were studied recently.[86,87] However, amongst the results obtained from these various studies, *Anthemishyalina* extract was found to be the most effective in containing the replication of coronavirus when compared to *Nigella sativa* and *Citrus sinensis* extracts.[86] Furthermore, recent reviews have suggested that the traditional Chinese medicine could be used for the prevention of Covid-19[88] or for the treatment of Covid-19 virus[89], while still acknowledging that many clinical studies are poorly designed or controlled.[90] Similar effects were seen in another study wherein twelve databases were screened through (12 May 2020) Randomized controlled trials (RCTs) and quasi-RCTs assessing the effects of herbal medicines for the treatment of Covid-19 and showed significant effect of the combined therapy of herbal medicine with Western medicine.[91,92] Another study conducted by Ang et al.[91] evaluated the effectiveness and adverse events of herbal medicines for the treatment of Covid-19 and have revealed the potential role of herbal medicine towards treating Covid-19.

*B. sacra* standardized extract is proven to have anti-inflammatory, antiasthma, anticancerous, antiviral properties and an immune-modulator as well. Since the virus affects mainly the respiratory organ causing inflammation of the lungs which further can lead to asthma, pneumonia and other related diseases, this BA standard extract, with the prior mentioned properties, could synergistically work when taken in combination with the other antiviral drug thereby combating the deadly Covid-19 infection by either preventing or treating the issue directly as per our hypothesis. The BA when combined with 5-LOX influences the re-programming of inflammatory enzyme into an anti-inflammatory enzyme. Similarly, when the enzyme 5-LOX was combined with other asthma drugs, or natural products, it was shown to inhibit its function, thus suppressing asthma. However, when taken alone, or in combination, it can act as an immune booster as well. Therefore, BA extract could be a potential candidate for drug discovery and development for an effective treatment of Covid-19 infection.[93-96]

## CONCLUSIONS

Based on the scientific evidences obtained by researchers across the globe, and the results accomplished so far by our team on *Boswellia* spp., focusing on *B. sacra* standardized extract, it appears that-

A. The standardized BA extract is found to be multi-channeled, multi-targeting, agent having multi-compounds that can modulate several molecular targets including kinases, growth factors, enzymes, receptors and others related for the survival of cells by suppressing the function influenced by the virus by counteracting on the enzyme receptors.

B. It is natural, safe and effective and above all, matches most of the criteria mentioned in our hypothesis.

C. Therefore, we can conclude that this standardized extract can be consumed as a supplementary medication for treating covid-19 virus in order to restore and/or ameliorate the immune system of the patient and/or decrease side effects while increasing the antiviral effects of the antivirals and other medications, when used in combination.

**Abbreviations List**

Covid-19 Coronavirus disease
FDA Food and Drug Administration
Covs Coronaviruses
MERS Middle East respiratory syndrome
SARS-Cods Severe acute respiratory syndrome coronavirus
SARS Severe acute respiratory disease
WHO World Health Organization
TCM traditional Chinese medicine
TAM traditional Arab medicine
PTA Pentacyclictriterpenic acids
Bas Beta Boswellic acids
CathepsinA single-chain glycoprotein
I*K*B Inhibitory kappa B kinase
EO Essential oils
TH1/TH2 Type 1 T-helper/ Type 2 helper cells
MD-AMB-231Human treated-resistant-metastatic breast cell line

MCF-cells Breast cancer cell line
ERK1/2 Extracellular signal-regulated kinase
MCL 1 Myeloid cell leukemia
FEO Frankincense essential oils
FM 94 cells Human melanoma cell line
HIV Human immunodeficiency virus
YFV Yellow fever virus
RSV Respirtaory viruses
VERO African green monkey kidney
BHK Baby Hamster Kidney fibroblasts
MT-4 Mock-infected cells
MTT assay 3-(4, 5-Dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide
LD50 Lethal dose, which causes the death of 50% of a group of test animals.
AM- Ayurvedic medicine
HPLC-MS-MS High pressure liquid chromatography with Tandem mass spectroscopy
LA Lupeolic acid
ALA- Acetyl boswellic acid
OVA Ovalbumin-specific
FEV Forced expiratory volume
FVC Forced vital capacity
ESR Erythrocyte sedimentation rate
ABA Acetyl boswellic acid alpha boswellic acid
Alpha ABA Alpha acetyl boswellic acid
Beta-BA Beta boswellic acid
AKB 11-keto-beta boswellic acid
AKBA 3-O-acetyl-11-keto-beta boswellic acid
ALA Acetyl lupeolic acid
Acetylated PTA Acetylated pentacyclictriterpenic acids
MRM Multiple reaction monitoring mode
HPLC High pressure liquid chromatoraphy
EPO Eosinophil selective peroxidase
NPO Neutrophil selective peroxidase
PEER Peak expiratory flow rate
COX2 Cyclogenease 2
5-Lox 5-Lipooxygenase
COX1 Cyclogenease 1
TNF-alpha tumor necrosis factor alpha
1L-1B Interleukin 1 beta
1L-4 Interleukin 4
1L-6 Interleukin 6
1L-10 Interleukin 10
*KB (NF-KB)* Kappa B kinase (kappa-light-chain enhancer of activated B cells
PC-3 Prostate cancer cell line
Ss RNA-ve Negative-strand RNA virus
Ss RNA +ve Positive-strand RNA virus
Vero 76 African green monkey kidney
BHK Baby hamster kidney cell
US-NIH United States National Institute of Health
RCTs Randomized clinical trial

**Declarations**

**Ethics Approval and Consent to Participate**: Not applicable.

**Consent for Publication**: Not applicable.

**Availability of Data and Materials**

This is a review article. All data generated or analysed during this study are included in this published article.

**Competing / Conflict of Interest**

None. The authors declare that there are no conflicts of / or competing interests.

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