Mini-Review

Thuja Occidentalis: an Unexplored Phytomedicine with Therapeutic Applications

Running title: *Thuja Occidentalis* as a Therapeutic Approach

Ankit Srivastava[1], Bimal Prasad Jit[2], Rutumbara Dash[3], Rishi Srivastava[4], Sameer Srivastava[1]

[1]Department of Biotechnology, Motilal Nehru National Institute of Technology, Allahabad-211004, India

[2]Department of Biochemistry, All India Institute of Medical Sciences, New Delhi-110029, India

[3]Departments of Gastroenterology, All India Institute of Medical Sciences, New Delhi-110029, India

[4]Department of Practice of Medicine, L R Shah Homeopathy Medical College, Saurashtra University, Rajkot-361162, India

Abstract

Background: The current outbreak of respiratory disease due to SARS-CoV-2 has received global attention, and recent studies show various limitations, including treatment. Phytomedicine has played a prominent role in the treatment and prevention of various epidemic and pandemic diseases.

Objective: Here, we attempt to focus on a safe and feasible approach for *Thuja occidentalis* to manage and alleviate the panic of respiratory viral infection including COVID-19 by strengthening an individual's immunity. The relevant information was collected from the web-based databases Pubmed, Google Scholar and MEDLINE as well as internet sources.

Conclusion: As an important phytomedicine and king of antipsychotics, *T. occidentalis* possesses a plethora of immunological properties that not only can be used effectively in the management of respiratory viral infection, but also have the potential to prevent the further progression of the disease. Importantly, this is only part of the approach to treatment for the current outbreak that should be considered along with other measures.

Keywords: Phytomedicine, *Thuja occidentalis*, COVID-19, Antiviral, Immunity, Upper respiratory infection, Immunomodulatory

1. A Pandemic that Changed the World: COVID-19

The World Health Organization (WHO) referred this outbreak as a Public Health Emergency of International Concern on 30 January 2020, and later on 11 March 2020 as a pandemic disease. There is very little clinical information on the novel Coronavirus (nCov), which poses a serious threat to public health worldwide [1]. Globally, a total of 205,338,159 confirmed cases have been updated, including 4,333,094 deaths as of August 13, 2021, for a total of 4,428,168,759 vaccine doses [2]. People with comorbidities such as diabetes, hypertension, cancer and respiratory disease are more sensitive to COVID-19 infection [3]. Respiratory infections caused by the "severe acute respiratory syndrome coronavirus-2" (SARS-CoV-2) impair immune homeostasis by altering the immune regulatory network, resulting in decreased responsiveness, alteration in T/B lymphocytes response, and a decreased macrophages function [4]. In a recent review, researchers deciphered that SARS-CoV-2 can alter the chromatin dynamics through the number of changes such as ACE2R methylation, histone mimicry, and also alter the interferon response and replication events to escape the hosts innate immunity [5]. Clinically, the adaptive immune response induced by nCoV occurs in 2 phases: the first is the immune-based defensive phase and the second is the inflammation-driven damage phase [6]. The first immune-based defensive phase is characterized by the recruitment of follicular T-helper cells, activated CD4 and CD8 T-cells, antibody-secreting cells and the binding of IgM and IgG antibodies to the virus is initiated [7]. The second phase leads to an uncontrolled cytokine release syndrome or cytokine storm, which is characterized by increased interleukins IL-6, IL-1β, granulocyte colony-stimulating factor (GM-CSF), interferon-gamma (IFN-γ) and tumor necrosis factor TNF-α (Fig. **1**). The induction of cytokine storms damages the tissues of the lungs, kidneys and heart, which leads to rapid multi-organ failure [8]. Globally, the rapid increase in asymptomatic COVID-19 patients poses a major threat to widespread transmission of the disease through the unwitting spread of the virus. Critical observations indicate that in symptomatic individuals, infection initiated during the maturation phase is identified by activation of CD4+ and CD8+, which has an important impact on the activation of the antibodies to neutralize the SARS-CoV-2 virus and protect the further development of the disease. However, if individuals fail to activate the antiviral immunity in the initial phase, it will certainly impair the adaptive immune responses, which could lead to excessive destruction of groups of cells by inflammation [4]. Therefore, strategies for enhancing and modulating immune activity are identified as useful approaches for reducing disease deterioration and mortality rates. In addition, an appropriate therapeutic approach that can target pre- and post-exposure prevention would be required.

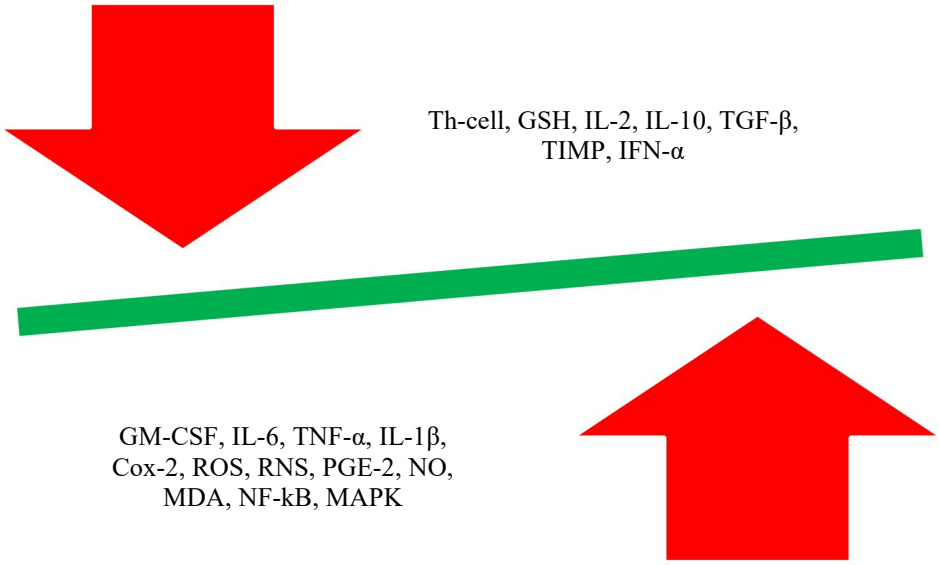

Fig. (1). Immunopharmacological potential of *T. occidentalis*. Immunopharmacological factors, including anti-inflammatory markers, show decreased expression, while pro-inflammatory cytokines, free radicals and signaling cascade stimulating inflammation tend to be higher, indicating the prevalence of viral infection.

2. Literature Survey

The literature survey for the present review was based on results obtained in PubMed, MEDLINE and Google Scholar database searches using the words *Thuja occidentalis* OR phytomedicine OR implication of thuja in respiratory distress OR pharmacological activities of *Thuja occidentalis* in the immune response OR therapeutic role of *Thuja occidentalis* in COVID-19. Selected literature under this review was published only in the English language. In addition, some relevant references from the selected articles have also been collected and included.

3. Strategies Currently Used to Target COVID-19

Many scientists and researchers are trying to find hope in the form of existing drugs or vaccines by repurposing their use to treat COVID-19 [9]. Several repurposed drugs are still in clinical trials, although no drugs or vaccines with clear clinical efficacy have been approved. HCQ (hydroxychloroquine) and chloroquine, which is used to treat malaria, chikungunya and other autoimmune diseases, are an immunomodulatory agent against malaria [10] and have also been studied in clinical practice for the treatment of COVID-19 due to its immunostimulatory effects and antiviral effects [10]. Based on experience from the past epidemics, antiviral drugs such as lopinavir, ritonavir and favipiravir have also been used with little success in COVID-19 [11]. In a report by Xu *et al*, tocilizumab has been shown to help in reducing the mortality rate of this infectious disease with some side-effects with prolonged use [12]. Baricitinib in combination with remdesivir is currently recommended by the Food and Drug Administration (FDA) [13] as an emergency medication, for COVID-19 patients, who require mechanical ventilation support and supplemental oxygen, with potentiating benefits for early treatment and quick recovery compared to remdesivir

alone[14]. In addition, according to Chinese guidelines, a low- to medium-dose corticosteroid can also be used briefly in patients with acute respiratory distress syndrome (ARDS) in COVID-19 treatment [15]. However, their excessive use can lead to complications in other body systems such as the liver and kidney, pregnant women and children under the age of twelve. In addition, their continued use may cause nausea and vomiting with immediate effect, thereby limiting or restricting use. In contrast to pharmacological agents, which are generally used to hinder the patient's symptoms, phytomedicine, as a complementary therapy, is increasingly becoming a method of treating various diseases, including respiratory distress, which is purported to enhance patient's immune response and natural defenses [16]. Hoping to tackle the current COVID-19 pandemic, the choice of phytotherapy could be the promising approach that can make a significant contribution in the current crisis.

4. Phytotherapy: A Holistic Approach

More than fifty vaccines against the novel coronavirus are currently available [17], but only a few of them have passed pre-clinical and clinical trials and are available for immunization worldwide. Considering the severity of the current outbreak, it is a priority to adopt multidimensional preventive measures. We need a combination of modern drugs, integrative medicines and more potent phytomedicine that can make the proper treatment of respiratory distress much easier.

In recent years there has been renewed interest in the phytotherapeutic system, which has been intensely picked up in the research community. The use of medicinal plants and their extracts has always been under constant investigation and is growing in popularity worldwide for several reasons such as safety, low side effects, long-lasting healing properties and a source of bioactive natural compounds with well-documented therapeutic potential. Much of the recent advances are based on clinically validated results and research with a better understanding of how phytomedicine work against chronic diseases such as cancer, diabetes, cardiac and respiratory illness. Medicinal herbs and the presence of specific secondary metabolites have an old track record of treating epidemics and are effective against viral infections such as flu [18]. The past has seen the influenza pandemic of 1918 to 1919 as one of the most severe ones. Around a quarter of the entire world population was infected with around 50 million deaths worldwide. In the US, this epidemic decreased the average lifespan by ten years. Phytomedicine is used extensively for both treatment and prophylaxis. As per reports, the average mortality with standard treatment ranged from 2.5% to 10%, while treatment with phytomedicine and other natural sources only 1% or fewer patients died [19]. Humans have seen different epidemics in succession, including scarlet fever in Europe, typhoid fever, yellow fever, and smallpox in America. Dengue, cholera, ebola, zika and polio have also been outbreaks in recent years and during these outbreaks phytomedicine had proven its effectiveness against the epidemics. Most deaths from flu or flu-like illnesses are due to pneumonia (98%). Pneumonia is the leading cause of child death worldwide. However, as per Saine A, 2020, the mortality rate of traditional medicine compared to pre-antibiotic allopathy (24.3%) and contemporary allopathy (13.7%) was only 3.4% while under the strict Hahnemann's principles even the same was lower at only 0.4% [20]. Similarly, several lines of evidence suggest that phytomedicine has potential prophylactic efficacy not only against flu-like symptoms including SARS-CoV-2, but also as a leading treatment strategy for other infections [21-23].

5. *Thuja occidentalis*: A Potential Phytomedicine Against Viral Infections

In the current pandemic, the Ministry of AYUSH, Government of India has suggested *Arsenicum album* 30 to curb the flu-like coronavirus infection along with WHO guidelines. Some commonly prescribed medicines as preventive measures against flu-like symptoms are *Bryonia alba* [24], *Gelsimium* [25], *Eupatorium perfoliatum* [26], *Arsenicum album* [27], *Influenzium* [28], *Pulsatilla* [29], *Phosphorus* [37], *Belladonna* [30], *Rhus Toxicodendron* [31], *Camphora officinalis* [32], *Thuja occidentalis* and others. Despite a large number of remedies available for respiratory viral infections summarized in (Table **1**), the limitation in treating upper respiratory infections (URI) is still relevant. In order to address the question outlined above, we comprehensively reviewed here that whether immunostimulating and antiviral properties of *T. occidentalis* could ideally be a strategy against acute and chronic respiratory viral infection or not.

Table 1. **Phytomedicine used in ancient epidemic and COVID-19.**

Treatment	Therapeutic activity	Biological function	References
Bryonia alba	Anti-inflammatory, antioxidant, antipyretic and cytotoxic, immunomodulatory and analgesic	Reduce inflammation in the serous tissue during pneumonia. *In-vitro* studies on immune cells reveals increase in leucocyte counts and stimulate the macrophages activity in animals as well as humans.	[24, 33-34]
Gelsimium	Antianxiety, analgesic, anti-inflammatory, cytotoxic, neurotropic and antitumor	In small doses it stimulates respiration in Influenza and Pneumonia	[25]
Eupatorium perfoliatum	Immunostimulatory, antioxidant, immunomodulatory and anti-inflammatory	Polyphenolic content shows antiviral activity by inhibiting the viral attachment to host cell.	[26]
Arsenic album	Anti-inflammatory, cytotoxic	Administration of Ars. Alb-30 results decreased in ROS level, DNA damage and minimize the intoxication.	[27, 35]

Influenzium	Immunostimulatory and immunomodulatory	It shows antiviral activity by inducing the cytokine production such as IFN-β and TNF-α during the Influenza and dry cough	[28]
Pulsatilla	Antiviral, immunostimulatory, anti-inflammatory	Enrich the immune system by enhancing the activity of macrophages. It also increases the SOD activity and prevents the hepatitis B viral infection.	[29, 36]
Phosphorus	Antiviral	Used in flu-like symptoms as prophylaxis and has also been explored in treatment of COVID-19 patients.	[37]
Atropa belladonna	Antiviral and Anti-inflammatory	Prescribed for the people having infection with intense temperature and inflammation of upper respiratory tract. Its potential as antiviral is confirmed by diminishing the Japanese encephalitis virus in chick chorioallantoic membrane.	[30, 38]
Aconitum napellus (Aconite)	Anti-inflammatory, immunostimulatory and antiviral	Enhances the natural immunity in influenza and acute respiratory viral diseases at different dilution level. It is also tested in mice for reducing the fever,	[39]

		inflammation, pain and circadian rhythm etc.	
Justicia Adhatoda	Immunomodulatory, cytotoxic, antioxidant	Increases the IgE level to fight against viruses. Relief cough and respiratory tract infections at higher potency	[40]
Rhus Toxicodendron	Antiviral, anti-inflammatory and immunomodulatory	Used for the treatment of rheumatic pains, influenza, cough etc. Shows the dual effect on inflammatory response by increasing the Cox-2 expression and decreasing the NO generation in MC3T3-e1 cell lines.	[31, 41]
Camphora officinalis	Antiviral, immunomodulatory, and antitussive (cough reliever)	Stimulate the immune response particularly in epidemic influenza.	[32]
Oscillococcinum	Antiviral	It is recommended for the treatment of influenza and influenza like epidemic.	[42]
Baptisia tinctoria	Antiviral, antibacterial	Raise the natural defense system against infection such as common cold, influenza and upper respiratory tract infection.	[43]
Antimonium arsenicosum	Antiviral	Frequently used in the case of pneumonia, emphysema, bronchitis and influenza.	[44]
Eryngium aquaticum	Antiviral, anti-	Found to be useful in	[45]

	inflammatory, antioxidant	epidemic influenza.	
Silicea	Antiviral, antibacterial	Prevent pulmonary fibrosis during fiberogranulation proliferation tissues in the small bronchioles.	[46, 47]
Cassia sophera	Cytotoxic, anti-inflammatory, antioxidant and anticancer	Remove respiratory distress	[48, 49]
Arsenicum iodatum	Antiviral and anti-inflammatory	Prevent pulmonary fibrosis during fiberogranulation proliferation tissues in the small bronchioles.	[46]
Lobelia	Anti-dyspnoetic agent	Respiratory stimulator	[50]
Natrum Muriaticum	Antiviral	Play a vital role in the treatment of fever, cold sores and flu-like epidemic such as Covid-19	[51]
Heper Sulphur	Antiviral, anti-inflammatory and immunostimulatory	Often prescribed for cold, dry cough, infection, emphysema, bronchitis etc.	[52]

ROS, reactive oxygen species; DNA, deoxyribonucleic acid; IFN-β, interferon-beta; TNF-α, tumour necrosis factor-alpha; SOD, superoxide dismutase; IgE, immunoglobulin E; NO, nitric oxide

The pathogenesis of the COVID-19 is characterized by various immunological behaviors. *T. occidentalis* possess diverse pharmacological properties (Fig. **2**) and only the most relevant biological activities listed in (Table **2**), which are intended to increase the natural immunity to URI by increasing the number of T-lymphocytes, B-lymphocytes producing antibodies and production of anti-inflammatory cytokines. It has been observed that *T. occidentalis* plays a prominent role in folk medicine in the treatment of several disorders such as bronchial catarrh, rheumatism, enuresis and uterine carcinoma, etc [53]. Previous studies have shown that aqueous extract of *T. occidentalis* has the ability to proliferate spleen cells, CD4-T cell count, nitric oxide (NO) and cytokine production such as GM-CSF, IL-1, IL-2, IL-3, IL-6 and TNF-α (Fig. **1**) [54]. Earlier studies have also shown that polysaccharides and flavonoid components derived from *T. occidentalis* have potential hepatoprotective, antioxidant, anti-ulcer, hypolipidemic, antiviral, anticancer and immunostimulatory activities (Fig. **2**) [55-56]. Additionally, *T. occidentalis* in combination

with other medicines like *Aconitum napellus*, *Arsenicum album*, *Asafoetida*, *Bryonia alba*, *Calcarea carbonica*, *Lachesis muta*, *Pulsatilla nigricans*, *Ricinus communis*, in various dilutions and formulations, is an important component of homeopathic medicine. This extract possesses the potential ability to activate macrophages, lymphocytes and cytokines in several immune-related disorders, as reviewed by Alves *et al* 2014 [57]. Evidence from the previous work also suggests that *T. occidentalis* has the potential to induce the gut-associated lymphoid tissue GALT and mucosal-associated immune response [58]. The results of Silva *et al* 2017 showed the potential anti-inflammatory effect of polysaccharides from *T. occidentalis*, which induce histamine, serotonin, PGE2 and bradykinin and can reduce vascular permeability and neutrophil migration to the affected site [59]. Furthermore, the polysaccharide fraction can lead to the decreased formation of pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 and significantly reduce the activity of COX-2 and iNOS and thus reduces oxidative stress during acute inflammation. The results of another study also indicated a possible antineoplastic and immunomodulatory activity of *T. occidentalis* [60-61].

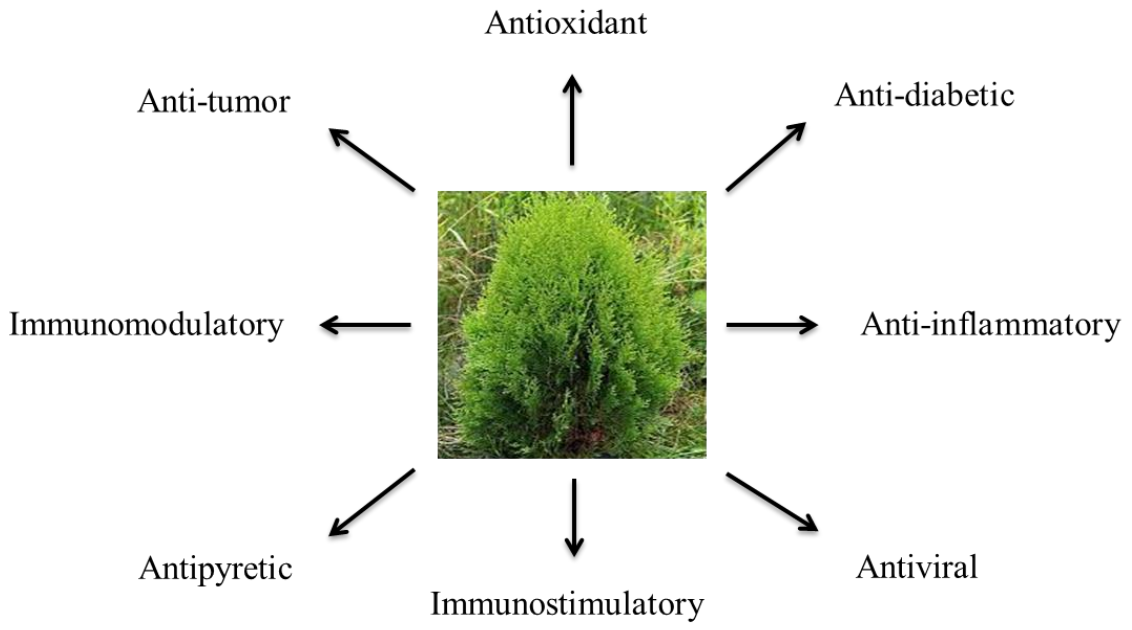

Fig. (2). Pharmacological properties. Phytochemical profiling of *T. occidentalis* possesses diverse pharmacological properties.

The potential anti-viral activity of *T. occidentalis* was previously investigated by several *in vivo* and *in vitro* test models and was published by Alves *et al* 2014 [57]. The results of the clinical study indicated that aqueous ethanolic extract of *T. occidentalis* or its herbal formulation was effective in mitigating the viral URI and common cold [67-68]. *T. occidentalis* consists of several flavonoids such as (+/-) catechin, (-) gallocatechin, mearusitrin, myricetin, procyanidin B-3, prodelphinidin, quercetin, quercitrin, bilobetin and amentoflavone. Among all, amentoflavone was shown to have potent antifungal and antiviral activity, specifically against the Respiratory Syncytial Virus (RSV) [57]. Earlier shreds of evidence showed that *T. occidentalis* derived polysaccharides have potential antiviral activity

against HIV and influenza type A virus (Table **2**) [60]. Furthermore, results from studies on mice have shown that the hydro-alcoholic extract of *T. occidentalis* exhibits potential inhibitory effect against the influenza virus [69]. In addition, the results of the commercial preparation Esberitox®N (Aspen Australia), consisting of *Echinacea purpurea*, *Echinaceae pallida*, *Baptisia tinctoria* and *T. occidentalis,* showed strong antiviral activity against acute and chronic URIs [70-71]. Another study by Zhang *et al* 2014 also argues for the potential antimicrobial and antiviral activity of the thuja genus [72].

Table 2. Therapeutic and biological activities of *T. occidentalis*.

Treatment	Therapeutic activity	Biological function	References
Thuja occidentalis	Immunomodulatory	Circulating antibody titer and Enhanced proliferation of B- and T-lymphoid cells	[61]
	Immunostimulatory	Immunostimulation of lymphocytes, enhanced tumouricidal performance	[62]
	Anti-viral	Presence of *in-vitro* polysaccharides shows antiviral activity against acute common cold and inhibition of HIV-1 as well as Influenza type A	[60, 63]
	Anti-oxidant	Methanolic extract has higher free radicals scavenging activities, results increase in DPPH, NO, GSH and anti-LPO activity.	[64,65]
	Anti-inflammatory	Colitis mice model induced with TNBS results decreased in inflammatory cytokines such as IL-6, TNF-α and COX-2	[66]

HIV-1, human immunodeficiency virus-1; DPPH, 2,2-diphenyl-1-picrylhydrazyl; NO, nitric oxide; GSH, glutathione; LPO, lactoperoxidase; TNBS, 2,4,6-trinitrobenzenesulfonic acid; IL-6, interleukin-6; TNF- α, tumour necrosis factor-alpha; COX-2, Cyclooxygenase.

There is strong evidence available in the present literature advocating the potential use of *T. occidentalis* as an immunostimulatory or immunomodulatory and antiviral effect. However, in some cases, the immunomodulatory potential of *T. occidentalis* alone has been considered less effective and can be improved if it is provided in the complex formulation. In order to increase the effectiveness of *T. occidentalis* in medical practice, it can therefore be proposed to use it as a complex preparation in different stages. This strategy would not only promote the relief of the symptoms of acute and chronic viral infection but it could also improve the body's protective response and quick recovery.

6. Does *T. occidentalis* Help in Ameliorating Symptoms of Respiratory Distress?

T. occidentalis is mainly native to North America and is widely used in homeopathy to treat respiratory diseases such as tonsillitis, cold sores, bronchitis, pneumonia and acute inflammation [57]. The biologically active compounds of this herb have been of research interest for decades, due to the presence of essential oils, coumarins, flavonoids and Thuja Polysaccharides (TPS) which are widely discussed for antiviral drug development. Essential oils contain a chemical called 'thujone' as their main constituent. A recent study showed that TPS can both stimulate T cells and induce the production of IFN-γ. Moreover, it also increases the secretion of TNF-α, IL-1, IL-6 and other cytokines in treated mice compared to control mice [59]. *T. occidentalis* also likely has potential as a treatment for a flu-like respiratory infection such as COVID-19 [73]. *In-vitro* and *in-vivo* investigations have revealed that *T. occidentalis* possesses antiviral effects and immunopharmacological potential mediated through the induction of cytokines, antibody production, macrophages initiation and other immunocompetent cells that can collectively enhance the immune response [60]. Other immunomodulating plants such as *Echinacea purpurea, Echinacea angustifolia*, *Baptisia tinctoria*, *Tinospora cordifolia and Eupatorium perfoliatum* should also be considered in acute and chronic infections of the upper respiratory tract and assessed using evidence-based therapy. In some cases, however, these phytomedicine induce higher levels of cytokine production, which can cause hyper-inflammation. On the other hand, the administration of *T. occidentalis* does not lead to a systemic increase in the cytokine titer, but can cause a local initiation of cytokine-producing cells, so that local contact with the immunostimulatory active components and cells are able to respond to additional stimulation to respond that leads to increased cytokine secretion to boost up the natural immunity and the ability to fight viral infections [69]. In various reports it has been suggested that phytomedicine is ideally recommended for the prevention and treatment of respiratory allergies such as hay fever, asthma, pollinosis, eczema, utricaria, and other allergies [74]. Several studies and meta-analyses have indicated the use of phytomedicine as a choice against certain respiratory illnesses. *Galphimia glauca* is shown to be effective against Hay fever/Rhinitis in different dilutions alone or in complex formulations and has consistently proven to be effective against respiratory distress symptoms [75]. Another group of researchers compared the phytomedicine consisting of *Galphimia glauca, Luffa operculata*, histamine, and sulfur in form of nasal spray with Cromolyn sodium spray as a conventional drug and concluded that both treatments were equally effective in 146

patients with seasonal allergic rhinitis [76]. Similarly, antiasthmatic and anti-anaphylactic effects of *Galphimia glauca* [77], *Blatta orientalis* MT [78], *Thuja occidentalis* [79], and others were evaluated and found an improvement in respiratory allergies which may be due to the suppression of IgE, mast cell stabilization and the reduction in eosinophil count. The efforts of most research groups were concentrated on reducing acute respiratory infection and their complications (pneumonia, pharyngitis, otitis media, acute sinusitis, cough, tonsillitis, etc). This was meticulously investigated in a recent report of Hawke & co-workers in 2018. Based on the outcomes, they documented that phytomedicine including *T. occidentalis* in combination is effective in treating viral URI in children when compared to other methods. Despite the proven success, this study has its own limitations particularly the use of phytomedicine in clinical practice for the treatment of respiratory distress in children [80]. It still appears to be an area of active research and in the light of respiratory distress and associated complication, phytomedicine offers a viable alternative therapeutic solution and possible prevention of recurrent respiratory distress. Although the literature on its specific use in SARS-CoV-2 infection is sparse, the above evidence elucidates that the *T. occidentalis* plant has tremendous potential to mitigate the complications associated with COVID-19 infection. In order to understand the mechanism and its potential application in SARS-CoV-2 infection in detail, diverse clinical studies and more depth studies are required.

7. Summary and Conclusion

COVID-19 is declared a global emergency. Therefore, it is crucial to search for an effective transdisciplinary or interdisciplinary approach to provide the scientific information primarily to design a new drug or utilize the existing drugs to combat COVID-19. Phytomedicine is an effective alternative treatment for various acute and chronic diseases. *T. occidentalis* is one of the well-known phytomedicine, which is an effective immune stimulator, helps to strengthen immunity or re-establish immunity. Moreover, our literature study also suggests it as an antiviral agent and an important medicine in the treatment and prophylactic measures for acute respiratory viral infection and flu-like symptoms such as COVID-19. Since COVID-19 affects the person's immunity, we suggest that *T. occidentalis* could have greater therapeutic efficacy against it, which could be attributed to its modulating activity of the innate immune responses.

8. Future Perspective

There is an urgent need to establish the link between therapeutics and the biological action of phytomedicine with the help of a modern approach. *T. occidentalis* is known to have immunomodulatory, immunostimulatory and antiviral effects, which is well documented through clinical studies. Interestingly, the existing kinds of literature also support the clinical efficacy of *T. occidentalis* in treating viral infection like HIV, HPV, Influenza type A, Herpes simplex virus type 1 and 2 (HSV-1, HSV-2), etc by stimulating the cytokines IFN-γ, G-CSF, IL-1, IL-6 and macrophages. Moreover, *T. occidentalis* also helps in regulating cytokines and prevents the patient from going into severe illness or death by preventing the cytokine storm [73]. Additional studies are required to confer the immunological properties of *T. occidentalis* with further study and experimentation. In recent years there has been renewed interest in researching the uses of phytomedicine, which can help reduce recovery time, improve the clinical cure rate, and prevent disease. One of the important advantages is limiting the transformation of mild to

moderate and moderate to the critical stage. Despite scientific explanations and some caveats, phytomedicine more specifically using *T. occidentalis* should be practiced with modern medicine to help control the current outbreak.

Highlights

1. Despite the number of treatments available for treating respiratory infections, the problem associated with it is still widespread.
2. Phytomedicine is more effective in reducing the severity or eliminating the infections of the upper respiratory tract.
3. *T. occidentalis* has been shown to exhibit significant antiviral, immunostimulatory, and immunomodulatory properties that could help to strengthen immunity and are considered a potent phytomedicine for acute and chronic respiratory viral infections such as COVID-19.
4. Hence, the choice of phytomedicine should be the promising approach that could make a significant contribution during the current crisis.

Abbreviations: COVID-19, coronavirus disease 2019; HCQ, hydroxychloroquine; FDA, Food and Drug Administration; ARDS, acute respiratory distress syndrome; URI, upper respiratory infections; GALT, gut associated lymphoid tissue; RSV, respiratory syncytial virus; TPS, Thuja polysaccharides. IL, interleukin; GSH, Glutathione; TGF, Transforming growth factor; TIMP, Tissue inhibitors of metalloproteinase; IFN, interferon; ROS, reactive oxygen species; RNS, reactive nitrogen species; PGE, Prostaglandin; COX, cyclooxygenase.

Consent for Publication: Not applicable

Source(s) of support: None

Conflicting Interest: The authors declare they have no conflicts of interest.

References

1. Hui, DS.; Azhar, IE.; Madani, TA.; Ntoumi, F.; Kock, R.; Dar, O.; Ippolito, G.; Mchugh, T.D.; Memish, Z.A.; Drosten, C.; Zumla, A. The Continuing 2019-Ncov Epidemic Threat of Novel Corona viruses To Global Health—The Latest 2019 Novel Coronavirus Outbreak In Wuhan, China. *International Journal of Infectious Diseases.,* **2020,** *91*, 264-266.
2. WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data. Available at: http://covid19.who.int. (Accessed August 30, **2021**).
3. Clinical Management Protocol for COVID19. Available at: https://www.mohfw.gov.in/pdf/ dated 27062020.pdf. (Accessed June 27, **2020)**.
4. Shi, Y.; Wang, Y.; Shao, C.; Huang, J.; Gan, J.; Huang, X.; Bucci, E.; Piacentini, M.; Ippolito, G.; Melino, G. COVID-19 infection: the perspectives on immune responses. *Cell Death & Differentiation.,* **2020,** *27*,1451–1454.
5. Jit, BP.; Qazi, S.; Arya, R.; Srivastava, A.; Gupta, N.; Sharma, A. An immune epigenetic insight to COVID-19 infection. *Epigenomics.,* **2021**, *13*(6),465-480.
6. Yan, G.; Lee, CK.; Lam, LT.; Yan, B.; Chua, YX.; Lim, AY.; Phang, K.F.; Kew, G.S.; Teng, H.; Ngai, C.H.; Lin, L. Covert COVID-19 and false-positive dengue serology in Singapore. *Lancet Infect Dis.,* **2020,** *1473-3099*(20), 30158-4.
7. Guo, XJ.; Thomas, PG. New fronts emerge in the influenza cytokine storm. *Semin Immunopathol.,* **2017,** *39*(5), 541-550.
8. Mehta, P.; McAuley, DF.; Brown, M.; Sanchez, E.; Tattersall, RS.; Manson, JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet.,* **2020,** *395*, 1033-1034.
9. Bharadwaj, KK.; Srivastava, A.; Panda, MK.; Singh, YD.; Maharana, R.; Mandal, K.; Singh, B.M.; Singh, D.; Das, M.; Murmu, D.; and Kabi, S.K. **Computational intelligence in vaccine design against COVID-19** K. Raza (Ed.), Computational Intelligence Methods in COVID-19: Surveillance, Prevention, Prediction and Diagnosis. Studies in Computational Intelligence, Springer, Singapore , **2021;** Vol *923*, pp. 311-329.
10. Ben-Zvi, I.; Kivity, S.; Langevitz, P.; Shoenfeld, Y. Hydroxychloroquine: From Malaria to Autoimmunity. *Clin. Rev Allergy Immunol*., **2012,** *42*(2), 145-153.
11. Zhang, L.; Liu, Y. Potential interventions for novel coronavirus in China: A systematic review. *J Med Virol*., **2020,** *92*, 479-490.
12. Xu, X.; Han, M.; Li, T.; Sun, W.; Wang, D.; Fu, B.; Zhou, Y.; Zheng, X.; Yang, Y.; Li, X.; Zhang, X. Effective treatment of severe COVID-19 patients with tocilizumab., *Proc Natl Acad Sci* USA., **2020,** *117*(20),10970-10975.
13. Mechineni, A.; Kassab, H.; Manickam, R. Remdesivir for treatment of COVID 19; review of the pharmacological properties, safety and clinical effectiveness. *Expert Opinion on Drug Safety.,* **2021,** DOI: 10.1080/14740338.2021.1962284

14. Langarizadeh, M.A.; Ranjbar, Tavakoli. M.; Abiri, A.; Ghasempour, A.; Rezaei, M.; Ameri, A. A review on function and side effects of systemic corticosteroids used in high-grade COVID-19 to prevent cytokine storms. *Excli J.,* **2021,** *15*(20), 339-365.
15. Russell, CD.; Millar, J.E,; Baillie, J.K. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet*., **2020,** *395*, 473-475.
16. Ullman, D.; Frass, M. A review of homeopathic research in the treatment of respiratory allergies. *Altern Med Rev.,* **2010,** *15*(1), 48-58.
17. Shah, SB.; Hariharan, U.; Chawla, R. Common anti-COVID-19 drugs and their anticipated interaction with anesthetic agents. *J Anaesthesiol Clin Pharmacol.,* **2021,** *37*(2),160-170.
18. Hasselaar, G.; Nijnatten, Wv.; Golden, I. A Pilot Study into the Comparative Effectiveness and Safety in the Elderly of a Homeopathic Flu Prophylaxis and the Regular Flu Vaccination in the Netherlands. *Homœopathic Links.,* **2016,** *29*(02), 120-126.
19. Winston, J. Treatment of Epidemics with Homeopathy - A History | National Center for Homeopathy. Available at: https://www.homeopathycenter.org/treatment epidemics-homeopathy-history. (Accessed February 17, **2020**).
20. Saine A. "Case Management of the Influenza and Pneumonia Patient with Homeopathy During the COVID-19 Pandemic". AIH Webinar, [Online] Available at: http://www.homeopathyusa.org; Accessed April 4, 2020
21. Robert, MT.; Elizabeth, BS.; Frye, J.; Chaturbhuja, N.; Rajkumar, M.; Peter, F. Homeopathic treatment of patients with influenza- like illness during the 2009 A/H1N1 influenza pandemic in India. *Homeopathy.,* **2013,***102*,187- 192.
22. Saeed- ul- Hassan, S.; Tariq, I.; Khalid, A.; Karim, S. Comparative clinical study on the effectiveness of homeopathic combination remedy with standard maintenance therapy for dengue fever. *Trop J Pharm Res.,* **2013,***12*, 767- 770.
23. Chaudhary, A.; Khurana, A. A review on the role of homoeopathy in epidemics with some reflections on COVID-19 (SARS-CoV-2). *Indian Journal of Research in Homoeopathy.,* **2020,** *14*(2), 100-109.
24. Manvi, M.; Prasad, G. Evaluation of pharmacognostical parameters and hepatoprotective activity in *Bryonia alba* Linn, *J. Chem. Pharm. Res.,* 2011, *3*(6), 99-109.
25. Raymond, H. Gelsemicine. Competes Rendus des Seancer de la Societe de Biologie et de ses Filiales., **1937,***126*,1151–4.
26. Derksen, A.; Kühn, J.; Hafezi, W.; Sendker, J.; Ehrhardt, C.; Ludwig, S.; Hensel, A. Antiviral activity of hydroalcoholic extract from Eupatorium perfoliatum L. against the attachment of influenza A virus. *J Ethnopharmacol.,* **2016,** *21*(188),144-152.
27. Kundu, SN.; Mitra, K.; Bukhsh, ARK. Efficacy of a potentized homeopathic drug (Arsenicum-Album-30) in reducing cytotoxic effects produced by arsenic trioxide in mice: IV. Pathological changes, protein profiles, and content of DNA and RNA. *Complementary Therapies in Medicine.,* **2000,** *8*, 157–165.

28. Siqueira, CM.; Costa, B.; Amorim, AM.; Gonçalves, M.; da, Veiga.; V.F.; Castelo-Branco, M.; Takyia, C.; Zancan, P.; Câmara, F.P.; Couceiro, J.N.; Holandino, C. H3N2 homeopathic influenza virus solution modifies cellular and biochemical aspects of MDCK and J774G8 cell lines. ***Homeopathy.,*** **2013,** *102*(1), 31–40.
29. Dai, L.; Wang, H.; Chen, Y. The immune-enhancing effect of PcG A – a glycoprotein isolated from dried root of Pulsatilla chinensis (Bunge) Regel. *Zhongguo Sheng hua Yuan Zazhi.,* **2000,** *21*, 230-31.
30. Dudgeon R.E. Hahnemann‟s discovery of the prophylactic powers of belladonna in scarlet fever allopathic testimony to this prophylactic. In: Dudgeon RE, editor. Lectures on the Theory & Practice of Homoeopathy. New Delhi: B Jain Publishers., **2002,** 540-544.
31. Saha, S.; Jana, B.; Basu, T. The two inducible responses, SOS and heatshock, in Escherichia coli act synergistically during Weigle reactivation of the bacteriophage ΦX174. *Int J Radiat Biol.,* **2007,** *83*,463-469.
32. Shuang, L.; Tancheng, D.; Peige, S.; Yufeng, L.; Lin, L.; Yiguo. "Synthesis of vitcamphor derivatives of camphor and its preliminary anti-inflammatory activity," *Proceedings 2011 International Conference on Human Health and Biomedical Engineering,* Jilin, China., **2011,** 88-91.
33. De, Oliveira. CC.; de, Oliveira, SM.; Godoy, LM.; Gabardo, J.; Buchi, Dde. F. Canova, a Brazilian medical formulation, alters oxidative metabolism of mice macrophages. *J Infect.,* **2006,** *52*(6),420-432.
34. Danno, K.; Colas, A.; Masson, JL.; Bordet, MF. Homeopathic treatment of migraine in children: results of a prospective, multicenter, observational study. *J Altern Complement Med*., **2013,** *19*(2),119-123.
35. Das, D.; De, A.; Dutta, S.; Biswas, R.; Boujedaini, N.; Khuda-Bukhsh, AR. Potentized homeopathic drug Arsenicum Album 30C positively modulates protein biomarkers and gene expressions in Saccharomyces cerevisae exposed to arsenate. *Zhong Xi Yi Jie He Xue Bao.,* **2011,** *9*(7),752-760.
36. Yao, D.; Vlessidis, AG.; Gou, Y.; Zhou, X.; Zhou, Y.; Evmirdis, NP. Chemiluminescence detection of superoxide anion release and superoxide dismutase activity: modulation effect of Pulsatilla chinensis. *Anal Bioanal Chem.,* **2004,** *379* (1), 171- 77.
37. Society of Homeopaths: Coronavirus COVID- 19. Available at: https://homeopathy-soh.org/coronavirus-covid-19. (Accessed April 15, **2020**).
38. Bandyopadhyay, B.; Das, S.; Sengupta, M.; Saha, C.; Das, KC.; Sarkar, D.; Nayak, C. Decreased intensity of Japanese encephalitis virus infection in chick chorioallantoic membrane under influence of ultradiluted Belladonna extract. *Indian J Res Homoeopathy.,* 2010, *6*(2), 24-28.
39. Pena, De. La. SS.; Sothern, RB.; López, FS.; Lujambio, IM.; Waizel-Bucay, J.; Sánchez, CO.; Monroy, C.P. Betancourt, E.T. Circadian aspects of hyperthermia in mice induced by *Aconitum napellus*. *Pharmacogn Mag.,* **2011,***7*(27),234-242.
40. Khan, I.; Ahmad, B, Azam S, Hassan F, Nazish, Aziz A, Rehman N, Ullah F, Liaqat Z. Pharmacological activities of *Justicia adhatoda*. *Pak J Pharm Sci.,* **2018**, *31*(2),371-377.

41. Lee, K.J.; Yeo, M.G. Homeopathic *Rhus toxicodendron* has dual effects on the inflammatory response in the mouse preosteoblastic cell line MC3T3-e1. *Homeopathy.,* **2016**, *105*(1),42-47.
42. Vickers, A.J.; Smith, C. Homoeopathic Oscillococcinum for preventing and treating influenza and influenza-like syndromes. In: Cochrane Database Syst Rev:(2): John Wiley & Sons, Ltd. Available at: https://www.cochranelibrary.com/ cdsr/doi/10.1002/14651858.CD001957.pub6/full. (Accessed Jan 28, **2015)**.
43. Banerji, P.; Banerji, P.; Das, G.C.; Islam, A.; Mishra, S.K.; Mukhopadhyay, S. Efficacy of *Baptisia tinctoria* in the treatment of typhoid: its possible role in inducing antibody formation. *J Complement Integr Med.,* **2012**; *9*(1).
44. Free materia medica books. Available at: https://www.materiamedica.info/en/materia-medica/william-boericke/antimonium-arsenicosum.
45. Ping, W.; Su, Z.; Yuan, W.; Deng, G.; Li, Shiyou. Phytochemical Constituents and Pharmacological Activities of Eryngium L. (Apiaceae). *Pharmaceutical Crops.,* **2012**, *3*, 99-120.
46. Vermeulen, F.E. Concordant Materia Medica: Allen, Boericke, Boger, Cowperthwaite, Clarke, Hering, Kent, Lippe, Phatak, Pulford, Vermeulen: Hering Included, Emryss bv. **1997**.
47. Chand, S.K.; Manchanda, R.K.; Batra, S.; Mittal, R. Homeopathy in the treatment of tubercular lymphadenitis (TBLN)- - an Indian experience. *Homeopathy.,* **2011**;*100*:157- 67
48. Nagore, D.H.; Ghosh, V.K.; Patil, M.J. Evaluation of antiasthmatic activity of *Cassia sophera Linn*. *Pharmacognosy magazine.,* **2009**,*5*(19), 109-118
49. Yadav, J.P.; Arya, V.; Yadav, S.; Panghal, M.; Kumar, S.; Dhankhar, S. *Cassia occidentalis L*: A review on its ethnobotany, phytochemical and pharmacological profile. *Fitoterapia.,* **2010**,*81*(4),223-230.
50. Joseph, Ep. Bronchitis and pneumonia. The Clinician's Handbook of Natural Medicine. 3rd ed.: Churchill Livingstone **2016**.
51. Dasgupta, A. Indian Authorities Propose Use of Homeopathy to Prevent Coronavirus. The Scientist. Available at: https://www.the-scientist.com/news-opinion/indian-authorities-propose-use-of-homeopathy-to-prevent-coronavirus-67075. (Accessed july 21, **2020).**
52. Demarque, D.; Jouanny, J.; Poitevin, B.; Saint-Jean, Y. Pharmacology and Homeopathic Materia Medica. 3rd ed. Sainte-Foy-lès-Lyon: CEDH; **2007**.
53. Offergeld, R.; Reinecker, C.; Gumz, E.; Schrum, S.; Treiber, R.; Neth, R.D.; Gohla, S.H. Mitogenic activity of high molecular polysaccharide fractions isolates the cuppressaceae Thuja occidentalis L. enhanced cytokine-production thyapolysaccharide, g-fraction (TPSg). *Leukemia.,* **1992**,*6*,189–191.
54. Hassan, H.T.; Drize, N.J.; Sadovinkova, E.Y.; Gan, O.I.; Gohla, S.; Schrum, S.; Neth, R.D. TPSg, an anti-human immunodeficiency virus (HIV-1) agent, isolated from the Cupressaceae *Thuja occidentale L*. (Arborvitae) enhances in vivo hemopoietic progenitor cells recovery in sublethally irradiated mice. *Immunol Lett.,* **1996,***50*,119–122.

55. Ojeswi, B.K.; Khoobchandani, M.; Hazra, D.K.; Srivastava, M.M. Protective effect of *Thuja occidentalis* against DMBA-induced breast cancer with reference to oxidative stress. *Human and Experimental Toxicology.,* **2010**, *29* (5), 369-375.
56. Madhuri, S.; Pandey, G. Some anticancer medicinal plants of foreign origin. *Current Science.,* **2009**, *96* (6), 779-783.
57. Alves, L.D.; Figueirêdo, C.B.; Silva, C.C.; Marques GS, Ferreira PA, Soares MF, Silva RM, Rolim-Neto PJ. *Thuja occidentalis* L.(Cupressaceae): Review of botanical, phytochemical, pharmacological and toxicological aspects. *Int J Pharm Sci Res.,* **2014**, *5*(4),1163.
58. Bodinet, C.; Lindequist, U.; Teuscher, E.; Freudenstein, J. Effect of an orally applied herbal immunomodulator on cytokine induction and antibody response in normal and immunosuppressed mice. *Phytomedicine.,* **2002a**, *9*, 606–613.
59. Silva, I.S.; Nicolau, L.A.D.; Sousa, F.B.M.; de Araújo, S,; Oliveira, A.P.; Araújo, T.S.L., Souza, L.K.M.; Martins, C.S.; Aquino, P.E.A.; Carvalho, L.L.; Silva, R.O. Evaluation of anti-inflammatory potential of aqueous extract and polysaccharide fraction of *Thuja occidentalis Linn*. in mice. *Int J Biol Macromol.,* **2017**, *105*, 1105–1116.
60. Naser, B.; Bodinet, C.; Tegtmeier, M.; Lindequist, U: *Thuja occidentalis* (Arbor vitae): A Review of its pharmaceutical, pharmacological and clinical properties. *Evidence-based complementary and alternative medicine.,* **2005**, *2*(1), 69-78.
61. Remya, V.; Kuttan, G. Homeopathic remedies with antineoplastic properties have immunomodulatory effects in experimental animals. *Homeopathy.,* **2015**,*104*, 211- 219.
62. Guimarães, F.S.; Abud, A.P.; Oliveira, S.M.; Oliveira, C.C.; César, B.; Andrade, L.F.; Donatti, L.; Gabardo, J.; Trindade, E.S; Buchi, D.F. Stimulation of lymphocyte anti-melanoma activity by co-cultured macrophages activated by complex homeopathic medication. *BMC Cancer.,* **2009**,*9*,293.
63. Gohla, S.H.; Zeman, R.A.; Bögel, M.; Jurkiewicz, E.; Schrum, S.; Haubeck, H.D.; Schmitz, H.; Hunsmann, G.; Neth, R.D. Modification of the in vitro replication of the Human Immunodeficiency Virus HIV-1 by TPSg, a Polysaccaride Fraction Isolated from the Cupressaceae *Thuja occidentalis* L. (Arborvitae). *Haematol Blood Transfus.,* **1992**, *35*, 140–149.
64. Bellili, S.; Aouadhi, C,; Dhifi, W.; Ghazghazi, H.; Jlassi, C,; Sadaka, C.; Beyrouthy, M.E.; Maaroufi, A.; Cherif, A.; Mnif, W. The influence of organs on biochemical properties of tunisian *Thuja occidentalis* essential oils. *Symmetry.,* **2018**, *10*, 649.
65. Nazir, M.Z.; Chandel, S.; Sehgal, A. In vitro screening of antioxidant potential of *Thuja occidentalis*. *J Chem. Pharm Sci.,* **2016**, *8*, 283–286.
66. Stan, MS.; Voicu, SN.; Caruntu, S.; Nica, I.C.; Olah, N.K.; Burtescu, R.; Balta, C.; Rosu, M.; Herman, H.; Hermenean, A.; Dinischiotu, A. Antioxidant and anti-inflammatory properties of a Thuja occidentalis mother tincture for the treatment of ulcerative colitis. *Antioxidants.,* **2019**, *8*: 416.
67. Vorberg, G. Bei Erkältung unspezifische Immunabwehr stimulieren. *Ärztl Prax.,* **1984**, *36*,97–8.

68. Wüstenberg, P.; Henneicke-von Zepelin, H.H.; Köhler ,G.; Stammwitz, U. Efficacy and mode of action of an immunomodulator herbal preparation containing echinacea, wild indigo and white cedar. *Adv Ther.,* **1999**,*16*,51–70.
69. Bodinet, C.; Mentel, R.; Wegner, U.; Lindequist, U.; Teuscher, E.; Freudenstein, J. Effect of oral application of an immunomodulating plant extract on Influenza virus type A infection in mice. *Planta Med.,* **2002b**, *68*(10), 896-900.
70. Zimmer, M. Specific conservative treatment of acute sinusitis in the ENT practice. *Therapiewoche.,* **1985**, *35*, 4024-4028.
71. Hauke, W.; Köhler, G.; Henneicke-Von Zepelin, H.H.; Freudenstein, J. Esberitox®N as supportive therapy when providing standard antibiotic treatment in subjects with a severe bacterial infection (acute exacerbation of chronic bronchitis). *Chemotherapy.,* **2002**, *48*, 259–266.
72. Zhang, X.W.; Choe, Y.H.; Park, Y.J.; Kim, B.S. Effect of Korean arbor vitae (Thuja koraiensis) extract on antimicrobial and antiviral activity. *African Journal of Pharmacy and Pharmacology.,* **2014**; *8*(10), 274-277.
73. Sytar, O.; Brestic, M.; Hajihashemi, S.; Skalicky, M.; Kubeš, J.; Lamilla-Tamayo, L,; Ibrahimova, U,; Ibadullayeva, S,; Landi, M. COVID-19 prophylaxis efforts based on natural antiviral plant extracts and their compounds. *Molecules.,* **2021**,*26*(3),727.
74. Kleijnen, J.; Knipschild, P.; ter Riet, G. Clinical trials of homoeopathy. *BMJ.,* **1991**,*302*,316-323.
75. Wiesenauer, M.; Haussler, S.; Gaus, W. Pollinosis therapy with Galphimia glauca. *Fortschr Med.,* **1983**,*101*,811-814.
76. Weiser, M.; Gegenheimer, L.H.; Klein, P. A randomized equivalence trial comparing the efficacy and safety of Lu$a comp.-Heel nasal spray with Cromolyn sodium spray in the treatment of seasonal allergic rhinitis. *Forsch Komplementarmed.,* **1999**,*6*,142-148
77. Lewith, GT.; Watkins, AD.; Hyland, ME.; Shaw, S.; Broomfield, JA.; Dolan, G.; Holgate, S.T. Use of ultramolecular potencies of allergen to treat asthmatic people allergic to house dust mite: double blind randomised controlled clinical trial. *BMJ* ., **2002**,324,520.
78. Chandrakant, NC.; Dattatray, PS.; Dinesh, KB. Anti-asthmatic and anti-anaphylactic activities of *Blatta orientalis* mother tincture. *Homeopathy.,* **2011**,*100*,138-43
79. Henneicke-Von Zepelin, H.; Hentschel, C.; Schnitker, J.K.; Kohnen, R.; Köhler, G .; Wüstenberg, P. Efficacy and safety of a fixed combination phytomedicine in the treatment of the common cold (acute viral respiratory tract infection): results of a randomised, double blind, placebo controlled, multicentre study. *Current Medical Research and Opinion.,* **1999**, *15*, 214–227
80. Hawke, K.; van Driel, ML.; Buffington, B.J.; McGuire, TM.; King, D. Homeopathic medicinal products for preventing and treating acute respiratory tract infections in children. Cochrane Database of Systematic Reviews 2018, Issue 4. Art. No.: CD005974. DOI: 10.1002/14651858.CD005974.