

SANGUINARIA CANADENSIS – A PROBABLE HOMOEOPATHIC MEDICINE FOR SEVERE VIRAL RESPIRATORY ILLNESS

A.S. Suman Sankar^{1*}, C.K. Mohan², N.V. Sugathan³ and S.T. Gopukumar⁴

^{1*}*Department of Repertory, Sarada Krishna Homoeopathic Medical College, Kulasekharam, India*

²*Department of Paediatrics, Sarada Krishna Homoeopathic Medical College, Kulasekharam, India*

³*Department of Practice of Medicine, Sarada Krishna Homoeopathic Medical College, Kulasekharam, India*

⁴*Department of Medical Research, Sarada Krishna Homoeopathic Medical College, Kulasekharam, India*

ABSTRACT

Viral infections affect respiratory tract commonly, Most of the infections are mild and in some it would be severe with direct or indirect complications. Homoeopathic medicines are extensively used to treat influenza since long time. Several of those medicines have been possess anti-viral properties in ultra-diluted doses. Similarity in the pharmacodynamic properties and patient signs are the basis of Homoeopathic treatment. The curing property of these drugs is based on its disease causing property. Sanguinaria canadensis is one such important medicine used in Homoeopathy to treat influenza and its complications, both individually as well as in combination preparations. The signs and symptoms of most of the severe viral respiratory infections are similar to that of the drug proving observations on Sanguinaria canadensis. The Sanguinaria respiratory symptoms are observed along with gastric and cardiac symptoms. The symptoms observed and recorded in Homoeopathic repertories are very similar to that of influenza like illness ranging from mild to severe respiratory illnesses. Secondary Metabolites action of Sanguinaria canadensis displays antiviral activity impeding HIV protease. Protopine in addition to allocryptopine are more vigorous against Parainfluenza Virus-3. Sanguinarine is seen as the inhibitor of aminopeptidase A, dipeptidyl peptidase IV and aminopeptidase N. APN inhibitors could meddle in certain processes of the pathogenetic course of aggravation, tumor infiltration through the basal membrane and viral infection. Numerous plants produce Antiviral phyto-constituents which can target viral proteins, lipid envelope, and viral nucleic acids. DNA-intercalating drugs curb DNA and RNA polymerases and protein biosynthesis, and diminish viral replication. Fundamental oils and polyphenols are dynamic against the free infection, the intercalators can likewise repress the viral replication inside the host cell. Among the intercalating PSMs, alkaloids of the isoquinoline, quinoline and β -carboline type give a few incredible antiviral mixes to model. sanguinarine, in Sanguinaria canadensis is a solid DNA intercalator with articulated cytotoxic, antibacterial and antiviral properties. Homoeopathic dynamizations of Sanguinaria Canadensis are safe and has been successfully used for viral respiratory pneumonia for long time. This medicine in homoeopathy potencies could have a potential for inhibiting viral replication and disease progression. Based on the clinical experience gained from the use of Sanguinaria on viral respiratory illness and the adjuvant facts noted above, the potentized homoeopathic medicine Sanguinaria canadensis can be further studied for its application in severe viral respiratory illness like SARS Covid-2 as a stand-alone treatment or as an adjuvant treatment.

KEYWORDS: Aminopeptidase, Coronavirus Homeopathic, Influenza, Respiratory, Sanguinaria Canadensis.

INTRODUCTION

Viral respiratory infections are more common yet a challenging one. Viral infections with mutation of common viruses may present as an epidemic or pandemic ^[1,2]. Homoeopathic system of medicine which works mainly on the principle of similar, individualization as well as drug dynamization has demonstrated its efficacy in treatment as well as prevention of such viral epidemics in outstanding manner ^[3,4].

Homeopathic medicines successfully used in treatment of influenza. Several medicines have been proven to have effective in viral respiratory illnesses with remarkable anti-viral properties^[39] in ultra-diluted doses^[40, 41]. Similarity in the pharmacodynamic properties and patient symptom is the basis of treatment. *Sanguinaria canadensis* is one such important medicine used in Homoeopathy for influenza, individually as well as in combination preparations^[26].

Homoeopathy relies on patient symptoms for finding the medicine suitable in a large scale viral infection like the present pandemic. In epidemics only one or few symptoms of the malady may be exhibited by an individual, its full image can only be perceptible when all the symptoms expressed by all the patients are put together. The symptoms may vary with respect to geographical conditions and the constitution of the person. In such situations its challenging to arrive at a single medicine which covers all the symptoms.

However this is an attempt to present the possibilities of *Sanguinaria canadensis* from homoeopathic point of view with reference to its phytochemical observations

VIRAL INFECTIONS

Viruses distress human beings as acute self-limiting disease^[1] affecting different organ systems like Respiratory, Nervous, gastro-enteric infection, HIV or others. Both DNA and RNA viruses survive only inside a suitable parasite and gets transmitted by vertical or horizontal transmission. Viral infection depends on viral load, susceptibility of the individual, environmental and sociological factors.

The incubation period of most of the common viruses ranges between 4-5 days or even weeks^[25]. Many viruses that were once present in only a few parts of the world are now spreading, new human viruses sometimes develop from viruses that usually affect animals.

Most commonly, viral infections involve the nose, throat, and upper airways, or systems such as the nervous, gastrointestinal, and reproductive systems. The most common viral infections of respiratory system involves Influenza viruses, Respiratory syncytial virus, Parainfluenza viruses, Rhinoviruses, Adenoviruses, Corona viruses^[26-28]. Viral infections with seasonal variations during summer (gastro-intestinal infection), winter (respiratory infection), rainy season (vector-borne infection) has also been reported in a review by Dr.Fisman^[29].

Numerous counteraction and treatment methods has been utilized to manage viral contaminations, plant based therapeutic preparations have a huge role in such practices. Numerous plants produce Antiviral phytoconstituents which can target viral proteins (polyphenols), the lipid envelope (basic oils and other lipophilic PSMs) and viral nucleic acids (intercalating alkaloids). DNA-intercalating drugs repress DNA and RNA polymerases and protein biosynthesis, and subsequently, popular replication. Though fundamental oils and polyphenols are dynamic against the free infection, the intercalators can likewise hinder the viral replication inside the host cell.

Among the intercalating PSMs, alkaloids of the isoquinoline, quinoline and β -carboline type give a few amazing antiviral mixes. Among these sanguinarine, in *Sanguinaria Canadensis* is an extremely solid DNA intercalator with articulated cytotoxic, antibacterial and antiviral properties^[46].

SANUGINARIA CANADENSIS

Sanguinaria an acaulescent perennial herb with white flowers, palmate leave with red cylindrical rhizome belongs to Papaveraceae family commonly grows in India, United States and Canada^[5].

The *Sanguinaria* is commonly known as blood root due to the reddish latex of the rhizome. Studies on *Sanguinaria canadensis* revealed various traditional uses of the plant as emetic, nauseant, expectorant, stimulant, sedative, emmenagogue, escharotic and diaphoretic for the treatment of wounds, rheumatism [6], bronchitis, headache, croup [7], influenza, chronic sinusitis [8], migraine [9], Rose cold [10], Eczema [11], Pneumonia, Skin cancer (as chemosurgery) [12] and menstrual problems [13,14]. The seeds of the plant are found to exhibit narcotic properties similar to *Stramonium* [15]. The root in powder form produces sneezing with nasal irritation. The tincture of *Sanguinaria* was found to be effective as an anti-plaque and anti-bacterial when employed along with Chewing gum [16].

Sanguinaria has been used in eclectic as well as homoeopathic system of medicine over years. In Homoeopathy, the fresh root is used to prepare mother tincture, it is reported to affect circulation producing congestion locally and depression of cardiac action; in mucous membrane it initially causes dryness followed by catarrh; in Uterus and ovaries it has produces polyp and excessive bleeding; in nervous system it leads to excitement [17]. It is mainly used in management of right sided Migraine [18] of periodical nature better by sleep, arthritis and climacteric problems [19-21]. A study conducted by Andrew croaker et al, shows that Homoeopathy formulations Hylands menopause treatment for climacteric complaints and Zee formulation for osteoarthritis with *Sanguinaria canadensis* as one of its content, improved the patients complaints [14].

Phytochemical studies on *Sanguinaria. canadensis* revealed the presence of alkaloids like sanguinarine, puccine, chelerythrine, sanguilutine, chelilutine, sanguirubine, chelirubine, protopine, beta- and gamma - homochelidonine, allocryptopine and other components like porphyroxin, resin, lignin, citric and malic acids, and starch [17].

The Respiratory employments of *Sanguinaria* (bloodroot) rhizomes are as bronchial muscle relaxant for asthma, a treatment for croup, flu and challenging hack, an expectorant, an antibacterial operator to treat diphtheria and pneumonia, a treatment for tuberculosis, and as a breathed in powder to treat nasal polyps.

PHYTOCHEMICAL ACTION OF SANGUNARIA CANADENSIS

Plant based studies showed HIV-1 protease inhibition activity of *Sanguinaria* -A screening study of 2000 drugs and natural products found sanguinarine had antiviral activity inhibiting HIV protease with an IC₅₀ of 13 µM. Sanguinarine also has activity against herpes simplex virus while protopine and allocryptopine are both active against Parainfluenza Virus-3 [14].

Chelerythrine, sanguinarine and an alkaloid extract from *macleanyacordata* and sanguiritrin were found to be inhibitors of aminopeptidase A and dipeptidyl peptidase IV, while fagaronine inhibited dipeptidyl peptidase IV only. At 50µM, chelerythrine, sanguinarine and sanguiritrin inhibited aminopeptidase N by 82%, 82%, 88%, DPP IV by 38%, 62%, 57%, and fagaronine by 34%, respectively. When bovine serum albumin (500 µg/mL) was added, the inhibition of both proteases by quaternary benzo[c] phenanthridine alkaloids (QBA) (50 µM) was significantly diminished. Strong interaction of chelerythrine and sanguinarine with bovine and human serum albumin was proved by electrophoretic determination of their respective conditional binding constant [44].

S. canadensis showed antimicrobial activity against enterotoxigenic *E. coli*. It may be used as feed additives to control diarrhea in neonatal or weaned pigs irrespective of its toxicity against IPEC-J2 cells *in vitro* [6].

Sanguinarine is a benzophenanthridine alkaloid which is considered to be the main active principle of *Sanguinaria canadensis* and is found to be deadly to organisms due to its cytotoxicity and is also found to have inhibitory effect on growth of microbes like bacteria, Fungi and even virus. The Sanguinarine chiefly acts by inhibiting oxidative decarboxylation of Pyruvate and in humans it inhibits butyryl- and

acetylcholinesterases. A study conducted in Pigs by Baisini *et al.*, explored the suppressive action of Sanguinarine in production of vascular endothelial growth factor [22]. It leads to respiratory paralysis and distress [12]. It exhibits its antiviral activity in HIV as well as Herpes simplex virus whereas the alkaloids protopine and allocryptopine act against Parainfluenza Virus-3 [14]. A study of Cynthia revealed the apoptotic activity of Sanguinarine on Cervical Cancer cells [23] and the study of David *et al.*, showed the immunomodulatory effect the same [24].

Sanguinarine extracts demonstrated immunosuppressive effects on production of the cytokines interleukin (IL)-2 and IL-8, and cell proliferation [45]. Bloodroot extracts stimulate macrophage cytokine production. The quantified phytochemical constituents were inversely related to TNF and IL-1 β , indicating that another constituent not yet identified may contribute to cytokine production by macrophages. Bloodroot extracts either had no effect on IL-8 production or, in the case of alcohol rhizome extract, decreased IL-8 production significantly. The alcohol rhizome extract had the highest level of sanguinarine and chelerythrine, raising the possibility that these constituents act to suppress IL-8 production [24].

CARDIOVASCULAR EFFECTS OF *S. CANADENSIS* ALKALOIDS

Sanguinarine has been found to have a vasodilatory effect, inhibiting α -1 and α -2 adrenoceptors with an IC₅₀ of 33.6 and 6.4 μ M, respectively. Sanguinarine has been shown to block angiotensin II in a slow, nearly irreversible and non-competitive manner [46].

Several bloodroot alkaloids interact with cardiac ion channels. Sanguinarine has been found to inhibit Na⁺-K⁺ ATPase activity [46].

ANTI-INFLAMMATORY ACTIONS OF *S. CANADENSIS* ALKALOIDS

Inflammation is induced by pro-inflammatory enzymes such as COX-2, NO and PGE2 and the inflammatory cytokines TNF- α , Interleukin IL1 and IL6. Protopine exerts an anti-inflammatory action being a potent NO inhibitor, reduces COX-2 expression and impairs the production of PGE2, IL-1B, IL-6 and TNF- α . This occurs through the inhibition of ERK 1/2 and JNK phosphorylation and NF- κ B activation in murine macrophages. Protopine has been found to inhibit carrageenan-induced rat paw oedema with a potency three-fold higher than acetylsalicylic acid. Chelerythrine has also been found to exert an anti-inflammatory action by inhibiting COX-2 and PGE2 production [46].

Polymorphonuclear leukocytes (PMN) release cytokines and lytic enzymes that fuel inflammation. However, when PMN undergo apoptosis, they are removed by the reticuloendothelial system without inflammatory mediator release. PMN apoptosis has been found to be a major mechanism of inflammation resolution in the gut, lung, joint and kidney. Chelerythrine induces rapid apoptosis in human PMN via a PKC (Protein Kinase C) independent mechanism preceded by rapid caspase-3 activation. 10 μ M chelerythrine chloride induces rapid and significant PMN apoptosis in less than 4 h [46]. Intercellular adhesion molecules (ICAM) and vascular cell adhesion molecules (VCAM) facilitate the migration of neutrophils into tissues and are key components of inflammatory disease processes such as asthma and inflammatory arthritis. Testing of 40 natural and synthetic alkaloids, terpenoids and phenolics found sanguinarine and isoliquiritigenin significantly down regulated VCAM-1. Of the 10 compounds that downregulated ICAM-1, sanguinarine had the greatest effect, reducing expression by 50.6% [46].

USE OF SANGUINARIA FOR RESPIRATORY ILLNESS

In an epidemic of the typhoid form of this affection which occurred in the eastern United States anterior to 1822, the efficacy of blood-root was proved and used this as an important adjuvant to the ordinary course of treatment adopted at that time for this affection [13].

Physicians give it in various stages of pneumonia, varying the dose according to the stage and condition of the system.^[13]

HOMOEOPATHY IN VIRAL INFECTION

Homoeopathic system of medicine has displayed its effectiveness in management both preventive and therapeutics of such viral infection during outbreak of Dengue, Chikungunia, Nipah virus, Ebola, Swine flu, Avian flu, influenza as well as Covid-19^[31-37]. Though the characteristics of most the common viruses are known, the treatment becomes challenging to the medical science due to their property of rapid adaptation through mutation^[30, 31].

Here homoeopathy medicine has its advantage with host oriented approach. The simillimum for the malady is sought from the drug proving symptoms matched with patient individual symptoms in a precise repertory approach.

Several medicines are used for patient care in homoeopathy. *Sanguinaria canadensis* is one such medicine with its phytochemical actions are proved to be effective against viral respiratory illnesses. Homoeopathically rather than its individual alkaloids, synergistic action of *Sanguinaria* in drug proving is observed and compared to the host reaction to the invading virus through subjective and objective observations.

Some of the signs and symptoms observed in severe acute respiratory syndrome are similar to that of the drug proving observations on *Sanguinaria canadensis*, providing an indication for Homoeopathicity of *Sanguinaria canadensis*.

SANGUINARIA FOR VIRAL INFECTION

The major compound in *Sanguinaria canadensis* is sanguinarine representing about 50% of the total alkaloids. In addition to sanguinarine, other alkaloids: chelerythrine, sanguilutine, allocryptopine, protopine, berberine and coptisine are usually present which forms the basis of homoeopathic action in a synergistic way by drug dynamization

A Summarising view of respiratory symptoms of *Sanguinaria canadensis* in Homoeopathic materia medica, from which Homoeopathic simillimum is arrived - Œdema of larynx. Trachea sore. Heat and tension behind the sternum. Aponia. Cough of gastric origin; relieved by eructation. Cough, with burning pain in chest; worse, right side. Sputum tough, rust-colored, offensive, almost impossible to raise. Spasmodic cough after influenza and after whooping-cough. Cough returns with every fresh cold. Tickling behind sternum, causes a constant hacking cough; worse at night on lying down. Must sit up in bed. Burning soreness in right chest, through to right shoulder. Severe soreness under right nipple. Hæmoptysis from suppressed menses. Severe dyspnœa and constriction of chest. Offensive breath and purulent expectoration. Burning in chest as of hot steam from chest to abdomen. Fibroid phthisis. Pneumonia; better, lying on back. Asthma with stomach disorders (Nux). Valvular disease with lung development, phosphates in urine and loss of flesh. Sudden stoppage of catarrh of air passages brings on diarrhœa^[20]. Dr. Clarke in his Dictionary of Practical Materia medica advised *Sanguinaria* for the treatment of Influenza^[38].

Sanguinaria canadensis met greater proportion of the tracheal and bronchial coughs of epidemic influenza than any other remedy. The chief features are: Violent, dry cough; wheezing, whistling, metallic; sputa almost impossible to raise. As Clarke states, "I have seen several cases of this kind rescued from apparently imminent death by *Sanguinaria*, the relief comes by the expectoration of a thick plug of mucus which was causing suffocation, and which the patient was too weak to dislodge"^[38].

Dr.Hering observations on *Sanguinaria Canadensis* - Influenza. Pneumonia ; rust colored sputum ; distressing dyspnoea ; hands and feet burning hot or very cold ; sometimes, even before amount of hepatization will account for it, there is failure of the heart's action ; heart weak and irregular in action. Pneumonia : left lung particularly affected ; with heart disease. Tough, rust-colored sputa in second and third stages of pneumonia. Pneumonia in second and third stages ; with dullness on percussion ; bronchial respiration, with red or gray hepatization and infiltration of parenchyma.^[47]

Gripp-Heel® a homeopathic preparation frequently used in the treatment of respiratory viral infections demonstrated dose-dependent in vitro activity (significant reductions of infectivity by 20% to 40%) against Human herpesvirus 1, Human adenovirus C serotype 5, Influenza A virus, Human respiratory syncytial virus, Human parainfluenza virus 3, Human rhinovirus B serotype 14, and Human coxsackievirus serotype A9^[39].

CONCLUSION

The treatment of respiratory viral infections are challenging. The Homoeopathic system of medicines with its individualised approach giving importance to host and with its treasure of ample medicines from various sources can play a major role in viral respiratory illnesses.

The Homoeopathic drug proving observations on *Sanguinaria canadensis* and the evidence from literature on phytochemical action of *Sanguinaria canadensis* by modern methods suggest this medicine as one of the choice for treatment of severe viral respiratory illnesses. The drug could be further studied for its possibilities in managing and preventing complications of severe viral acute respiratory syndromes

REFERENCES

- [1] Burrell CJ, Howard CR, Murphy FA. Epidemiology of Viral Infections. Fenner and White's Medical Virology. 2017:185.
- [2] 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 Apr 1;14(2):100.
- [3] Jacobs J. Homeopathic prevention and management of epidemic diseases. Homeopathy. 2018 Aug;107(03):157-60
- [4] Hasan N, Nayem MU, Mohshinuzzaman M, Biswas AH, Kayes ME, Hakim MA, Uddin N, Alom MJ. Homeopathic Approach to COVID-19: A Review. Malaysian Journal of Medical and Biological Research. 2020 Apr 26;7(1):39-44.
- [5] Rai N. Homoeopathic Pharmacopoeia of India (HPI), Tenth Volume: A Review. Research & Reviews: A Journal of Drug Formulation, Development and Production. 2018 Apr 3;4(3):6-11.
- [6] NandaKafle G. Antimicrobial Activity, Cytotoxicity and Phytochemical Analysis of *Sanguinaria canadensis* Native to South Dakota. Open Access Library Journal. 2017;4(12):1.
- [7] Leonard JP. On the use of *Sanguinaria*. The Boston Medical and Surgical Journal. 1845 Jul 9;32(23):457-9.
- [8] Nayak C, *et al.* Homeopathy in chronic sinusitis: a prospective multi-centric observational study. Homeopathy. 2012 Apr;101(02):84-91.
- [9] Wandile PM. Migraine and the Scope of Homeopathy. Homœopathic Links. 2017 Sep;30(03):189-94.

- [10] Wandile PM. Treatment of Chronic Allergic Rhinitis and Sinusitis with Homeopathy. *Homœopathic Links*. 2017 Jun;30(02):123-8.
- [11] Graber JD. Sanguinaria in Eczema. *Journal of the American Medical Association*. 1907 Aug 24;49(8):705.
- [12] Becci PJ, Schwartz H, Barnes HH, Southard GL. Short-term toxicity studies of Sanguinarine and of two alkaloid extracts of *Sanguinaria canadensis* L. *Journal of Toxicology and Environmental Health, Part A Current Issues*. 1987 Jan 1;20(1-2):199-208.
- [13] Gibb GD. The *Sanguinaria canadensis*: Its natural history, properties, and medical uses. *British Medical Journal*. 1860 Feb 11; 1(163):104.
- [14] Croaker A, King GJ, Pyne JH, Anoopkumar-Dukie S, Liu L. *Sanguinaria canadensis*: traditional medicine, phytochemical composition, biological activities and current uses. *International journal of molecular sciences*. 2016 Sep; 17(9):1414.
- [15] Smith DB. On *Sanguinaria canadensis*. *The Boston Medical and Surgical Journal*. 1832 Jan 31;5(25):393-5.
- [16] Da Silveira Moretti AB, et al. Effect of *Sanguinaria canadensis* Tincture Associated to a Chewing Gum on the Bacterial Biofilm. *The Open Complementary Medicine Journal*. 2009 Sep 7;1(1).
- [17] Gibson DM. *Sanguinaria*, a study. *British Homeopathic Journal*. 1971 Oct; 60(04):296-300.
- [18] Land ST. 20 years ago: *British Homœopathic Journal*, January 1984. *Homeopathy: the journal of the Faculty of Homeopathy*. 2004 Jan; 93(1):54-5.
- [19] Lasser R. Proving of *Sanguinaria*. *British Homœopathic journal*. 1993 Jan 1; 82(1):65.
- [20] W, B., 2020. SSS - Homœopathic Materia Medica - By William BOERICKE. [online] Homeoint.org. Available at: <<http://www.homeoint.org/books/boericmm/s/sang.htm>> [Accessed 1 August 2020].
- [21] Bordet MF, Colas A, Marijnen P, Masson JL, Trichard M. Treating hot flushes in menopausal women with homeopathic treatment—results of an observational study. *Homeopathy*. 2008 Jan;97(01):10-5.
- [22] Basini G, Santini SE, Bussolati S, Grasselli F. The plant alkaloid sanguinarine is a potential inhibitor of follicular angiogenesis. *Journal of Reproduction and Development*. 2007:0702150064-.
- [23] Leaver CA, Yuan H, Wallen GR. Apoptotic Activities of *Sanguinaria canadensis*: Primary Human Keratinocytes, C-33A, and Human Papillomavirus HeLa Cervical Cancer Lines. *Integrative Medicine: A Clinician's Journal*. 2018 Feb; 17(1):32.
- [24] Senchina DS, Flinn GN, McCann DA, Kohut ML, Shearn CT. Bloodroot (*Sanguinaria canadensis* L., Papaveraceae) enhances proliferation and cytokine production by human peripheral blood mononuclear cells in an in vitro model. *Journal of herbs, spices & medicinal plants*. 2009 Mar 18;15(1):45-65.
- [25] Lessler J, Reich NG, Brookmeyer R, Perl TM, Nelson KE, Cummings DA. Incubation periods of acute respiratory viral infections: a systematic review. *The Lancet infectious diseases*. 2009 May 1;9(5):291-300.
- [26] Bondarenko L, Gorchakova N, Galkin A. Efficacy Profile of the Homeopathic Combination for Influenza and Acute Respiratory Viral Diseases Treatment and Prevention. *InnovBiosystBioeng*, 2018, vol. 2, no. 4, 252–261.
- [27] Couch RB, Englund JA. Respiratory viral infections in immunocompetent and

- immunocompromised persons. *The American journal of medicine*. 1997 Mar 17;102(3):2-9.
- [28] Beckham JD, Cadena A, Lin J, Piedra PA, Glezen WP, Greenberg SB, Atmar RL. Respiratory viral infections in patients with chronic, obstructive pulmonary disease. *Journal of Infection*. 2005 May 1;50(4):322-30.
- [29] Fisman D. Seasonality of viral infections: mechanisms and unknowns. *Clinical Microbiology and Infection*. 2012 Oct 1;18(10):946-54.
- [30] Tan SL, Ganji G, Paeper B, Proll S, Katze MG. Systems biology and the host response to viral infection. *Nature biotechnology*. 2007 Dec;25(12):1383-9.
- [31] Chakma A. Homoeopathic Perspectives in Few Major Viral Diseases Emerging & Re-emerging in India | Homeopathy Resource by Homeobook.com [Internet]. Homeobook.com. 2020. Available from: <https://www.homeobook.com/homoeopathic-perspectives-in-few-major-viral-diseases-emerging-re-emerging-in-india/>
- [32] Pillai S, Punnen, 2020. A. Swine Flu – The Real Facts and Homoeopathy Perspectives | Homeopathy Resource by Homeobook.com [online] Homeoint.org. Available at: <<https://www.homeobook.com/swine-flu-the-real-facts-and-homoeopathy-perspective/>> [Accessed 1 August 2020].
- [33] K. Saji. Nipah, 2020. A Homoeopathic Perspective | Homeopathy Resource by Homeobook.com [Internet]. Homeobook.com. 2020 [online] Homeoint.org. Available at: <<https://www.homeobook.com/nipah-a-homoeopathic-perspective/>> [Accessed 1 August 2020].
- [34] Banu S. Influenza and Homoeopathic management | Homeopathy Resource by Homeobook.com [Internet]. Homeobook.com. 2020. Available from: <<https://www.homeobook.com/influenza-and-homoeopathic-management/>> [Accessed 1 August 2020].
- [35] Department of Homoeopathy Govt of Kerala preventive for Avian flu (Bird flu) | Homeopathy Resource by Homeobook.com [Internet]. Homeobook.com. 2020. Available from: <<https://www.homeobook.com/department-of-homoeopathy-govt-of-kerala-preventive-for-avian-flu/>> [Accessed 1 August 2020].
- [36] N.S.Sheik S, S N. Sheik. Ebola outbreak, it's catastrophic consequences and Homoeopathic management | Homeopathy Resource by Homeobook.com [Internet]. Homeobook.com. 2020. Available from: <<https://www.homeobook.com/ebola-outbreak-its-catastrophic-consequences-and-homoeopathic-management/>> [Accessed 1 August 2020].
- [37] Chaukkar S. Effective management & Homoeopathy medicines for swine Flu | Homeopathy Resource by Homeobook.com [Internet]. Homeobook.com. 2020. Available from: <<https://www.homeobook.com/effective-management-homoeopathy-medicines-for-swine-flu/>> [Accessed 1 August 2020].
- [38] Clarke J H. A Dictionary of Practical MateriaMedica. Available from: <<http://www.homeoint.org/clarke/s/sang.htm/>> [Accessed 1 August 2020].
- [39] Glatthaar-Saalmüller B, In vitro evaluation of the antiviral effects of the homeopathic preparation Gripp-Heel on selected respiratory viruses *Can J PhysiolPharmacol*. 2007 Nov; 85(11):1084-90.
- [40] Bukhsh AR. Ultra-Highly Diluted Homeopathic Remedies Have Demonstrable Anti-Viral Effects: A Commentary on Our Published Findings Related to Experimental Phage Infectivity in Bacteria. *Biomedical Journal*. 2018 Sep 11;1:5.
- [41] Bhaswati Bandyopadhyay *et al*. Decreased Intensity of Japanese Encephalitis Virus Infection in Chick Chorioallantoic Membrane Under Influence of Ultradiluted Belladonna Extract, *American Journal of Infectious Diseases* 2010. 6 (2): 24-28.

- [42] Pan L, Mu M, Yang P, Sun Y, Wang R, Yan J, Li P, Hu B, Wang J, Hu C, Jin Y. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study. *The American journal of gastroenterology*. 2020 May 1;115.
- [43] Yamamoto N, Yang R, Yoshinaka Y, Amari S, Nakano T, Cinatl J, Rabenau H, Doerr HW, Hunsmann G, Otaka A, Tamamura H. HIV protease inhibitor nelfinavir inhibits replication of SARS-associated coronavirus. *Biochemical and biophysical research communications*. 2004 Jun 4;318(3):719-25.
- [44] Šedo A, Vlašicová K, Barták P, Vespalec R, Vičar J, Šimánek V, Ulrichová J. Quaternary benzo [c] phenanthridine alkaloids as inhibitors of aminopeptidase N and dipeptidyl peptidase IV. *Phytotherapy Research*. 2002 Feb;16(1):84-7.
- [45] Perera MA, Robinson JR, Shearn CT, Noble TM, Hallam JE, Kohut ML, Senchina DS. Effects of bloodroot (*Sanguinaria canadensis* L.) rhizome ethanol extracts on cytokine production by blood mononuclear cells during flowering and fruiting. *Journal of Herbal Medicine*. 2014 Mar 1;4(1):18-23.
- [46] Wink Michael, Potential of DNA Intercalating Alkaloids and Other Plant Secondary Metabolites against SARS-CoV-2 Causing COVID-19, *Diversity* 2020, 12(5), 175; <https://doi.org/10.3390/d12050175>
- [47] Hering Constantine, *The Guiding Symptoms of our Materia Medica*, Available from: <<http://www.homeoint.org/hering/s/sang-4.htm#29>>[Accessed 5 August 2020].

