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Review paper

Combinatory therapeutic approaches for common cold and SARS-CoV-2



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ABSTRACT

Many countries in the world face the new challenge of having human coronavirus infection to manage commendably - the large affliction of human health. Together, each country has modern drugs and a variety of medicinal products developed from their traditional medical practitioners to treat a common cold. In this review, we describe potentially synergistic therapeutics of traditional and complementary medicine available for common cold which might be useful for prevention or for the adjuvant treatment of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Further, we provide a phylogenetic overview of SARSCoV-2 based on a complete genome sequence of common cold viruses. We suggest modern and traditional medicine and preventive strategies which might control the disease to offer more suitable and acceptable common cold management including coronavirus. A substantial proportion of medicinal products developed by traditional medicine against common cold as well as modern medicine mainly focus on symptoms suppression. The recombinant interferon alpha-2b and lactoferrin derived from modern medicine in combination with herbal based products from traditional medicine may support the prevention of novel coronavirus infections. An integrated approach against common cold viruses to establish efficacy and safety through modern and traditional medicine and regular physical exercise along with preventive dietary sources is proposed.

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1. Introduction

The infections in upper respiratory tract of humans and distress of the nasal part of the respiratory mucosa is called common cold. The main symptoms are nasal stuffiness and discharge, sneezing, sore throat and cough. These symptoms appear from 2 to 14 days, depending on the immune status of the human body. The usual recovery period of infected people ranges from 7 to 10 days [1]. The common cold is caused by numerous viruses that belong to several different families [2]. In general, the common colds affects adults two to four times a year and children four to eight times a year [3].

The common cold is not a serious concern to people but rather accepted a part of human life. The infection rate and economic losses due to common cold are not well studied in the world except in the United States of America, where a 40 % of time lost in work is reported [4] and the economic loss is estimated to be around \$20

billion/per year by the impact of cold-related issues [5]. The influenza pandemic or Spanish flu was recorded as the most severe in recent history, this outbreak was caused by H1N1 virus in 1918. Around 500 million people were infected globally with a mortality of 50 million [6]. The rare and presently scaring outbreak of human coronavirus SARS-CoV-2 (COVID-19) in the world cause severe health issues as well as a massive economic loss globally.

Now a days, scientists are keenly working on resolving the challenge of the novel human coronavirus infection. In this article, we aimed to describe the existing data available on therapeutics towards common cold viruses and to suggest (preventive) treatments towards human coronavirus based on their molecular profile and available knowledge on their modes of action. The electronic database search was conducted with the search terms of common cold, therapeutic ways and human coronavirus.

2. History

People believe that the term “common cold” is derived from cold weather, as this disease is very common in cold climate [7].

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Although common cold was found in early centuries around the globe, researchers discovered the root cause for respiratory illness only between 1950s and 1960s. During this stage, the detection and control aspects like isolation procedures for infected person had been developed and many viruses responsible for upper respiratory tract infection were identified [8]. After the invention of the Polymerase chain reaction technique, the description of viral structures, the molecular characterization and the antigen detection have been significantly increased [9]. New viral strains, not only related to seasonal common cold, were identified such as dengue virus (DENV-1-4) [10], Hepatitis C virus [11], new Human Immunodeficiency virus from Gorilla [12], MERS-CoV [13], Teviot virus (TevPV) from bats [14], including the Novel Corona -2019.

3. Cause

Occasionally, people may misunderstand and compare air-borne allergies with common cold, as allergies are likely to cause similar (common cold) symptoms. Allergies are caused by allergens such as dust mites, pollens, animal dander, mold and certain foods, however common cold is caused by viruses, which infect the upper respiratory tract of human beings. A total of 200 viral serotypes belonging to eight major virus groups are associated with colds [15]. According to Heikkinen and Jarvinen [2], the infective rate of rhinoviruses is higher than the one of other viruses group (Fig. 1). In the past three decades, the average rate of infections by coronaviruses was 12.5% [2], nevertheless these virus infections are common throughout the world and their average infection rate was 0.9% of world human population between December 2019 and November 2020 [16].

4. Pathogenesis

The development of common cold in the human body is not completely understand due to the variety of virus strains. In each phase of the disease, different types of viral strains invade into the respective system [17]. It is yet unknown whether the common

cold viruses enter into the respiratory tract only through nose and mouth or through the tear ducts [18] and their pathogenesis is not well understood [17]. Among common cold viruses, rhinovirus infections are more common in the upper respiratory tract compared to other viruses [19]. Rhinoviruses have more than one hundred serotypes or strains since the rate of mutations of the same virus strain differs during every cold season.

The common cold viruses trigger primarily immune responses which vary virus-specifically. The rhinoviruses invading the upper respiratory tract primarily bind to the host epithelial cell intercellular adhesion molecule-1 (ICAM-1) and cadherin related family member 3 (CDHR3) receptors which activate the release of inflammatory mediators like kinins, leukotrienes, histamines, interleukin-1, interleukin-6 interleukin-8, tumor necrosis factor and regulate the activation of normal T-cells. [20-22]. Fortunately, the higher infective rate caused by rhinoviruses does not cause damage to the nasal epithelial cells, however other common cold viruses may cause cell damage [17].

5. Human coronavirus

Next to rhinoviruses, the coronavirus infective rate accounts for about 15% of all upper respiratory tract infections in adults [9]. The vital thing is that human coronaviruses caused 2.3% of mortality of the total infective cases between December 2019 and November 2020 [16]. The human coronaviruses were discovered during 1960s [6]; four novel strains of B814 [23], 229E [24], infectious bronchitis virus (IBV) [25] and organ culture 43 (OC43) [26] were isolated. In successive years, studies on 229E and OC43 strains were sustained, but the B814 strain was lost due to unknown reason [27]. Later, other strains of severe acute respiratory syndrome-related coronaviruses (SARS-CoV) were identified: in 2003 the human coronavirus NL63 (HCoVNL63); in 2004 the HCoV HKU1; in 2005 and 2012 the middle-east respiratory syndrome related coronavirus (MERS-CoV); in 2019 the SARS-CoV-2 (COVID-19) [28,29].

Owing to the serious outbreak of SARS-CoV-2, scientists carried out research on coronaviruses in different ways covering molecular

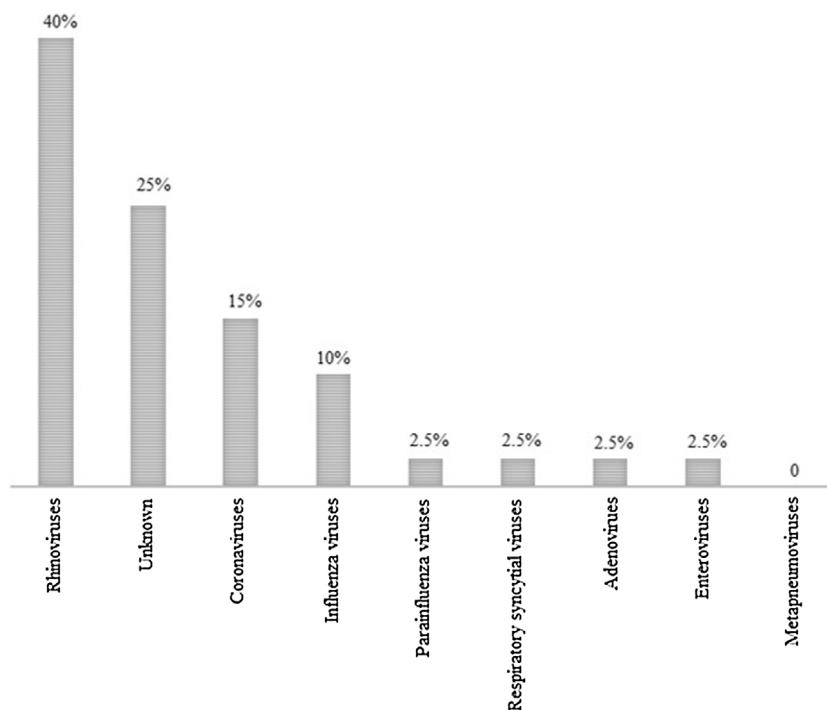


Fig. 1. Infective rate of viruses per year for common cold (Modified according to [2]).

profiles of the mode of action of the virus, studying the symptomatic effects of an infection, the community aspects and therapeutic aspects. In this review, we compared the common cold causing viruses based on their complete genome sequence submitted in the NCBI GenBank for demonstrating the relationship between common cold viruses especially to coronaviruses. We took 22 viral complete genome sequences belonging to eight major types of viruses. These sequences were subjected to multiple sequence alignment methods by Clustal W [30]. Two phylogenetic models, ML and NJ (Maximum Likelihood and Neighbor Joining) were applied by using MEGA 7 [31].

The ML and NJ models formed the same phylogenetic tree, which leads to two separate clades (Fig. 2). In the first clade, seven major type of common cold viruses were grouped. The second clade includes the different strains of the human coronaviruses. HCoV shares a common ancestor with the human adeno- and rhinoviruses. SARS-CoV shares a common ancestor with a HCoV229E. The SARS-CoV-2 emerged from SARS-CoV with a 100 % bootstrap value. The phylogenetic tree supports the origin of SARS-CoV-2 from different strains in a time manner. As novel COVID-19 shares 99 % with common cold viruses (rhino and adenoviruses), the outlook of treatments available for common cold would reasonably support the treatment of SARS-CoV-2 infections.

6. Therapeutic strategies

Today, two major categories are often differentiated - modern and traditional medicine. The science-based modern medicine is effective and popular among the majority of people whereas the traditional medicine often lacks biological plausibility and is often experimentally disproven. The treatment for common cold is available in both type of therapies. The present study provides an overview about the therapies for common cold based on the available data bases.

6.1. Modern medicine

Several studies have been conducted to treat acute respiratory tract infections of human. The drugs used for reducing the symptoms

of common cold are summarized in Table 1. They are grouped into two categories: 1) antibiotics and 2) other substances. In addition, anti-allergic drugs are used for reducing symptoms and a fast recovery from common cold (eg. Cetirizine). Based on the literature survey, there is no specific medicine available for viruses causing common cold [51]. In general, a broad range of over-the counter medicines like analgesics, antihistamines, decongestants, nasal steroids, mucus dilutants, anti-tussives and lozenges are used for inhibiting symptoms produced by acute respiratory infections.

The MERS-CoV outbreak occurred in Saudi Arabia in 2012. Since its outbreak the disease lead to a high mortality rate in 12 countries with Saudi Arabia reporting 2121 cases from 2012 with a 37.1 % fatality rate (WHO report). The urgency in treatment from MERS-CoV to COVID-19 made us to concentrate on different aspect of treatment strategies. INF α 2b and ribavirin were chosen to treat rhesus macaque monkeys infected with MERS-CoV. Treated animals did not shown any breathing abnormalities and less symptoms of pneumonia [52]. In previous studies INF α showed a remarkable inhibitory effect against SARS-CoV in *in-vitro* and *in-vivo* studies [53–55,49].

6.2. Traditional medicine

Traditional medicine is often followed from generation to generation. Before the development of modern medicine, 80 % of the human population used their indigenous medicine [56]. In particular, Africa, China, and India practice traditional medicine. Recently, traditional medicine is increasingly accepted in the scientific community. The disciplines of ethnobotany, ethnomedicine, herbalism and medical anthropology developed. Since there is no specific drug in modern medicine available for controlling viruses causing common cold, the drugs used in traditional medicine for controlling common cold are reviewed in this study.

Several traditional medicine are available for cough, sneezing, fever and bronchitis all over the world. Appropriate drugs related to common cold are summarized in Table 2, for example, lime flowers in European medicine, purple *perilla* porridge and scallion stalk porridge in Chinese medicine, six herbal formulas in Korean medicine, Akinyele

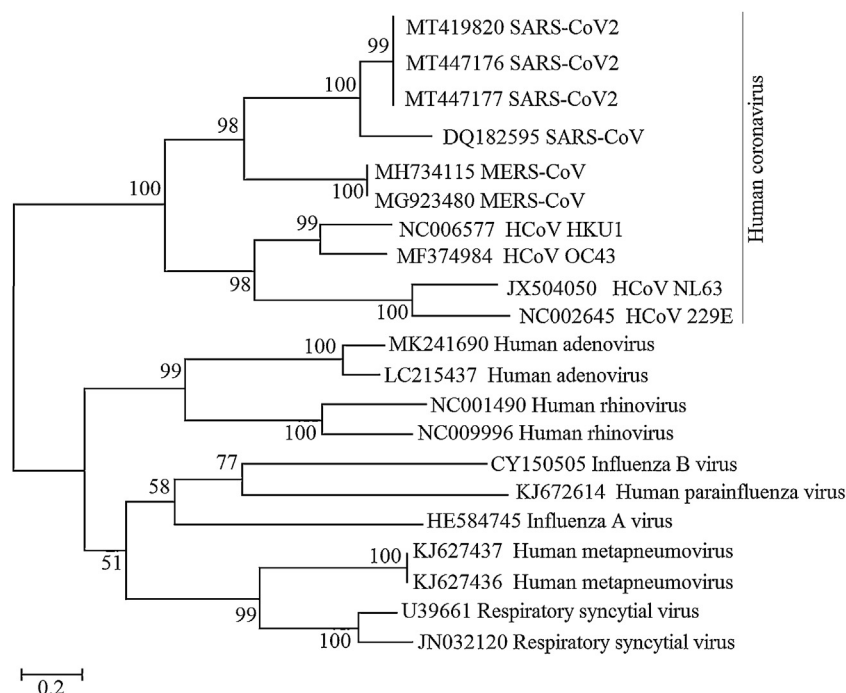


Fig. 2. Maximum Likelihood phylogenetic tree for common cold viruses with SARS-CoV-2 based on complete genome sequences (Bootstrap value shows in the above clade).

Table 1
Modern medicine used for common cold.

Chemical	Treatment	References
Antibiotics		
Cephalosporins	Uncomplicated acute respiratory tract infections	[32]
Gatifloxacin	Acute respiratory infections	[33]
Penicillin V	Pharyngitis	[34]
Amoxicillin	Pharyngitis	[34]
Cephalexin	Pharyngitis	[34]
Cefadroxil	Pharyngitis	[34]
Clindamycin	Pharyngitis	[34]
Azithromycin	Pharyngitis	[34]
Clarithromycin	Pharyngitis	[34]
Doxycycline	Acute Rhinosinusitis	[34]
Levofloxacin	Acute Rhinosinusitis	[34]
Moxifloxacin	Acute Rhinosinusitis	[34]
Terfenadine	Allergic rhinitis	[35]
Cetirizine	Allergic rhinitis	[36]
Astemizole	Allergic rhinitis	[37]
Acrivastine	Allergic rhinitis	[38]
Azelastine	Allergic rhinitis	[39]
Loratadine	Allergic rhinitis	[40]
Ebastine	Allergic rhinitis	[41]
Mizolastine	Allergic rhinitis	[42]
Fexofenadine	Allergic rhinitis	[43]
Others		
Procalcitonin	Acute respiratory infections	[44]
Vitamin D supplementation	Acute respiratory infections	[45]
Zinc	Acute respiratory infections	[46]
Brompheniramine	Rhinovirus colds	[47]
Pleconaril	Rhinovirus infections	[48]
Recombinant Interferon alpha-2b	Influenza A & B, parainfluenza 1–3, and adenovirus B	[49]
Interferon-beta and gamma	SARS-CoV	[50]

Table 2
Treatment for common cold by using traditional medicine of the world.

Name of the product/Plant	Type of medicine	Treatment	References
Lime flowers, blackcurrant and camomil	European Medicine	Common cold, Flu	[57]
Purple perilla porridge and Scallion stalk porridge	Chinese Medicine	Common cold with weak patients	[58]
CAM products such as <i>Andrographis paniculata</i> (Kalmcold), <i>Echinacea purpurea</i> , and <i>Pelargonium sidoides</i> (geranium) extract	Chinese Medicine	Common cold	[59]
Jade Wind-Barrier Powder	Chinese Medicine	Common cold with weak patients	[60]
Six herbal formulas (SHF): <i>Galgueuntang</i> , <i>Gumiganghwal-tang</i> , <i>Insamgaedoksan</i> , <i>Samsoum</i> , <i>Socheongryong-tang</i> and <i>Sosiho-tang</i>	Korean Medicine	Common cold	[61]
Akinyele LGA and Anjio LGA	African Medicine	Common cold	[62]
Leaves of <i>Ajuga remota</i> , <i>Clematis brachiata</i> , <i>Englerina woodfordioides</i> , <i>Lantana camara</i> , <i>Lippia javanica</i> , <i>Melia azadirachta</i> , <i>Ocimum basilicum</i> , <i>Piper capense</i> , <i>Pistacia aethiopica</i> , <i>Psidium guajava</i> , <i>Rhamnus prinoides</i> , <i>Schkuhria pinnata</i> , <i>Tithonia diversifolia</i> , <i>Urtica massaica</i> , <i>Withania somnifera</i> , etc.	African Medicine	Common cold	[63]
<i>Lippia javanica</i> , <i>Eucalyptus grandis</i> , <i>Tetradenia riparia</i> and <i>Senecio serratulloide</i>	African Medicine	Respiratory infections	[64]
Gertoufa (<i>Brocchia cinerea</i> Viss.), Fersig (<i>Tamarix gallica</i> L.)	African Medicine	Respiratory diseases	[65]
Maryam goliye sfahan (<i>Salvia reuterana</i> Boiss), Avishane denaei (<i>Thymus daenensis</i> Celak.)	Iranian Medicine	Common cold	[66]
Opium poppy (<i>Papavera somniferum</i> L)	Iranian Medicine	Common cold	[67]
Akkoub (<i>Gundelia tournefortii</i> L.), Zoufa (<i>Micromeria myrtifolia</i> Boiss. et Hohen), Kase'en, Mayramyie (<i>Salvia rubifolia</i> Boiss)	Arabic Medicine	Common cold	[68]
Latumoni (<i>Abrus precatorius</i>)	North-east Indian Medicine	Common cold	[69]
Nelli (<i>Emblia officinalis</i>)	Ayurvedic Medicine	Respiratory disorders	[70]
Sivanar amirtham, Pavala parpam	Siddha Medicine	All kinds of respiratory ailments	[71]
Arque Ajeeb (inhalation), Nuqu Nazla, Itriphal Ustakhuddus, Habbe Shifa, Khamira Nazla, Sharbat Unnab	Unani Medicine	Upper respiratory tract infections	[72]

LGA and Anjio LGA in African medicine, Maryam goliye sfahan in Iranian medicine, Akkoub and Zoufa in Arabic medicine, Latumoni in North-east Indian medicine, Nelli in Ayurvedic medicine, Sivanar amirtham and Pavala parpam in Siddha medicine and Nuqu Nazla in Unani medicine (for details see Table 2).

6.3. Vaccine

The common cold viruses can cause serious illness and death for children and elderly people. Medical biologists are curious to discover a solution through the development of vaccines [73].

However, the development of vaccines for common cold viruses is difficult due to the existence of diverse viral serotypes (more than 200 serological distinct strains) and frequent mutations of viral proteins in each year especially the RNA viruses [73]. Presently the pandemic of SARS-CoV-2 and its fatal rate demand the development of vaccines to prevent or protect their infection. Three types of vaccines have been recently announced to be made available by the end of 2020. However, the process of vaccinating the population requires time. The required time horizon is presently difficult to predict. In the meanwhile, we may supposedly suggest that the combination of binding protein and replicative genes of available common cold strains coupled in a single genome with a virus may be developed and used as an effective vaccine for preventing the disease of common cold.

6.4. Physical exercises

Evidence based studies highlight that physical exercises reduced the number of days subjects suffered from upper respiratory tract infections including the severity of their symptoms [74,75]. As yet common colds cannot be prevented or controlled [76]. However, meditation can reduce experienced stress and negative emotions of people affected by respiratory tract illness [77]. Thus, first evidences propose that training in meditation and exercise reduce the susceptibility to upper respiratory tract infections [78]. Besides, yoga therapy (*pranayama*), significantly improved lung function subjectively [79].

7. Prevention

The common cold is not serious until SARS-CoV-2 acted as pandemic. Modern and traditional medicine research against common cold viruses have often lead to drugs achieving symptom control, even though the exact drug for controlling the cause of common cold is still missing. Plenty of drugs are available for suppressing symptoms. At this moment, prevention would be one of the best solutions to avoid a coronavirus infection. The reduction of personal contacts or the isolation of infected persons is presently the measurement of choice. Indeed, traditionally, if a person suffered from chicken pox disease caused by Varicella zoster virus, the suffered person's family members isolated from their society till the recovery, a system still followed in South India. In addition, the intake of dietary supplements of vitamin C rich foods [80], lactoferrin [81] and garlic extracts [82] has been proposed. Furthermore, following self-hygienic procedures are recommended to avoid common cold infections.

8. Conclusion

Although, many therapies have a scientific evidence of activity against common cold viruses, there is no specific medicine available for curing common cold. Instead effective symptom reducing products are available in modern and traditional medicine. The literature review revealed that the recombinant interferon alpha-2b and lactoferrin derived from modern medicine in combination with herbal based products from traditional medicine may be interesting for further investigations for the prevention of novel coronavirus infections. An integrated approach against common cold viruses to establish efficacy and safety through modern and traditional medicine and regular physical exercise along with preventive dietary sources is proposed.

Declaration of Competing Interest

The authors report no declarations of interest.

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