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TRP channels in COVID-19 disease: Potential targets for prevention and treatment

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ABSTRACT

Coronavirus disease 2019 [COVID-19] is a global health threat caused by severe acute respiratory syndrome coronavirus 2 [SARS-CoV2] that requires two proteins for entry: angiotensin-converting enzyme 2 [ACE2] and -membrane protease serine 2 [TMPRSS2]. Many patients complain from pneumonia, cough, fever, and gastrointestinal (GI) problems. Notably, different TRP channels are expressed in various tissues infected by SARS-CoV-2. TRP channels are cation channels that show a common architecture with high permeability to calcium [Ca^{2+}] in most sub-families. Literature review shed light on the possible role of TRP channels in COVID-19 disease. TRP channels may take part in inflammation, pain, fever, anosmia, ageusia, respiratory, cardiovascular, GI and neurological complications related to COVID-19. Also, TRP channels could be the targets for many active compounds that showed effectiveness against SARS-CoV-2. Desensitization or blocking TRP channels by antibodies, aptamers, small molecules or venoms can be an option for COVID-19 prevention and future treatment. This review provides insights into the involvement of TRP channels in different symptoms and mechanisms of SARS-CoV-2 , potential treatments targeting these channels and highlights missing gaps in literature.

1. Introduction

Coronavirus disease 2019 [COVID-19] is one of the worst pandemics in the world. According to new estimates from the World Health Organization [WHO] published in May 25, 2021, over 4.1 million new cases and 84,000 new deaths were globally reported in a week [1]. Although in some cases COVID-19 patients were asymptomatic, many people complained from pneumonia, cough, fever, and gastrointestinal [GI] problems [2,3]. Recently, the long haul COVID-19 illness started to gain recognition whereby some patients suffer from symptoms in the long term even when their viral tests were confirmed negative [4].

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 [SARS-CoV2], which acts via a spike protein [S protein] that binds to host cell receptors and regulates viral infection [5]. It is widely accepted that two key proteins are required for SARS-CoV2 entry: angiotensin-converting enzyme 2 [ACE2] and *trans*-membrane protease serine 2 [TMPRSS2] [6]. Accumulating evidence showed that calcium [Ca^{2+}] channel blockers inhibited SARS-CoV-2 infectivity in epithelial lung cells proving that Ca^{2+} ions are required for the viral entry into host cells [7]. Since transient receptor potential [TRP] channels are cation channels with high permeability to Ca^{2+} in most sub-families [8], they could be involved in certain steps of SARS-CoV-2 life cycle.

TRP channels are divided according to the amino acid sequences into different subgroups including TRPM [melastatin], TRPML [mucolipin], TRPA [ankyrin], TRPV [vanilloid], TRPP [polycystin] and TRPC [canonical or classical] channels [8]. In fact, most TRP channels are widely expressed in tissues that are infected by SARS-CoV2 virus. Therefore, TRP channels can be valuable targets interfering with COVID-19 life cycle. It was noted that uncoating of the viral envelope is a crucial step for the entry of enveloped viruses, including SARS-CoV-2 virus that enters host cells through endocytosis. In order for this step to occur, different receptors are needed to trigger fusion of the viral envelope with the endolysosomal membrane [9,10]. Importantly, a TRP channel, TRPML2 channel, plays a key role in this process. It enhances the efficiency of viral trafficking in the endosomal system, thus affecting the viral entry [9,10]. Therefore, TRP channels can be valuable targets interfering with COVID-19 life cycle.

Despite the surge of papers published about COVID-19, the mechanisms that underpin this disease are still inconclusive. In fact, many COVID-19 symptoms result from the activation of different TRP channels. It has been suggested that TRPV1 desensitization [e.g. by

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Abbreviations

ACE2	Angiotensin-converting enzyme 2
ARDS	Acute respiratory distress syndrome
ATP	Adenosine triphosphate
Ca^{2+}	Calcium
CBD	Cannabidiol
COVID-19	Coronavirus disease 2019
CTX	Ciguatoxin
3D	Three dimensional
DRG	Dorsal root ganglia
EC	Enterochromaffin cells
EECs	Enteroendocrine cells
ER	Endoplasmic reticulum
GI	Gastrointestinal
HSP70	Heat shock protein 70
HSR	Heat shock response
ICU	Intensive care unit
IFNγ	Interferon gamma
IL	Interleukin
IL-1β	Interleukin 1 beta
Nrf2	Nuclear factor erythroid 2–related factor 2
NSAIDs	Non-steroidal anti-inflammatory drugs
NTS	Nucleus tractus solitarius
PIP2	Phosphatidylinositol 4,5-bisphosphate
ROS	Reactive oxygen species
RTX	Resiniferatoxin
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SP	Substance P
S protein	Spike protein
TG	Trigeminal ganglia
TMPRSS2	*Trans*-membrane protease serine 2
TNFα	Tumor necrosis factor alpha
TRP	Transient receptor potential
TRPA	Transient receptor potential ankyrin
TRPC	Transient receptor potential canonical or classical
TRPM	Transient receptor potential melastatin
TRPML	Transient receptor potential mucolipin
TRPP	Transient receptor potential polycystin
TRPV	Transient receptor potential vanilloid
WHO	World Health Organization

resiniferatoxin (RTX)] in the afferent neurons can decrease complications associated with the standard therapy in severely compromised COVID-19 patients; thus can improve their immune and inflammatory responses [11]. Notably, headache and myalgia are common symptoms in COVID-19 disease [12,13]. Unfortunately, the use of non-steroidal anti-inflammatory drugs [NSAIDs] to alleviate these symptoms may increase the susceptibility to coronavirus by upregulating ACE2 receptors therefore enhancing viral entry [14]. In this context, it is well established that several TRP channels are involved in pain sensation such as TRPV1 channel [15]. Therefore, these channels represent promising targets for pain relief in COVID-19.

Worthy to mention, around 53% of COVID-19 mortalities resulted from acute respiratory distress syndrome [ARDS] caused by edema in the lungs [16,17]. It has been demonstrated that TRPV4 and TRPC6 channels are implicated in pulmonary edema [18,19] while TRPV4 and TRPM7 channels are regulators for pulmonary fibrosis [20,21]. Thus, TRPV4 channel was recently emerged as a therapeutic target in SARS-CoV-2 infection [22]. Taken together, the aim of this review is to explore the possible involvement of TRP channels in different COVID-19 symptoms in line with potential trends in the prevention and treatment of this disease.

2. Methods

Literature search was done for articles using the following keywords: angiotensin-converting enzyme 2, ageusia, anosmia, cardiovascular, cough, coronavirus disease 2019, desensitization, diet, edema, fever, gastrointestinal, headache, hearing, inflammation, medicinal plants, myalgia, natural products, pain, pulmonary, respiratory, severe acute respiratory syndrome coronavirus 2, tachyphylaxis, transient receptor potential channels, and venom. PubMed and Google scholar were used to search for the articles.

3. Results

3.1. TRP channels

There are different types of TRP channels being involved in many physiological and pathological responses. TRPV1 (capsaicin receptor) is a non-selective cation channel correlated with several inflammatory conditions such as airway obstruction [23]. Compelling lines of evidences revealed that TRPA1, a Ca^{2+}-permeable channel, is co-localized with TRPV1 channel in neuronal and non-neuronal cells [15]. Importantly, TRPV2 and TRPV3 channels are selective to Ca^{2+} and take part in Ca^{2+} homeostasis [24]. TRPV6 is another channel that exhibits higher selectivity to Ca^{2+} [100:1 ratio] compared to 3:1 ratio in TRPV2 channel [24]. Additionally, TRPM2 channel has the ability to respond to oxidative stress and is permeable to Ca^{2+} as well as to other ions [25,26]. This channel is considered a suicidal channel that compromises the cell by overloading it with Ca^{2+} under stress conditions [27]. In more detail, TRPM2 channel is activated by reactive oxygen species [ROS] and is involved in the production of pro-inflammatory chemokines [25]. On the other hand, TRPM5 channel has an unusual characteristic compared to other TRP channels [15]. It is a Ca^{2+} impermeable channel with high selectivity to Na^{+} that leads to depolarization, action potential and release of adenosine triphosphate [ATP] transmitter in the afferent neurons [15]. Further, it was revealed that TRPM8 channel has Ca^{2+} and Na^{+} dual selectivity [28].

TRPC channels are non-selective cation channels that have 1.1:9 Ca^{2+}:Na^{+} selectivity ratio and are involved in several responses [29]. A point of interest is that the existence of multiple TRP channels in a tissue can form heterodimers that trigger different responses compared to monomers and this fact adds a complexity to validating the mechanism of action of TRP channels in a response [30]. Importantly, TRPML channels are non-selective cation channel expressed in the endosomal vesicles [31]. TRPML2 channel is expressed in immune cells, thymus and spleen compared to the ubiquitous expression of TRPML1 channel [31].

3.2. TRP channels and different symptoms of COVID-19

3.2.1. TRP channels and inflammatory response in COVID-19

Several studies demonstrated the existence of a hyperinflammatory state [cytokine storm] in COVID-19 cases due to the upregulation of several pro-inflammatory mediators [32]. In more detail, multiple reports showed that COVID-19 patients had high levels of interferon gamma [IFNγ], interleukin 1 beta [IL-1β], IL-6 and IL-10 [33,34]. Additionally, it was noted that COVID-19 patients admitted to the intensive care unit [ICU] in Wuhan had higher amounts of tumor necrosis factor alpha [TNFα] and other cytokines compared to healthy individuals [34].

Several studies shed light on the role of different TRP channels in

immune and inflammatory responses suggesting that there is an interplay between these channels and the production of inflammatory mediators in COVID-19 patients. For instance, it was reported that TRPV4 channel is a regulator for pulmonary inflammation due to its expression in alveolar macrophages [35]. Particularly, TRPV4 channel is involved in the recruitment of neutrophils and macrophages during lung injury [20].

The possible role of TRPA1 channel in inflammation in COVID-19 was also highlighted [36]. Several natural compounds and diets reduced inflammatory symptoms in COVID-19 patients in a TRPA1 dependent mechanism [36]. Examples include broccoli, black pepper, ginger, green tea and curcuma whereby their consumption improved nasal obstruction and cough in COVID-19 patients [36].

TRPM2 is another channel that takes part in stress-related inflammatory and immune processes [37]. Also, the communication between immune cells and TRPV1-expressing fibers was found to be critical in mediating airway inflammation caused by inhaled allergens or viral infection [38]. Collectively, all the aforementioned TRP channels can be positive targets in alleviating COVID-19 symptoms that are related to immune and inflammatory processes.

3.2.1.1. ***TRP channels and pain in COVID-19.*** It is widely accepted that COVID-19 patients suffer from several types of pain such as referred pain, myalgia, hyperalgesia and headache [12,13]. Caution must be observed when using the currently available drugs for pain relief in COVID-19 patients [14]. Unfortunately, inconclusive reports indicated that the use of NSAIDs may increase the susceptibility to Coronavirus by upregulating viral entry through ACE2 receptors [14]. These facts urge the need to explore new therapeutics that can alleviate rather than aggravate COVID-19 symptoms. In this regard, accumulating knowledge showed that several TRP channels (e.g. TRPV1 channel) are promising targets for pain. Besides, the involvement of TRPA1 channel in mechanical hyperalgesia and inflammatory pain is an indication for its role in pain [39]. Of the receptors belonging to TRPM subfamily, it was found that TRPM2, TRPM3 and TRPM8 channels are associated with the processing of noxious stimuli; thus pain sensation [39]. Other TRP receptors are also considered transducers of pain such as TRPV2, TRPV3, TRPV4, TRPC1 and TRPC6 channels [39]. Noteworthy to mention, several interventional procedures (e.g. dextrose injections) that were used to reduce pain in COVID-19 patients interact with TRPV1 channel [40]. Similarly, Bonvini et al. reported the activation of TRPM3 and TRPV4 channels by hypoosmolar solutions that were used to challenge cough [28]. Taken together, TRP channels are promising targets for alleviating pain in COVID-19 patients.

3.2.2. TRP channels and fever in COVID-19

Fever is one of the symptoms reported in 98% of COVID-19 patients [34]. It was demonstrated that a continuous fever that lasts for long term is responsible for heat shock protein 70 [HSP70] depletion, ARDS and death [16]. Also, it is widely accepted that the expression of thermosensitive ion channels (e.g. some TRP channels) plays a key role in thermoregulation conducted by hypothalamus [41]. These channels allow hypothalamic neurons to respond to minor thermal fluctuations in the body in addition to other functions [41]. Particularly, high expression of TRPV1, TRPV2, TRPV3 and TRPV4 channels compared to lower expression for TRPA1 and TRPM8 channels was revealed in the hypothalamus [41]. Of note , TRPV1, TRPV2, TRPV3, TRPV4 and TRPM3 channels are gated by warm temperatures [16].

When body temperature progressively increases, the heat shock response [HSR] is activated leading to plasma membrane fluidization and a transient opening of TRPV1 channel [42,43]. It was revealed that using TRPV1 agonists such as capsaicin and RTX up-regulated the accumulation of several HSP proteins (e.g. HSP70, HSP27 and HSP90) in epithelial cells [44] while the use of TRPV1 siRNA and TRPV1 antagonists [e.g. capsazepine, or AMG-9810] attenuated HSPs [44]. Also, it was documented that TRPV1 trafficking can be modulated by HSP70 proteins [44]. Interestingly, Bromberg and Weiss proved the co-precipitation of TRPV1 and HSP70 from the lungs of septic rats treated with HSP70-expressing adenovirus [42].

TRPV4 immunoreactivity was found in the anterior hypothalamic structures that are involved in the integration of thermal and osmotic signals [45]. Importantly, it was reported that TRPM2 channel is a heat sensor in the hypothalamus contributing to hypothermia during fever [46]. Another aspect that can link TRP channels and fever is their sensitization by phosphatidylinositol 4,5-bisphosphate [PIP2] which is highly abundant in the membrane [42]. All these data suggest that TRP channels can play a crucial role in fever in COVID-19 patients and can be promising targets in developing antipyretic drugs.

3.2.3. TRP channels and respiratory complications in COVID-19

Pursuant to many published researches, Ca^{2+} is needed for the entry, morphogenesis, replication, assembly, release and immune evasion of SARS-CoV viruses [47]. Due to the high selectivity of many TRP channels to Ca^{2+}, it is expected that several TRP channels contribute to the respiratory complications associated with COVID-19. In this context, it was noted that the upper and lower respiratory tracts are densely populated by sensory afferent neurons in dorsal root ganglia [DRG] and nodose vagal ganglia that express high levels of TRPV1 channel [38]. Additionally, several reports showed that TRPV1 channel is expressed in the epithelial cells of lungs [20].

3.2.3.1. Pulmonary edema. Around 53% of COVID-19 mortalities resulted from ARDS caused by the accumulation of protein-rich inflammatory edema leading to cell death of alveolar cells in the lungs [16,17]. Notably, pulmonary edema and disruption of the alveolo-capillary barrier are key drivers to the critical stages of COVID-19 infection [48]. Further, it was mentioned that there is link between the increase in intracellular Ca^{2+} and ROS levels in mitochondria, an important matter that contributes to the functions of many viruses including members of *Coronaviridae* family [47]. In this line, earlier reports showed that several TRP channels [such as TRPM2, TRPV4, TRPV1, TRPC1, TRPC4 and TRPC6 channels] are involved in enhancing the vascular permeability in lung endothelium [19] (Fig. 1). In fact, many TRP channels are expressed in the lung, including TRPV2, TRPV5 and TRPV6 channels [49]. In addition, in primary afferent neurons, TRPV1 channel can be activated by ROS or heat produced during tissue injury and inflammation [43,50]. Besides, several studies pointed to TRPA1 channel as a molecular target for ROS and other oxidative stress byproducts [28].

TRPV4 channel was recently emerged as a therapeutic target in many respiratory diseases including SARS-CoV-2 infection [22]. TRPV4 can be activated by osmotic gradients that occur during edema [18]. TRPV4 activation also contributes to the formation of nitric oxide, ROS in alveolar macrophages and mediates vasoconstriction in pulmonary artery smooth muscle cells [49]. Thus, the use of TRPV4 inhibitors in a model of acute lung injury prevented edema, reduced arterial pressure and hyperactivity in the airways [20]. Besides, Balakrishna et al. reported that blocking TRPV4 is correlated with inhibiting inflammation and edema [18].

Worthy to mention, the depletion of Ca^{2+} stores from the endoplasmic reticulum (ER) can activate other channels such as TRPC1 and TRPC4 channels [51]. This activation increases Ca^{2+} influx and endothelial contraction in lung endothelium [52]. Also, it was reported that platelet-activating factor causes recruitment of TRPC6 channel into lung endothelial cells and increases Ca^{2+} influx and endothelial permeability [53]. Of note, George and colleagues depicted that there could be fibrotic consequences after SARS-CoV-2 infection [54].

Using proteomics and metabolomics of data obtained from 85 confirmed COVID-19 cases in Guangxi, China, it was revealed that the interplay between TRP channels and inflammatory pathways is a crucial factor for pulmonary fibrosis; in terms of occurrence and development

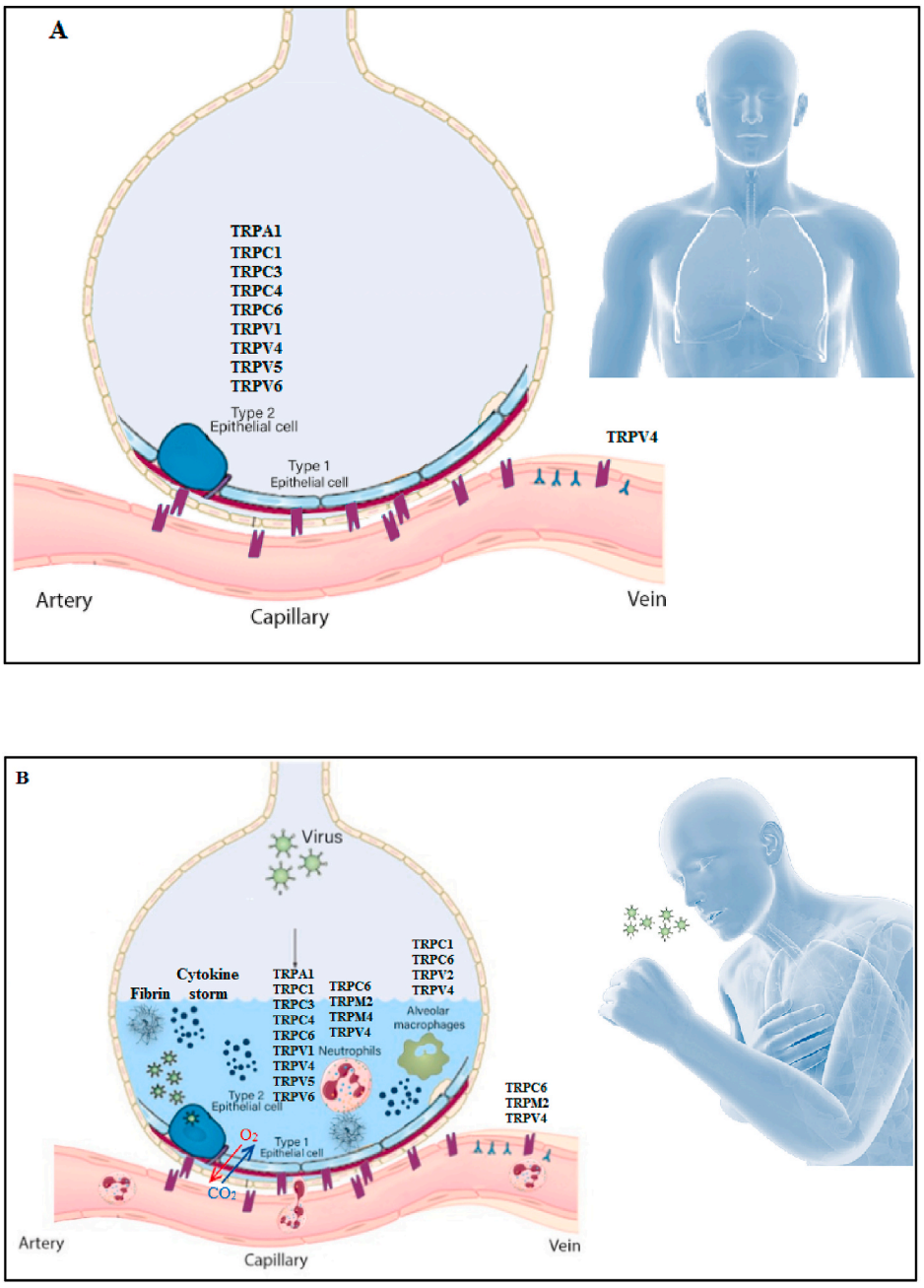

Fig. 1. Alveolus in lung A] Normal state B] Pulmonary edema in COVID-19 disease.

[55]. In this context, previous studies showed that TRPV4 and TRPM7 channels are regulators for pulmonary fibrosis [20,21]. More research is needed to investigate the involvement of TRP channels in COVID-19-associated fibrosis. Furthermore, Jian and co-workers affirmed the link between TRPV4-induced Ca^{+2} uptake and lung congestion, dyspnea as well as the increase in pulmonary vascular pressure [56]. With respect to dyspnea, previous studies published that restoring serotonin levels can convert silent hypoxemia into symptomatic hypoxemia at an early stage in SARS-CoV-2 patients, thus can help them to seek early treatment [57]. Importantly, several researches highlighted the relation between serotonin release and TRP channels suggesting that TRP channels can play a vital role in hypoxemia in COVID-19 patients [58–63]. Consistent with the previously mentioned information, TRP channels can be therapeutic targets for alleviating pulmonary edema in COVID-19 patients.

3.2.3.2. Cough. Cough was documented in 76% of COVID-19 patients [34]. Several TRP channels are involved in respiratory complications associated with COVID-19 infection [36]. In general, the activation of TRP channels in sensory nerves of the airways causes Ca^{2+} influx, depolarization and action potential that collectively lead to cough [27]. Additionally, previous works affirmed that the respiratory viral infection up-regulates TRPA1 and TRPV1 channels in airway cells [64]. Importantly, the administration of TRPA1, TRPV4 and TRPV1 agonists evoked cough in a dose dependent manner in preclinical studies [65]. Also, the use of gabapentin neuromodulator was effective in patients suffering from chronic cough in a mechanism that involved blocking subtypes of TRP channels [65]. Interestingly, it was documented that pulmonary viral exposure can convert the low-threshold cough mechanoreceptors into nociceptors due to the expression of TRPV1 and substance P [SP] [65]. In fact, the role of TRPV1 channel in cough was highlighted in several studies whereby one study drew attention to the finding that capsaicin oral administration improved cough through

desensitization of TRPV1 channel [66]. Moreover, it was demonstrated that using a TRPV4 antagonist reversed cough induced by a TRPV4 agonist in a mechanism that involves P_2X_3 receptor [67]. Also, it was hypothesized that black pepper, ginger, green tea and curcuma improved nasal obstruction and cough in a TRPA1 dependent mechanism [36]. All of these studies display the possible involvement of TRP channels in cough reflexes in COVID-19.

3.2.4. TRP channels and neurological alterations in COVID-19

Accumulating lines of evidences showed that several neurological alterations are associated with COVID-19 including headache, and symptoms of muscle damage (e.g. soreness and weakness of limbs) [14,68]. SARS-CoV-2 virus is one of the neuroinvasive viruses detected in the brain parenchyma and cerebrospinal fluid in human and animal models [69]. Thus, the virus contributes to neurological alterations that are associated with COVID-19 [69].

3.2.4.1. Headache. Headache is a frequent symptom observed in COVID-19 patients in the emergency rooms [14]. It was documented that viral proliferation in lung tissues can disrupt alveolar exchange and can cause hypoxia in CNS, obstruction of cerebral blood flow and accordingly headache due to ischemia [69]. Cerebral edema and coma may also develop if hypoxia persisted [69].

It is accepted that many TRP channels play crucial roles in headache and migraine symptoms since these channels (e.g. TRPV1 channel) are expressed in trigeminal ganglia [TG] neurons and dural nerve fibers [70]. One of the drugs that proved effectiveness in alleviating headache is sumatriptan that inhibits TRPV1 channel [71]. Also, it was found that the use of civamide [an intranasal TRPV1 agonist] reduced the frequency of headache attacks in patients [72]. Furthermore, TRPV4 mRNA is expressed in TG neurons compared to the minimal expression of TRPM8 mRNA [70,73]. According to Wei et al., TRPV4 activation contributed to headache-like behavior in rats [74]. Similarly, TRPA1 channel is expressed in peripheral sensory neurons and contributes to the emergence of headache [70]. The importance of TRP channels in the occurrence of headache can be manifested by the fact that these channels are activated by many stimuli that cause headache such as low pH [70].

3.2.4.2. Myalgia. Myalgia is a common symptom in 44% of COVID-19 patients [34]. Earlier reports showed that SARS-CoV-2 can affect skeletal muscle cells by direct binding to ACE2 or via indirect routes [75]. Also, several hypotheses were proposed about the mechanisms that underlie myofascial pain syndrome [13]. One of them is the muscle contracture and energy crisis hypothesis in which Ca^{2+} leakage from the sarcoplasmic reticulum in injured muscles can cause taut bands, energy crisis and production of different sensitizers that lead to pain [13]. The involvement of Ca^{2+} raises the possibility of TRP channels' involvement in muscular disorders. In this regard, previous studies reported that TRPV channels have a role in delayed onset muscle soreness that occurs after strenuous exercise [13]. Moreover, the interaction between TRPV1 channel and other receptors (e.g. acid sensing ion channels) is widely accepted to take part in ischemic muscle [76].

3.2.5. TRP channels anosmia, ageusia and hearing loss in COVID-19

Worldwide, it was emerged that COVID-19 infection causes a reduction or loss of taste and smell [77]. Notably, ACE2 and TMPRSS2 proteins are expressed in the olfactory epithelial support cells [sustentacular cells] but not olfactory sensory neurons [6]. Also, it was found that taste buds don't express ACE2 while epithelial cells of the tongue do [78].

TRP channels are abundant in oral mucosal cells, epithelial cells of the tongue and taste buds [32]. For instance, TRPV1 channel is expressed in the neurons that innervate the oral cavity [15]. Additionally, TRPM4 channel is expressed in type I and II cells [79] while TRPM5 channel is expressed in type II cells [15]. Therefore, a loss of either TRPM4 or TRPM5 channels may significantly impair taste [79]. In more detail, the tastants interact with their G-protein coupled receptors leading to an increase in intracellular Ca^{2+} and TRPM5 activation; hence, taste recognition [15]. Importantly, Dnate' Baxter and co-workers documented that mouse TRPM5-expressing cells showed expression of different transcripts that take part in immunity, inflammation and viral infection such as TMPRSS2 transcript [80]. This fact points to the potential role of TRPM5 channel in smell loss [80], albeit not directly. Noteworthy, the nasal and oral TG nerve endings are activated by irritant chemicals that can be recognized by TRP channels such as menthol, capsaicin, thymol and allicin resulting in different sensations [81] suggesting that TRP channels can contribute to anosmia and ageusia in COVID-19 patients. Interestingly, many of the taste chemicals (e.g. eugenol, menthol and linalool) can activate TRPV1 and TRPM8 channels [82]. Others (e.g. eugenol and allicin) can activate TRPV1 and TRPA1 channels [82]. Collectively, this information highlights the possible involvement of TRP channels in anosmia and ageusia in COVID-19 disease as summarized in Fig. 2.

The authors of this review need to point to hearing loss/impairment symptom in patients infected with the new strain of SARS-CoV-2 (B.1.617 variant) in addition to other symptoms of COVID-19 (nausea, vomiting, diarrhea and abdominal pain) [83]. There is relationship between one type of the TRP channels (TRPV4) and hearing impairment as reported by Tabuchi and collaborators who found that there was a hearing impairment in TRPV4-knockout mice [84]. Future studies may indicate the involvement of TRP channels in the complications of the new strain of SARS-CoV-2.

3.2.6. TRP channels and GI complications in COVID-19

Nausea, anorexia, vomiting and diarrhea are reported symptoms in many patients infected with SARS-CoV-2 [3]. In addition, it became well-recognized that appetite loss is a common and may be severe symptom in COVID-19 patients especially in people infected with the SARS-CoV-2 variant B.1.617 [83,85].

There are several mechanisms hypothesized to be involved in the viral induced symptoms in the GI system (e.g. nausea and vomiting) (Fig. 3). In the first days post-infection, the virus can induce the release of hormones and neuroactive agents [e.g. serotonin and SP] from the enteroendocrine cells [EECs] in the upper GI tract or cytokines from inflamed GI epithelia [3]. These mediators act systemically by binding to their receptors in the area postrema or locally by sensitizing the abdominal vagal afferent neurons leading to nucleus tractus solitarius [NTS] stimulation [86]. This stimulation evokes motor pathways responsible for the vomiting reflex and sends signals to the higher brain regions to generate the sensation of nausea [86]. In delayed onset symptoms, the viral attack to the area postrema in the dorsal brainstem that regulates the digestive system can be another mechanism for SARS-CoV-2 in inducing these complications [3].

Importantly, previous studies highlighted the broad expression of several TRP channels in the GI tract and their role in response to noxious irritants [87]. TRPV1 expression had been well described in esophageal sensory neurons, stomach-labeled vagal nodose neurons and colon labeled afferent neurons [58,88,89]. In this line, Hammer and Vogelsang reported that capsaicin infusion into the proximal small intestine of human volunteers evoked sensations of pain, cramps, pressure, warmth and nausea [59]. Likewise, it was reported that TRPA1 channel was co-expressed with TRPV1 channel in the esophagus, stomach, intestine and colon [60–62]. Importantly, the *in vitro* activation of TRPA1 channel with allyl isothiocyanates evoked serotonin release from enterochromaffin cells [EC], leading to the stimulation of vomiting [90]. Also, TRPM8 channel was expressed in colonic afferent neurons, esophageal vagal jugular, stomach-labeled nodose and jugular neurons [63,89]. Additionally, there is broad expression of TRPV4 channel in the GI tract including the primary sensory neurons [20]. On the other hand, it was documented that there is close interplay between some TRP channels and food intake suggesting the possible role of TRP channels in appetite

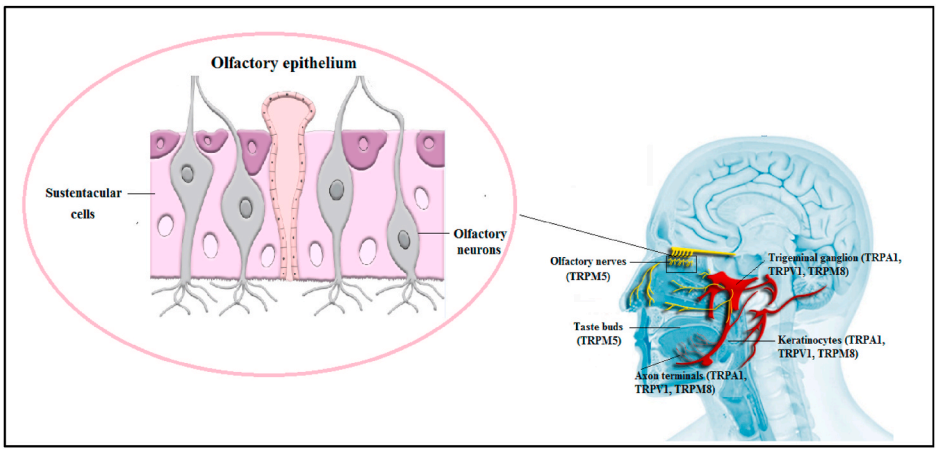

Fig. 2. TRP channels, anosmia and ageusia in COVID-19.

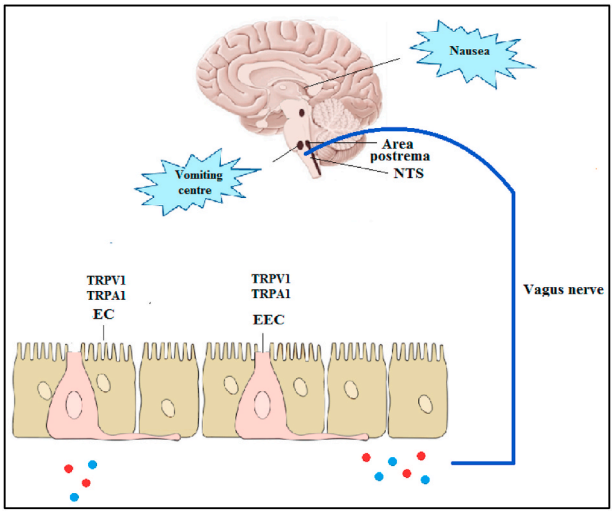

Fig. 3. Possible involvement of TRP channels in nausea and vomiting in COVID-19.

loss in COVID-19 patients [91,92]. For instance, TRPA1 channel has a role in satiety and food intake [91]. Moreover, TRPV1 channel plays a fundamental role in the control of appetite via influencing key hormones or modulating the signaling of GI vagal afferent nerve [92]. The involvement of TRP channels in COVID-19-associated GI symptoms needs further consideration in future studies.

3.2.7. TRP channels and cardiovascular complications in COVID-19

Cardiovascular complications are one of the risks that are associated with COVID-19 particularly in elderly and individuals suffering from hypertension [93]. Also, arrhythmias, cardiac fibrosis and myocyte hypertrophy were reported in many COVID-19 patients [94,95]. Importantly, several studies exemplified that multiple TRP channels are expressed in the heart and contribute to several cardiac complications [21,96]. For instance, TRPC channels is involved in the development of cardiac hypertrophy and heart failure while TRPM4 channel is implicated in cardiac arrhythmias [96]. Also, it was reported that TRPM7 channel contributes to the pathogenesis of cardiac fibrosis [21].

In fact, TRPC3, TRPC4 and TRPM2 channels act as endothelial redox sensors meanwhile TRPC1, TRPC4, TRPC6, TRPV4 and TRPM2 channels have been implicated in endothelial barrier dysfunction [97]. TRPM2 channel is involved in facilitating Ca^{2+} entry in response to oxidative stress and regulating endothelial barrier integrity [97]. Also, Xu and collaborators reported that TRPV4 activation limited atherosclerosis and vascular inflammation [98]. In the endothelial cells of carotid artery, TRPV4 loss of function caused problems in blood pressure and vascular tone [99]. In another study, it was demonstrated that TRPV4 loss of function induced Ca^{2+} release from internal stores, thus affecting vascular homeostasis [72]. The relation between TRP channels and Ca^{2+} ions that are needed for the viral activities suggests that TRP channels can be targeted in COVID-19 disease. Table 1 summarizes the possible involvement of TRP channels in COVID-19 symptoms.

Table 1
TRP channels and COVID-19 symptoms.

Symptom	TRP channel(s) involved in the symptom	Reference
Inflammation	TRPV4	[20]
Inflammation	TRPA1	[36]
Stress-related inflammatory processes	TRPM2	[37]
Airway inflammation induced by viral infection	TRPV1	[38, 40]
Pain	TRPV1	[15]
Pain	TRPM2, TRPM3,TRPM8	[39]
Pain	TRPV2, TRPV3, TRPV4, TRPC1, TRPC6	[39]
Fever	TRPM2	[46]
Pulmonary edema	TRPM2, TRPV4, TRPV1, TRPC1, TRPC4, TRPC6	[19]
Ventilator-induced lung injury	TRPV4	[48]
Oxidative stress	TRPV1	[43]
Oxidative stress	TRPA1	[28]
Nitric oxide and ROS production in alveolar macrophages	TRPV4	[49]
Increase in the endothelial permeability of pulmonary blood vessels	TRPC6	[53]
Pulmonary fibrosis	TRPV4, TRPM7	[20, 21]
Cough	TRPA1, TRPV4, TRPV1	[65]
Headache	TRPV1	[71]
Headache	TRPV4	[74]
Headache	TRPA1	[70]
Myalgia	TRPV channels	[13]
Ischemic muscle Myalgia	TRPV1	[76]
Loss of taste	TRPM4, TRPM5	[79]
Loss of smell	TRPM5	[80]
Hearing impairment	TRPV4	[84]
Vomiting	TRPA1	[90]
Nausea	TRPV1	[59]
Loss of appetite	TRPA1	[91]
Loss of appetite	TRPV1	[92]
Cardiac arrhythmia	TRPM4	[96]
Cardiac fibrosis	TRPM7	[21]
Endothelial redox sensors	TRPC3, TRPC4, TRPM2	[97]
Endothelial barrier dysfunction	TRPC1, TRPC4, TRPC6, TRPV4, TRPM2	[97]

3.3. Potential trends for the prevention and treatment of COVID-19

3.3.1. Blocking/desensitization of TRP channels

Finding optimal therapies for the relief of symptoms in COVID-19 patients relies on understanding the pathways and signaling mechanisms that are activated by the viral entry. The complexity lies in the multi-organ systems that are affected by the infectious virus. However, Ca^{2+} signaling was reported to be an important contributor [47]. As shown in previous studies, TRP channels provide a favorable environment for viruses and contribute significantly to the increase in cellular Ca^{2+} levels and viral infection [64,100]. Accordingly, blocking TRP channels can be an effective measure in controlling different viruses including SARS-CoV-2. In more detail, it was found that blocking the function of TRP channels using antagonists, antibodies or aptamers is a well-known strategy for treating certain diseases. Some TRP antagonists are already in clinical trials for this purpose. For example, a TRPV4 antagonist (GSK2798745) was developed as a novel therapeutic intervention for the treatment of pulmonary edema associated with heart failure [101]. A TRPC4 and TRPC5 inhibitor [Hydra/Boehringer Ingelheim] is currently in clinical trial phase I for treating anxiety disorder and depression [102]. Noteworthy, there is trend towards using concentrations of compounds that cause desensitization of TRP channels rather than blocking them [103]. Tachyphylaxis, defined as a reduction in the response after repeated applications of agonists, is another form of desensitization and can be considered in targeting TRP channels in this context [104]. The importance of the agonistic approach relies on the fact that using agonists inhibits the function in the entire nociceptor compared to using antagonists that only blocks the channel's activation [103]. Other reason is that the intake of many antagonists produces undesirable effects [105]. For instance, the use of TRPV1 antagonists causes hyperthermia and block of thermosensation [105]. Several researches showed the benefits of using TRP agonists in this context. It appeared that silencing TRPV1-expressing pulmonary sensory neurons using RTX improved survival in a mouse model of cytokine storm lethal pneumonia induced by *Staphylococcus aureus* [106]. Therefore, TRPV1 desensitization [e.g. by using RTX] in afferent pathways can decrease the severity of ARDS syndrome in COVID-19 patients [11]. Additionally, TRPV1 desensitization by the non-pungent synthetic analogue of capsaicin (olvanil) inhibited nociceptive processing in DRG neurons and decreased capsaicin-induce thermal hyperalgesia [107]. Also, it was proposed that rapid desensitization of TRPA1 channel could reduce complications of COVID-19 symptoms [36]. Importantly, it is well-known that TRP channels are targets for venomous toxins (Fig. 4) [108]. The use of toxins (e.g. RTX) for COVID-19 treatment has been suggested [11]. Previous researches showed that the spider toxins from *Psalmopoeus cambdridgei* [e.g. vanillotoxins 1–3] and *Ornithoctonus huwena* [Earth Tiger] [e.g. double-knot toxin] can specifically activate TRPV1 channel [109]. Bv8 is another toxin (obtained from the skin of *Bombina variegata* frog) that causes hyperalgesia in a TRPV1 dependent mechanism [110]. Besides, it was documented that polycyclic ether toxins [e.g. brevetoxin and gambierol] extracted from marine dinoflagellates act as allosteric modulators for TRPV1 channel [111]. Furthermore, previous reports showed that multiple toxins inhibit TRPV1 channel including the venom of the tropical sea anemone *Heteractis crispa*, the analgesic polypeptide toxin and two toxins extracted from *Agelenopsis aperta* spider, named as AG505 and AG489 [112,113].

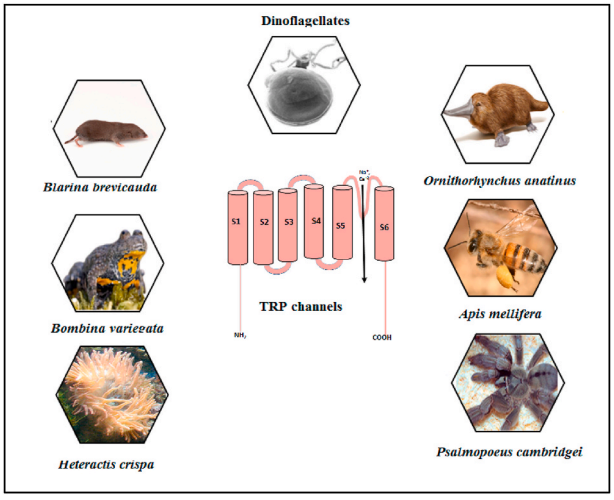

Fig. 4. Examples of venoms that modulate the functions of TRP channels.

Other TRP channels can be also targeted by toxins. For example, it was reported that soricidin (extracted from the salivary glands of *Blarina brevicauda* shrew) inhibits TRPV6-induced Ca^{2+} uptake [114]. Also, melittin venom from bee [*Apis mellifera*] can target TRPC and TRPV1 channels while the venoms from *Ornithorhynchus anatinus* platypus and fish-containing ciguatoxin [CTX] affect TRPA1 channel [108,115]. Besides, TRPC6 channel can be blocked by the tarantula peptide, GsMTx-4 [116]. All of this information suggests that venoms can be used to target TRP channels to alleviate COVID-19 symptoms .

3.3.2. Potential use of medicinal plants and phytochemicals interacting with TRP channels for the prevention and treatment of COVID-19

Medicinal plants are considered rich sources for active ingredients that proved to be valuable in treating different diseases including viral diseases. In a randomized, open label, placebo-controlled, multi-center clinical trial, the administration of *Nigella sativa* L. with honey for thirteen days caused viral clearance and a reduction in the severity of COVID-19 symptoms [117]. To add, it was shown that thymoquinone, the active compound in *N. sativa*, caused 98% inhibition of SARS-CoV-2 [118]. Another study provided a solid evidence for the effectiveness of *N. sativa* in decreasing coronavirus load in HeLa-infected cells as well as its effect on the expression of several TRP genes [119].

In a study conducted by Wang et al., the researchers cultivated 800 types of *Cannabis sativa* L. containing high amount of the non-psychotropic phytocannabinoid cannabidiol (CBD) which shows anti-inflammatory properties [120]. The authors identified 13 *C. sativa* extracts that are high in CBD and low in 9-tetrahydrocannabinolic acid and showed that these extracts can decrease ACE2 and TMPRSS2 protein levels as proved in artificial three dimensional (3D) human models of oral, airway and intestinal tissues [120]. Noteworthy, TRP channels (e.g. TRPV1-4, TRPA1, and TRPM8 channels) are putative cannabinoid receptors [121]. Thus, CBD might decrease the viral load through direct or indirect interaction with TRP channels.

In addition, several phytochemicals that interact with TRP channels can be potential treatments for COVID-19 [122–143]. However, the implication of the involvement of TRP channels in their mechanism of action had not been investigated yet.

Berbamine is a bis-benzylisoquinoline alkaloid used in traditional Chinese medicine, Berberis [122]. This alkaloid potently inhibited the infection of various coronaviruses (e.g., SARS-CoV-2), inhibited TRPML channels and compromised the endolysosomal tracking of viral receptors, such as ACE2 [122]. As mentioned previously, TRPML channels are Ca^{2+} permeable, non-selective cation channel present in the endosomes and lysosomes [31] suggesting that targeting TRML channels to inhibit SARS-CoV-2 entry to the host cells is a useful strategy that can be involved in the antiviral effect of this alkaloid. . In fact, this information opens a door for future *in silico* and *in vitro* studies to discover lead compounds that can inhibit TRML channels and SARS-CoV-2 entry to host cells.

To add, some natural compounds have the potential for inhibiting SARS-CoV-2 as well as treating at least some symptoms of COVID-19. Examples include, but not limited to, resveratrol, spermidine, spermine, naringenin, quercetin, curcumin and baicalin.

Resveratrol is a polyphenol present in peanuts, berries, and red

grapes 122]. This polyphenol is a ligand for TRPV1, TRPA1, TRPM2, and TRPC5 channels [124–127]. In Vero E6 cells, resveratrol and its structurally related compound (pterostilbene) inhibited SARS-CoV-2 infection effectively by interfering with the post-entry steps of viral replication cycle [128]. Resveratrol is currently in several clinical trials for COVID-19 treatment [123]. Meanwhile, its exact mechanism of action against SARS-CoV-2 and its interaction with various types of TRP channels to alleviate COVID-19 symptoms needs further investigation.

Spermidine and spermine are potent TRPV1 ligands. It was documented that these polyamines inhibited SARS-CoV-2 infection possibly by inducing viral degradation in the endolysosomes [129,130]. Furthermore, spermidine attenuated bleomycin-induced lung fibrosis and inhibited ER stress-induced cell death in mice [131].

Naringenin targets several TRP channels producing analgesic effects [132]. In more detail, it reduced TRPV1 activation and blocked TRPM3 channel [132]. Also, naringenin inhibited human coronaviruses infection effectively [133] suggesting that this inhibition can be mediated by interaction with one or more of TRP channels.

Quercetin is a well known ligand for TRPM7, TRPV1 and TRPA1 channels [134–136]. In a prospective, randomized, controlled, and open-label study, a daily dose of 1000 mg of quercetin was given for 30 days to 152 COVID-19 outpatients to study its adjuvant effect in treating the early symptoms and in preventing the severe consequences of the disease. Quercetin was effective in improving COVID-19 early symptoms as well as preventing the severity of the disease [137].

Curcumin is a ligand for TRPM8, TRPV1 and TRPA1 channels while piperine is a TRPV1 ligand [138,139]. It was revealed that COVID-19 patients with mild, moderate, and severe symptoms who received curcumin/piperine treatment showed recovery from early symptoms [fever, cough, sore throat, and breathlessness] accompanied with better ability to maintain oxygen saturation above 94% and better clinical outcomes [140]. Moreover, *in silico* drug discovery suggested that curcumin acts as SARS-CoV-2 main protease inhibitor [141].

Finally, baicalin exhibited potent antiviral activities and was identified as the first non-covalent, non-peptidomimetic inhibitor of SARS-CoV-2 3CLpro [142]. Notably, earlier reports showed that baicalin caused down-regulation of TRPV1 mRNA expression levels in DRG neurons [143]. Taken together, all of the aforementioned studies suggest that TRP channels contribute to several symptoms of COVID-19 and can be seriously considered as targets for the treatment of this disease.

It is out of space to mention all the researches that were conducted about the effects of medicinal plants and active compounds on SARS-CoV-2. We suggest reading reviews that can be helpful in this context and that demonstrate the broad spectrum of TRP activation by active compounds [144–147]. TRP channels are targets for many of the active compounds that exhibited effectiveness against SARS-CoV-2 [148] and can be valuable targets for future subjective studies.

3.3.3. Use of dietary constituents and vitamins interacting with TRP channels for the prevention and treatment of COVID-19

There is substantial evidence revealing that variations in COVID-19 death rates between countries can be, partly, related to differences in dietary habits [149]. Notably, several diet varieties interact with TRP channels in different contexts. For example, many spices and fermented vegetables [e.g. allicin, capsaicin, curcumin, gingerol, piperine and Wasabi] interact with TRPA1 and TRPV1 channels [36]. Further, it was hypothesized that some diets can activate the nuclear factor erythroid 2–related factor 2 [Nrf2] and desensitize TRP channels, thus can alleviate several symptoms of COVID-19 [150]. For example, the consumption of spicy food caused desensitization of TRP channels in synergy with Nrf2 [149]. Of note, Nrf2 is a potent antioxidant that can inhibit SARS-CoV-2 induced oxidative stress [150]. Moreover, in a trial conducted during the first 2 phases of COVID-19 infection, it was found that there was a reduction in cough, fatigue, nasal and GI symptoms in patients who consumed either broccoli and paracetamol or broccoli with the agonists of TRPA1/TRPV1 and paracetamol [36]. Of note, broccoli capsules are considered potent agonists for Nrf2 and weak TRPA1 agonists [36]. In addition, open-labeled induced cough challenges were carried out in a COVID-19 patient using different treatments [137]. The results of this study suggested that there could be fast desensitization of TRPA1 and TRPV1 channels as well as a crosstalk with Nrf2 [137]. In more detail, the study was performed using nutrients that have different agonistic activities for Nrf2, TRPA1 and TRPV1. It was depicted that the use of red pepper [has high TRPV1 agonistic activity] or curcumin and black pepper [both are potent TRPA1 agonists] were effective in decreasing cough with a 3-h persistent effect. The use of broccoli [has strong Nrf2 agonistic activity] reduced cough with an effect that lasted for 6 h. The combination of broccoli, curcumin and black pepper was more effective in cough reduction and this effect persisted for more than 9 h.

In another study, the authors referred to a Korean traditional food [Kimchi] as a food that may be associated with low COVID-19 mortalities in Korea [151]. Kimchi is prepared by fermenting baechu cabbage with cruciferous vegetables and other ingredients such as ginger, red pepper and garlic [151]. These ingredients are known to be activators for Nrf2 and certain TRP channels [e.g. TRPA1, TRPV1] [150].

Worthy to emphasize on, it was speculated that vitamin D deficiency is associated with severe symptoms and a high fatality rate in COVID-19 patients [152]. Recently, it was shown that 25-hydroxyvitamin D is a partial agonist for TRPV1 channel contributing to a decrease in T-cell activation and Ca^{2+} signaling mediated by TRPV1 channel in TG neurons [153]. This fact suggests that there could be link between several symptoms of COVID-19, vitamin D and TRP channels.

4. Conclusions

Several studies provided foundations for the possible involvement of TRP channels in different pathophysiological mechanisms in COVID-19. Since TRP channels contribute to several symptoms of COVID-19, they can be seriously considered as targets for the prevention and treatment of this disease. However, the specific role of TRP channels in COVID-19 symptoms needs further investigation.

The authors of this review suggest that using TRP channel- targeted therapy (e.g. venoms and agonists) to desensitize TRP channels can alleviate COVID-19 symptoms. Particularly, the desensitization of TRPV1 channel using RTX or venoms may decrease the severity of ARDS syndrome in COVID-19 patients. To add, the inhibition of TRPML2 channel can be used as a strategy to inhibit SARS-CoV-2 entry into the host cells. Further investigation is recommended. New insights will undoubtedly arise in the future.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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