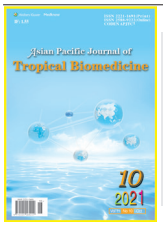

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Potential immunomodulatory role of sesamin in combating immune dysregulation associated with COVID−19

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ABSTRACT

The ongoing outbreak of novel coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused an unprecedented global health crisis. Development of a cure for this devastating disease is currently at full speed, with several vaccines against COVID-19 already authorized and administered. Currently, demand for these vaccines far exceeds supply. As such, boosting immunity represents a viable route to halt the rapid spread of SARS-CoV-2 and limit fatalities until vaccines become more readily and widely available. The use of phytochemicals appears to be a promising panacea. Sesamin, a lignan isolated from *Sesamum indicum* seeds, is known for its potent pharmacological properties, and is therefore hypothesized as a potential candidate in the therapeutic regimen against COVID-19. Herein, we highlight the confirmed therapeutic anti-inflammatory and immune-modulatory potential of sesamin against myriads of respiratory disorders, and tentatively suggest that sesamin may exert similar potent effects against COVID-19. Precisely, we speculate that sesamin may help alleviate COVID-19 *via* restoring Th1/Th2 balance and preventing inflammation and cytokine storm development. Additionally, we further support the promising role of sesamin against COVID-19 by underscoring the direct evidence, which suggests that sesamin may demonstrate promising inhibitory potential against three important SARS-CoV-2 targets, namely main protease, spike protein, and angiotensin-converting enzyme 2 receptor. Although preliminary, there is ample evidence to propose sesamin as a potential phytotherapeutic and prophylactic candidate against COVID-19. Further *in vitro*, *in vivo*, and preclinical studies are required to further substantiate the role of sesamin in the prevention and/or treatment of COVID-19.

KEYWORDS: Sesamin; SARS-CoV-2; COVID-19; Immunomodulation; Anti-inflammatory; Cytokine storm; Th1/Th2 balance

1. Introduction

Viruses are ubiquitous infectious agents which may induce classical inflammation *via* activating innate and adaptive immune responses. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent for the 2019 coronavirus disease (COVID-19) is one such example known to induce inflammation, mainly in the lungs. Thus far, the ongoing outbreak of this virus has spread to more than 220 countries with over 163 million confirmed cases and over 3 million deaths worldwide as of May 2021[1]. The virus belongs to the coronavirus (CoV) family of Coronavirida, which consists of four major subfamilies, out of which α- and β-CoVs can infect mammals, including humans[2]. SARS-CoV-2 is identified as a β-CoV with a positive-sense single-stranded RNA genome, encapsulated by a membrane envelope. The virus is wrapped in a lipid bilayer in which viral surface proteins, like spike protein (S protein), are embedded[2]. Like the two previous β-CoV outbreaks, namely SARS-CoV, which occurred in China in 2002 and Middle East respiratory syndrome, which first appeared in Saudi Arabia in 2012, SARS-CoV-2 is a respiratory pathogen. Once SARS-CoV-2 gains entry to the respiratory tract, it damages the airway epithelial cells making it difficult for the lungs to filter

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out dirt and dust, eventually leading to pneumonia. The most-reported clinical symptoms of COVID-19 include fever, dry cough, fatigue, myalgia, and dyspnea[3,4]. In severe cases, COVID-19 may also lead to cytokine storm development, a systemic inflammatory response arising from increased oxidative stress due to the rapid release of free radicals and cytokines[5,6]. If not managed, cytokine storm may result in acute respiratory distress syndrome (ARDS), a respiratory failure characterized by the rapid onset of inflammation in the lungs, and a condition that is regarded as a major reason for fatality in COVID-19 patients[5]. Currently, multiple vaccines have been developed with the promise of protection against COVID-19. Nevertheless, it is estimated that it could take up to a year for enough of the vaccine to be manufactured to help inoculate the general public, leaving most of the population at risk of developing COVID-19 until vaccines become more readily accessible. Developing and maintaining strong immunity then becomes a necessity, and there is ample evidence supporting the exceptional pharmacological benefits that natural products may have against myriads of infections, of which COVID-19 is no exception[7].

Sesamin, with a molar mass of 354.35 g/mol and a molecular formula of $C_{20}H_{18}O_6$, is a lipid-soluble furanofuran-type lignan isolated from *Sesamum indicum* seeds. The health-promoting benefits of sesamin have been recently reviewed[8]. Besides its ability to regulate macrophage cholesterol homeostasis[9,10], sesamin has been shown to exert potent anti-hyperlipidemic[11], anti-carcinogenic[12], immunomodulatory and anti-inflammatory[13] effects *in vitro* and *in vivo*. Thymoquinone (in *Nigella sativa*), curcumin (in *Curcuma longa*), and allicin (in *Allium sativum*) are examples of natural anti-inflammatory agents proposed to exert promising antiviral effects against COVID-19[14,15]. Despite its promising immunomodulatory and anti-inflammatory properties, very few studies examined the therapeutic potential of sesamin against COVID-19. In this review, more light will be shed on the therapeutic anti-inflammatory and immunomodulatory potential of sesamin that is believed to be of relevance in the fight against COVID-19. Precisely, the role of sesamin in restoring Th1/Th2 balance and in preventing inflammation and cytokine storm development in a plethora of respiratory disorders will be highlighted, tentatively suggesting that sesamin may exert similar potent anti-inflammatory effects against COVID-19. Additionally, direct evidence indicating the inhibitory potential of sesamin against main protease (M^{pro}) and other critical SARS-CoV-2 molecular targets will be highlighted. Taken together, this review sets the foundation for the potential use of a potent and natural anti-inflammatory and immunomodulatory agent like sesamin for the prophylaxis and/or treatment of the dreaded disease, COVID-19, and highly encourages future endeavors to further confirm its therapeutic role against this infection.

2. Role of sesamin in modulating Th1/Th2 responses in lung tissue

T lymphocytes are a major source of cytokines. There are two major subsets of T lymphocytes, distinguished by the presence of cell surface molecules known as CD4 and CD8. Type 1 helper (Th1) cells, along with type 2 helper (Th2) cells belong to the $CD4^+$ T helper cell subset, which are formed following the activation of naïve Th cells[16]. These two divisions work antagonistically, with Th1 and Th2 cells combating intracellular and extracellular pathogens, respectively[17]. Interleukin 2 (IL-2), IL-12, IL-18, tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ) are examples of Th1-related cytokines. These are primarily pro-inflammatory and are responsible for killing intracellular parasites and for perpetuating autoimmune responses[16]. On the other hand, IL-4, IL-5, IL-10, and IL-13 are examples of Th2-related cytokines, which are associated with elimination of extracellular pathogens and promotion of immunoglobulin E (IgE) and eosinophilic responses in atopy[16]. Having well-balanced immune responses that are suited to the immune challenge is key to orchestrate a well-coordinated immune response to eliminate pathogens. Evidence suggests that sesamin possesses promising immunomodulatory properties that may prove to be useful for promoting Th1 immune responses and suppressing Th2 immune responses, thus striking a balance between these two divisions.

Th1/Th2 imbalance can exacerbate disease outcomes in many different types of ailments, including respiratory disorders. Several studies point to the role of sesamin in modulating Th1/Th2 immune responses in different types of allergic disorders. In one *in vivo* study, sesamin was found to restore the balance between Th1- and Th2-related immune responses in female BALB/c mice with ovalbumin (OVA)-induced allergic asthma[18]. In particular, the oral administration of sesamin (200 mg/kg/day) for 3 d was found to result in a significant drop in the Th2 cytokines IL-4, IL-5, and IL-13, after their levels have been significantly increased following OVA-sensitization in female mice. Additionally, sesamin administration (200 mg/kg/day) was also found to significantly elevate the levels of IFN-γ, a key Th1 cytokine known to play a role in inhibiting airway eosinophilia, after its levels were decreased following OVA-sensitization in mice. The Th1 and Th2 modulatory effects of sesamin were found to result in a significant attenuation of allergic airway inflammation in OVA-sensitized mice. Collectively, findings from this study point to the importance of Th1/Th2 modulation for alleviating allergic airway inflammation and support the promising potential of sesamin to bring about the Th1/Th2 modulatory effects. Similar results also reported in another *in vivo* study conducted by Lin and colleagues, whereby sesamin was found to significantly decrease OVA-induced immune responses in male BALB/c mice with allergic asthma *via* suppression of Th2-cytokine release[19]. In particular, administering sesamin (1, 10, and 20 mg/kg) daily for 6 d to OVA-sensitized mice was associated with

a significant suppression in IL-4, IL-5, and IL-13 levels, all of which play critical roles in mediating Th2 responses. An *in vitro* study by Hsieh and colleagues found that sesamin may have the potential to alleviate asthmatic inflammation through downregulating the expression of both Th1- and Th2-related chemokine expression in the human monocytic cell line (THP-1) and human primary monocytes[20]. In particular, pre-treating THP-1 cells with sesamin (1-10 μM) for 2 h before lipopolysaccharide (LPS) stimulation was found to result in a significant reduction in the levels of macrophage-derived chemokine, a Th2 chemokine shown to be elevated in asthmatic patients, and interferon gamma-induced protein 10 (IP-10), a Th1 chemokine implicated in inflammation and hyperreactivity in asthmatic patients. Similar, but less potent, effects were also reported in human primary monocytes, whereby pre-treatment of monocytes with sesamin (1-10 μM) for 2 h resulted in a significant decrease in macrophage-derived chemokine, but not IP-10 levels after these cells were stimulated with LPS for 24-48 h. Collectively, findings from all these studies strongly encourage the propensity of sesamin in restoring Th1/Th2 balance and in potentially alleviating several types of respiratory disorders. As it stands, research on the promising restorative effects of sesamin on Th1/Th2 balance is restricted to *in vitro* and *in vivo* studies conducted on rodents, preventing any definite conclusions on its potent immunomodulatory effects to be drawn in humans. Future endeavors should therefore be aimed at exploring the potential therapeutic modulatory effects of sesamin on Th1/Th2 immune responses on different types of lung disorders in humans.

3. Role of sesamin in preventing cytokine storm development in lung tissue

The potential propensity of sesamin in striking a balance between Th1/Th2 immune responses has important implications for the modulation of inflammatory responses against infections, including respiratory infections. Overexaggerated inflammatory responses due to an unregulated immune system can result in an activation cascade of auto-amplifying pro-inflammatory cytokines, leading to a cytokine storm. Development of cytokine storm is prevalent in several types of allergic disorders and is suspected to be the main reason for mortality in these patients. Paramount experimental evidence indicates that a natural compound like sesamin may help prevent cytokine storm development due to its well-documented anti-inflammatory, immunomodulatory, and anti-oxidative effects[13].

The potent anti-inflammatory effects of sesamin were found to be useful in the amelioration of various disorders, from metabolic[21–30], to neurological[31–36], to even cancer[37–43]. Additionally, and most relevant to this review, sesamin was shown to mitigate a variety of lung disorders by decreasing cytokine and chemokine production both *in vitro* and *in vivo*, indicating its possible potential in managing lung pathology in patients suffering from respiratory and allergic conditions. For example, in one *in vivo* investigation, sesamin was found to significantly attenuate histopathologic changes, lung edema, and cytokine production in BALB/c mice induced with the stressor LPS[44]. In particular, administering sesamin (25, 50, and 100 mg/kg) to mice 1 h post LPS stimulation was found to be associated with a dose-dependent reduction in LPS-induced IL-1β, IL-6, and TNF-α levels, indicating an inhibitory potential against cytokine storm development. Findings from another *in vivo* study by Ye and colleagues showed that sesamin administration (50 and 100 mg/kg/day) for 2 d was able to mitigate carrageenan-induced lung inflammation in male Sprague-Dawley rats *via* downregulating the levels of IL-1β, IL-8, and TNF-α levels[45]. Similar results were also reported in another *in vitro* study by Li and colleagues, whereby sesamin treatment (25-100 μM) of human mast cells (HMC-1) induced with phorbol 12-myristate 13-acetate (PMA) plus A23187, a calcium ionophore, for 4 h, successfully reversed the PMA/A23187 induced increase in IL-6 and TNF-α levels[46]. Collectively, these findings suggest the potent propensity of sesamin in inhibiting excess cytokine production, which may therefore aid in the potential prevention of cytokine storm development.

4. Role of sesamin in attenuating other inflammatory mediators in lung tissue

Besides its direct inhibitory effects on cytokine levels, sesamin may also contribute to cytokine storm suppression *via* attenuation of other inflammatory indices that seem to increase following lung infection. For example, in an *in vivo* investigation, feeding male Sprague-Dawley rats a diet containing sesamin and α-tocopherol (0.5% wt) for 3 weeks was found to result in a significant reduction in lung leukotriene C4 levels, a vasoconstrictor implicated in allergy and asthma[47]. Additionally, the sesamin and α-tocopherol combination diet was found to be associated with a significant reduction in plasma histamine levels, an effect that could potentially reverse bronchoconstriction. Findings from a study by Li and colleagues also reported a drop in histamine release, and hence a suppression in anti-dinitrophenol IgE-mediated anaphylactic reaction, in rat peritoneal mast cells following its pre-incubation with sesamin (25-100 μM) for 30 min[46]. Specifically, sesamin pre-treatment was found to result in a concentration-dependent drop in histamine release, whereby adding 50 μM, 100 μM, and 200 μM of sesamin resulted in a 13%, 43%, and 62% decrease in histamine release, respectively. Evidence also indicates a protective role of sesamin against allergic asthma. In an *in vivo* study, Li and colleagues found the oral administration of sesamin (200 mg/kg/day) for 3 d to OVA-induced BALB/c mice resulted in a significant attenuation in OVA-induced inflammatory cell infiltration in the peribronchiolar and perivascular regions, indicating the role of sesamin in suppressing antigen-induced airway inflammation[18]. In another *in vivo* investigation, sesamin demonstrated an inhibitory potential on OVA-induced immune responses in allergic asthma in male BALB/

c mice[19]. Specifically, the intraperitoneal injection of sesamin (1, 10, and 20 mg/kg/day) for 6 d was found to result in significantly lower eosinophil and inflammatory cell influx into the lungs. Additionally, sesamin (1, 10, and 20 mg/kg/day) was also capable of inhibiting goblet cell hyperplasia, airway mucus occlusion, and even suppressed the mRNA expression levels of mucin 5AC (*MUC5AC*), a mucin prevalent in multiple respiratory conditions including chronic respiratory inflammatory disease. In another *in vivo* study, sesamin has also been shown to be capable of suppressing pleurisy, a condition whereby the membranes that surround the lungs become inflamed causing chest pain and shortness of breath, in male Sprague-Dawley rats[45]. Precisely, the oral administration of sesamin (50 and 100 mg/kg/day) for 2 d was shown to reverse the effects of the inflammatory compound carrageenan, whereby it inhibited both the infiltration of polymorphonuclear neutrophils and reduced total exudate volume of lung tissue in rats. Additionally, sesamin was also found to reduce the levels of the inflammatory biomarker, myeloperoxidase, and β-glucuronidase, indicating reduced polymorphonuclear neutrophil activation. Besides its effects on multiple inflammatory indices, sesamin may also be useful for promoting the activity of natural killer (NK) cells, key players in innate immunity known to play a role in mediating cancer cell killing and destruction of virus-infected cells during acute infection. Indeed, an *in vitro* study by Majdalawieh and colleagues demonstrated that the addition of *Sesamum indicum* extract (10, 50, and 100 μg/mL) to a co-culture of NK cells (derived from C57BL/6 mice) and YAC-1 tumor cells for 4 h significantly elevated NK cytotoxic activity by 2.9, 9.0, and 9.0-folds, respectively[48]. Although promising, further analysis from another *in vitro* investigation suggests that elevation in the cytotoxic activity of NK cells (against Raji cells derived from Burkitt's lymphoma) is more likely attributed to sesamolin, another major lignan found in sesame seed, than to sesamin[49]. The potential role of sesamin in stimulating the cytotoxic activity of NK cells cannot be ruled out however given the scarcity of research on this topic. Future *in vitro* and *in vivo* studies are therefore highly warranted to investigate the role of sesamin on NK cells. Collectively, it is clear from the evidence presented that sesamin exhibits strong inhibitory potential on a variety of cytokines, chemokines, and other inflammatory indices that seem to be elevated following lung inflammation in allergic and other types of respiratory disorders. Sesamin may therefore prove to be an attractive candidate drug to mitigate cytokine storm development in patients suffering from respiratory problems.

5. Potential role of sesamin in preventing and treating COVID-19

SARS-CoV-2 infection may lead to damage to multiple bodily systems, including the circulatory, urogenital, and digestive systems. However, this deadly virus has been shown to cause the most deleterious damage to the respiratory system. Although multiple pathophysiological processes are to blame for the exacerbation of lung dysfunction in COVID-19 patients, inflammation and cytokine storm development are suspected to play an imperative role in determining the severity of this infection. Indeed, studies on patients with COVID-19 revealed an increase in the levels of chemokines, including IP-10 and chemokine C-C motif ligand 2, in the bronchoalveolar lavage fluid cells of these patients[50]. Additionally, the levels of white blood cells, neutrophils, C-reactive proteins, and other inflammatory indices, including IL-6, in COVID-19 patients, were found to be significantly higher in intensive care unit (ICU) cases compared to those in non-ICU cases[51]. Furthermore, post-mortem examination of the lungs of those who died because of COVID-19 demonstrated the existence of acute respiratory distress syndrome, a deleterious outcome that follows from cytokine storm, if left untreated[52]. The reported rise in inflammatory indices and cytokine storm development in COVID-19 patients has been shown to be mediated, at least in part, *via* the COVID-19-induced dysregulations in immune responses. Precisely, SARS-CoV-2 infection seems to result in an imbalance in Th1/Th2 responses, causing a significant increase in both responses. Consequently, the levels of Th-1 and Th-2 related cytokines, including TNF-α, IL-2, IL-4, and IL-10 rise in the lung tissue, resulting in inflammation and cytokine storm development[53]. Collectively, these findings clearly indicate that inflammation, cytokine storm development, and Th1/Th2 imbalance in lung tissue are linked with poor prognosis in COVID-19 patients. Given the potent anti-inflammatory and immunomodulatory effects of sesamin reported in the aforementioned sections, sesamin may prove to be useful for the prevention and mitigation of COVID-19. Figure 1 provides a detailed summary of the immune-related and inflammatory cascades activated following SARS-CoV-2 infection and the proposed potential modulatory effects of sesamin on such cascades.

Sesamin has previously been shown to be useful for mitigating viral infections like influenza virus type A H1N1[54] *via* attenuating cytokine storm and inflammation, and it is tentatively suggested that sesamin may exert similar potent anti-inflammatory and immunomodulatory effects against the dreaded disease, COVID-19. Unlike its well-documented protective effects against a plethora of respiratory and viral disorders, literature published on the therapeutic potential of sesamin specifically against COVID-19 is very scarce. So far, only three computational studies have investigated the inhibitory potential of sesamin against COVID-19. Data from molecular docking and molecular modeling analyses from all three studies strongly suggest the propensity of using a nutraceutical like sesamin for the prevention and possible amelioration of COVID-19. Specifically, sesamin has been shown to be capable of inhibiting the activity of a SARS-CoV-2 protein shown to exhibit a protease activity[55]. The inhibition of this protease is of critical importance as it indicates suppressed viral replication ability in the host, and thus a possible treatment route against SARS-CoV-2. Indeed, in an

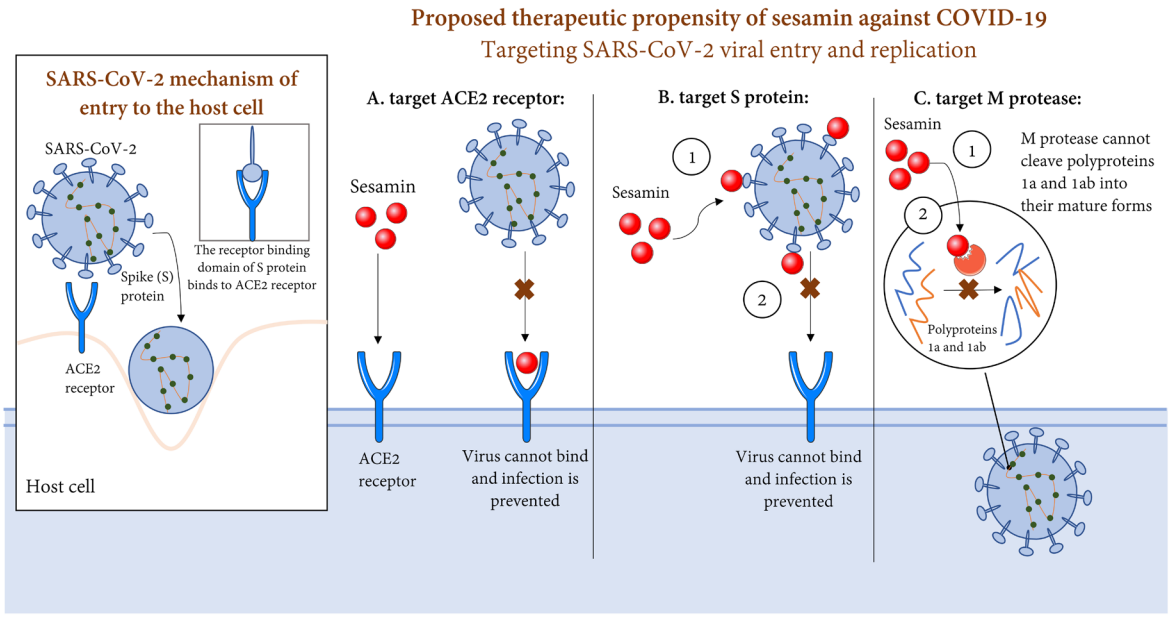

Figure 1. The proposed therapeutic potential of sesamin against three important targets in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): angiotensin-converting enzyme 2 (ACE2) receptor, spike protein (S protein), and main protease (M^{pro}). A: Sesamin may interrupt the binding of S protein to ACE2 receptor by binding to ACE2 receptor. B: Sesamin may interrupt the binding of S protein to ACE2 receptor by binding to the receptor binding domain of S protein. C: Sesamin may halt SARS-CoV-2 replication by binding to M^{pro} and preventing the cleavage of polyproteins 1ab and 1a into their mature forms.

in silico investigation, out of 17 compounds screened for potential protease binding abilities (7 human immunodeficiency virus protease inhibitors, 8 natural compounds, and 2 flu drugs), sesamin was demonstrated to have the second-highest binding affinity (–7.7 Kcal/mol) to SARS-CoV-2 protease, indicating its promising potential to attenuate coronavirus replication. Subsequent studies identified M^{pro} as the key protease in SARS-CoV-2. Further investigation on this protease found that it regulates viral replication mainly *via* cleaving viral replicase polyprotein 1a and 1ab into their mature forms[56]. The same study further confirmed the inhibitory potential of sesamin on M^{pro} by *in silico* analysis. In this study, out of five natural antioxidants tested (sesamin, galangin, ellagic acid, capsaicin, and epicatechin), sesamin was demonstrated to exhibit the strongest negative binding energy (–8.93 Kcal/mol) and the greatest inhibition constant (Ki value: 285.02 nM) to M^{pro}, indicating the potential for inhibiting the activity of M^{pro} and consequently less viral replication. Interestingly, the inhibition constant of sesamin was found to be even higher than that of the native M^{pro} inhibitor, carmofur, which has been extensively studied for its possible use as a potential drug against COVID-19[57]. Collectively, findings from this study strongly suggest that sesamin may have the potential to inhibit M^{pro} activity in a highly effective manner and may therefore be employed as a potential therapeutic drug against COVID-19. Besides M^{pro}, sesamin was also demonstrated to exhibit an inhibitory effect on two other potential targets of SARS-CoV-2, namely S protein and angiotensin-converting enzyme 2 (ACE2) receptor[58]. M^{pro} and S protein both play critical roles in regulating viral replication and transmission, whereas ACE2 acts as the main receptor wherein S protein binds and infects the host cells. As such, binding to these targets may halt the viral replication process or slow down its infectivity in humans. Findings from a computational investigation by Natesh and colleagues indicated that sesamin demonstrated a binding efficiency similar to that of the standard drug remdesivir, which was previously used for HIV treatment and which has also been shown to shorten recovery time for COVID-19 patients due to its action as a protease inhibitor[58]. Specifically, compared to remdesivir, sesamin demonstrated a higher affinity towards S protein (sesamin: –7.2 Kcal/mol, remdesivir: –6.6 Kcal/mol) and an almost similar affinity to remdesivir towards M^{pro} (sesamin: –8.2 Kcal/mol, remdesivir: –8.3 Kcal/mol) and ACE2 human receptor (sesamin: –6.4 Kcal/mol, remdesivir: –6.4 Kcal/mol). Collectively, findings from this study strongly support the inhibitory propensity of sesamin towards M^{pro}, S protein, and ACE2 receptor, suggesting a possible therapeutic role of sesamin against SARS-CoV-2.

A summary of the proposed mechanisms of action underlying the potential of sesamin to interfere with SARS-CoV-2 entry and replication is presented in Figure 2. While *in vitro* and *in vivo* experimental evidence is still lacking, findings from all these studies strongly support the potential of using sesamin-based nutraceuticals to provide relief from COVID-19 complications. Future research should therefore be directed at confirming the potentially promising inhibitory effects of sesamin on SARS-CoV-2 targets both *in vitro*

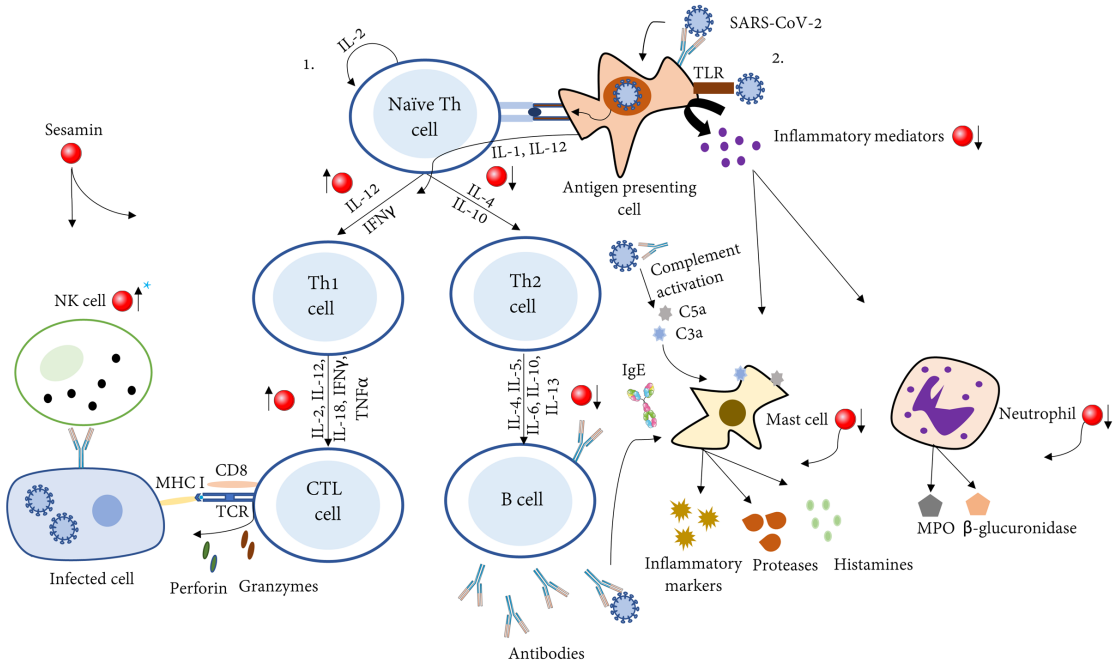

Figure 2. The inflammatory cascade following SARS-CoV-2 entry and the proposed therapeutic modulatory role of sesamin on multiple steps in this cascade. 1. Detection of SARS-CoV-2 by antigen presenting cells like macrophages and dendritic cells stimulates the differentiation of naïve Th cells into Th1 cells, which signals apoptosis of infected cells *via* CTL sensitization, or Th2 cells, which activate B cells and produces antibodies to fight against SARS-CoV-2. 2. Attachment of SARS-CoV-2 to TLR on antigen presenting cells also stimulates innate immune responses by releasing inflammatory markers, cytokines, and chemokines, which help activate mast cells and other types of immune cells. Activation of immune cells in turn triggers the overexaggerated release of cytokines, chemokines and inflammatory markers, leading to cytokine storm. Sesamin is proposed to modulate adaptive immune responses *via* regulating Th1/Th2 differentiation and its associated cytokine release. Additionally, sesamin is proposed to modulate innate immune responses *via* downregulating excessive cytokine, chemokine, and inflammatory marker release from various immune cells. *Potential modulatory effect of sesamin on NK cells is inconclusive and requires further investigation. NK: natural killer, CTL: cytotoxic T lymphocytes, TLR: toll-like receptor, MPO: myeloperoxidase, MHC Ⅰ: major histocompatibility class Ⅰ, TCR: T cell receptor.

and *in vivo*. Once confirmed, sesamin may be used to provide relief from the complications that accompany COVID-19. In addition to its possible role in alleviating COVID-19 symptoms, sesamin may also be used as a prophylactic agent with minimal side effects to strengthen immunity and provide protection against COVID-19.

6. Conclusion

Various studies have been published confirming the anti-inflammatory and immunomodulatory potential of sesamin on a plethora of allergic and other types of respiratory disorders. Ample experimental evidence suggests that sesamin exerts its anti-inflammatory and immunomodulatory potential *via* restoring Th1/Th2 balance and attenuating inflammatory indices and cytokine storm development. COVID-19 has emerged as a very serious threat to global health and the economy. Inflammation and dysregulated immune responses play a significant role in the pathophysiology of this dreaded disease. Sesamin, being a potent anti-inflammatory and immunomodulatory agent, may prove to be useful for prophylaxis and possible treatment against SARS-CoV-2 infection. Studies suggest that sesamin may exert an inhibitory potential on three important SARS-CoV-2 targets, namely M^{pro}, S protein, and ACE2 receptor. Additionally, the well-documented immunomodulatory and anti-inflammatory properties of sesamin render it a promising candidate that may help potentially restore Th1/Th2 balance and prevent exaggerated immune responses and cytokine storm development in COVID-19 patients. It is noteworthy that although promising, the existing information about the potential effects of sesamin on COVID-19 is very preliminary, with the majority of claims based on data from computer-aided docking studies. Well-planned *in vitro* and *in vivo* studies confirming the inhibitory potential of sesamin against SARS-CoV-2 targets and its potential immunoprotective effects on regulating Th1/Th2 balance and cytokine storm development are therefore highly warranted to establish the safe dose and clinical efficacy of sesamin against COVID-19 infection.

Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

AFM, SMY, and IAA performed the literature analysis and wrote the original draft of the article. AFM and SMY generated the figures. AFM and SMY critically reviewed and revised the final draft of the article.

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