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Natural Products as A Promising Therapy for SARS COV-2; An Overview

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Abstract

Recently emerging pandemic SARS CoV-2 conquered our world since December 2019. Continuous efforts have been done to find out effective immunization and precise treatment stetratigies. A way from therapeutic options that were tried in SARS CoV-2, an increased attention is directed to predict natural products and mainly phytochemicals as collaborative measures for this crisis. In this review, most of the mentioned compounds specially flavonoids (biacalin, hesperidin, quercetin, luteolin,, and phenolic (resveratrol, curcumin, and theaflavin) exert their effect through interfering with the action of one or more of this proteins (spike protein, papain-like protease, 3-chymotrypsin-like cysteine protease, and RNA-dependent RNA polymerase) that are involved in viral life cycle beside the anti-inflammatory effect of these compounds. The triterpenoids (celastrol, escin and glycyrrhizin) and the alkaloids (lycorine and cepharanthine) mediated their effect mainly through anti-inflammatory activity. Glycyrrhetinic acid (glycyrrhizin metabolite) dawn regulates ACE-2, and reduces protease expression, thus reduce viral entry. This review may be representing an initial step in long path for designing the successful and effective treatment or vaccine for this pandemic.

Keywords: SARS CoV-2, Remedsiver, Antiviral, Phytochemical, Interleukin.

المنتجات الطبيعية كعلاج واعد لسارس CoV-2 :نظرة عامة

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الخلاصة

غزت جائحة السارس CoV-2 الناشئة مؤخرًا عالمنا منذ ديسمبر ٢٠١٩. وقد بذلت جهود مستمرة لاكتشاف التحصين الفعال والإجراءات العلاجية المحددة.

بعيدا عن الخيارات العلاجية التي تم استعمالها لسارس CoV-2، يتم توجيه اهتمام متزايد للتنبؤ بالمنتجات الطبيعية والمواد الكيميائية النباتية بشكل أساسي كعلاجات مساندة في هذه الأزمة . في هذه المراجعة، معظم المركبات المذكورة وخاصة مركبات الفلافونويد (بايكالين ، هيسبيريدين ، كويرسيتين ، لوتيولين ، والفينولات (ريسفيراترول ، كركمين ، وثيافلافين) تظهر تأثيرها من خلال التداخل مع عمل واحد أو أكثر من هذه البروتينات (spike protein, papain-like protease, 3-chymotrypsin-like cysteine protease, and RNA-dependent RNA polymerase) التي تشارك في دورة الحياة الفيروسية بجانب التأثير المضاد للالتهابات لهذه المركبات. الترايتيربينويدات (سيليسترول ، إيسين ، جليسيرر هيزين) والقلويدات (ليكورين وسيفارانثين) تعطي تأثيرها بشكل رئيس من خلال النشاط المضاد للالتهابات. حمض الجليسيرر تينيك (مستقلب الجليسيرر هيزين) يثبط الإنزيم المحول للأنجيوتنسين ٢ ، ويقلل من تعبير البروتياز ، وبالتالي يقلل من دخول الفيروس.قد تمثل هذه المراجعة خطوة أولية في مسار طويل لتصميم ناجح وعلاج أو لقاح فعال لهذا الوباء.

الكلمات المفتاحية: السارس CoV-2, ريميدسفير,مضاد فايروسي,المركبات النباتية الكيميائية,انترلوكينز.

Introduction

One of the main pathogens that mainly goals the respiratory system in human is coronavirus (CoV), which is be allied to the *Coronaviridae* family. Under the electron microscope CoV signifies spike like projections on its outer surface granting it a crown-like appearance; therefore the designation coronavirus [(1)]. CoVs are miniature in size as well as consist of a single stranded RNA .The CoV family subgroups include alpha (α), beta (β), gamma (γ) in addition to delta (δ) coronavirus [(2)]

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Earlier outbreaks of CoV consist of Middle East respiratory syndrome (MERS)-CoV as well as the severe acute respiratory syndrome (SARS)-CoV which have been previously categorized as agents that form abundant public health hazard [3]. Recently Coronavirus disease 2019 (COVID-19), a new developed respiratory disease resulted from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has turn out to be pandemic [4].

SARS-CoV-2 is contemplating a novel human infecting β CoV. Phylogenetic studies of the SARS-CoV-2 genome show that the virus is closely correlated (by 88% identity) to two bat-derived SARS like CoVs and genetically distinct from SARS-CoV (by around 79% similarity) as well as MERS-CoV [5].These studies point out that bats may aid as the virus natural host , signifying that mammals are the almost certainly link between SARS-CoV-2 and humans [6].

Transition

Numerous reports have proposed that human to human transmission is a possible route for SARS-CoV-2 infection dispersal [7]. All age groups are prone to infection which is transmitted via large droplets generated by both symptomatic and asymptomatic people. The infection can be transmitted even before onset of symptoms during patient coughing and sneezing. Even on clinical recovery patients could be infectious provided that the symptoms last [8]. It has been stated that the virus can endure from 2 hours to few days in the droplets on the surfaces or else ground and may infect individuals at a distance of about 1.8 meters radius [9]. Infection is acquired either by inhalation of the droplets or touching the mouth, nose, as well as eyes after contact with contaminated objects or surfaces. Both stool and contaminated water may also contain virus. As a result consequent transmission through aerosolization and/or fecal - oral route is strongly hypothesized [10].

Pathogenesis

Afterwards human body entrance , SARS-CoV-2 primary enters the host cells prior to replication [11]. The upper respiratory tract mucosal lining epithelium is the main site for viral replication. Additional multiplication occurs in lower respiratory tract and alimentary mucosa [12]. Angiotensin converting enzyme 2 (ACE2) which is broadly expressed in heart , lung and kidney has been recognized as the functional receptor by which SARS-CoV-2 enters the body mucosa [13].

The binding of the virus spike (S) protein (separated to the S1 and S2 part) to ACE2 activate SARS-CoV-2 infection. The attachment of the virus to the target host cells surface is expedites via binding of S1 part of the virus S protein to the ACE2 cellular receptor of the host. Viral S protein priming then requires S protein cleavage of S1 from S2 (and at another S2' site) by the host cell serine protease TMPRSS2. The fusion of the cell membranes of both virus and host is driven by the S2 subunit of the virus [14]. Moreover, variance response through T helper cells (type 1 and type 2) activates cytokine storm and both respiratory dysfunction besides hypoxemia induced by SARS-CoV-2 can cause myocardial cells impairment [15]. This progress is related to inflammatory cytokines elevation including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A in addition to TNFα [16]. ***Symptoms***

The clinical manifestations of SARS-CoV-2 varying from asymptomatic infection to acute respiratory distress syndrome (ARDS) and multiple organ impairment. The average incubation period assessed to be 5.2 days [17]. Commonly observed symptoms include fever, sore throat, cough, myalgia or fatigue, dyspnoea, headache, diarrhea as well as conjunctivitis [16, 18]. In some severe cases serious respiratory syndromes, pneumonia, kidney impairment and even death may occur. Severe clinical patterns are witnessed in individuals with coexisting health conditions like cardiovascular disease, diabetes, lung disease and cancer [15, 19]. Adverse outcomes are also more common in aged as well as frail patients [20].

Diagnosis

The initial identification of SARS-CoV-2 patients is based on the clinical manifestation incidence related to early disease stage development. Different diagnostic methods are used as confirmatory test for patients with SARS-CoV-2. Real-time Polymerase Chain Reaction (Rt-PCR) considered as a standard diagnostic test which is based on the recognition of the SARS-CoV-2 sequence [21]. Since the virus RNA has been isolated from both upper as well as lower respiratory tract samples, the collection of nasopharyngeal besides oropharyngeal swabs is the main method for diagnosis [22]. Detection of SARS-CoV-2 RNA in stool and blood specimens has also been proved by numerous studies [23, 24].

Distinctive range of laboratory anomalies can be considered as an additional nonspecific laboratory characteristics for patients with SARS-CoV-2 [15, 25]. An elevated level of serum C-reactive protein, alanine aminotransferase, lactate dehydrogenase and aspartate aminotransferase can be observed. High percentage of patients showed reduced albumin level [26]. Hematological abnormality include lymphopenia, mild thrombocytopenia, prothrombin time prolongation and elevated D-dimer values [25, 27, 28]. Both D-dimer and lymphopenia to a minor degree seem like to have the main prognostic associations [28].

Besides to the previously designated methods, antigen-antibody reaction based kits offer rapid diagnostic technique. This test exploits immune reaction of combined human antibodies i.e., immunoglobulin M (IgM) in addition to IgG through spike proteins of SARS-CoV-2 from the blood sample of patient [29].

Additional specific and more sensitive diagnostic tool for SARS-CoV-2 is computerized topography or CT. Related features of CT images are shown in the majority of patients including ground glass opacity and bilateral patchy infiltrates [30]. Conventional chest X ray is less sensitive tool comparing to CT. In a very limited cases, ultrasound has been used as a diagnostic tool [31].

Treatment

Presently, there are no definite drugs or vaccine for potential treatment of SARS-CoV-2 till now. Treatment strategies are basically symptomatic and supportive. Nevertheless, to manage this disease some perspectives have been used [32]. The single choice available is the practice of broad-spectrum antiviral agents such as Nucleoside analogues as well as HIV-protease inhibitors that could weaken virus infection till availability of precise antiviral drug. In preclinical trials for both SARS-CoV and MERS-CoV infections, remdesivir as per a nucleotide analogue has been stated to be effective agent through acting on the coronaviruses polymerase. Remdesivir acts by impeding into the RNA chain of budding viral and then results in its premature termination [33].

The combination of lopinavir/ritonavir, a protease inhibitor demonstrated a potent efficacy against SARS-CoV-2. A reduction in the viral load in SARS-CoV-2 patients was also observed with this combination [34]. Another antiviral agent which is suggested as probable therapy is nelfinavir, a selective HIV protease inhibitor that revealed strong SARS-CoV-2 inhibition [35].

Other therapeutic options suggested for treatment are arbidol (antiviral agent with a broad-spectrum activity)[36], interferons (antiviral cytokines)[37], monoclonal antibody[38], convalescent plasma (plasma acquired from individuals recovered from SARS-CoV-2)[39] and intravenous immunoglobulin [40].

Conceivable natural products against SARS-CoV-2

Resveratrol

It is a (*trans*-3,4′,5-trihydroxystilbene) [40] (figure 1). This polyphenol was at first detected in 1940 in white hellebore roots and synthesized by not less than 72 plant species, grapes, cranberries, and huzhung are included [41, 42]. Resveratrol is a phytoalexin exhibits antiviral effect against several viruses as pseudorabies virus, African swine fever virus, herpes simplex virus, influenza A virus, human immune deficiency virus, and respiratory syncytial virus [43, 44]. Lin et al (2017) proved the antiviral action of resveratrol against MERS-CoV. The antiviral effect was the product of several mechanisms which ultimately result in opposing viral-induced apoptosis and promotion or stimulation of cell survival [42].

Marenella perspective (2020) was that resveratrol might be effective supportive management for SARS COV-2. ACE2 (angiotensin-converting enzyme -2) receptors are the target of SARS-CoV. Receptors–virus interaction influences viral entrance, clearance, and it has a crucial role in determining ARSD (acute respiratory distress syndrome) symptom severity. Following viral infection, the expression of the receptors is downregulated which may affect pathogenesis and disease prognosis [45].

Horne JR and a college perspective' (2020) was based on previous studies in the animals and in vitro study on human aortic smooth muscles, these studies demonstrate that resveratrol alone or dietary fat lessening in combination with resveratrol causes ACE2 upregulation. They suggest a probable mechanism whereby dietary fat reduction and/or rise resveratrol intake may modify responses to SARS-CoV 2 [46].Wahedi HM et al (2020) in a molecular docking studies showed that stilbene-based natural constituents and especially resveratrol might be an auspicious SARS-CoV 2 drug candidate which disrupted SARS-CoV-2 spike S glycoprotein and human ACE2 receptor complex [47].

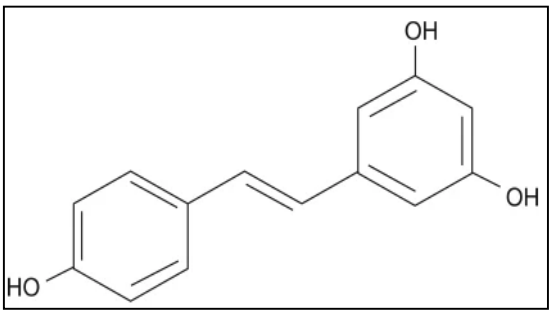

Figure 1. Chemical structure of resveratrol [48]

Curcumin

It is a polyphenolic compound [1,7-Bis(4-hydroxy-3-methoxyphenyl)-1,6-hep tadiene 3,5-dione] (figure 2), and the main curcuminoid obtained from turmeric (*Curcuma longa*).Various interesting biological activities have been displayed by curcumin, such as antimicrobial, antioxidant, anticancer, antiviral, and others [49, 50].

Zahedipour et al (2020) mentioned a suitable justification based on modern and previous studies (curcumin impeding viral cell entry, inhibiting virus encapsulation and viral protease enzyme as well as modifying diverse cellular signaling pathways) that encourage the planning of modern studies and clinical trials using curcumin as a therapeutic agent for SARS-CoV-2 [51].

Chen et al (2020) evaluate the effect of a combination of phytochemicals (vitamin C, curcumin, and glycyrrhizic acid abbreviated as VCG Plus) against the coronavirus utilizing systems biology. The study revealed that this combination can have an action on 88 hub targets that are closely coupled and linked with immune and inflammatory responses. VCG Plus can modulate or regulate the innate immune response by influence NOD-like and

Toll-like signaling pathways to stimulate interferon generation, activation and balancing T-cells, and for regulating the inflammatory response by inhibiting of certain signaling pathways (PI3K/AKT, NF-κB, and MAPK). The inhibition of inflammatory response, in turn, prohibit cytokine storm which is observed in certain SARS-CoV-2 [52]. In addition to the proved antiviral effect of curcumin against other viruses.

Rosha et al (2020) postulated that this phytochemical probably beneficial in SARS-CoV 2 patients through various actions as; antithrombotic activity since an elevated number of thrombotic events occur in those patients, anti-cytokines and antifibrotic effects could assist in lung involvement. The main pathway for SARS-CoV-2 cell entry might be interposed by curcumin [53].

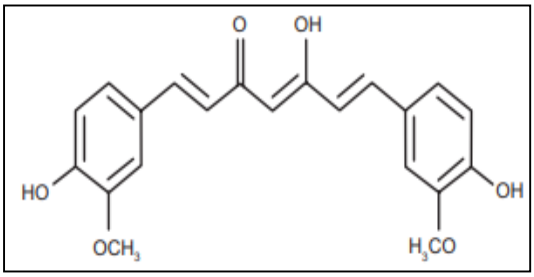

Figure 2. Chemical structure of curcumin [54]

Biacalin

Baicalin is (7-glucuronic acid, 5,6-dihydroxyflavone, or 7-O-glycoside 0f biacalein) (figure 3). It is the main bioactive compound from the root of *Scutellaria baicalensis*, also it is present in the *Thymus vulgaris* L. leaves [55, 56]. Chu et al (2015) proved through in vitro and in vivo (in mice) the antiviral activity of biacalin against influenza virus A (H1N1) as a powerful inducer of interferon-gamma (IFN-γ) in major IFN-γ producing cells [57]. Jelic D et al (2016) showed in two assays that biacalin (the glycoside) and biacalein (the aglycone) are significant inhibitors for Src tyrosine kinase, inhibition of this receptor is associated with the decreased generation of inflammatory cytokines, one of which IL-6 in LPS-stimulated THP-1 cells. The inhibitory effect (anti-inflammatory effect) of biacalein is more than that of biacalin. In MTS cytotoxicity assay in THP-1 cells both of these flavonoids demonstrated no cytotoxicity [56].

Haixia Su et al (2020) investigated the inhibitory effect of biacalin and biacalein vs SARS-CoV-2 3CLpro. [58]. 3CLpro is a 3-chymotrypsin-like cysteine protease this enzyme rules replication of coronavirus and is crucial for its life cycle [59]. The antiviral effect of these compounds was also evaluated against a clinical isolate of SARS-CoV-2 in Vero E6 cells. Biacalin and biaclein have a distinctive binding mode with SARS-CoV-2 3CLpro which was determined by X-ray protein crystallography. A core of substrate-binding pocket formed by the interaction of two catalytic residues, the first is decisive S1/S2 subsites and the second is an oxyanion loop. To this pocket, the biacalin is ensconced acting or behaving as a shield opposite the catalytic dyad to avoid the peptide substrate from getting near the active site. So Haixia Su et al. stated that biacalin because of its simple chemical structure, ubiquitous mode of action and powerful antiviral effect along with safety profile could be tried as antiviral agent [58].

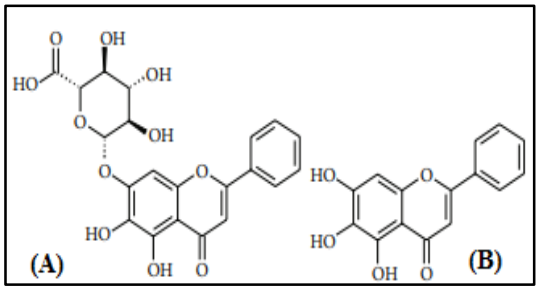

Figure 3. Chemical structure of (A) biacalin and (B) biacalein [56]

Hesperidin

It is a flavonoid glycoside, its aglycone is hesperetin (figure 4). Hesperidin was initially isolated from the citrus peel [60] and it is present in large amounts in sweet oranges and lemons [61]. Hesperidin is used in diosmin manufacturing [62, 63]. Hesperidin has anti-inflammatory, antiviral, antioxidant, and other pharmacological activities [61].

Haggag et al (2020) visualized the probability of using hesperidin as a prophylactic and adjuvant curative candidate for SARS-CoV-2. Haggag declared this vision according to previously reported outcomes that confirm the effectiveness and safety of this phytochemical. Hesperidin bans SARS-CoV-2 ingress to the lung cell through the disruption of ACE2 and SARS-CoV-2 receptor binding domain interaction by targeting the binding interface of SARS-CoV-2 Spike and ACE2 human receptors. Hesperidin ameliorates the host cellular immunity, minify inflammatory mediators' release. Simultaneous administration of a mixture of hesperidin and diosmin along with heparin is essential for protection against thromboembolism [62, 63].

Meneguzzo et al (2020) mentioned that hesperidin could be an effective antiviral agent against SARS CoV-2 and its further mutations. Hesperidin is outperforming the other natural molecules as well as antiviral drugs that were advised in SARS-CoV-2 clinical trials as the binding tendency of it for all the major viral and cellular targets is robust. Hesperidin can interrupt the viral infection at different stages starting from virus entrance to the steward human cell, to the viral genome transcription and replication. It was

suggested that hesperidin might be effective prophylaxis since it prohibits virus spreading to other cells, it has a high safety index, short life span in the human body, and at high doses, hesperidin showed no sign of cytotoxicity. Hesperitin also displayed a good binding affinity to one or more targets [64].

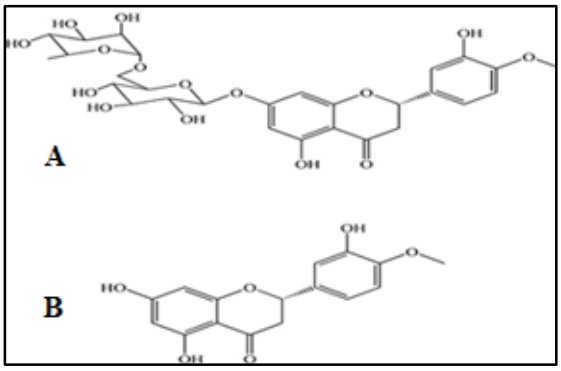

Figure 4. Chemical structure of :A. hesperidin B. hesperitin [60]

Quercetin

Is flavonol aglycone; (3,3′,4′,5,7-pentahydroxy-flavone) (figure 5), found in various vegetables and fruits. Quercetin demonstrated numerous effects such as antioxidant, antiproliferative, antibacterial, antiviral, and others [65, 66]. Previous studies reported that quercetin could reduce mortality resulted from severe pandemic influenza A complications [66].

In a previous study, quercetin was shown to inhibit SARS-CoV entry to host cell [67].

Biancatelli et al (2020) pointed for the use of a combination of vitamin C and quercetin for prophylaxis and early management of SARA COV-2 respiratory tract infections. Quercetin affects various enzymes and targets that are involved in the virus life cycle as reverse transcriptase enzymes, SARS 3CL protease in SARS-COV. Hydroxyl groups in quercetin and its derivatives inhibit SARS 3CL protease through binding to Gln189 site on this enzyme. Because SARS COV-2 protease 3CL has the same binding site (Gln189) as SARS-COV so quercetin assumed to be effective for this pandemic. Vitamin C display immunomodulatory effect, boosting interferon formation, restrictive cytokine-mediated organ damage, enhance survival rate in lethal infection. Regarding this combination, a synergistic effect is gained, vitamin C is an antioxidant compound, has the ability for the generation of quercetin from oxidized quercetin derivatives. At the same time, both of these nutraceuticals exert antiviral and immunomodulatory effects [68].

Glinsky (2020) showed the feasibility of using putative combinations one composed of quercetin and vitamin D and the other quercetin, vitamin D, and estradiol for SARS-COV-2. These combinations were more effective as treatment agents showed statistically more powerful effects on expression of SARS-CoV-2 target genes as compared to monotherapies These agent separately or in combination alter the expression of genes encoding SARS-CoV-2 targets to varying degree which ultimately modulate the functions of viral proteins [69].

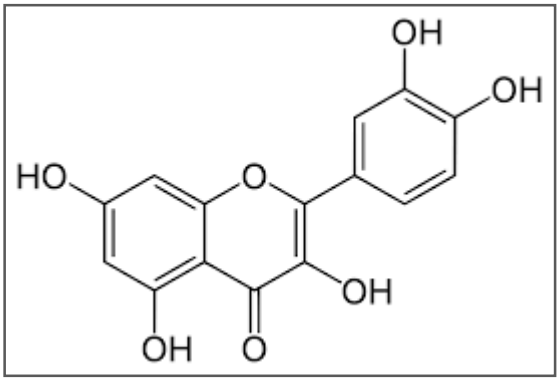

Figure 5. Chemical structure of quercetin [69]

Luteolin

This flavone aglycone displayed antiviral effect (figure 6). Theoharides (2020) discussed the effective role of luteoline in SARS COV-2. Luteolin suppress viral entrance to host cell through binding to the SARS-CoV-2 spike S glycoprotein. Serine proteases, like SARS-CoV 3CL protease and other proteases were inhibited by luteolin. This flavone has anti-inflammatory effect. Tetramethoxyluteolin (luteolin derivative) decrease the secretion of the TNF and IL-1β (pro-inflammatory cytokines) from the mast cells. chemokines CCL2 and CCL were also inhibited [70].

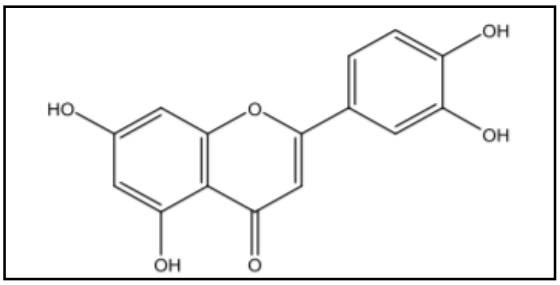

Figure 6. Chemical structure of luteolin [71].

Theaflavin

Theaflavin is a polyphenolic compound that has a benzotropolone skeleton (figure 7), it results from catechin oxidative condensation. This reddish-orange pigment (theaflavin) mainly founded in fermented tea, and anyhow very small quantities might be present in non-fermented tea (green tea) [72, 73]. Theaflavin has antiviral and anti-inflammatory properties [74].

Chen et al (2005) in a study using fluorogenic substrate assay demonstrated that theaflavin-3,3′-digallate inhibit SARS-CoV 3CLpro more than theaflavin which might be explained by

the absence of gallate group in theaflavin [75]. Lung et al (2020) based on molecular docking studies demonstrated the probability of using theaflavin as a lead compound for evolving an inhibitor for SARS-CoV-2. According to the result of Lung's study theaflavin has the ability to docking in or targeting the catalytic pocket nearer the active site of RdRp (RNA-dependent RNA polymerase) in MERS-CoV, SARS-CoV, and SARS-CoV-2. RdRp is crucial for catalyzing the RNA replication from RNA templates. In the used molecular docking studies, theaflavin possess the lowest idock score and lower binding energy in the catalytic pocket of SARS-CoV-2 RdRp which may be explained by the fact that further hydrogen bonds along π-cation interaction were formed between theaflavin and the catalytic pocket of RdRp in SARS-CoV-2 [76].

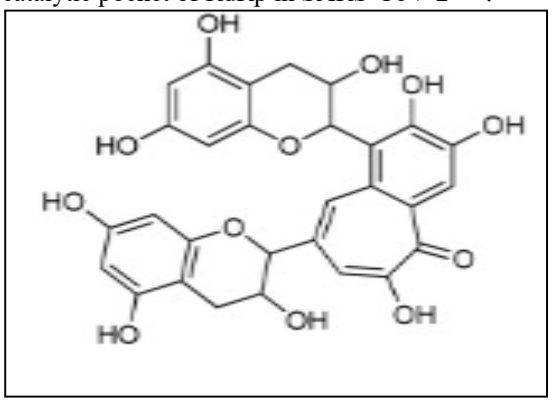

Figure 7. Chemical structure of theaflavin [72]

Glycyrrhizin

Is a licorice bioactive compound that belongs to an acidic type of saponin glycosides (figure 8). This glycoside exhibits various clinical effects, one of which is the antiviral effect [77].

Luo P et al (2020) perspective debates the possible use of glycyrrhizin as a SARS-COV-2 drug candidate based on its various pharmacological actions. The proposed mechanisms for using glycyrrhizin to conflict SARS-COV- 2 may be via binding to ACE2, thus prevent the formation of SARS-COV- 2 and ACE2 complex, inhibition of proinflammatory cytokines, thrombin, and cumulating IROS (intracellular reactive oxygen species). Airway exudates overproduction is inhibited while stimulating endogenous interferon [78].

Harald Murck (2020) discussed the protective effect of glycyrrhizin in SARS CoV-2 patients and its role in mitigating disease severity. His point of view was based on two main effects related to glycyrrhizin and its metabolite glycyrrhetinic acid (GA). GA firstly restrain an enzyme named 11-beta-hydroxysteroid dehydrogenase type 2, through the inhibition of this enzyme cortisol activate mineralocorticoid receptors which in turn dawn regulate ACE2 expression and thus reduce entry points of SARS CoV-2. Type 2 transmembrane serine protease serves as a cofactor for virus uptake by ACE2. GA reduces protease expression and offers a supplementary mechanism that limits virus entrance [79]. GA exerts anti-inflammatory effect through antagonism of Toll-like receptor 4, and thus decreases inflammation in many tissues including lungs. The production of inflammatory cytokines as TNFα, IL6, and IL1ß are reduced.

As a result, GA neutralizes the mitigation of the ACE2 protective anti-inflammatory effect gained from reduced ACE2 expression due to GA used. ACE2 possesses an anti-inflammatory effect by the formation of angiotensin 1-7 and angiotensin 1-9 [79].

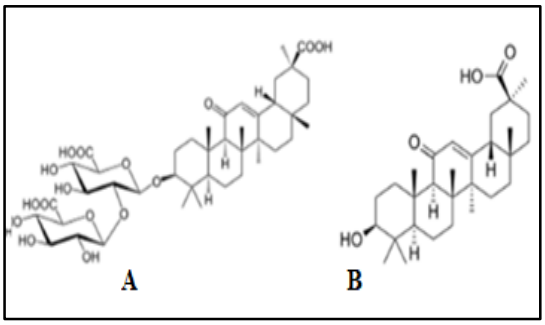

Figure 8. Chemical structure of A. glycyrrhizin and B. glycyrrhetinic acid [80]

Escin

Escin is a natural mixture of triterpenic saponins rather than a pure compound (figure 9), consisting of A, B, C and D escin, it is extracted from the horse chestnut seeds [81]. Previous studies reported the potent escin anti-inflammatory and anti-edematous actions [82]. Michelini et al (2018) proved the antiviral effect of β-escin against HSV-1 infection (*herpes simplex virus type 1). By the meaning of screening assay escin showed inhibitory effect vs SARS-CoV* [83] .

Gallelli et al (2020) demonstrated the possibility of using escin in combination with another antiviral agent as remdesivir as an effective therapeutic option for SARS CoV-2 patients suffering from acute lung injury. Gallelli and colleagues based in their outcome on the powerful anti-inflammatory effect of escin that is analogous to dexamethasone and methylprednisolone. In the late stage of SARS CoV-2 infection, the cytokine storm produces acute lung injury, escin might reduce the secretion of inflammatory mediators in addition to attenuate the acute lung injury. Several on ongoing clinical trials using escin oral and intravenous dosage form in SARA CoV-2 patients [84].

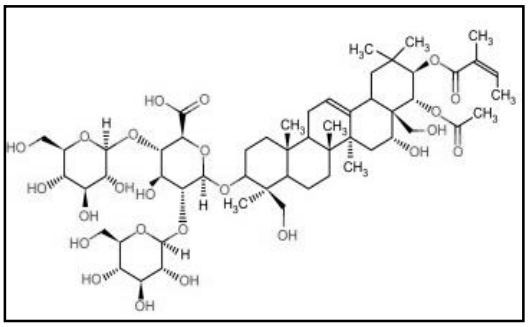

Figure 9. Chemical structure of escin [81]

Celastrol

Is a pentacyclic triterpenoid of quinone methide type (figure 10), extracted from the root bark of *Tripterygium wilfordii*. It is used for the treatment of many conditions; tumors and rheumatoid arthritis in particular [85]. Celastrol targets NFkB, anti-inflammatory, antioxidant mediators, and certain cell signaling molecules, exhibiting a potent anti-inflammatory effect [86]. In a previous study celastrol along with other quinone methide triterpeniods proved as a potent inhibitor for SARS-CoV 3CLpro [87].

Law et al (2020) concluded that celastrol is an effective therapeutic option for SARS CoV-2 based on its powerful anti-inflammatory effect. Celastrol perhaps acts through inhibition of lipopolysaccharide and subsequent protein and mRNA expression that is encoding for pro-inflammatory cytokines like IL-6, IL8, and MCP-1 (Monocyte chemoattractant protein 1). The reduction in pro-inflammatory cytokines suppresses the phosphorylation step of the NF-κB, IKKα/β and Iκβα. By suppression of this step, P56 is inactivated and the cascade of the inflammatory process is inhibited [88].

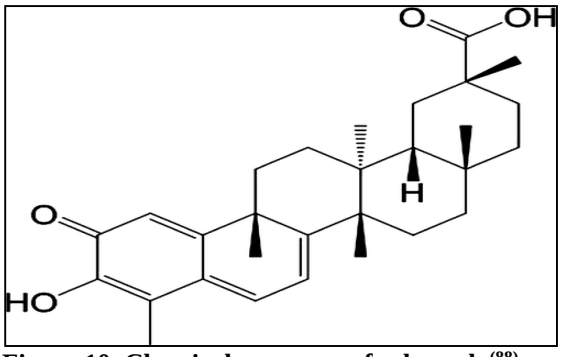

Figure 10. Chemical structure of celastrol [88]

Lycorine

Is a pyrrolo[de]phenanthridine ring-type alkaloid [89] which was isolated from bulbs of *Narcissus pseudonarcissus* [90]. Lycorine proved in a study to have an antiviral effect against SARS-CoV (Severe Acute Respiratory Syndrome associated coronavirus) [91]. Shen et al (2020) showed the antiviral effect of 36 compounds against alpha and beta coronavirus that infect human among these virus HCoV-OC43 which cause encephalitis in mice. Lycorine demonstrated powerful antiviral action against multiple genetically distinct coronavirus in vitro and protected mice against lethal HCoV-OC43 infection in vivo [92].

Zank et al (2020) examined the antiviral effect of lycorine along with gemcitabine, and oxysophoridine vs SARS-CoV-2 in cell culture. These compounds demonstrated a dose-dependent antiviral effect that is not related to compound mediated cytotoxicity. Lycorine demonstrates various mechanisms as an antiviral agent for viruses other than SARS-CoV-2, but for the SARS-CoV-2 antiviral mechanism probably related to hosting factors modulation instead of targeting viral factors directly [93].

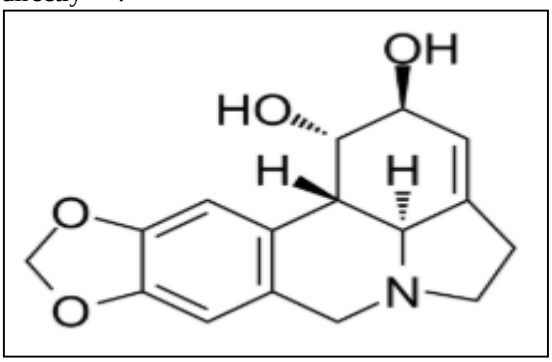

Figure 11. Chemical structure of lycorine [94]

Cepharanthine

This is benzylisoquinoline alkaloid (figure 11), isolated from *Stephania cephalantha*. it has anti-inflammatory, antioxidant properties used for the treatment of leukemia, alopecia, and other diseases [95].

Rogosnitzky et al (2020) et al (2020) in a review showed that cepharanthine might be a drug of choice and therapeutic option for SARS CoV-2. Cepharanthine interfered with certain enzymes and mediators generation that are involved in the viral entrance, replication, and in a cytokine storm. Among these deactivations of the nuclear factor-kappa B (NF-κB), cyclooxygenase expression, lipid peroxidation, nitric oxide, and cytokine formation [96].

Jeon et al (2020) evaluated the antiviral effect of 48 FDA- approved drugs as a candidate for SARS CoV-2 using chloroquine, lopinavir, and remdesivir as standards or reference drugs. Among the 48 tested drugs only 24 demonstrated the antiviral effect for SARS CoV-2, cepharanthine is included [97].

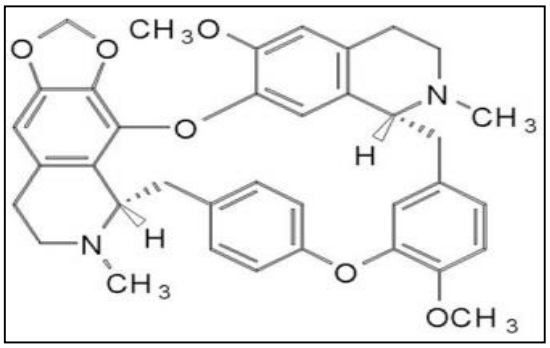

Figure 12. Chemical structure of Cepharanthine (98)

Other natural products

Narkhede et al (2020) reported in a study using molecular docking studies the potential antiviral effect of several phytochemicals including berberine, tryptanthrine, indirubin, indican rhein, β-caryophyllene, β-sitosterol, these compound act via inhibition of viral protease [(99)].

Conclusion

Different phytochemicals and natural products were tried as possible treatment for SARS CoV-2. Alkaloids, phenolic, terpenes, and others were examples of these compounds. Flavonoids and phenolics were the compounds that are discussed in this review followed by triterpenes and lastly alkaloids. The pharmacological activities of these candidates were mediated through the direct effect on virus life cycle and / or via the anti-inflammatory effect which are beneficial in cytokine storm. Almost all the acquired data or information based on molecular docking studies (theoretical studies) and or previous studies related to MERS and SARS CoV. Further, in vitro and in vivo studies are required to find out the effective treatment for this pandemic.

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