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Anti-SARS-CoV and Anti-cancer Effects of Emodin

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Abstract

Background and aims: The SARS-CoV-2 disease 2019 (COVID-19), whose spread started in the late December in 2019 in China, is the main concern in the world today. Potential anti-coronavirus targets can be categorized into two classes depending on the target, one is operating on the host immune system or human cells, and the other is on coronavirus itself. Anthraquinones are generally extracted from the Polygonaceae family, and have many beneficiary characteristics such as being antibacterial, anti-cancer and anti-diabetes. Emodin anthraquinones represent an important role in human health and have golden healthful features making them a drug to cure many illnesses. The aim of this study was to review the inhibiting effect of emodin on cancer and SARS-CoV-2.

Methods: This comprehensive literature review was performed on papers that have been published from 1994 till 2020 in various data resources such as NCBI, Science direct, Springer and Web of science. The selected keywords were emodin, medicinal plant, anticancer plant and medicinal herbs, cancer and SARS-CoV-2.

Results: Different studies were found that emodin is known as an effective agent to obstruct the interaction of the S protein of SARS-CoV and the host ACE2 (Angiotensin converting enzyme 2) and the infection caused by the retrovirus. In addition, the outbreak of cancer in patients infected by SARS-CoV-2 (COVID-19) is more than it among the general population.

Conclusion: Therefore, the present research is going to outline and highlight the anti SARS-CoV-2 therapeutic strategies of emodin and the anti-cancer characteristics' of this drug.

Keywords: Emodin, SARA-Cov-2, Cancer.

Review article

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Introcuction

The SARS-CoV-2 disease (COVID-19), whose breakout started in the late December in 2019 in Wuhan-China, is the main concern in the world today. It has had a quick breakout across China and then different countries [1, 2]. The virus belongs to the β-coronavirus family and evolved evolutionarily by bats, and then it was transferred to human beings [3,4]. The genome sequence of SARS-CoV-2 shows 96.2% similarity with SARS-related coronavirus (SARSr-CoV; RaTG13), 79% with SARS-CoV, and 50% with MERS-CoV [4,5]. SARS-CoV-2's receptor is the angiotensin converting enzyme II (ACE2) and uses a spike protein as an attachment to its receptor [6-8]. It is believed that partial spike gene of novel corona virus is produced by a pangolin type[9-12] coronavirus. SARS-CoV-2 contains a positive RNA genome, and it has at least four structural proteins: Spike (S) protein, envelope (E) protein, membrane (M) protein, and nucleocapsid (N) protein[12,13]. The results of several recent studies have represented a correlation between cancer and COVID-19[14]. Patients suffering from cancer have weaker immune systems in comparison with the general population both due to the nature of the disease and its treatment processes. The rates of infection and mortality are high among cancer patients. Research shows that the outbreak of cancer has been more among patients infected by SARS-CoV-2 (COVID-19) than among the general population [15]. In China, it is known that 1% of the patients infected to COVID-19 have had a history of cancer. Lung cancer is the most common cancer among these patients while colorectal, breast, and bladder cancer, lymphoma, papillary thyroid cancer, renal cell carcinoma, adrenal carcinoma are in the forthcoming ranks [15].

Potential anti-coronavirus therapies

Potential anti-coronavirus targets can be categorized into two classes depending on the target, one is operating on the host immune system or human cells, and the other is on coronavirus itself [16]. Regarding human targets, the SARS-CoV-2 , similar to SARS virus, binds to the angiotensin-converting enzyme 2 (ACE2) receptor which is expressed abundantly in lung, kidney, heart and some other organs [17],[18]. The virus uses transmembrane protease, serine2 (TMPRSS2) in order to spike protein activation. Spike is broken into S1 and S2 by TMPRSS2. This plays a crucial role in SARS and coronavirus infection:therefore, TMPRSS2 could be a novel antiviral strategy against coronavirus and some influenza viruses [19-27].

Drug Targets for Coronavirus

The pharmacological targets of coronavirus are as follows:

1-Papain-like proteinase (PLpro) is responsible for the production of Nsp1, Nsp2 and Nsp3 through an N-terminus breakage of the replicase poly-protein. These proteins are important for virus

genome replication [28]. PLpro works as an antagonism of the host's innate immunity [29-31].

2-3C-like main protease (3CLpro or Nsp5) is another therapeutic target for the novel coronavirus. This enzyme is essentially maturates itself using polyproteins and then produces an Nsp4–Nsp16 [32].

3-RNA-dependent RNA polymerase (RdRp or Nsp12) is a very important protein in novel virus structure which contains Ser-Asp-Asp motif in an active site, and its activity is enhanced through NSP12 [33, 34].

4- Helicase (Nsp13) is utilized for separating double-stranded (ds) DNA and RNA and contains two domains: zinc binding domain located on N-terminal, and a helicase domain [35].

5-Some non-structural proteins which are involved in virus RNA synthesis can be targets for drug design. In this regard, NSP-3b, 3e, 7, 9. 10, 14, 15 and NSP7-8 complexes are candidates of the virus inhibition[16]. Structural proteins: Spike is the vital structural protein which is important in virus interaction to host cell receptors [36]. Spike protein is broken into S1 and S2 by the TMPRSS2 which corporate in attachment and fusion of virus to host cell [37].

6- Virulence factors of coronavirus: Nsp1, Nsp3c and ORF7a are recognized as virulence factors. Nsp1 leads to the inhibition of producing type-I interferon and degradation of mRNA by attaching to host 40S ribosomal subunit [38,39]. Nsp3c is involved in resistance of the novel virus to host innate immunity. The process occurs via attachment of this virus to host ADP-ribose [40]. Bone marrow stromal antigen 2 (BST-2 or tetherin) is a pre-B-cell growth activator [41,42], and it is a marker of type I interferon-producing cells (IPC)[43]. BST-2 has an antiviral activity which diminishes the release of human coronavirus 229E (hCoV-229E) and many other viruses [44]. Antiviral activity of BST-2 is restricted by ORF7a via direct interaction of ORF7a with BST-2 [45]. It has been shown that SARS-CoV and other coronaviruses have an open reading frame ORF-3a that encodes a monovalent cations-permeable channel in the infected host cells. The activity of this channel affects virus release and it entails a higher selectivity of K+ compared to Na+ [46-48].

Emodin and its beneficiary effects on Human Health

Anthraquinones are generally extracted from the Polygonaceae family, such as Rheum palmatum and Rheum officinale. Anthraquinones have many beneficiary features such as being antibacterial, anti-cancer, anti-diabetes [49,50]. Emodin anthraquinones (1,3,8-trihydroxy-6-ethylanthraquinone) (Fig-1) plays important roles in human health and it entails golden healthful features making it a drug for the treatment of the following illnesses: gallstones, inflammation and inflammatory diseases, hepatitis [51,52]. Emodin has been utilized as a laxative therapy for many years and some laxative mechanisms of emodin are as follows: the reduction of Na+-K+-ATPase activity in intestinal mucosa, inhibition of somatostatin, and enhancing the release of acetyl choline [52-54]

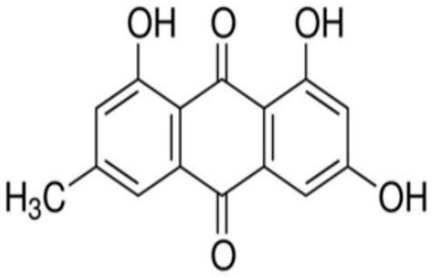

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Figure1- structure of emodin (55)

It has been shown that emodin is an anti-inflammatory, anti-ulcerogenic, anticancer, immunosuppressive, antibacterial, antiviral [56,57], vasorelaxant, and a chemo preventive factor [58].

Anti-cancer effects of emodin

Emodin induces apoptosis in a dose-dependent manner, and activates caspase-3 [59] and -9 enzymes [60], induces p53 protein [61], generates reactive oxygen species (ROS) [62], downregulates androgen receptors [63], suppresses lipid raft coalescence [64], inhibits Janus-activated kinase 2 [65], and it utilizes some apoptotic and anticancer mechanisms in various cell types (Fig-2).

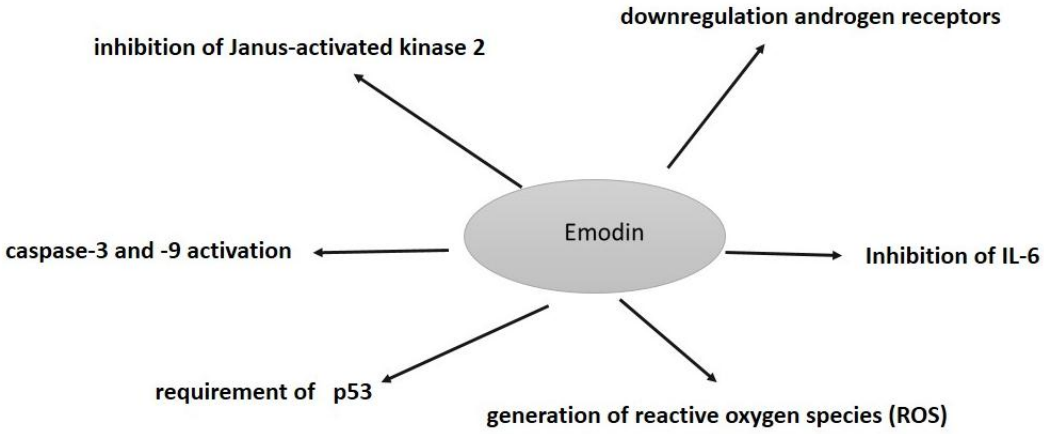

Figure2- Anti-cancer mechanisms of emodin

The Vital Role of Emodin in Novel Coronavirus Treatment

Various studies have demonstrated four drug targets of Emodin in inhibiting the coronavirus. This compound is a potent inhibitor of the 3a ion channel (Fig-3). Inhibition of this channel can counteract the release of the virus. The reduction of extracellular viral RNA copied by emodin is an evidence of inhibition of the virus release. This drug leads to decrease intracellular scripts of the virus 'RNA' in the presence of high concentrations. This indicates that emodin can inhibit other stages of the virus' life cycle at higher concentrations [66, 67]. Another

mechanism of emodin in inhibiting the coronavirus is approved regarding SARS-Cov by blocking the virus binding to its receptor, the angiotensin-converting enzyme [68]. The binding of the S protein to ACE2 is inhibited in 200 μM of emodin and 80% inhibition is achieved in 50 μM dosage [65]. Also emodin is a strong inhibitor of the 3a channel in about 20 M [66].

Still another emodin treatment strategy is inhibition of the 3C like protease (3CLpro) enzyme in novel virus which automatically cleaves polyproteins to produce mature enzymes, and its cleavage site is the downstream area of the non-structural protein leading to release the non-structural protein NSP4-NSP16s. As a result, this enzyme is involved in the maturation of non-structural proteins and therefore; it is considered as an essential enzyme for the viral life cycle to be utilized as a new drug target [69].

It has been shown that when 3CLpro enzyme is inhibited, the replication of the SARS-cov virus in the host cell is inhibited [70], and emodin leads to the inhibition of this enzyme which is present in Covid-19 virus structure [69-71]. It has been shown that Aloe emodin (1,8-dihydroxy-3-(hydroxymethyl) anthraquinone) is a another type of emodin which is present in aloe latex, in dose-dependently manner inhibited cleavage activity of the SARS coronavirus 3CLpro, in cell-free (the IC50 values were 132μM), and in cell-based assays [72].

Emodin inhibit the Janus-activated kinase-2 enzyme and the JAK2 / STAT3 signaling pathways induced by interleukin-6 [65]. Furthermore, it leads to the inhibition of the cytokine storm because the release of interleukin-6 releases other cytokines, resulting in inflammatory storms and the death of the infected patients[73]. It is worth mentioning that there are at least 36 IL-6 inhibitors which only two of them are monoclonal antibodies: Tocilizumab and Sarilumab, approved by the FAD. It has been shown that dietary Emodin has antioxidant properties and reduces oxidative damage to organs [74].

Side effects of emodin:

Emodin also has some side effects, if it is consumed in high dosages for a long period of time. In this regard, genotoxic effects of emodin are reported in some studies[75]. Furthermore, Emodin is carcinogen in rodents, and leads to cancer in some animals. Others studies have rejected the results of the carcinogenicity of emodin[76-79]. However, evaluating the genotoxity profile of emodin did not show any concerns on its genotoxity in humans [79]. Because emodin is a potent inhibitor of cytochrome P4501A1, and most pro-oncogen compounds need to be activated by detoxifying enzymes, emodin has been shown to inhibit this protein and thus counteracts the mutating effects of P4501A1. According to the above sources [80] , the lack of genotoxicity of emodin in humans is supported.

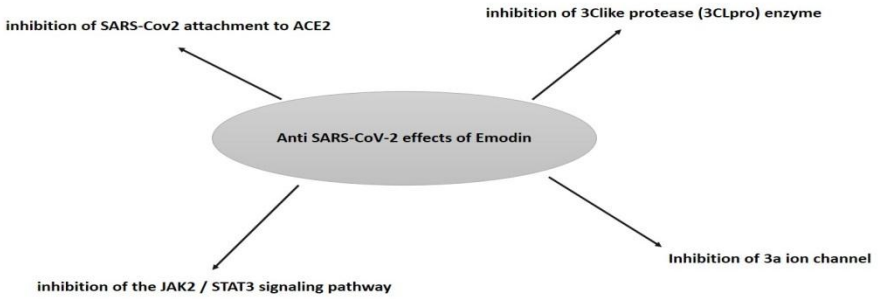

Figure 3 - Anti SARS-CoV -2 mechanisms of emodin

Conclusion

Emodin may operate as an antiviral drug by obstructing virus infection and its release. In addition, it shows anticancer effects using various mechanisms. Hence, emodin may open the horizons to novel therapeutics in treatment of coronaviruses. It can be considered as a basis for drug development against coronavirus infections and various cancers.

Acknowledgement

None reported.

Conflict of Interest

All authors report no conflicts of interest relevant to this article.

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