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IJBLS 2023; 2(1):105-114

International Journal of BioLife Sciences

Review paper

Hypericum perforatum against SARS-CoV-2. A Narrative Review

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***Received**: 20 June 2023* ***Revised**: 25 June 2023* ***Accepted**: 8 July 2023*

Abstract

Background and Aim: Viral infection dissemination and cytokine storm play an important role in the aggravation of COVID-19 disease, thus developing a drug that provides both antiviral and anti-inflammatory properties is essential.

Method: In this study, we reviewed the remarkable properties of two major active compounds (hyperforin and hypericin) in *Hypericum perforatum* plant with a special focus on the molecular pathways that have been involved in their anti-inflammatory and antiviral effects.

Results: Hyperforin can inhibit inflammation and regulate the function of the immune system by inhibiting the phosphorylation of three main signaling pathways including JAK/STAT, NF-κB, MAPK and increasing T_{reg} cells. Hypericin by destruction of viral membrane, proteins, and nucleic acids can inactivate only enveloped viruses.

Conclusion: Recently, studies have shown that hypericin has the ability to bind to the SARS-CoV-2 NSP14, ACE2 recognition region of SARS-CoV-2's S-protein. The antiviral and anti-inflammatory properties of hypericin and hyperforin increase the probability of *H. perforatum* effectiveness against SARS-CoV-2. We believe that *H. perforatum* extract has the potential to be considered as an antiviral herbal medicine.

Keywords: *Hyperforin, Hypericin, COVID-19, Inflammation, Cytokine storm, Hypericum perforatum, SARS-CoV-2*

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Introduction

The spread of SARS-CoV-2 in 2019 faced the world community with many challenges [1], [2]. Many new variants have emerged since the SARS-CoV-2 has been identified [3]. The reports show, two factors play a crucial role in the aggravation of the disease in Covid-19 patients: viral infection dissemination and cytokine storm. The cytokine storm causes acute respiratory distress syndrome (ARDS), organ damage, and even death. Therefore, the anti-inflammatory drugs are used to counteract the progression of the cytokine storm. However, these drugs have side effects and are unable to function selectively. Unfortunately, anti-inflammatory drugs may inhibit the production of anti-viral cytokines by affecting inflammatory pathways, thereby delaying the fight against the virus and triggering secondary infection [4]. Therefore, there is an urgent need to develop new and highly effective antiviral and anti-inflammatory drugs to prevent and control viral infections. Medicinal plants and purified natural products are an appropriate alternative for developing this kind of medicine. This study aims to consider the extraordinary properties of hypericin and hyperforin in the *H. perforatum* plant to investigate the possibility of its influence on SARS-CoV-2.

Hypericum perforatum

Hypericum L. (Hyepricaceae) is a large genus with about 490 flowering species. Among them *Hypericum perforatum* L. is an important species in terms of both economics and medicine [5]. *H. perforatum* is a widespread and well-known species native to Asia, North Africa, Western Europe and North America [6], [7]. There is a long history of its use in traditional medicine. It's no secret that the amazing properties *H. perforatum* are a hot topic among scientists. *H. perforatum* has been used for a variety of therapeutic purposes, including anti-virus [8], [9], [10], [11], anti-tumor [12], and anti-depressant [13]. It has also demonstrated remarkable anti-inflammatory properties [14], [15], [16], [17], [18], [19]. Hypericin and hyperforin (Figure 1) are two important components of *H. perforatum* which are responsible for its potent pharmacological effects [20]. A range of concentrations of 1-5 % hyperforin and 0.1-0.3 hypericin usually present in the total hydro-alcoholic *H. perforatum* extract.

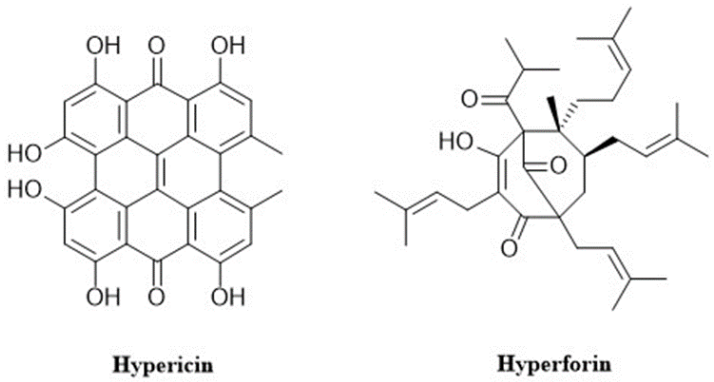

Figure 1. Chemical structures of hyperforin and hypericin

Method

In this review article, different resources have been used including journals and conferences in various languages such as English, Chinese, Persian, etc. We obtained gathered information from search engines including Scopus, Science Direct, Research Gate, Google Scholar, PubMed, and Embase. The keywords for searching are ‘Hypericin’ ‘Hyperforin’ ‘*Hypericum perforatum*’ ‘St. John’s wort’ ‘COVID-19’ ‘2019-nCoV’ ‘SARS-CoV-2’ that were explored in combination with

‘inflammation’ ‘antiviral’ ‘cytokine storm’ and separately.

Chemistry:

H. perforatum contains anthraquinone (e.g., hypericin, pseudohypericin and isohypericin which are derivate from naphthodianthrones) [21], Flavonoids (e.g., flavonols, flavones and glycosides) [22], phenols (e.g., caffeic, chlorogenic and vanillic acids) [23], prenylated phloroglucinols (e.g., hyperforin, adhyperforin and tannins) [23], [24], [25], volatile oils and other constituents [23]. Hypericin and hyperforin are the major active constituents in *H. perforatum* [26]. The antiviral effects of hypericin [8], [9], [10], [11] and anti-inflammatory effects of hyperforin [17], [18], [19] has been reported in many studies. However, the antiviral and anti-inflammatory efficacy of *H. perforatum* may not be attributed to these two compounds alone, as the synergic effect with other compounds may provide more efficacy.

Anti-Inflammatory Effects of Hyperforin:

Hypericin, flavonoids, hyperforin, and other compounds found in *H. perforatum* extract (HPE) have anti-inflammatory activities. However, hyperforin has the highest anti-inflammatory properties due to its effects on various inflammatory pathways [15], [17], [18], [19], [27]. The anti-inflammatory effects of hyperforin and HPE (which contain hyperforin) have been proven against inflammation caused by viral infections such as influenza A virus (IAV) and infectious bronchitis virus (IBV) [28], [29], [30], [31]. Pu et al. [28] described that HPE was able to slow the loss of arterial oxygen saturation, prevent lung consolidation, reduce lung weight, lower the viral titer of IAV-infected mice, and eventually prevent mortality. Another study found that oral administration of HPE decreased the secretion of tumor necrosis factor (TNF)-α and interleukin (IL)-6 while increased the levels of interferon (IFN)-ϒ and IL-10 in serum and the lungs of IAV-infected mice [29].

Further study on IBV also indicated that HPE could reduce the level of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and through affecting on the NF-κB signaling pathway could decrease the mRNA expression of IL-6 and TNF-α. It was interesting that HPE was able to diminish reactive oxygen species (ROS) generation which caused by IBV [30], [31]. Importantly, hyperforin has been shown to alleviate autoimmune diseases such as EAE (encephalomyelitis), IBS (irritable bowel syndrome), Parkinson's disease, Alzheimer's disease, and type 1 diabetes [17], [18], [19], [32], [33], [34], [35], [36]. Several studies have demonstrated that HPE and hyperforin can function as immunoregulators, reduce leukocyte infiltration into the central nervous system, increase regulatory T (Treg) cells in the spleen, and subsequently regulate autoreactive T-cells [32], [37], [38].

HPE and hyperforin inhibited phosphorylation of three important signaling pathways, including Janus kinase/signal transducer and activator of transcription (JAK/STAT), NF-κB, and mitogen-activated protein kinases (MAPK), in pancreatic β-cell lines and isolated rat and human pancreatic islets (Figure 2) [17], [18], [39].

HPE and its active compounds also suppress the transcription of target genes involved in apoptosis and inflammation. Many studies have also found that HPE decreases IL-6, TNF- and NF-κB mRNA expression levels [17], [19]. Furthermore, experimental results showed that HPE could reduce ROS production in carrageenan-induced pleurisy [40], [41].

Hyperforin suppresses the production of nitric oxide (NO) and prostaglandin E2 (PGE2) in RAW 264.7 macrophages, which is related to the inhibition of inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX)-2 gene expression [42]. In another study, the capability of hyperforin to inhibit cellular and cell-free PGE2 production by interfering with the microsomal PGE synthase (mPGES)-1 and suppression of leukotriene formation via the inhibition of 5-lipoxygenase (5-LO)

has been proposed as a molecular basis for its anti-inflammatory effects [43].

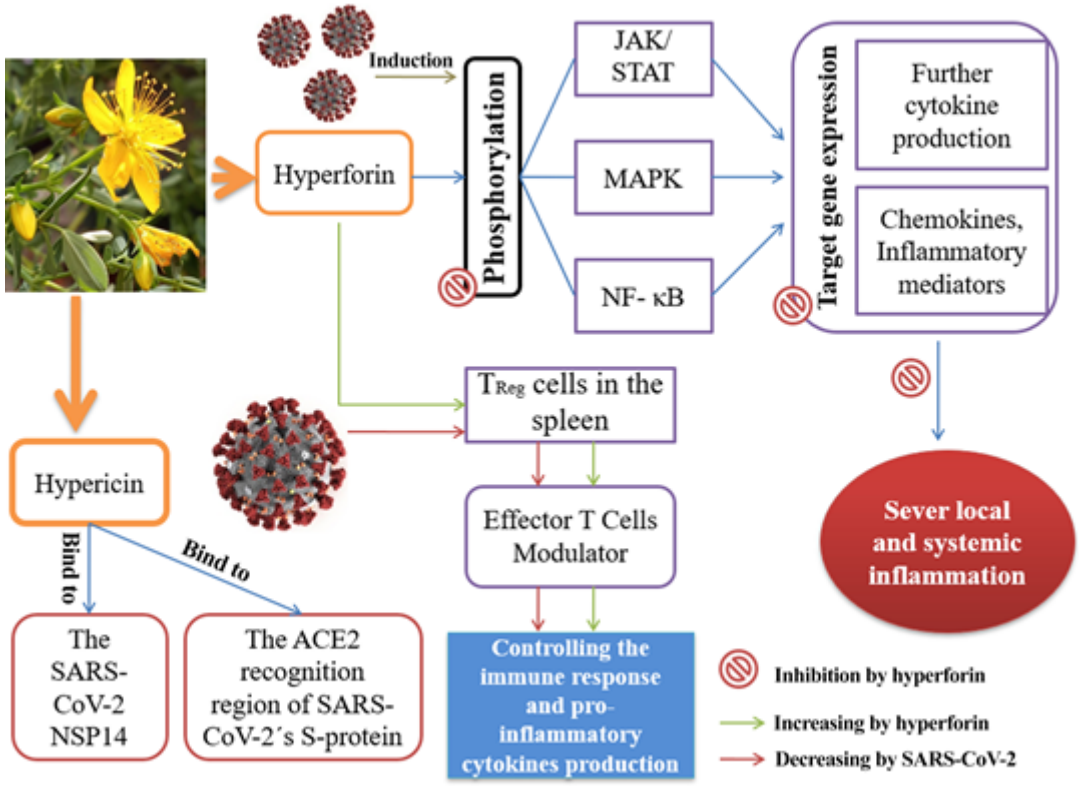

Figure 2. The possible mechanism of hypericin and hyperforin against SARS-CoV-2

Antiviral Effects of Hypericin:

A wide range of studies have shown that hypericin has antiviral activity against type 1 and 2 herpes simplex virus [44], [45], human immunodeficiency virus [46], [47], [48], influenza virus [28], [29], avian influenza virus [49], duck hepatitis B and chronic hepatitis C viruses [50], friend leukemia virus, radiation leukemia virus [51], [52], and novel duck reovirus [53]. The antiviral effects of hypericin are reported in several studies. Hypericin can function as the antiviral via three different mechanisms: I) Degradation of the viral lipid coat; Tang et al. [54] found that hypericin can inactivate viruses that are enveloped by lipid, however it cannot inactivate non-enveloped viruses. This suggestion would be in consistent with the findings of cell studies [55]. Lenard et al. [56] found that hypericin can inactivate the fusion activity of many viruses in a light-dependent process. Hypericin can be embedded in the phospholipid bilayer of cell plasma membranes, as evidenced by the fluorescent microscopic observations [57], [58]. One of the main possible reason for why only enveloped viruses are inactivated is the loss of the fusion function [56]. II) Destruction of viral membrane: Hudson et al. [59] suggested that in the presence of hypericin, viral membranes can be destroyed. Hypericin has the potential to damage proteins and nucleic acids. As a result, the virus is no longer able to encode viral antigens in infected cells, and its infectivity has been lost. III) Formation of immature or abnormally assembled cores: It's possible that hypericin interferes with the processing of precursor polyproteins encoded by viral genes because cells treated with it had immature or abnormally constructed cores [48].

Effects of Hypericin on SARS-CoV-2:

Coronaviruses (CoVs) are grouped into the Coronavirinae subfamily, Coronaviridae family within the Nidovirales order that are enveloped, single-stranded and positive-sense RNA viruses [60]. CoVs have been isolated into 4 genera: alfa-CoV, beta-CoV, gamma-CoV and delta-CoV. The SARS-CoV-2, which belongs to beta-CoVs [61] and causes severe and acute respiratory disease that called coronavirus disease 2019 (COVID-19) [62]. The clinical trials show that an increase in the expression level of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6 as well as chemokine like IL-8 causes cytokine storm (CS) in all COVID-19 patients [63], [64], [65], [66], [67], [68].

According to the findings, most patients show lymphocytopenia as well as a decrease in natural killer (NK) cells, T cells, T_{reg} cells, and especially induced regulatory T cells. In severe patients, these changes are much more dramatic [69], [70]. Furthermore, autopsy findings reveal that critical patients have spleen atrophy, necrosis lymph nodes with decreased number, and diffused alveolar injury in the lungs [4].

According to the studies, hypericin has exhibited strong binding affinity to the active site of the SARS Coronavirus main peptidase (SARS-CoVMpro) enzyme and interacts with the amino acids (ASN142 and HIS164) of the active site of the target site. The SARS-CoVMpro plays an essential role in the replication cycle of the Coronaviridae family [71].

Furthermore, recent studies have shown that hypericin inhibits SARS-CoV-2 activity by two mechanisms: I) Hypericin can bind to the amino acids (involving ASN-252, GLY-93 and HIS-268) of N-terminus of SARS-CoV-2 NSP14 (Nonstructural Protein 14) by three hydrogen bonds, and bind to the amino acids (involving ASN-306, ARG-310, ASN-422 and LY-336) of the C-terminus of it by six hydrogen bonds. NSPs play an important role in the replication and transcription of CoVs. NSP14 is the most important protein in coronaviridae family. NSP14 harbors both RNA cap guanine N7-methyl transferase (N7-MTase) and 3′-5′ exoribonuclease (ExoN) activities. Therefore, hypericin can disrupt NSP14 activity by binding to it [62]. II) Hypericin can bind to the Angiotensin-converting enzyme 2 (ACE2) recognition region of SARS-CoV-2's S-protein (Figure 2). Structural proteins like spike (S) protein have an essential role in virion assembly and infection of CoVs and it is the main key for the viral attachment to the receptor of host [72].

Conclusion

Studies showed, it is necessary to strike a balance between the use of antiviral and anti-inflammatory drugs in COVID-19 patients. As mentioned, hyperforin can inhibit the cytokine storm and it has the potential to be used as an anti-inflammatory drug. In addition, hypericin can disturb viral replication cycle and bind to the ACE2 recognition region of SARS-CoV-2's S-protein. Therefore, hypericin has an important role in preventing the spread of viral infection. Based on research and the synergistic effects that these two compounds have along with other compounds in plant extract, we recommend the use of plant extract. Unfortunately, it remains uncertain whether novel variants of SARS-CoV-2 will pose a threat in the future. But undoubtedly, the Omicron variant will not be the last variant of concern [73]. Therefore, the need for anti-COVID-19 drug along with vaccination is still necessary.

Acknowledgment

We thank and appreciate Imam Reza and all those who helped us in conducting this research.

Conflict of interests

The authors declare that there are no competing interests.

Reference

[1]. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. The Lancet. 2020;395(10223): 470-3.
[2]. Organization WH. WHO Director-General's opening remarks at the media briefing on COVID-19. 11 March 2020. Geneva, Switzerland. 2020.
[3]. https://www.who.int/activities/tracking-SARS-CoV-2-variants.
[4]. Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, Wang J, Qin Y, Zhang X, Yan X. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The Perspectives of clinical immunologists from China. Clin Immunol. 2020; 214:108393.
[5]. ROBSON NK. Studies in the genus Hypericum L.(Guttiferae) 4 (2). Section 9. Hypericum sensu lato (part 2): subsection 1. Hypericum series 1. Hypericum. Bull Nat Hist Mus. 2002;32(2):61-123.
[6]. Bombardelli E, Morazzoni P. Hypericum perforatum. Fitoterapia. 1995;66(1):43-68.
[7]. Riazi A, Majnoun HN, Naghdi BH, Naghavi M, Rezazadeh S, Ajani Y. The study of morphological characteristics of St. John's Wort (Hypericum perforatum L.) populations in Iran's natural habitats. J Med Plant. 2011.
[8]. Naesens L, Bonnafous P, Agut H, De Clercq E. Antiviral activity of diverse classes of broad-acting agents and natural compounds in HHV-6-infected lymphoblasts. J Clin Virol. 2006;37 Suppl 1.S69-75.
[9]. Birt DF, Widrlechner MP, Hammer KD, Hillwig ML, Wei J, Kraus GA, Murphy PA, McCoy J, Wurtele ES, Neighbors JD, Wiemer DF, Maury WJ, Price JP. Hypericum in infection: Identification of anti-viral and anti-inflammatory constituents. Pharm Biol. 2009;47(8):774-82.
[10]. Marrelli M, Conforti F, Toniolo C, Nicoletti M, Statti G, Menichini F. Hypericum perforatum: Influences of the habitat on chemical composition, photo-induced cytotoxicity, and antiradical activity. Pharm Biol. 2014;52(7):909-18.
[11]. Wölfle U, Seelinger G, Schempp CM. Topical application of St. John's wort (Hypericum perforatum). Planta med. 2014;80(02/03):109-20.
[12]. Mirmalek SA, Azizi MA, Jangholi E, Yadollah-Damavandi S, Javidi MA, Parsa Y, Parsa T, Salimi-Tabatabaee SA, Ghasemzadeh-Kolagar H, Alizadeh-Navaei R. Cytotoxic and apoptogenic effect of hypericin, the bioactive component of Hypericum perforatum on the MCF-7 human breast cancer cell line. Cancer Cell Int. 2015;16(1):3.
[13]. Zhai X-j, Chen F, Chen C, Zhu C-r, Lu Y-n. LC–MS/MS based studies on the anti-depressant effect of hypericin in the chronic unpredictable mild stress rat model. J Ethnopharmacol. 2015;169:363-9.
[14]. Panossian A, Gabrielian E, Manvelian V, Jurcic K, Wagner H. Immunosuppressive effects of hypericin on stimulated human leukocytes: inhibition of the arachidonic acid release, leukotriene B4 and Interleukin-Iα production, and activation of nitric oxide formation. Phytomedicine. 1996;3(1):19-28.
[15]. Hammer KD, Yum M-Y, Dixon PM, Birt DF. Identification of JAK–STAT pathways as important for the anti-inflammatory activity of a Hypericum perforatum fraction and bioactive constituents in RAW 264.7 mouse macrophages. Phytochemistry. 2010;71(7):716-25.
[16]. Dellafiora L, Galaverna G, Cruciani G, Dall'Asta C, Bruni R. On the Mechanism of Action

of Anti-Inflammatory Activity of Hypericin: An In Silico Study Pointing to the Relevance of Janus Kinases Inhibition. Molecules. 2018;23(12):3058.
[17]. Novelli M, Menegazzi M, Beffy P, Porozov S, Gregorelli A, Giacopelli D, De Tata V, Masiello P. St. John's wort extract and hyperforin inhibit multiple phosphorylation steps of cytokine signaling and prevent inflammatory and apoptotic gene induction in pancreatic β cells. Int J Biochem Cell Biol. 2016;81:92-104.
[18]. Menegazzi M, Novelli M, Beffy P, D'Aleo V, Tedeschi E, Lupi R, Zoratti E, Marchetti P, Suzuki H, Masiello P. Protective effects of St. John's wort extract and its component hyperforin against cytokine-induced cytotoxicity in a pancreatic beta-cell line. Int J Biochem Cell Biol. 2008;40(8):1509-21.
[19]. Novelli M, Masiello P, Beffy P, Menegazzi M. Protective role of St. John's wort and its components hyperforin and hypericin against diabetes through inhibition of inflammatory signaling: Evidence from in vitro and in vivo studies. Int J Mol Sci. 2020;21(21):8108.
[20]. Vollmer JJ, Rosenson J. Chemistry of St. John's wort: Hypericin and hyperforin. J Chem Educ. 2004;81(10):1450.
[21]. Vanhaelen M, Vanhaelen-Fastre R. Quantitative determination of biologically active constituents in medicinal plant crude extracts by thin-layer chromatography densitometry: I. Aesculus hippocastaneum L., Arctostaphyllos uva-ursi Spreng, Fraxinus excelsior L., Gentiana lutea L., Glycyrrhiza glabra L., Hamamelis virginiana L., Hypericum perforatum L., Olea europea L., Salix alba L. and Silybum marianum Gaertn. J Chromatogr A. 1983;281:263-71.
[22]. Berghöfer R, Hölzl J. Biflavonoids in Hypericum perforatum1; Part 1. Isolation of I3, II8-Biapigenin. Planta med. 1987;53(02):216-7.
[23]. Barnes J, Anderson LA, Phillipson JD. St John's wort (Hypericum perforatum L.): a review of its chemistry, pharmacology and clinical properties. J Pharm Pharmacol. 2001;53(5):583-600.
[24]. Brondz I, Greibrokk T, Groth PA, Aasen AJ. The relative stereochemistry of hyperforin-an antibiotic from hypericum perforatum L. Tetrahedron Lett. 1982;23(12):1299-300.
[25]. Ayuga C, Rebuelta M. A comparative study of phenolic acids of Hypericum caprifolium Boiss and Hypericum perforatum L. An Real Acad Farm. 1986;52:723-8.
[26]. Nahrstedt A, Butterweck V. Biologically active and other chemical constituents of the herb of Hypericum perforatum L. Pharmacopsychiatry. 1997;30 Suppl 2(S 2):129-34.
[27]. Hammer KD, Hillwig ML, Solco AK, Dixon PM, Delate K, Murphy PA, Wurtele ES, Birt DF. Inhibition of prostaglandin E2 production by anti-inflammatory Hypericum perforatum extracts and constituents in RAW264. 7 mouse macrophage cells. J Agric Food Chem. 2007;55(18):7323-31.
[28]. Pu X-y, Liang J-p, Wang X-h, Xu T, Hua L-y, Shang R-f, Liu Y, Xing Y-m. Anti-influenza A virus effect of Hypericum perforatum L. extract. Virol Sin. 2009;24(1):19.
[29]. Xiuying P, Jianping L, Ruofeng S, Liye Z, Xuehong W, Yan L. Therapeutic efficacy of Hypericum perforatum L. extract for mice infected with an influenza A virus. Can J Physiol Pharmacol. 2012;90(2):123-30.
[30]. Chen H, Muhammad I, Zhang Y, Ren Y, Zhang R, Huang X, Diao L, Liu H, Li X, Sun X, Abbas G, Li G. Antiviral Activity Against Infectious Bronchitis Virus and Bioactive Components of Hypericum perforatum L. Front Pharmacol. 2019;10:1272.
[31]. Chen H, Feng R, Muhammad I, Abbas G, Zhang Y, Ren Y, Huang X, Zhang R, Diao L, Wang X, Li G. Protective effects of hypericin against infectious bronchitis virus induced apoptosis and reactive oxygen species in chicken embryo kidney cells. Poult Sci. 2019;98(12):6367-77.
[32]. Nosratabadi R, Rastin M, Sankian M, Haghmorad D, Tabasi N, Zamani S, Aghaee A,

Salehipour Z, Mahmoudi M. St. John's wort and its component hyperforin alleviate experimental autoimmune encephalomyelitis through expansion of regulatory T-cells. J Immunotoxicol. 2016;13(3):364-74.
[33]. Mozaffari S, Esmaily H, Rahimi R, Baeeri M, Sanei Y, Asadi-Shahmirzadi A, Salehi-Surmaghi MH, Abdollahi M. Effects of Hypericum perforatum extract on rat irritable bowel syndrome. Pharmacogn Mag. 2011;7(27):213-23.
[34]. Mohanasundari M, Sabesan M. Extract on astrocytes in MPTP induced Parkinson's disease in mice. Eur Rev Med Pharmacolog Sci. 2007;11:17-20.
[35]. Kraus B, Wolff H, Heilmann J, Elstner EF. Influence of Hypericum perforatum extract and its single compounds on amyloid-beta mediated toxicity in microglial cells. Life Sci. 2007;81(11):884-94.
[36]. Griffith TN, Varela-Nallar L, Dinamarca MC, Inestrosa NC. Neurobiological effects of Hyperforin and its potential in Alzheimer's disease therapy. Curr Med Chem. 2010;17(5):391-406.
[37]. Dell'Aica I, Niero R, Piazza F, Cabrelle A, Sartor L, Colalto C, Brunetta E, Lorusso G, Benelli R, Albini A, Calabrese F, Agostini C, Garbisa S. Hyperforin blocks neutrophil activation of matrix metalloproteinase-9, motility and recruitment, and restrains inflammation-triggered angiogenesis and lung fibrosis. J Pharmacol Exp Ther. 2007;321(2):492-500.
[38]. Cabrelle A, Dell'Aica I, Melchiori L, Carraro S, Brunetta E, Niero R, Scquizzato E, D'Intino G, Calza L, Garbisa S. Hyperforin down-regulates effector function of activated T lymphocytes and shows efficacy against Th1-triggered CNS inflammatory-demyelinating disease. Wiley Online Library. 2008.
[39]. Novelli M, Beffy P, Menegazzi M, De Tata V, Martino L, Sgarbossa A, Porozov S, Pippa A, Masini M, Marchetti P. St. John's wort extract and hyperforin protect rat and human pancreatic islets against cytokine toxicity. Acta Diabetologica. 2014;51(1):113-21.
[40]. Menegazzi M, Di Paola R, Mazzon E, Muia C, Genovese T, Crisafulli C, Suzuki H, Cuzzocrea S. Hypericum perforatum attenuates the development of carrageenan-induced lung injury in mice. Free Radic Biol Med. 2006;40(5):740-53.
[41]. Menegazzi M, Masiello P, Novelli M. Anti-Tumor Activity of Hypericum perforatum L. and Hyperforin through Modulation of Inflammatory Signaling, ROS Generation and Proton Dynamics. Antioxidants. 2021;10(1):18.
[42]. Berköz M, Allahverdiyev O, Yıldırım M. Investigation of the effect of hyperforin and hypericin on inflammatory response in RAW 264.7 macrophages. Van Med J. 2018;25(2):124-31.
[43]. Koeberle A, Rossi A, Bauer J, Dehm F, Verotta L, Northoff H, Sautebin L, Werz O. Hyperforin, an anti-inflammatory constituent from St. John's wort, inhibits microsomal prostaglandin E2 synthase-1 and suppresses prostaglandin E2 formation in vivo. Front Pharmacol. 2011;2:7.
[44]. Wood S, Huffman J, Weber N, Andersen D, North J, Murray B, Sidwell R, Hughes B. Antiviral activity of naturally occurring anthraquinones and anthraquinone derivatives. Planta med. 1990;56(06):651-2.
[45]. Weber N, Murray B, North J, Wood S. The antiviral agent hypericin has in vitro activity against HSV-1 through non-specific association with viral and cellular membranes. Antivir Chem Chemother. 1994:83-90.
[46]. Steinbeck-Klose A. HIV-negative by hypericin or living with inactivated HIV virus after four years of hypericin therapy?. Forsch Komplementarmed. 1995;2:33-5.
[47]. Valentine F, Itri V, Kudler N, Georgescu R. Synthetic hypericin enters blood lymphocytes and monocytes in vitro and decreases culturable HIV in blood obtained from infected individuals.

International Conference on AIDS. 1991:p97.
[48]. Degar S, Prince AM, Pascual D, Lavie G, Levin B, Mazur Y, Lavie D, Ehrlich LS, Carter C, Meruelo D. Inactivation of the human immunodeficiency virus by hypericin: evidence for photochemical alterations of p24 and a block in uncoating. AIDS Res Hum Retroviruses. 1992;8(11):1929-36.
[49]. Zhao X, Liang J, Zhu Y, Shang R, Wang W, Cui Y. Study on the antiviral activity of hypericin proteinbound complex on H5N1 subtype of AIV in vitro. J Trad Chinese Vet Med. 2006;3:13-5.
[50]. Furuta A, Tsubuki M, Endoh M, Miyamoto T, Tanaka J, Salam KA, Akimitsu N, Tani H, Yamashita A, Moriishi K. Identification of hydroxyanthraquinones as novel inhibitors of hepatitis C virus NS3 helicase. Int J Mol Sci. 2015;16(8):18439-53.
[51]. Meruelo D, Lavie G, Lavie D. Therapeutic agents with dramatic antiretroviral activity and little toxicity at effective doses: aromatic polycyclic diones hypericin and pseudohypericin. Proc Nat Acad Sci. 1988;85(14):5230-4.
[52]. Degar S, Lavie G, Meruelo D. Photodynamic inactivation of radiation leukemia virus produced from hypericin-treated cells. Virology. 1993;197(2):796-800.
[53]. Du X, Xiao R, Fu H, Yuan Z, Zhang W, Yin L, He C, Li C, Zhou J, Liu G, Shu G, Chen Z. Hypericin-loaded graphene oxide protects ducks against a novel duck reovirus. Mater Sci Eng C Mater Biol Appl. 2019;105:110052.
[54]. Tang J, Colacino JM, Larsen SH, Spitzer W. Virucidal activity of hypericin against enveloped and non-enveloped DNA and RNA viruses. Antiviral Res. 1990;13(6):313-25.
[55]. Duráan N, Song PS. Hypericin and its photodynamic action. Photochem Photobiol. 1986;43(6):677-80.
[56]. Lenard J, Rabson A, Vanderoef R. Photodynamic inactivation of infectivity of human immunodeficiency virus and other enveloped viruses using hypericin and rose bengal: inhibition of fusion and syncytia formation. Proc Nat Acad Sci. 1993;90(1):158-62.
[57]. Lavie G, Valentine F, Levin B, Mazur Y, Gallo G, Lavie D, Weiner D, Meruelo D. Studies of the mechanisms of action of the antiretroviral agents hypericin and pseudohypericin. Proc Natl Acad Sci U S A. 1989;86(15):5963-7.
[58]. Thomas C, Pardini RS. Oxygen dependence of hypericin-induced phototoxicity to EMT6 mouse mammary carcinoma cells. Photochem Photobiol. 1992;55(6):831-7.
[59]. Hudson JB, Lopez-Bazzocchi I, Towers GH. Antiviral activities of hypericin. Antiviral Res. 1991;15(2):101-12.
[60]. Chen Y, Liu Q, Guo D. Emerging coronaviruses: genome structure, replication, and pathogenesis. J Med Virol. 2020;92(4):418-23.
[61]. Wu F, Zhao S, Yu B, Chen Y-M, Wang W, Hu Y, Song Z-G, Tao Z-W, Tian J-H, Pei Y-Y. Complete genome characterisation of a novel coronavirus associated with severe human respiratory disease in Wuhan, China. BioRxiv. 2020.
[62]. Liu C, Zhu X, Lu Y, Zhang X, Jia X, Yang T. Potential treatment with Chinese and Western medicine targeting NSP14 of SARS-CoV-2. J Pharm Anal. 2021;11(3):272-7.
[63]. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
[64]. Conti P, Ronconi G, Caraffa A, Gallenga CE, Ross R, Frydas I, Kritas SK. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. J Biol Regul Homeost Agents. 2020;34(2):327-31.

[65]. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62.
[66]. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020;46(5):846-8.
[67]. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-13.
[68]. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Zhou X, Chen D, Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J, Song Y. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020;180(7):934-43.
[69]. Wan S, Yi Q, Fan S, Lv J, Zhang X, Guo L, Lang C, Xiao Q, Xiao K, Yi Z. Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). MedRxiv. 2020.
[70]. QinC Z. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis. 2020.
[71]. Agrawal A, Jain NK, Kumar N, Kulkarni GT. Molecular docking study to identify potential inhibitor of covid-19 main protease enzyme: An in-silico approach. ChemRxiv. 2020.
[72]. Smith M, Smith JC. Repurposing therapeutics for COVID-19: Supercomputer-based docking to the SARS-CoV-2 viral spike protein and viral spike protein-human ACE2 interface. ChemRxiv. 2020.
[73]. Fan Y, Li X, Zhang L, Wan S, Zhang L, Zhou F. SARS-CoV-2 Omicron variant: recent progress and future perspectives. Signal Transduction and Targeted Therapy. 2022;7(141).