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Network Pharmacology and bioinformatics analyses identify intersection genes of niacin and COVID-19 as potential therapeutic targets

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Abstract

Objectives: Patients with colorectal cancer (CRC) may be susceptible to the coronavirus disease-2019 (COVID-19). However, anti-CRC/COVID-19 treatment options are currently unavailable. Since niacin is a vitamin with cytoprotective and anti-inflammatory functions, this study aimed to evaluate the possible functional roles and underlying mechanisms of action of niacin as an anti-COVID-19 and -CRC therapy.
Interventions: We used a series of network pharmacology-based and computational analyses to understand and characterize the binding capacity, biological functions, pharmacological targets and therapeutic mechanisms of niacin in CRC/COVID-19.
Measurements and main results: We revealed the clinical characteristics of CRC patients and COVID-19 patients, including predisposing genes, survival rate and prognosis. Moreover, the results of molecular docking analysis indicated that niacin exerted effective binding capacity in COVID-19. Further, we disclosed the targets, biological functions and signaling pathways of niacin in CRC/COVID-19. The analysis indicated that niacin could help in treating CRC/COVID-19 through cytoprotection, enhancement of immunologic functions, inhibition of inflammatory reactions and regulation of cellular microenvironment. Furthermore, five core pharmacological targets of niacin in CRC/COVID-19 were also identified, including *BCL2L1*, *PTGS2*, *IL1B*, *IFNG* and *SERPINE1*.
Conclusions: This study, for the first time, revealed the niacin-associated molecular functions and pharmacological targets for treating CRC/COVID-19, as COVID-19 remains a serious pandemic. But the findings were not validated in actual CRC patients infected with COVID-19, so further investigation is needed to confirm the potential use of niacin for treating CRC/COVID-19.

Key words: colorectal neoplasms; COVID-19; niacin; network pharmacology; computational biology; prognosis

BACKGROUND

Coronavirus disease-19 (COVID-19), a fatal pandemic, has shown a gigantic increase in incidence and mortality rates worldwide [1]. As severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is newly-found, effective anti-COVID-19 medicines are limited, especially during the early outbreak in China [2]. Hydroxychloroquine is being administered as a potential treatment for COVID-19, and some of its curative effects can be found in clinical practice [3]; however, other pieces of

evidence show limited therapeutic effectiveness [4]. Therefore, potential bioactive agents against COVID-19 need to be urgently screened and validated. Additionally, patients with cancer, such as colorectal cancer (CRC), lung cancer and breast cancer, have shown a high incidence of COVID-19 than those with noncancer diseases in China [5]. CRC is a severe, life-threatening neoplasm that can induce malignant invasiveness or metastasis [6]. In China, the incidence of CRC has increased in recent years due to the urbanized lifestyle and modern diet [7]. As per the 2020 cancer statistics, incidence rates for CRC rank among the top three cancer cases worldwide [8]. Further, during the early outbreak of COVID-19, hospitals were the main place for infection [9]. Thus, in-hospital patients with CRC are at an increased risk of COVID-19 infection. If CRC patients get infected with COVID-19, treatment for these patients will be difficult due to poor immunity and lack of medicines against COVID-19 [10]. Therefore, effective treatments should be screened in such patients.

Niacin, a B-type vitamin, is essential for normal functions in the gastrointestinal tract and nervous system [11]. It is a functional precursor of nicotinamide adenine dinucleotide, a bioactive coenzyme responsible for maintaining cell respiration and metabolism [12]. Moreover, niacin helps regulate energy metabolism, methylation, DNA rehabilitation and immune function [13]. Reports suggest that deficiency of niacin can increase the risk of neurodegeneration, immunological disorder and inflammation stress [14]. Additionally, niacin exerts its anti-inflammatory effect by suppressing the NF-κB pathway [15]. A high concentration of niacin has antiproliferative activity against colon cancer stem cells [16]. Furthermore, it can effectively inhibit inflammatory reaction in the colon tissue and tumorigenesis by activating G-Protein Coupled Receptor 109A (GPR109A) [17]. Interestingly, niacin is a potent antipneumonia agent that modulates specific genes, such as *niaR*, *niaX* and *pnuC* [18]. However, the pharmacological targets and mechanism by which niacin can combat COVID-19 in CRC patients remain to be studied in detail.

Network pharmacology is a useful bioinformatics tool to discover all candidate targets, functions and mechanisms of bioactive components to treat disease [19, 20]. Our previous bioinformatics analyses identified core targets, biological functions and signaling pathways downstream to few bioactive compounds, such as plumbagin and Vitamin-C in clinical disorders, including liver cancer, pneumonia and sepsis [21–23]. In the present study, using the network pharmacology approach, we aimed to elucidate the detailed anti-COVID-19/CRC mechanisms of niacin for network visualization. Further, a visible graphical abstract for the current flowchart is provided to demonstrate the anti-COVID-19/CRC functions and mechanisms exerted by niacin (Figure 1).

Materials and methods

Identification of CRC/COVID-19–associated genes

To identify the CRC/COVID-19–associated genes, transcriptome profiles of CRC patients were downloaded from The Cancer Genome Atlas (TCGA) database (https://portal.gdc.cancer.gov/) on 05 May 2020. The differential genes in CRC were screened and obtained using the 'limma' package of R-language Bioconductor with false discovery rate < 0.05 and | log$^{\text{fold change (FC)}}$ | > 1. Furthermore, genes related to COVID-19 were selected from the Genecard database, OMIM database and NCBI gene

function module. Finally, these genes were compared to obtain the overlapping targets in CRC and COVID-19 [28, 29].

Clinicopathological analysis of CRC and COVID-19–associated genes

The 'survival' package in R package was used to analyze the correlation of CRC/COVID-19-associated genes and survival rates in patients with CRC/COVID-19. Prognostic analyses were performed using univariate Cox proportional hazards regression. Moreover, different characteristics of diseased genes and patients with CRC/COVID-19 were analyzed using a multivariate Cox proportional hazards regression model. Finally, based on the average risk score, patients were categorized into low- and high-risk groups [30].

Acquisition of niacin-pharmacological target in CRC/COVID-19

All pharmacological targets of niacin were screened and collected from accessible online tools, such as Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP), Swiss Target Prediction, TargetNet, Batman, Drugbank and HitPick [31]. The overlapping candidate genes were identified after data correction using reviewed (Swiss-Prot) and Human settings in the Uniprot database [32].

Enrichment analyses and network visualization

R-language packages, including 'ClusterProfiler,' 'ReactomePA,' 'org.Hs.eg.Db' and 'GOplot,' were used for enrichment analysis and visualization of gene ontology (GO) biological process (BP) and KEGG pathways of the overlapping gene targets of niacin in CRC/COVID-19. GO information was obtained using "org.Hs.eg.Db." P-value cutoff = 0.05 and q-value cutoff = 0.05 were set for enrichment, and output was used for plotting the bubble chart, bar chart and Circos plot [33, 34]. Cytoscape software (3.7.1 version) was used to construct a graphical representation of drug-target-GO function-pathway-disease for creating GO BP and pathway in response to targeting CRC and COVID-19 intersecting genes [35].

Identifying core targets of niacin against CRC/COVID-19

The overlapping targets of niacin treatment and CRC/COVID-19 were queried in the STRING database (version 11.0) to obtain the interaction network of the target–target function-related proteins, target interaction in protein–protein interactions (PPI) network map, and .tsv data. The Network-Analyzer setting from Cytoscape software was applied for analyzing the topological parameters. The median degree of freedom of the target network was 3.231, and the maximum freedom of degree was 7. Thus, the core target screening condition range was set to 4–7. Further, core targets were collected according to the Degree-value of the algorithm [36].

Molecular docking

Using molecular docking analysis, the binding situation and interaction force of protein and small molecules can be predicted and obtained. The molecular structure of niacin was obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) [24]. The protein structure of COVID-19 associated proteins
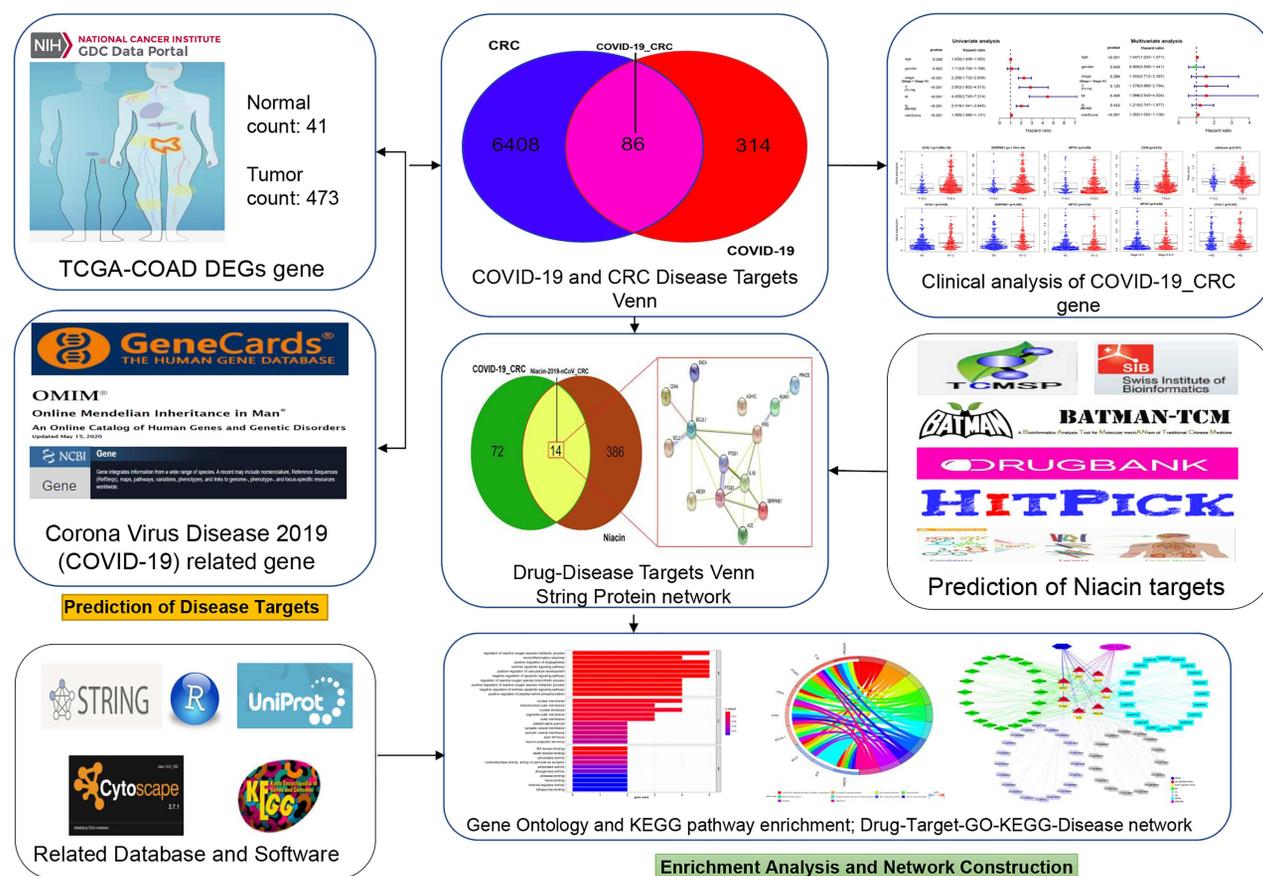
Figure 1. Workflow of the study. The figure indicates the antiviral action and mechanism of niacin against CRC/COVID-19 using the network pharmacology and computational bioinformatics analysis approach.

Table 1. Univariate Cox proportional hazards regression analysis of COVID-19 combined with CRC gene

Symbol	HR	HR.95 L	HR.95H	P-value
IL16	1.324457	1.042209	1.683142	0.021558
SERPINE1	1.005443	1.002007	1.00889	0.001883
CR2	1.053227	1.013614	1.094388	0.008018
FCER2	1.134922	1.070732	1.20296	2.04E-05
NPTX1	1.232645	1.015844	1.495716	0.034071
TLR10	1.691648	1.029342	2.780101	0.038074
UCHL1	1.067599	1.033462	1.102865	7.98E-05
NCF1	1.28472	1.021642	1.615543	0.032104
CD79A	1.019596	1.003902	1.035537	0.014209
CD36	1.063087	1.014473	1.11403	0.010417
FGF2	1.208832	1.024961	1.425689	0.02427
CD40LG	1.435032	1.010346	2.038229	0.043648
ADA	1.052907	1.005433	1.102622	0.028514

was obtained from the PDB database (https://www.rcsb.org/) [25]. MM2 force field optimization was performed using the three-dimensional structure of the compound downloaded by the ChemBio3D Draw module in the ChemBioOffice software (version 2010). The Protein Data Bank, Partial Charge (Q), & Atom Type (T) (PDBQT) structure file necessary for virtual screening were created using the Raccoon software [26]. The supporting tool MGLTools 1.5.6 of Autodock Vina software was used to process the corresponding protein, hydrogenation and Gasteiger charge for merging nonpolar hydrogen atoms [27].

The original pdb file format was converted to the pdbqt file format recognized by the Autodock Vina program, providing a ligand basis for molecular docking. Further, the docking active center (including all residues around the original ligand) was set through the grid box function in the software, based on the size of the root mean square deviation (RMSD) of the docked ligand molecule and original ligand molecule with a reasonable setting of docking parameters. RMSD ≤ 4 was considered the threshold for conformation of the ligand after docking to match the conformation of the original ligand.
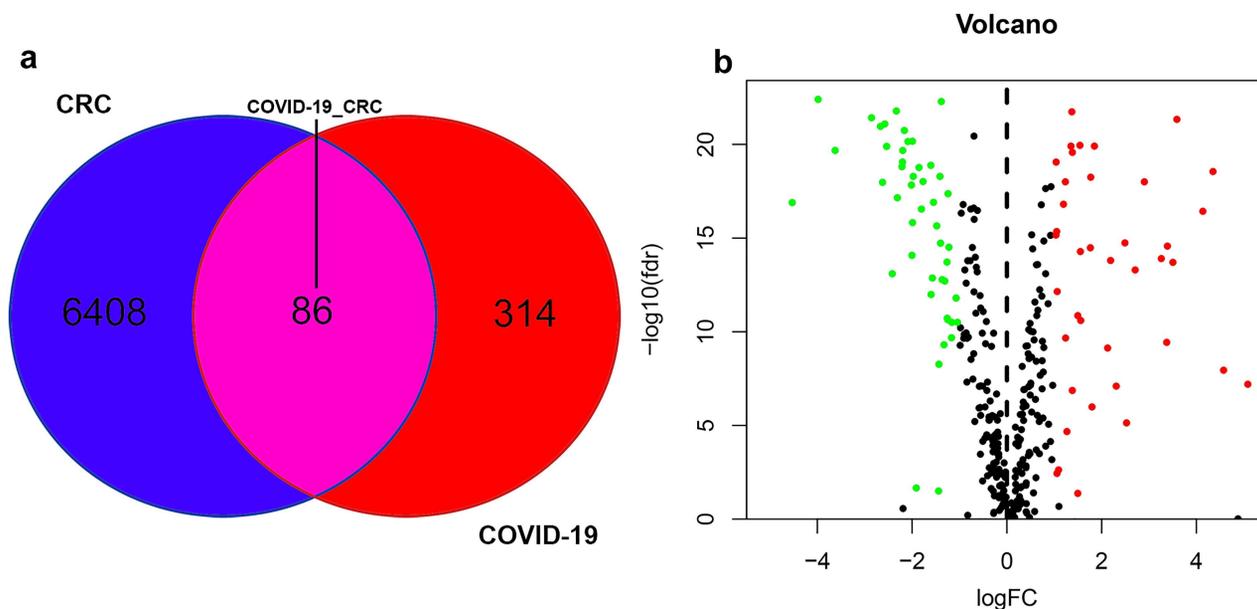
Figure 2. Analysis of intersecting genes in CRC/COVID-19. (**A**) Venn diagram depicting intersecting genes in CRC/COVID-19. (**B**) Volcano-plot representation of differential gene expression (DGE).

Table 2. Multivariate Cox proportional hazards regression analysis

Symbol	coef	HR	HR.95 L	HR.95H	*P*-value
IL16	−0.42431	0.654221	0.392304	1.091003	0.103915
SERPINE1	0.005727	1.005743	1.00178	1.009722	0.004473
FCER2	0.355835	1.427372	1.093811	1.862653	0.008787
NPTX1	−0.49767	0.607946	0.342335	1.079639	0.089422
UCHL1	0.045768	1.046832	0.998118	1.097923	0.059771
CD36	0.058166	1.059891	0.989731	1.135024	0.095998
ADA	0.051072	1.052398	1.003059	1.104165	0.037102

Results

Identification of COVID-19/CRC targets

First, network pharmacology collected 400 genes associated with COVID-19 from the Genecard, OMIM and NCBI databases (Figure 2A). Whereas, 6494 CRC-associated differentially expressed genes were identified using the TCGA database (Figure 2A). A comparison of these two gene clusters identified 86 intersection genes in COVID-19 and CRC (Figure 2A). Further, we checked the differential gene expression (DGE) of the intersected genes using R-language, in which 39 genes were upregulated and 47 were down-regulated in CRC (Figure 2B).

Clinicopathological analysis of CRC/COVID-19-associated genes

To understand the correlation of CRC/COVID-19-associated genes and pathology of CRC/COVID-19, the 86 differential genes were subjected to univariate and multivariate Cox analyses. First, the univariate Cox analysis identified 13 genes, including *IL16, SERPINE1, CR2, FCER2, NPTX1, TLR10, UCHL1, NCF1, CD79A, CD36, FGF2, CD40LG* and *ADA* to be significantly (*P* < 0.05) associated with CRC/COVID-19 (Figure 3A, Table 1). Whereas, multivariate Cox analysis identified seven targeting genes out of 13, including *IL16, SERPINE1, FCER2, NPTX1, UCHL1, CD36* and *ADA* (Table 2). Moreover, based on the coef values of Multivariate Cox

proportional hazards regression analysis representing patient risk (Table 2), we categorized the patients into high- and low-risk groups. Next, in the overall survival analysis, no significant differences were observed between the high- and low-risk groups (Figure 3B). Further, each CRC patient's risk score, survival status and expression distribution of the seven genes mentioned above were analyzed. The results showed that greater risk value in patients correlated with higher risk score (Figure 3C) and increased expression levels of the three genes—*UCHL1, SERPINE1* and *ADA* (Figure 3E). Furthermore, we conducted an independent single factor and multifactor prognostic analysis with the seven genes. Moreover, the clinical prognostic analysis of the seven genes showed that the expression of four genes— *CD36, NPTX1, SERPINE1* and *UCHL1*—was closely associated with advanced stages of CRC. The expression of *NPTX1, SERPINE1* and *UCHL1* was also related to the number and scope of lymph node metastasis and spread in the lymph node area, while the expression of *NPTX1* in CRC stage I and II disease was higher than that in stage III and IV. Additionally, the expression of *UCHL1* was higher in older than that in younger patients (Figure 4, Table 3).

Identifying niacin targets and intersection with COVID-19 and CRC

TCMSP databases and Swiss Target Prediction software were used to determine the pharmacological targets of niacin. After
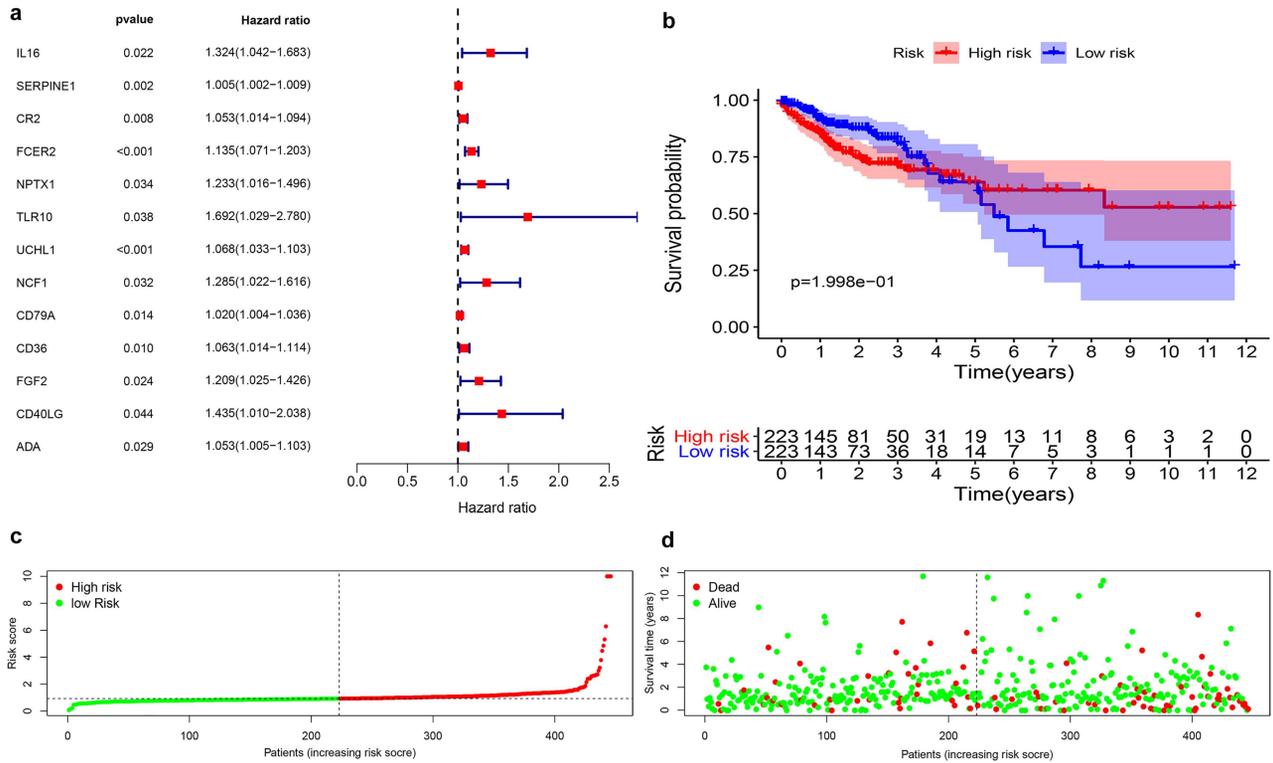
Figure 3. Prognostic value of CRC/COVID-19 associated genes. (**A**) Univariate Cox analysis identified 13 genes, including *IL16*, *SERPINE1*, *CR2*, *FCER2*, *NPTX1*, *TLR10*, *UCHL1*, *NCF1*, *CD79A*, *CD36*, *FGF2*, *CD40LG* and *ADA*. (**B**) Survival analysis indicated no difference in overall survival between high- and low-risk groups. (**C**) Analysis of patients' risk score using Cox proportional hazards regression. (**D**) Expression levels of genes in the high- and low-risk groups.

Table 3. Clinical correlation analysis

Symbol	Age (≤65 versus >65)	Gender (male versus female)	Stage (stage I and II versus stage III & IV)	T (T1 & 2 versus T3 & 4)	M (M0 versus M1)	N (N0 versus N1–2)
IL16	0.981(0.327)	−0.546(0.586)	0.517(0.605)	−0.16(0.873)	0.489(0.626)	0.156(0.876)
SERPINE1	−0.048(0.962)	−0.18(0.857)	−1.922(0.056)	−3.894(1.161e−04)	−1.265(0.211)	−2.071(0.040)
FCER2	1.217(0.225)	−1.346(0.180)	−0.908(0.365)	−1.342(0.181)	−0.85(0.399)	−0.969(0.334)
NPTX1	1.038(0.300)	−0.665(0.506)	−2.084(0.039)	−2.787(0.006)	−0.975(0.333)	−2.14(0.034)
UCHL1	2.048(0.042)	0.05(0.960)	−1.713(0.088)	−4.862(1.696e−06)	−1.416(0.162)	−1.989(0.048)
CD36	1.725(0.086)	1.07(0.285)	−1.437(0.152)	−2.515(0.012)	−1.128(0.263)	−1.638(0.102)
ADA	−0.586(0.558)	−0.132(0.895)	0.024(0.981)	0.025(0.980)	−0.416(0.679)	−0.16(0.873)
Risk score	0.884(0.378)	−1.425(0.156)	−1.48(0.141)	−2.172(0.031)	−1.507(0.137)	−1.507(0.134)

biological correction and depletion of repetitive genes using the UniProt database, 400 niacin-associated targets were obtained. An overlap of COVID-19/CRC genes with niacin-associated targets identified 14 intersection genes of niacin against COVID-19/CRC (Figure 5A; Supplementary Table 1, Supplemental Digital Content 1). The 14 intersection genes were submitted for GO and KEGG enrichment analyses, which indicated niacin to affect a series of BPs, including regulation of reactive oxygen species metabolic process, neuroinflammatory response, positive regulation of angiogenesis, extrinsic apoptotic signaling pathway, positive regulation of vasculature development, negative regulation of apoptotic signaling pathway, regulation of reactive oxygen species biosynthetic process, positive regulation of reactive oxygen species metabolic process, negative regulation of extrinsic apoptotic signaling pathway, positive regulation of peptidyl-serine phosphorylation, prostaglandin biosynthetic process, prostanoid biosynthetic process, positive regulation of alcohol biosynthetic process, reactive oxygen species metabolic process, reactive oxygen species biosynthetic process, peptidyl-serine phosphorylation, negative regulation of signal transduction in the absence of ligand, negative regulation of extrinsic apoptotic signaling pathway in the absence of ligand, peptidyl-serine modification, and regulation of peptidyl-serine phosphorylation (Figure 5B; Supplementary Table 2, Supplemental Digital Content 2). Additionally, in the KEGG pathway analysis, 48 KEGG pathways related to all core targets were found (P-adjust < 0.05). These included the AGE–RAGE signaling pathway in diabetic complications, NF-kappa B signaling pathway, p53 signaling pathway, Leishmaniasis, small cell lung cancer, Chagas disease (American trypanosomiasis), HIF-1 signaling pathway, African trypanosomiasis, measles, influenza A, chronic myeloid leukemia, EGFR tyrosine kinase
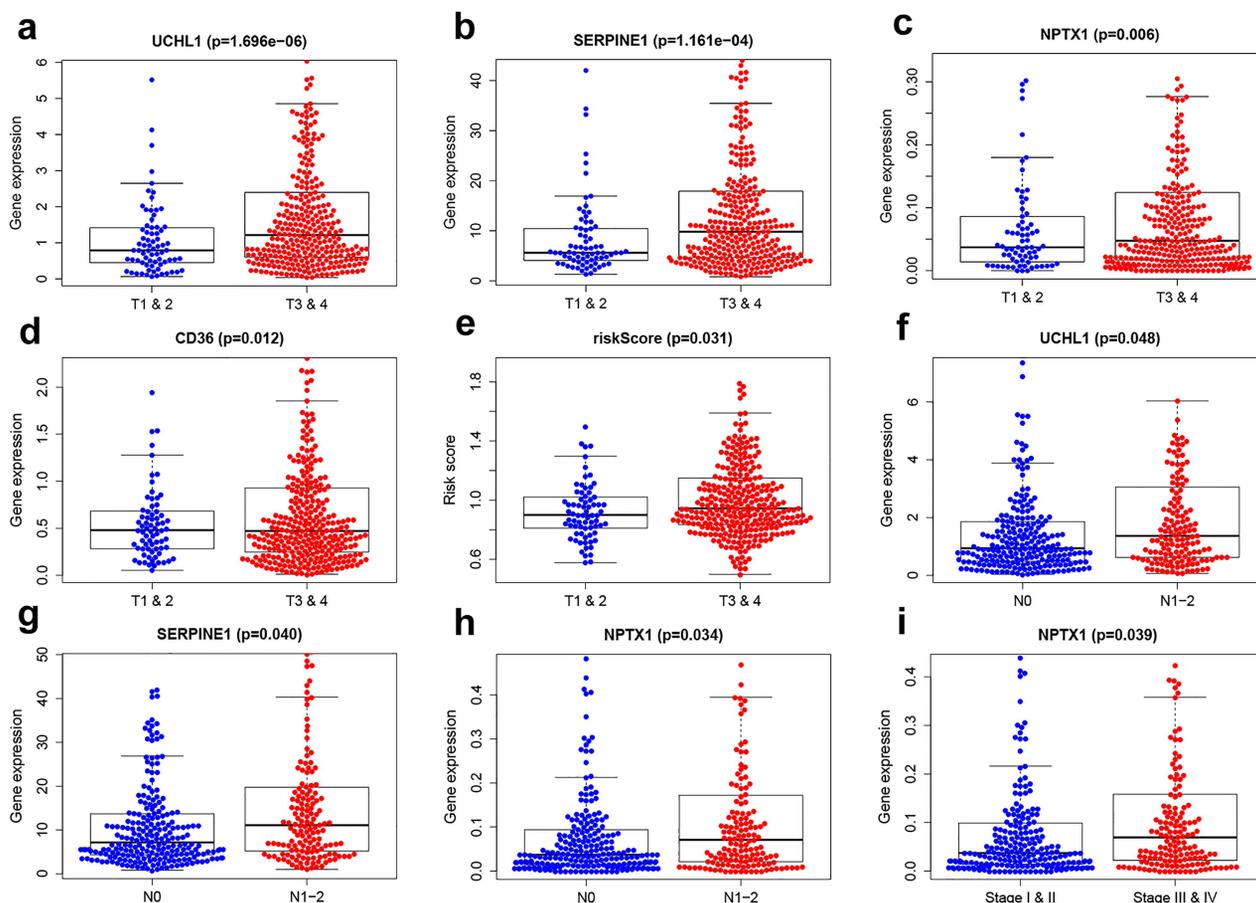
Figure 4. Clinical prognostic analysis of the 7 genes. (**A–D**) Association of gene expression of *UCHL1*, *SERPINE1*, *NPTX1* and *CD36* with tumor stage and metastasis in colorectal cancer (CRC) patients. (**E**) Association of risk score with tumor stage of CRC. (**F–H**) Association of expression of *SERPINE1*, *UCHL1* and *NPTX1* with the number of lymph node metastasis. (**I**) Association of expression of NPTX1 with staging in CRC.

inhibitor resistance, human cytomegalovirus infection, IL-17 signaling pathway, Amoebiasis, Th17 cell differentiation, toxoplasmosis, serotonergic synapse, apoptosis-multiple species, and MicroRNAs in cancer (Figure 5C; Supplementary Table 3, Supplemental Digital Content 3).
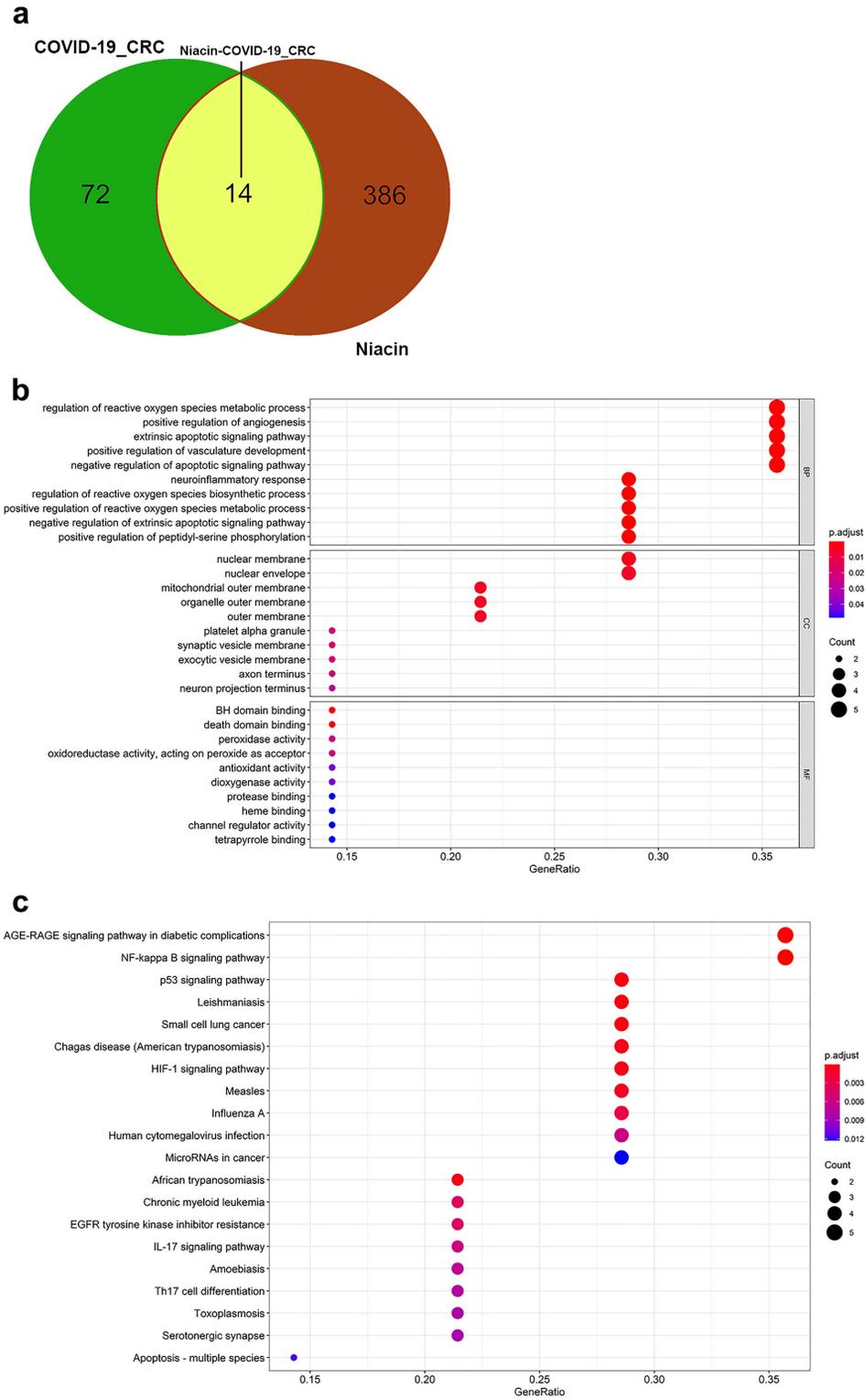
Identification of core targets of niacin against COVID-19 and CRC

Next, STRING analysis was used to determine the PPI-networking mediated by 14 intersection targets of niacin against COVID-19/CRC (Figure 6A). All mapped intersecting proteins were input to the Cytoscape software to calculate the topological parameters of PPI-network related to niacin against COVID-19/CRC. The analysis identified five core gene targets, including *BCL2L1*, *PTGS2*, *IL1B*, *IFNG* and *SERPINE1* (Figure 6B; Supplementary Table 4, Supplemental Digital Content 4).

## Binding of niacin to COVID-19 intersecting potential target genes

In order to determine the possible binding of niacin with the COVID-19 and the identified core targets, molecular docking analysis was performed. The crystal structure of the COVID-19 main protease was collected from the PDB database (http://www.rcsb.org/structure/5R84) with PDB ID 5R84, for docking analysis with niacin (Figure 7). The active cavity box parameter setting center_x, y, z was 10.162, 0.119 and 20.548, respectively, and size_x, y, z was 11.25, whereas RMSD of the original ligand was 2.304 Å. Thus, the hydrogen bond between the proto-ligand 2-cyclohexyl-~{N}-pyridin-3-yl-ethanamide (GWS) of 5R84 and 5R84 protein acted on two amino acid residues, *viz.* HIS-163 (1.7 Å) and GLU-166 (2.1 Å) (Figure 7A). Our result showed that niacin forms a hydrogen bond with the amino acid residue HIS-163 (2.0 Å) of 5R84 (CONVID-19) (Figure 7B), the bond action suggested that niacin had a good binding activity with the 5R84 protein (COVID-19). Further, we analyzed the possible binding between niacin and the five COVID-19/CRC core targets (*BCL2L1*, *PTGS2*, *IL1B*, *IFNG* and *SERPINE1*) identified from STRING analysis. Our result showed that niacin only bind to IL1B. We collected the crystal structure of IL1B from the PDB database (http://www.rcsb.org/structure/5R85), the active cavity box parameter setting center_x, y, z was 41.653, 4.192 and 71.476, respectively, and size_x, y, z was 11.25, whereas RMSD of the original ligand was 2.328 Å. The analysis suggested that hydrogen bonding between pro-ligand 3,3,3-tris(fluoranyl)-1-piperazin-1-yl-propan-1-one (S7A) of 5R85 and the 5R85 protein acted on the amino

Figure 5. Functional characterization of niacin against CRC/COVID-19 intersecting genes. (**A**) Venn diagram depicting intersecting genes of niacin and CRC/COVID-19. (**B**) Gene ontology analysis of intersecting genes of niacin and CRC/COVID-19. (**C**) Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway of intersecting genes of niacin and CRC/COVID-19.
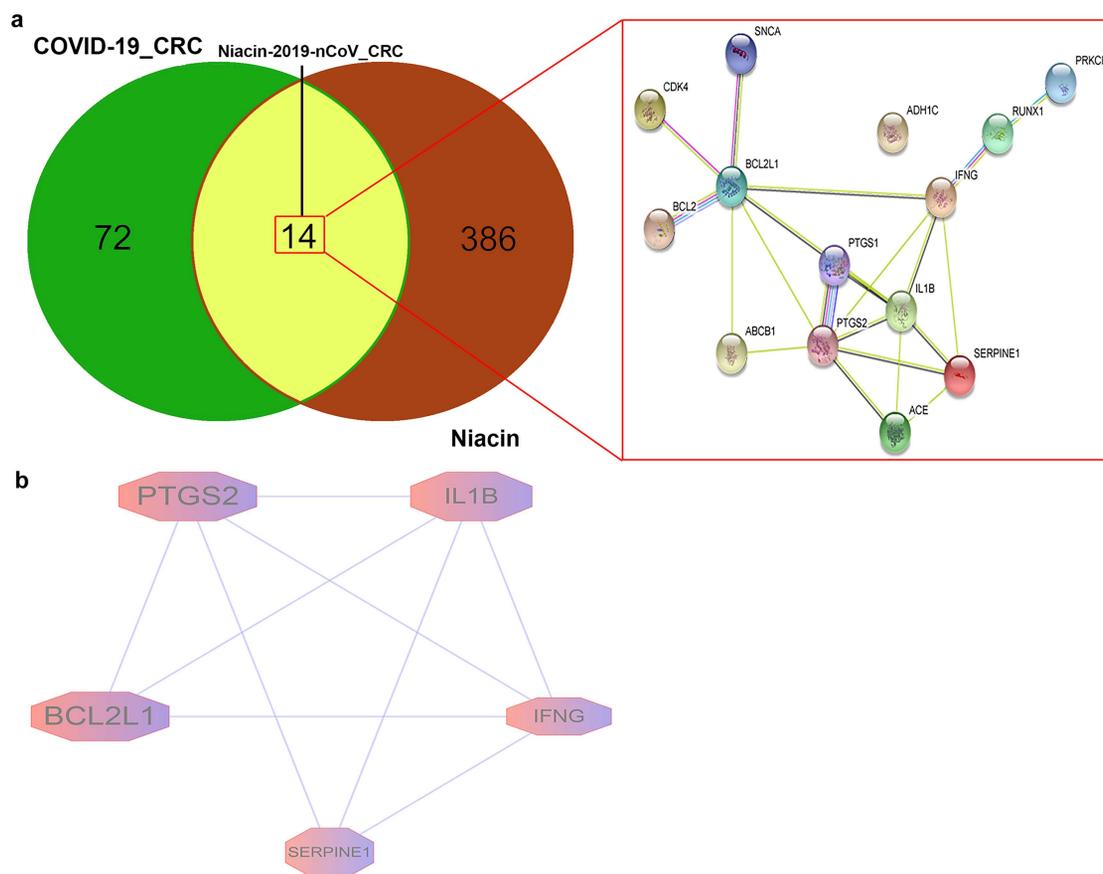
Figure 6. Gene network analysis of niacin against CRC/COVID-19. (**A**) STRING analysis indicating protein–protein interaction networking mediated by 14 intersecting targets of niacin against COVID-19/CRC. (**B**) Cytoscape analysis representing the protein interaction network related to the action of niacin against COVID-19/CRC. Five core targets—*BCL2L1*, *PTGS2*, *IL1B*, *IFNG* and *SERPINE1*—are highlighted.

acid residue LEU-26 (2.3 Å) (Figure 7C). Moreover, the binding of niacin was consistent with pro-ligand S7A's hydrogen-bonding amino acid residue Leu-26 (2.3 Å) of IL1B (Figure 7D), indicating its high-affinity association between niacin and IL1B.

DISCUSSION

COVID-19 is an emerging, rapidly evolving pandemic with an increasing infection and death rate worldwide [37]. Moreover, specific therapy against COVID-19 remains undeveloped to overcome this life-threatening epidemic disease. Additionally, COVID-19 in humans is increasing every day [38]. As per statistics, the COVID-19-infected population is huge in several countries globally [39], including China, India and Brazil. In developing countries, the incidence of malignant diseases, such as cancers, has rapidly increased in recent decades [40]. As the immune system of cancer patients is weakened due to immunosuppression and immunological dysfunction [41], any external infection can deteriorate their health. However, given the current COVID-19 prevalence, hospital in-patients with cancer may have an increased risk of being infected with the novel coronavirus (SARS-CoV-2), as hospitals are a high-risk place for exposure to coronavirus [42]. As per cancer statistics in 2020, CRC is the second leading cause of death by cancer in the USA [43]. Additionally, the COVID-19 infected cases in the USA are increasing [44]. Moreover, CRC patients may be susceptible to infection with COVID-19 under current ineffective management. Thus, the incidence of COVID-19 in CRC patients may worsen the treatment outcome and decrease the survival rate in such patients.

In a previous reference analysis, niacin showed beneficial action against CRC cells [16]. Thus, based on the viral inhibitory effects of niacin [45], we hypothesize that niacin may exert potent pharmacological activity in patients with CRC combined with COVID-19. In the current computational analysis, we first screened out and identified hub genes and 86 intersecting genes of COVID-19 combined with CRC. The DGE analysis showed 39 upregulated and 47 downregulated genes in patients with CRC and/or COVID-19. The DGE-based analysis may be used for determining clinical characteristics in CRC patients with COVID-19. As per the independent prognostic and survival analyses, few of the important DGE, including *IL16*, *SERPINE1*, *CR2*, *FCER2*, *NPTX1*, *TLR10*, *UCHL1*, *NCF1*, *CD79A*, *CD36*, *FGF2*, *CD40LG* and *ADA*, may function as potent biomarkers for screening and characterizing different stages of CRC patients with COVID-19. Taken together, these 86 intersection genes in CRC and COVID-19 may be used as potential treatment targets. Further, using
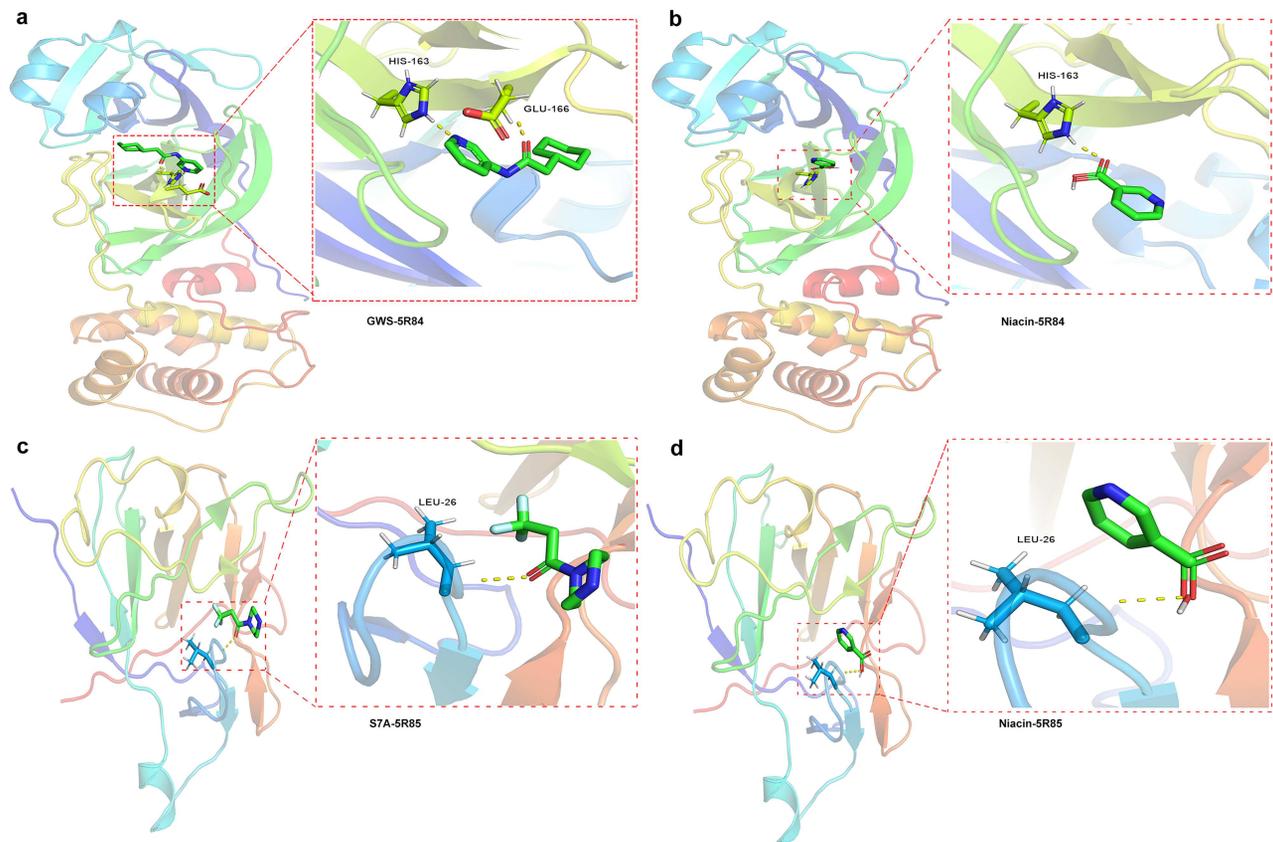
Figure 7. Binding of niacin to COVID-19 and the core target IL1B using molecular docking analysis. (**A**) Sites of niacin with SARS-CoV-2 main protease (PDB ID 5R84). (**B**) Hydorgen bond formed between niacin and and 5R84 protein of COVID-19 on HIS-163. (**C**) Sites of niacin with Human Interleukin-1 Beta (PDB ID: 5R85). (**D**) Hydorgen bond formed between niacin and and 5R85 protein of IL1B on LEU-26.

the network pharmacology approach, we identified 14 intersection genes with niacin treatment against CRC and COVID-19 before DGE analysis. The DGE-analysis identified significant differences in the expression of *SERPINE1* and *BCL2L1*. Moreover, CRC and COVID-19 showed increased expression of *SERPINE1* and *BCL2L1*, along with a lower survival rate. *SERPINE1* is a serpin peptidase inhibitor that was found to be induced in recurrent CRC tumors compared to nonrecurrent tumors [46]. It has been reported that *SERPINE1* interacted with different growth factors such as AKT1, VEGFA and TGFB1 in CRC [47]. Further, increased expression of SERPINE1 was associated with tumor cell migration and invasion through the activation of the PI3K-Akt pathway [48]. *BCL2L1* is an oncogenic driver and antiapoptotic factor in CRC [49–50]. It was reported that the induction of *BCL2L1* led to a reduction of apoptosis in CRC cell lines [51]. These findings indicated that these 14 intersection genes might be potent pharmacological targets of niacin against CRC and COVID-19. Based on the GO and KEGG enrichment analysis, the findings suggested that anti-CRC and anti-COVID-19 effects exerted by niacin were directed via cytoprotection, antiviral and anti-inflammatory actions, immunoregulation, as well as regulation of related signaling pathways, including the NF-kappa B, p53, HIF-1 and IL-17, Th17 cell differentiation, and MicroRNAs in cancer. Moreover, the anti-CRC/COVID-19 action

of niacin could be modulated by core molecules/genes, including *BCL2L1*, *PTGS2*, *IL1B*, *IFNG* and *SERPINE1*. Using molecular docking analysis, we identified best binding activities of niacin with GWS_5R84 structures in COVID-19 and S7A_5R85 in the core target IL1B, indicating that niacin can effectively bind to specific proteins in the novel coronavirus. These bindings suggested that niacin may be able to bring the IL1B to target the COVID-19. Additionally, we believe that adjuvant supplementation of niacin may enhance the therapeutic efficacy of current clinical antiviral agents and immunotherapy to treat the fatal COVID-19, or CRC combined with COVID-19.

Conclusions

Taken together, the bioinformatics and computational findings highlight antivirus, anti-inflammation and immunity-modulation as key targets/pathways of niacin treatment in CRC/COVID-19 (Figure 8). Further, niacin may be used clinically to treat CRC/COVID-19, based on the identified BPs (pharmacological functions) and signaling pathways (therapeutic mechanisms). Moreover, the potent pharmacological targets of niacin against CRC/COVID-19 were identified, paving the way for further clinical trials.
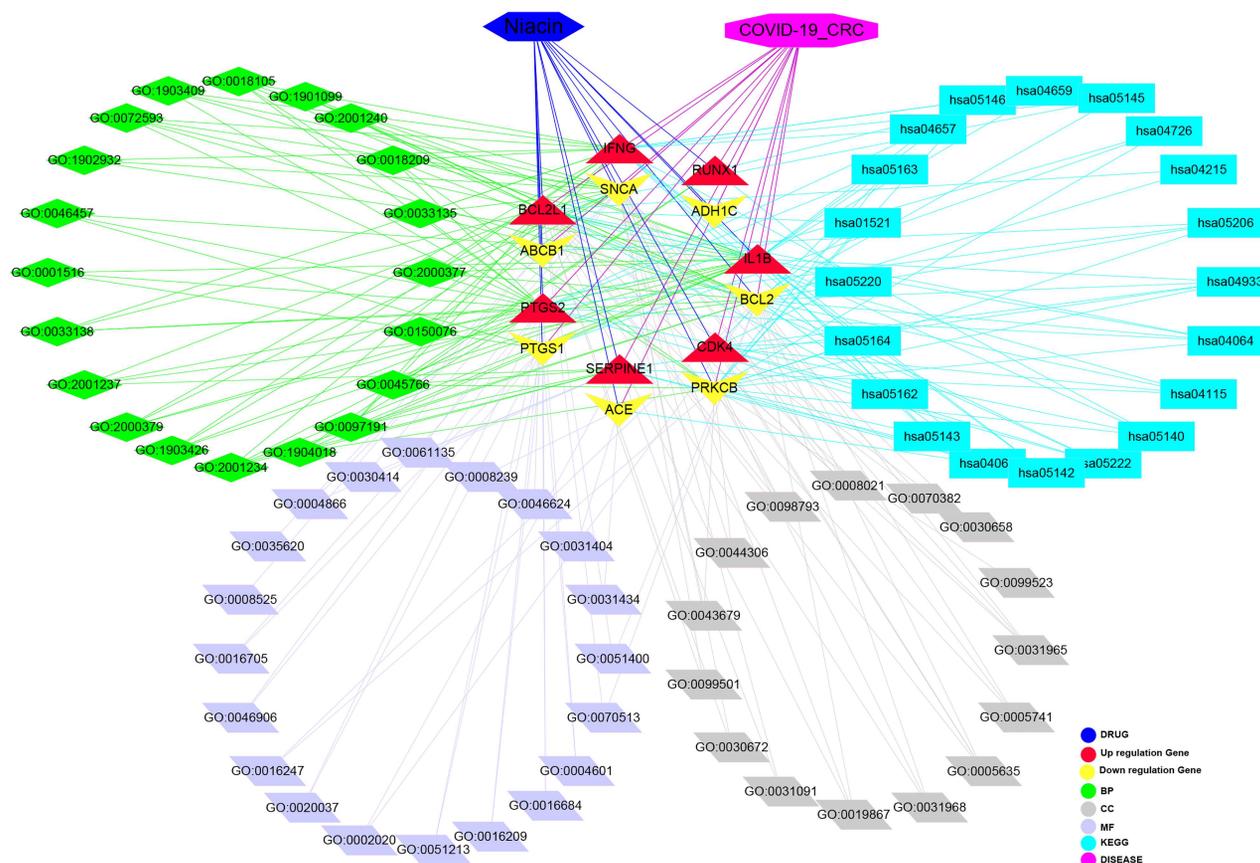
Figure 8. Interaction network showing core biotargets, pharmacological functions, and signaling pathways of niacin against CRC/COVID-19.

Authors' contributions

R.L, K.P.L. and M.S. conceived and designed the study. X.L. and L.M. performed data analysis and data interpretation. X.L., L.Y. and L.M. conducted the bioinformatics and statistical analyses. R.L and K.P.L prepared the manuscript.

Key Points

- The clinical characteristics of colorectal cancer (CRC) patients and COVID-19 patients, including predisposing genes, survival rate and prognosis, were uncovered.
- Molecular docking analysis indicated that niacin exerted effective binding capacity in COVID-19.
- The targets, biological functions and signaling pathways of niacin in CRC/COVID-19 were revealed.
- Five core pharmacological targets of niacin in CRC/COVID-19, including *BCL2L1*, *PTGS2*, *IL1B*, *IFNG* and *SERPINE1*, were identified.

Supplementary data

Supplementary data are available online at https://academic.oup.com/bib.

Abbreviations

CRC   colorectal cancer
COVID-19   coronavirus disease-2019
SARS-CoV-2   severe acute respiratory syndrome coronavirus 2
GPR109A   G-Protein Coupled Receptor 109A
TCGA   The Cancer Genome Atlas
GO   gene ontology
BP   biological process
KEGG   Kyoto Encyclopedia of Genes and Genomes

PDB   Protein Data Bank
PDBQT   Protein Data Bank, Partial Charge (Q), & Atom Type (T)
RMSD   root mean square deviation
TCMSP   Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform.

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