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Original Research

Simple Theoretical Criterion for Selection of Natural Compounds with Anti-COVID-19 Activity

Veljko Veljkovic[1,*], Sanja Glisic[2], Vladimir Perovic[2], Milena Veljkovic[1], Slobodan Paessler[3]

[1]Biomed Protection, Galveston, TX 77550, USA
[2]Laboratory for Bioinformatics and Computational Chemistry, Institute of Nuclear Sciences Vinca, National Institute of the Republic of Serbia, University of Belgrade, 11001 Belgrade, Serbia
[3]Department of Pathology, Galveston National Laboratory, University of Texas Medical Branch, 301 University Boulevard, Galveston, TX 77550, USA
*Correspondence: veljko@biomedprotection.com (Veljko Veljkovic)
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Abstract

Background: A novel human coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become the leading threat to global health. An effective antiviral could not only help those still vulnerable to the virus but could be a critical treatment if a virus emerges toward evading coronavirus disease 2019 (COVID-19) vaccines. Despite the significant efforts to test already-approved drugs for their potential to kill the virus, researchers found very few actually worked. **Methods**: The present report uses the electronic molecular descriptors, the quasi-valence number (AQVN), and the electron-ion interaction potential (EIIP), for the analysis of natural compounds with proven therapeutic activity against the COVID-19. **Results**: Based on the analysis of the electronic properties of natural compounds which are effective against SARS-CoV-2 virus the simple theoretical criterion for the selection of candidate compounds for the treatment of COVID-19 is proposed. **Conclusions**: The proposed theoretical criterion can be used for the identification and optimization of new lead compounds for the treatment of the COVID-19 disease and for the selection of the food and food supplements which could have a beneficial effect on COVID-19 patients.

Keywords: natural compounds; secondary metabolites; flavonoids; coronavirus; COVID-19; electron-ion interaction potential; average quasi-valence number

1. Introduction

The outbreak of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) has led to coronavirus disease-19 (COVID-19); a pandemic disease that represents the global health, social and economic threat. Currently, SARS-CoV-2 is spreading worldwide very rapidly and its control is very difficult because there is no available effective vaccine or drugs. As of October, 2021 globally, more than 247 million people have been diagnosed with COVID-19, 223 countries have been affected and more than 5 million deaths have been reported. Therefore, it is an urgent need for development of effective drugs for treatments of the COVID-19 disease.

Natural products have been the primary source of medicines in all cultures with a vast diversity of terrestrial and marine organisms; also, they are the most successful source of drug leads for the treatment of many diseases [1]. Flavonoids are extensively distributed natural products produced by plants having an essential role in plant physiology, with a potential anti-inflammatory, anticancer, antibacterial, antifungal, and antiviral activity [2].

Around ten years of research is needed for the development of de-novo medicines. Thus, the repurposing of natural products could be an efficient strategy against SARS-CoV-2 infection [3].

Some natural compounds have been shown to possess antiviral activities against various viruses (influenza virus, human immunodeficiency virus (HIV), hepatitis C and B viruses, measles-virus, herpes simplex virus, poliovirus and human coronaviruses SARS and MERS) [4–11]. The potential treatments for viral diseases using natural plant compounds are actively studied worldwide, especially against viruses from the coronavirus group were intensified last year. Furthermore, in recent years, understanding the antiviral mechanisms of complex plant extract and isolated plant-derived compounds have been actively studied. In addition to molecular docking studies, *in silico* analyses of extracted compounds were used in these studies [12]. To date, numerous Chinese herbs and herbal formulations have been reported to possess antiviral activities [13–15]. This suggests the natural phyto compounds and medicinal plant-based formulations as a base for the development of novel drugs for the treatment of the COVID-19 disease.

Previously, it was showed that the biological properties of organic molecules are determined by the physical parameters the electron-ion interaction potential (EIIP) and the average quasy-valence number (AQVN) [16]. These electronic molecular descriptors served as a base for the *in silico* screening of different molecular libraries for candidate drugs against HIV, influenza virus, Ebola virus, Leish-

mania disease, malaria disease and antibiotic-resistant bacteria [17–23]. The purpose of this study is to develop the criterion for *in silico* selection of natural compounds that have promising antiviral effects against SARS-CoV-2 virus.

2. Materials and Methods

It has been previously proposed the model of the molecular interactions in biological systems which encompass two steps [16,24]. The first step is determined by the selective long-range forces which allow specific recognition and targeting between interacting molecules at a distance longer than one linear dimension of the interacting macromolecules (102–103 Å). These forces directly influence the number of productive collisions between interacting molecules. The second step is the chemical binding between interacting molecules which involves the weak noncovalent forces (van der Waals, hydrogen bonding, ionic interactions, etc.) which operate over a short distance range (<5 Å).

The number of valence electrons and the electron–ion interaction potential (EIIP), are the molecular descriptors which determine the long-range properties of biological molecules [16]. These physical parameters are derived from the general model pseudopotential [25,26] and for organic molecules are determined by the following equations.

$$W = 0.25Z^* \sin(1.04\pi\, Z^*)/2\pi \quad (1)$$

where Z* is the AQVN determined by

$$Z^* = \sum_m n_i Z_i / N \quad (2)$$

where Z_i is the valence number of the i-th atomic component, n_i is the number of atoms of the i-th component, m is the number of atomic components in the molecule and N is the total number of atoms. The EIIP values calculated according to Eqns. 1 and 2 are in Rydbergs (Ry = 13.5eV).

We will further use these molecular descriptors for analysis of natural compounds with the anti-COVID-19 activity.

3. Results

Several laboratory and clinical studies have demonstrated remarkable efficacy of different herbal preparations in prevention and treatment of the COVID-19 disease [27–31]. This especially concerns the traditional Chinese medicine (TCM) which successfully used for clinical treatment of mild, moderate, severe and critical cases and convalescence [32]. However, these studies still leave the question of whether these extraordinary health effects are the consequence of some unique properties of the herbal ingredients in these preparations. In order to answer this question, we analyzed the electronic properties, represented by the molecular descriptors AQVN and EIIP, of chemical ingredients of 22 therapeutic TMC preparations recommended for COVID-19 in China [33]. The molecular descriptors AQVN and EIIP, calculated for 92 essential compounds from these preparations, are given in Table 1 (Ref. [30]) and Fig. 1 (Ref. [30]).

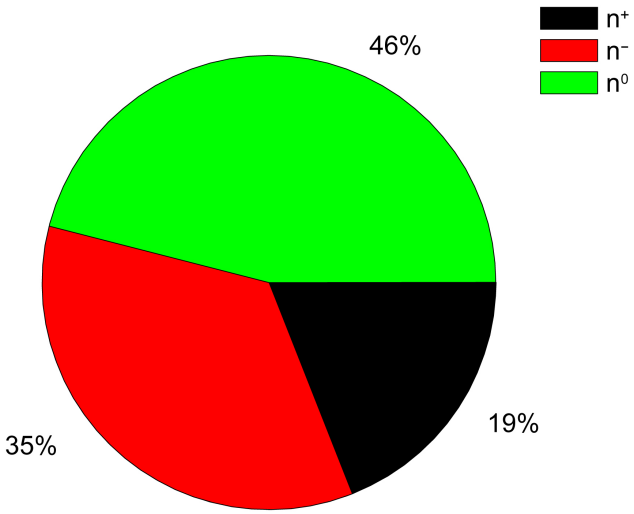

Fig. 1. The distribution of electron donors (n^+) and electron-acceptors (n^-) in TMC [30].

Recently, 105 herbs from 24 TCM prescriptions that are highlighted in the guidelines for the treatment of COVID-19, were analyzed [34]. The results of this analysis showed that the combination of Amygdalus Communis Vas (ACV) and Ephedra sinica Stapf (ESS) is the best for the treatment of patients in almost all the stages of COVID-19, so ACV and ESS (AE) were selected as the most important herbal pair [34]. The molecular descriptors AQVN and EIIP, calculated for 26 active ingredients of the herbal pair AE is given in Table 2 (Ref. [31]) and Fig. 2 (Ref. [31]).

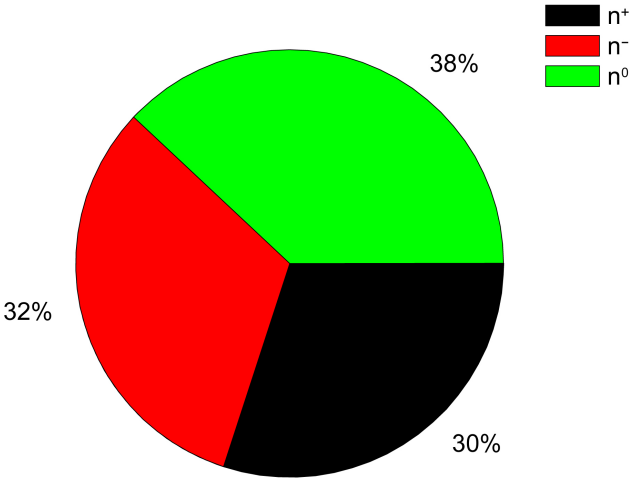

Fig. 2. The distribution of electron donors (n^+) and electron-acceptors (n^-) in the herbal preparation AE [31].

Table 1. The AQVN and EIIP parameters of the essential chemical ingredients of the therapeutic TMC preparations recommended for COVID-19 in China [30].

Compound	Formula	AQVN	EIIP [Ry]
kaempferol	C15H10O6	3.419	0.1339
quercetin	C15H10O7	3.500	0.1260
luteolin	C15H10O6	3.419	0.1339
glycyrrhetinic acid	C30H46O4	2.375	0.0941
indigo	C16H10N2O2	3.200	0.1092
β-sitosterol	C29H50O	2.150	0.0578
naringenin	C15H12O5	3.188	0.1060
isorhamnetin	C16H12O7	3.371	0.1341
formononetin	C16H12O4	3.125	0.0879
isoflavone	C15H10O2	3.037	0.0577
licochalcone B	C16H14O5	3.086	0.0750
glyasperin C	C21H24O5	2.760	0.0435
licochalcone a	C21H22O4	2.766	0.0416
3-methoxyglabridin	C21H22O5	2.833	0.0188
anhydroicaritin	C21H20O6	2.979	0.0359
stigmasterol	C29H48O	2.180	0.0644
6-(3-oxoindolin-2-ylidene) indolo (21-b)	C23H13N3O2	3.220	0.1138
quinazolin-12-one	C14H8N2O2	3.308	0.1293
bicuculline	C20H17NO6	3.136	0.0915
physciondiglucoside	C28H32O15	3.120	0.0863
dihydroverticillatine	C27H41N02	2.271	0.0820
licoisoflavanone	C20H18O6	3.046	0.0608
574'-trihydroxy-8-methoxyflavone	C16H12O6	3.294	0.1275
acacetin	C16H12O5	3.212	0.1121
irisolidone	C17H14O6	3.189	0.1064
wogonin	C15H10O5	3.333	0.1319
baicalein	C15H10O5	3.333	0.1319
glycyrrhizic acid	C42H62O16	2.717	0.0564
hesperidin	C28H34O15	3.065	0.0678
hyperoside	C21H20O12	3.321	0.1308
andrographolide	C20H30O5	2.546	0.0906
gallic acid	C7H6O5	3.556	0.1150
rosmarinic acid	C18H16O8	3.238	0.1179
rutin	C27H30O16	3.206	0.1105
chlorogenic acid	C16H18O9	3.163	0.0993
tanshinone II A	C19H18O3	2.800	0.0304
hydroxysafflor yellow A	C27H32O16	3.147	0.0946
paeoniflorin	C23H28O11	3.000	0.0439
chlorogenin	C27H44O4	2.347	0.0918
5-Hydroxy-67345-pentamethoxyflavone	C20H20O8	3.083	0.0742
isokaempferol	C15H10O6	3.419	0.1339
morin	C15H10O7	3.500	0.1260
gardenin E	C19H18O9	3.217	0.1133
artemisetin	C20H20O8	3.083	0.0742
genistein	C15H10O5	3.333	0.1319
dryobalanone	C30H50O3	2.265	0.0810

Table 1. Continued.

Compound	Formula	AQVN	EIIP [Ry]
curcumin	C21H20O6	2.979	0.0359
elemicin	C12H16O3	2.645	0.0742
chrysoeriol	C16H12O6	3.294	0.1275
apigenin	C15H10O5	3.333	0.1319
scutellarin	C21H18O12	3.412	0.1342
oroxylin-7-O-glucuronide	C22H20O11	3.283	0.1259
forsythin	C27H34O11	2.889	0.0016
forsythiaside E	C20H30O12	2.935	0.0193
ursodeoxycholic acid	C24H40O4	2.353	0.0923
chenodeoxycholic acid	C24H40O4	2.353	0.0923
ophiopogonin D	C44H70O16	2.631	0.0772
ginsenoside rg 2	C42H72O14	2.531	0.0921
methyl ophiopogonanone A	C19H18O6	3.023	0.0526
ginsenoside Rb2	C56H92O25	2.694	0.0626
ginsenoside R0	C48H76O19	2.671	0.0682
ophiopogon A	C44H70O18	2.682	0.0656
sanchinoside rd	C48H82O18	2.581	0.0860
ophiopogonanone E	C19H20O7	3.000	0.0439
schisanlactone E	C30H44O4	2.410	0.0959
N-transferuloyltyramine	C20H23NO5	2.816	0.0248
angeloylgomisin O	C28H34O8	2.771	0.0399
gomisin-A	C23H28O7	2.793	0.0327
gomisin R	C22H24O7	2.906	0.0079
changnanic acid	C29H44O4	2.390	0.0985
kadsulactone	C30H44O3	2.364	0.0932
kadsulignan B	C23H26O7	2.857	0.0102
ginsenoside rh2	C36H62O8	2.396	0.0953
bisindigotin	C32H18N4O2	3.178	0.1036
irisolidone	C17H14O6	3.189	0.1064
8-isopentenyl-kaempferol	C20H18O6	3.046	0.0608
neobaicalein	C19H18O8	3.156	0.0972
dihydrooroxylin A	C16H14O5	3.086	0.0750
chrysin-5-methylether	C16H12O4	3.125	0.0879
catechin	C15H14O6	3.143	0.0934
72-dihydroxy-58-dime thoxyflavone	C17H14O6	3.189	0.1064
7-hydroxy-58-dimethoxy-2-phenylchromone	C17HH14O5	3.054	0.0639
57-dihydroxy-8-methoxy-2-(2-methoxyphenyl)chromone	C17H14O7	3.263	0.1227
formononetin	C16H12O4	3.125	0.0879
Isoglabrolide	C30H44O4	2.410	0.0959
glabrolide	C30H44O4	2.410	0.0959
ebeiedinone	C27H43NO	2.250	0.0784
peimisine	C27H41NO3	2.389	0.0949
verticinone	C27H43NO3	2.351	0.0922
imperialine	C27H43NO3	2.351	0.0922
ussuriedinone	C27H35NO3	2.515	0.0935
euchrenone A5	C25H26O4	2.727	0.0534
glycyrol	C21H18O6	3.067	0.0684

Table 1. Continued.

Compound	Formula	AQVN	EIIP [Ry]
indirubin	C16H10N2O2	3.200	0.1092
acacetin	C16H12O5	3.212	0.1121
syrigin	C17H24O9	2.920	0.0134
emodin	C15H10O5	3.333	0.1319
7-Omethylisomucronulatol	C18H20O5	2.837	0.0174
formononetin	C16H12O4	3.125	0.0879
ellagic acid	C14H6O8	3.929	0.0416
39-di-O-methylnissolin	C17H16O5	3.000	0.0439

Table 2. The molecular descriptors AQVN and EIIP calculated for the active ingredients of the herbal pair AE for treatment of the COVID-19 disease [31].

Compound	Formula	AQVN	EIIP [Ry]
Quercetin	C15H10O7	3.500	0.1260
Kaempferol	C15H10O6	3.419	0.1339
Luteolin	C15H10O6	3.419	0.1339
β-sitosterol	C29H50O	2.150	0.0578
Naringenin	C15H12O5	3.188	0.1060
Stigmasterol	C29H48O	2.180	0.0644
Herbacetin	C15H10O7	3.500	0.1260
Genkwanin	C16H12O5	3.212	0.1121
Taxifolin	C15H12O7	3.352	0.1333
Pectolinarigenin	C17H14O6	3.189	0.1064
(+)-catechin	C15H14O6	3.143	0.0934
Diosmetin	C16H12O6	3.294	0.1275
Eriodictyol	C15H12O6	3.273	0.1243
Truflex OBP	C20H30O4	2.482	0.0956
Leucopelargonidin	C15H14O6	3.143	0.0934
Resivit	C15H14O7	3.222	0.1144
(+)-Leucocyanidin	C15H14O7	3.222	0.1144
Mandenol	C20H36O2	2.207	0.0702
24-Ethylcholest-4-en-3-one	C29H48O	2.180	0.0644
poriferast-5-en-3beta-ol	C29H50O	2.150	0.0578
campest-5-en-3beta-ol	C28H48O	2.156	0.0591
Stigmasterol	C29H48O	2.180	0.0644
l-SPD	C19H21NO4	2.800	0.0304
Estrone	C18H22O2	2.534	0.0928
Glabridin	C20H20O4	2.818	0.0242
Machiline	C17H19NO3	2.750	0.0466
Licochalcone	C21H22O4	2.766	0.0416
Phaseol	C20H16O5	3.073	0.0707
(+)-catechin	C15H14O6	3.143	0.0934
Glycyrol	C3H8O3	2.714	0.0570
Liquiritin	C21H22O9	3.077	0.0769
CLR	C27H46O	2.162	0.0606
Sitosterol	C29H50O	2.150	0.0578
Spinasterol	C29H48O	2.180	0.0644
gondoic acid	C20H38O2	2.167	0.0616
11,14-eicosadienoic acid	C20H36O2	2.207	0.0702
Mairin	C22H22O8	3.038	0.0582

Natural polyphenols, playing a relevant role in reducing inflammation and preventing the onset of serious chronic diseases, have been recently reviewed as promising agents to fight COVID-19 [35]. The AQVN and EIIP values calculated for 50 natural polyphenols with demonstrated anti-COVID-19 activity [35] are given in Table 3 (Ref. [32]) and Fig. 3 (Ref. [32]). The molecular descriptors AQVN and EIIP were also calculated for hypericin which is nathodyanthrone and not a typical phenolic compound [36].

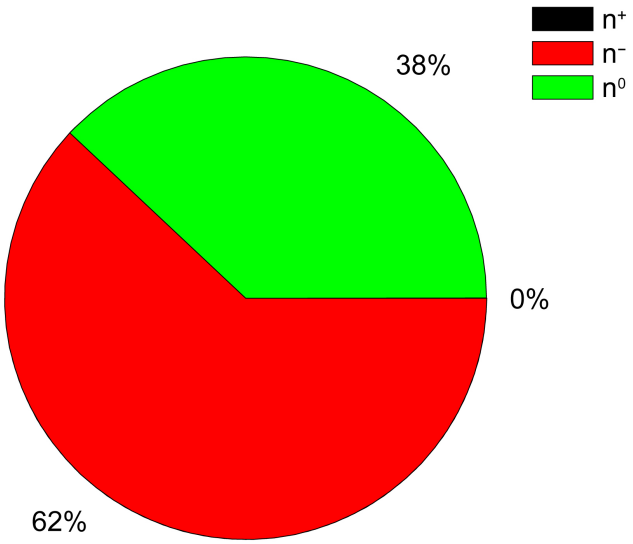

Fig. 3. The distribution of electron donors (n^+) and electron-acceptors (n^-) in polyphenols which are active against the COVID-19 disease [32].

The previous analysis of 45,010,644 compounds randomly selected from the PubChem database [37] showed that 90.5% of these compounds have EIIP and AQVN values in the intervals (0.00–0.10 Ry) and (2.4–3.2), respectively (Fig. 4, Ref. [33]) [24]. This part of the EIIP/AQVN space, encompassing the majority of analyzed compounds, was referred as the "basic chemical space" (BCS) [24]. The small fraction (4.3%) of analyzed compounds from the PubChem, representing the strong electron donors and are located left of BCS. The compounds with the strong electron-acceptor properties (5.3% of analyzed compounds from the PubChem) are in the domain right of BCS. Results presented in Table 4 show that the percentage of strong electron-acceptors and electron-donors in preparations with anti-COVID-19 activity is significantly higher in the comparison with compounds in the PubChem [37], approved drugs [38], natural compounds [39] and collection of small molecules that are relevant to biological systems (KEEG) [40].

Table 3. The molecular descriptors AQVN and EIIP calculated for polyphenols which are active against the COVID-19 disease [32].

Compound	Formula	AQVN	EIIP [Ry]
Cyanidin	C15H11O6	3.344	0.1327
Daidzein	C15H10O4	3.241	0.1185
Dieckol	C36H22O18	3.605	0.1016
Genistein	C15H10O5	3.333	0.1319
Mearnsitrin	C22H22O12	3.250	0.1202
Myricitrin	C21H20O12	3.321	0.1307
Psoralidin	C20H16O5	3.073	0.0707
Quercetin 3-O-D-glucoside	C21H19O12	3.365	0.1339
Rutin	C27H30O16	3.205	0.1105
Xanthoangelol E	C21H22O6	2.898	0.0050
Benzoic acid	C7H6O2	3.067	0.0684
Ellagic acid	C14H6O8	3.929	0.0416
Gallic acid	C7H6O5	3.556	0.1150
Kaempferol 3-O-rutinoside	C27H30O15	3.167	0.1004
Naringenin	C15H12O5	3.188	0.1060
Oleuropein	C25H32O13	3.000	0.0439
Quercetin	C15H10O7	3.500	0.1260
Quercetin 3-O-rutinoside	C27H30O16	3.206	0.1105
Resveratrol	C14H12O3	2.966	0.0308
Scutellarein	C15H10O6	3.419	0.1339
Cyanidin 3-O-glucoside	C21H21O11	3.226	0.1154
Epigallocatechin	C22H18O11	3.373	0.1342
Epigallocatechin gallate	C22H18O11	3.373	0.1342
Hypericin	C30H16O8	3.407	0.1343
Kaempferol	C15H10O6	3.419	0.1339
Cryptotanshinone	C19H20O3	2.714	0.0570
Luteolin	C15H10O6	3.419	0.1339
Afzelin	C21H20O10	3.216	0.1130
Apigenin	C15H10O5	3.333	0.1319
Baicalin	C21H18O11	3.360	0.1337
Biorobin	C27H30O15	3.167	0.1004
Caffeic acid	C9H8O4	3.238	0.1179
Catechin	C15H14O6	3.143	0.0934
Chlorogenic acid	C16H18O9	3.163	0.0993
Chrysin	C15H10O4	3.241	0.1185
Curcumin	C21H20O6	2.979	0.0359
Delphinidin	C15H11O7	3.424	0.1337
Ferulic acid	C10H10O4	3.083	0.0742
Galangin	C15H10O5	3.333	0.1319
Hesperetin	C16H14O6	3.167	0.1004
Isoferulic acid	C10H10O4	3.083	0.0742
Nobiletin	C21H22O8	3.020	0.0513
Nympholide A	C30H26O15	3.324	0.1310
Pinocembrin	C15H12O4	3.100	0.0787
Rhoifolin	C27H30O14	3.127	0.0885
Rutin	C27H30O16	3.206	0.1105
Taiwanhomoflavone A	C33H24O10	3.224	0.1148
Tangeretin	C20H20O7	3.021	0.0519
Viniferin	C28H22O6	3.036	0.0572
Artepillin C	C19H24O3	2.565	0.0882

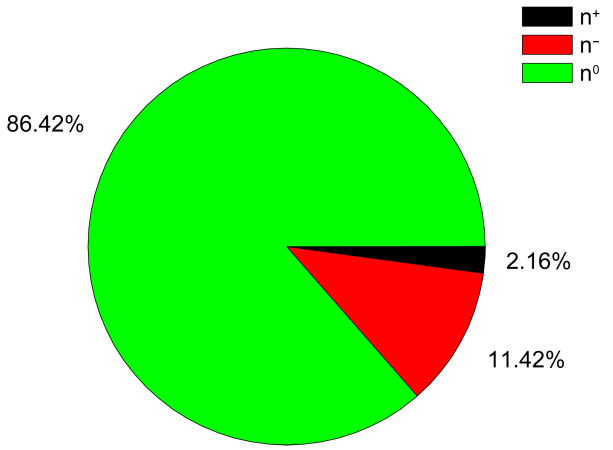

Fig. 4. The distribution of electron donors (n^+) and electron-acceptors (n^-) in compounds from the PubChem database [33].

Table 4. The content of the electron-donors (n^+) and the electron-acceptors (n^-) in the different sources of compounds.

Source of compound	Number of compounds	n^+[%]	n^-[%]	n^++n^-[%]
TMC	93	18	29	47
AE	37	27	32	59
Polyphenols	50	0	29	29
Approved drugs	1469	8	9	17
KEEG	7638	8	9	17
Natural compounds	4668	11	16	25
PubChem	4,5010,644	4	5	9

4. Discussion

The COVID-19 pandemic is one of the greatest challenges modern medicine has ever faced. Doctors and scientists are trying to find treatments and drugs that can cure and prevent this disease. Unfortunately, nearly two years into the pandemic there is no cure yet for COVID-19 disease. A handful of therapies—remdesivir, monoclonal antibodies and the steroid dexamethasone—have improved the care of COVID patients, but these drugs are not cure-alls and they are not for everyone. On the other hand, efforts to repurpose other drugs, or discover new ones, have not had much success.

At the beginning of the COVID-19 pandemic the National Health Commission of the People's Republic of China released the Dignosis and treatment protocol for COVID-19 which includes the TCM treatment [41]. TCM's preventing and curative effect was outstanding. As of March 2020 new cases of COVID-19 in China have significantly decreased and more than 70,000 people were cured of COVID-19 and discharged from the hospital with the total treatment time of approximately 2 months [42]. China has today the lowest number of the daily new cases and the lowest COVID-19 mortality in the world [43].

Presented results show that most essential ingredients of analyzed TCM preparations (Table 1) can be represented by the specific groups of organic compounds according to their basic electronic properties AQVN and EIIP, and these differ from the vast majority of known chemicals which are located in BCS. These ingredients are in the domains of the AQVN/EIIP space that are situated left and right of BCS. The distribution of the essential ingredients of the important herbal pair AE (Table 2) in the AQVN/EIIP space is similar with distribution of ingredients of other analyzed TCM preparations with anti-COVID-19 activity. Previously, we reported that the domains left and right outside BCS contain the strong electron-donors and electron-acceptors, respectively [23,24].

Polyphenols have been recently suggested as promising agents to fight COVID-19, and some clinical trials have already been approved with polyphenols to treat COVID-19. It was suggested that these compounds possess a potential immunomodulatory therapeutic value against SARS-CoV-2-induced immune response dysregulation [35]. In Table 1, the authors also analyzed emodin, a precursor of nathodyanthrones fagopyrin characterized by antiviral potential [44].

Results presented in Table 3 show that the main fraction (58%) of analyzed polyphenols with anti-COVID-19 activity are the strong electron-acceptors which are located in the AQVN/EIIP space right of BCS. Of note also is that ingredients with the electron-acceptors properties dominate in the analyzed TCM, compared to the electron-donor compounds.

Knowledge of the possible active mechanisms of TCM preparations in the treatment of COVID-19 may provide meaningful information for further study to investigate the mechanisms of TCMs as a therapeutic approach to overcoming COVID-19. TMC could treat COVID-19 through multiple components, multiple targets, and multiple pathways. Polyphenols are most abundant ingredients in all TCM preparations with the anti-COVID-19 activity. Among these polyphenols kaempferol, quercetin, baicalein and luteolin are the main components of Chinese patent medicine representing an indispensable part of TCM [33]. These flavonoids also are within natural polyphenols with demonstrated anti-COVID-19 activity [35] (Table 3).

Previously, to identify human proteins that represent the most probable candidates for interactors with flavonoids, we analyzed human proteins from the UniProt database [45], using the informational spectrum method (ISM) [46]. Results of this analysis suggest that among the human proteins NF-kB represents one of the more likely targets for flavonoids. The role of NF-kB pathway in the COVID-19 pathogenesis was confirmed in numerous studies. The investigation of the host-virus interaction provides evidence that SARS-CoV-2 modulates NF-κB signaling and inflammatory cytokine expressions [47]. The experimental and *in silico* study suggests that compound from some TCM preparation interfere with the NF-κB signaling pathway, leading to the inhibition of release of proinflammation factors, such as TNF-α, IL-1β, IL-8 which may induce the inflammation storm in COVID-19 [48]. Zhao *et al*. [49] analyzed the treatment mechanism of this TCM preparation from molecular, pathway, and network levels and show in experiments *in vitro* that baicalin can suppres NF-κB signaling and downregulate the expression of IL6 and TNF-α. It was found that the SARS-CoV-2 infection activates the NF-κB pathway, driving unchecked inflammation that contributes to total organ failure in COVID-19 patients [50,51]. Based on the evidence of the role which the NF-κB plays in the COVID-19 pathogenesis, this pathway was suggested as a potential target for treatment of critically ill patients [52]. We previously reported the active anti-HIV flavonoid compounds are grouped in the AQVN interval (3.34–3.59) and the EIIP interval (0.1100 and 0.1350 Ry) [53]. Of note is that this domain of the AQVN/EIIP space overlaps the domain encompassing the electron-aceptor compounds with anti-COVID-19 activity.

Quercetin represents a most investigated natural compound with the anti-COVID-19 activities. Antiviral, immunomodulatory, and anticoagulant effects of quercetin and its derivatives are recently reviewed and its potential role in prevention and management of COVID-19 were suggested [54]. It is also suggested that quercetin could prevent the cell-to-cell transmission of SARS-CoV-2 [55]. Currently, therapeutic effect of quercetin is investigated in 14 clinical studies [56].

5. Conclusions

The simple EIIP/AQVN criterion described in this paper can be used for powerful and rapid *in silico* screening of natural compounds that are active against SARS-CoV-2 virus and for identification and optimization of new lead compounds for treatment of the COVID-19 disease. These results, together with data from the USDA Food Database [57] (http://www.nal.usda.gov/fnic/) also can be used for selection of food and the food supplements which could have a beneficial effect for COVID-19 patients.

Author Contributions

VV and SP designed the concept. VV, MV and SG done formal analysis. VP, MV and SG performed data curation. VV and SP prepared the original draft. VV, VP, SG, MV and SP wrote and reviewed the manuscript. VP implemented the software. VV and VP done the visualization, VV and VP designed the methodology. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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