ISBN 978-1-960740-01-4

PLANT AND FOOD PHENOLICS – CHEMISTRY, FUNCTIONALITY AND PRACTICAL APPLICATIONS

Editors

Muhammad Kamran Khan & Sadia Hassan

Review Based Book Chapter

THERAPEUTIC POTENTIAL OF CARICA PAPAYA FLAVONOIDS AGAINST VIRUSES

July 10, 2024

doi: 10.5281/zenodo.12677393

Scientific Knowledge Publisher (SciKnowPub), USA

info@sciknowpub.com

REVIEW BASED BOOK CHAPTER

THERAPEUTIC POTENTIAL OF CARICA PAPAYA FLAVONOIDS AGAINST VIRUSES

Ghulam Zahara Jahangir[1]*, Rida Farooq[1], Saima Younas[1], Uroosa Tabarak[1], Muhammad Zafar Saleem[1], Aisha Younas[2], Maria Rafique[2]

[1]*Centre for Applied Molecular Biology (CAMB), University of the Punjab, Lahore, Pakistan*
[2]*Lahore College for Women University (LCWU), Lahore, Pakistan*

For Correspondence
zahra.camb@pu.edu.pk

Abstract

The papaya, or Carica papaya, is a popular tropical fruit that has been gaining attention for its purported health advantages. Flavonoids are among the most important bioactive components in papaya. These are a large and varied class of plant secondary metabolites with potential medicinal utility. The presented study has been conducted to explore the antiviral effects of the flavonoids found in Carica papaya. Quercetin, kaempferol, and their glycosides are some of the flavonoids found in abundance in papaya. Antioxidant, anti-inflammatory, and antibacterial characteristics have been documented as most promising pharmacological benefits of these flavonoids. Additionally, flavonoids from Carica papaya were studied for their potential antiviral properties against several viruses. Papaya flavonoids have been shown to have antiviral properties in vitro and in vivo tests, and they may be able to inhibit the viruses spread including HIV, dengue virus and HSV. These antiviral actions are the result of processes that block the entrance, replication, and protein production of the invading virus. The antiviral effect of papaya flavonoids is due, in part, to their ability to boost the body's immunological response to viral infections; as their immunomodulatory characteristics. These results point to Carica papaya flavonoids as a possible natural antiviral agent. Conclusively, Carica papaya's flavonoids have powerful antiviral actions against many different viruses. In deep, studies can effectively find best dose and formulation of papaya flavonoids, as well as assess their safety and effectiveness for therapeutic use. There is hope for the creation of cutting-edge therapeutic treatments against viral infections by drawing on Carica papaya as a source of natural antiviral chemicals.

Keywords

Carica Papaya, Antiviral Effects, Flavonoids, Anti-inflammatory, Fruits, SARS COV-2

1. Overview of Carica Papaya

The traditional medications are also subject to specialized regulatory criteria, which take into account verified scientific studies on comparable products in the market [1]. Herbs and the plants, which are exploited for health benefits and curative purposes, have always remained a center of attention for scientists. Medicinal plants have been used from ancient times. Owing to their industrial significance, such medicinally important plants are of prime importance. Among all the plant species found on earth, about 32% species contain the therapeutic characteristics and the number of species employed globally for their valuable properties are about 7500 [2]. Papaya plant is of great therapeutic relevance for herbal medicines that have been discovered over centuries. During 2017, production of papaya was increased approximately 13 million metric tons with Brazil and India contributing more in the global share, trailed by Indonesia, Nigeria, Mexico and Dominican Republic [3]. Papaya belongs to the family Caricaceae and is famous all over the world due to its nutritional and therapeutic values [4]. Papaya is small i.e. 5-10m tall single stem (16-33ft), branched trees, or spirally arranged leaves. Their leaves are large with a diameter of 50-70 cm, with deeply palmately seven lobes. Leaves and fruits are borne with the lower trunk (Table 1) [5]. There are more than 50 known varieties of papaya, however owing to unregulated papaya pollination, pure breeding variants are dwindling. Papaya can reduce the level of lipid per oxidation and increase the amount of antioxidants level in the blood. Papaya is used for development of various pharmaceutical and industrial products. The presence of vitamin A, B, C and E in papaya improves immunity. Diseases like tonsils, nausea and jaundice are also treated with the help of papaya plant. It also includes minerals like potassium, magnesium, and iron. Additionally, it includes the digestive enzyme papain, renowned for its use in the treatment of cuts, rashes, wounds, allergies and burns [6]. Numerous small-scale research studies and case reports suggest that patients' platelet counts improve quickly after receiving papaya leaf extract, and they attribute this effect to the fruit's potential to stabilize erythrocyte membranes. In-vitro tests on human leukemia monocytic cell line (THP-1) by leaf extract of papaya (PLE) revealed a major reduction in the expression of envelope of DENV and in influenza protein NS1, a decrease in viral load as well as rise in the expression level of interferons

Type I (IFN-). This proved direct antiviral efficacy. The in-vivo investigation using mice infected with DENV revealed that treatment with PLE altered the genes' expression related to the control of endothelial permeability in the liver [7]. Papaya leaves, seeds, fruits, stems, and other plant parts are higher in phenols, flavonoids and alkaloids. They have a lot of medicinal and antimicrobial activities as shown in Figure 1 [8]. Carotenoids, Phytosterols, Phenolic compounds and Cyanogenic compounds are densely packed photochemical present in papaya seeds and leaves [3].

Table 1 Phytoconstituents found in different parts of plants [9]

Fruits	Vitamins, protein, carbohydrates, volatile compound, glycosides, alkaloids, minerals, fat
Seed	Fatty acid, crude fibers, benzyl thiourea, papaya oil, carpaine, benzyl isothiocyanate, caricin, enzyme myrosin, crude protein
Root	Enzyme myrosine and caproside
Juice	N-butyric acid, n-octanoic acid, plamitic, myristic, linoleic, stearic, linolenic acid, lipid, oleic acid, n-hexanoic acid
Leaves	Pseudocarpain, choline, vitamin C and E, alkaloids, carpain
Latex	Glutamincyclotranferase, proteolytic enzyme papain, chymopapain A, B, C, chemopapain
Bark	Fructose, xylitol, galactose, β-sitosterol

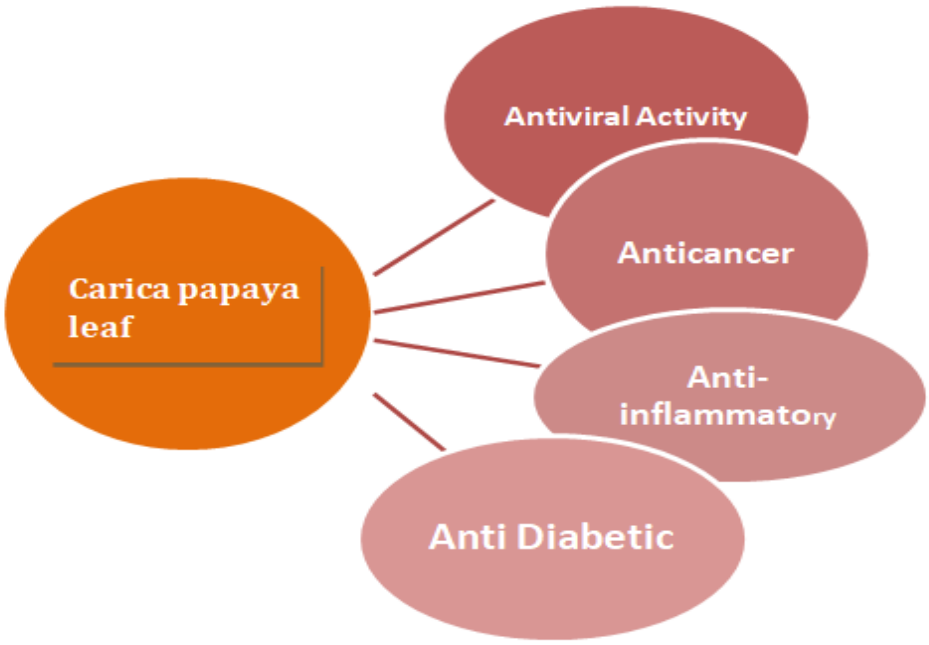

Figure 1 Medicinally importance of Carica papaya

2. Medicinally Valuable Active Components of Carica Papaya

Secondary metabolites are organic compound which play important role in protection, competition and specie interaction. According to species, organs, growth conditions and developmental stages, it can widely distribute in different amount. There are many secondary metabolites in the Carica papaya which are all antioxidants. Phenolic compounds that are most abundantly obtained from vegetables and fruits are most important for the development and generation of the plant. These compounds give exclusive taste and vigor to human body and are produced commonly as secondary metabolites in reaction to certain damage or extreme ecological influence like drought [10]. Flavonoids are the active constituents of Carica papaya. Seven important flavonoids consist of quercetin, kaempferol, Quercetin 3-(2G-rhamnosylrutinoside), Quercetin3-rutinoside, Kaempferol 3-(2G rhamnosylrutinoside), kaempferol 3-rutinoside, myricetin3-rhamnoside [11, 12]. The content and bioavailability of these biologically active flavanols depends upon the food source, consumption quantity, and extent of ripeness, growth conditions of the plant, foodstuff preparation and treatments [13]. Flavonoids have great importance for their therapeutic qualities as well [14]. These flavonoids are able to reduce fever and infection, protection of cranial nerves. They have anti-viral activity against dengue virus, zika virus, Japanese encephalitis virus, influenza virus, hepatitis B virus, type 2 and 3 dengue virus infection. The therapies of allergic rhinitis are also done by flavonoids [15]. The pharmacological characteristics of flavonoid compounds are improved by glycosylation, which makes them more water-soluble and increases their bioavailability. An essential trait of flavonoids is their solubility in both aqueous and organic solvents. Flavonoids can rapidly oxidize and create an insoluble polymer despite being poorly soluble in water. Despite the fact that flavonoids' phenolic group makes them weakly acidic and easily soluble in alkaline solutions, the majority of their sources of food are acidic. Whereas, solubility of flavonoids in lipophilic solvents greatlyinhibitstheir oxidization in food sources, their bioavailability from food is typically improved by their solubility in water, and glycosylation typically promotes aqueous solubility [2]. Depending on the kind of sugar, the presence of sugar moieties typically results in improved bioavailability of the corresponding flavonoid aglycone. Because, the human intestine contains hydrolyzing enzymes for sugar glucosides, sugar-

containing flavonolglucosides e.g. astragalin (kaempferol 3-O-glucoside) andisoquercetin (quercetin 3-O-glucoside) are absorbed by it more rapidly as compared to other gut glucosides [16].

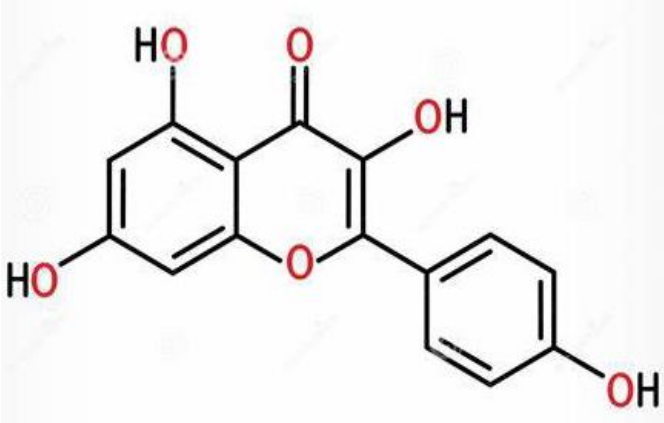

Figure 2 Structure of kaempferol [12]

Several edible plants, including cabbage, tea, endive, broccoli, beans, kale, tomatoes, leeks, grapes and strawberries contain kaempferol, a yellow bioactive flavonoid [12]. The ability of kaempferol is to penetrate the bodily tissues is necessary for their bioactivity in humans. When evaluating a compound's mode of action, one possible step is to look at how well it is digested, absorbed, and processed after food has been consumed. Kaempferol is effectively bioavailable in conjugate form than free form, according to several pharmaceutical studies. According to recent research, the liver swiftly metabolizes the absorption of kaempferol [17]. It leaves the liver and circulates throughout the entire body as methyl, glucuronide, and sulphate conjugates. Measurements of these conjugates in human blood and urine can be used to determine the bioactivity of both of these flavones. Kaempferol, an antioxidant, causes the reduction in emergence of reactive nitrogen and oxygen species as well asprevent the formation of superoxide ions [16]. Additionally, it diminishes hydroxyl radicals, peroxynitrite, and radicals generated by Fenton. Additionally, kaempferol increases the catalase activities, superoxide dismutase and heme oxygenase-1, while decreasing the activity of xanthine oxidase. In addition, kaempferol inhibits the expression of VEGF and angiogenesis, controls the activity of HIF-1, induces apoptosis, causes arrest of G2/M cell cycle and results in apoptosis that is caspase-3-dependent. This study concentrates

on the current understanding of kaempferol's role in lowering risk, disease prevention and cure (including cancer), as well as its underlying action mechanisms. This is because of numerous treatment benefits of kaempferol i.e. chemotherapeutic compoundfor the treatment of various maladies [18].

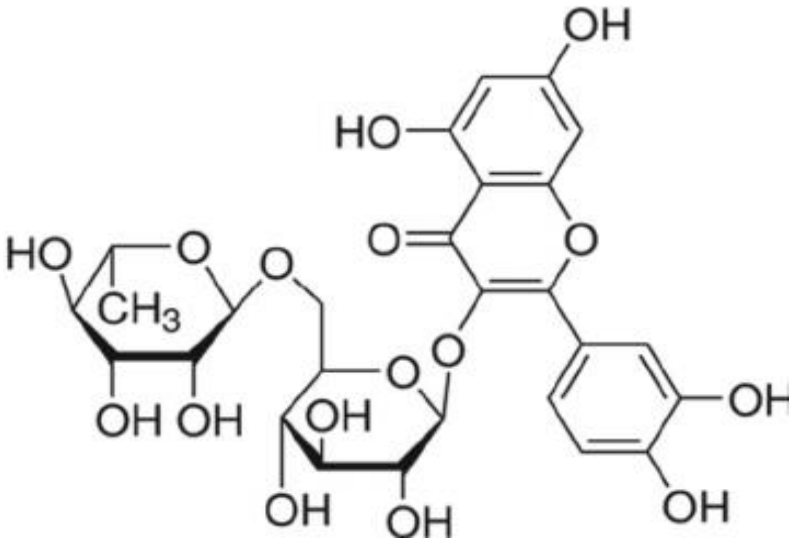

Figure 3 Structure of rutin [19]

Rutin, also recognized as vitamin C and quercetin-3-O-rutinoside, is a polyphenolic natural flavonoid. Due to its lipophilic nature, rutin becomes soluble in methanol, ethanol and pyridine [19]. It has poor stability and bioavailability, which are mostly caused by the substance's low water solubility [20]. Buckwheat is a well-known source of natural rutin. Many plant species, e.g. Labisiapumila (Blume), Sophora japonica L., and Mez (Primulaceae), naturally produce rutin (Fabaceae). It is the result of phenylpropanoid's metabolic interaction. The conversion of amino acid phenylalanine to 4-coumaroyl-CoA happens as part of this metabolic process. Flavonoids are created through a biosynthetic process that combines malonyl-CoA with 4-coumaroyl-CoA. Additionally, it can be through various enzymatic changes. Various plants are employed for the extraction of rutin and derivatives using several different techniques, for example, heat reflux extraction, mechanochemically dependent extraction, ultrasound-assisted extraction, solid-phase micro-extraction, infrared assisted extraction, supercritical fluid extraction, pressurized liquid extraction and microwave-assisted extraction [21]. Likewise citrus fruits, vegetables and beverages made from plants

contain rutin. Also due to its reducing properties against several oxidizing species like superoxides, hydroxyl radicals and peroxyl. It also has pharmacological benefits like anti-cancer, anti-inflammatory andanti-microbial properties. Moreover, rutin has demonstrated superiority in the treatment of diabetes, hypolipidemia, and several malignancies [22]. It has been demonstrated that rutin inhibits several flavonoids' prooxidant effects by enhancing theoxygen radicals' production. It also has benefits over aglycones, that have limited medicinal benefits because of their mutagenic and cytotoxic attributes. Additionally, this compound is considered to be a non-toxic substance with potential biomedical uses [23].

The precious flavonoid named Quercetin can be acquired naturally from Carica papaya [13]. Green vegetables e.g. spinach, cauliflower contain high amount of quercetin whereas apples have lower quantity of these flavonols [24]. It is typically present in the diet as rutin and isoquercetin [25]. Quercetin is active anti-viral activity and our topic of interest. Quercetin enhances the absorption and plasma quercetin blood level. Consumption of quercetin at least 5 consecutive days can reduce the itching, sneezing, and help to live a more comfortable life. Quercetin and kaempferol can suppress the reverse transcriptase, proteases, binding viral capsid entities and polymerases. It can inhibit the nonstructural proteins' (NS5A, NS2, NS5B and NS3) activity that are involved in replication of HCV [26]. Docking result proves that quercetin potentially inhibits protease action of NS2 in HCV [27]. Quercetin also inhibits the entry of HSV by reducing the gD expression. It acts simultaneously between early and rapid protein expression. It blocks influenza virus (A & B) RNA polymerase. It play important role in dengue virus and COVID 19 [28]. It suppresses the early stages of viral infection which can bind with the protease and involved in viral replication. Endocytosis that involves up-taking the virus into the cell is blocked by preventing the phosphatidylinositol 3-kinase activity. It can inhibit the viral protein translation and RNA polymerase by enhancing the breakdown of eukaryotic initiation factor 4G which blocks the transcription process. Quercetin enhances the mitochondrial responses which increases the viral clearance.

2.1. Quercetin

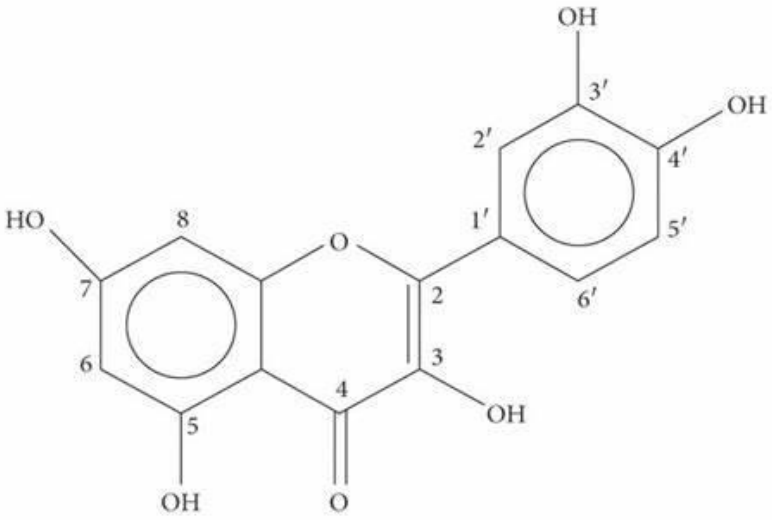

Figure 4: Structure of quercetin [29]

Quercetin (2-(3, 4-dihydroxyphenyl)-3, 5, 7-trihydroxy-4H-chromen-4-one) is a primary category of flavonoids having5 hydroxyl groups at 4', 5, 3, 3' and 7 of the centralframe of flavonol [30]. This flavanol is found in two forms glucoside (having attached sugar molecule) and aglycone (no linked sugar). Various quercetin glycosides were glycosylated to these hydroxyl groups and constituent a major derivative of quercetin [31]. From plants, we get its form named Quercetin 3-o-glucoside that is involved in giving color to the plant's fruits that may also be a vegetable [32]. A unique flavonoid subclass, quercetin, is naturally occurring biologically active substance based on the flavone nC6 (ring A)-C3 (ring C)-C6 (ring B) structure. This major flavonoid is that polyphenol which is present in higher amounts of some species of flavonoids producing plants. It is richly produced in Carica papaya with its antioxidant quality thus it is a low-cost and valuable dietary supplement obtained naturally [2]. Numerous physiological functions in plants, including photosynthesis, pollen development, antioxidant machinery, and seed germination, are made easier by quercetin. In rats, pigs, and humans, quercetin from isoquercetin is more readily absorbed than rutin and quercetin [33]. However, because there are more glycosidic moieties and sugar positions in the glycosylated flavonoid than in the comparable aglycones, it has lower antioxidant

effectiveness [15]. It also promotes healthy plant growth and development. Due to its high antioxidant properties; quercetin effectively protects plants from a variety of biotic and abiotic stressors. Quercetin supplements may boost antioxidant (anticarcinogenic, antidiabetic) activity and prevent many chronic diseases due to their ability to reduce lipid per oxidation, platelet aggregation, capillary permeability, and promote mitochondrial biogenesis [34]. Because it is highly soluble and bioavailable, quercetin is being employed more frequently in novel pharmaceutical formulations for people's health. It is used for the cure and remedy of many diseases mainly cancer, cardiovascular, asthma and diabetes. Besides it has antioxidant and anti-inflammatory qualities. It has also been found antiviral and effective against COVID-19 [35]. This is also effective against obesity [36]. So it can be used both as therapy and as supplement in diet [13, 32]. It is also effective Quercetin a major polyphenol has been found to greatly affect the activities of cancer cells thus can be used as substitute to medications for inhibition and handling of various forms of cancers [37].

In vitro as well as in vivo findings revealed that it has also been found helpful in progress of wound soothing and in bone formation [38]. Quercetin can obstruct the blemishing mechanism of cornea when it happens after some injury or pathogen encounter to the eye. It also helps in the cure of oral mucous lining and gastric mucosa. Quercetin can help in healing and recovery of liver and skin as well [39]. Because of its potential in inhibiting polymerases, proteases and reversetranscriptaseaction being anticancer, declining DNA gyrase, binding capsid proteins of virus, it has also been investigated in variousviral infections' models and types. No antiviral medications derived from plant components have yet received approval, despite the fact that several small compounds obtained from plants are recognizeddue to their antiviral characteristics [40]. Due to unwanted effects and interactions between herbs and medications, it may be difficult to assess the safety and efficacy of herbal remedies. The privileged molecule quercetin is known to inhibit the inflammatory response at various levels. Additionally, it affects the host's immune system as well as the pathways involved in viral translation. Additionally, it has been discovered to impede replication by concentrating on several of these viruses' vital targets. Quercetin has been shown to aid in the recovery from some of these viral infections in preclinical and clinical trials because of

its capacity to inhibit viral targets, alter host variables, or a combination of both. As a result, it may be a pharmacological candidate for use in treating a variety of viral illnesses as shown in Figure 5 [30, 41]. In order to prevent apoptotic neuronal cell death, quercetin inhibits some expressions in glial cells like TNF, IL-1, or IL-8. It will reduce the expression of IL-4 and inhibit cyclooxygenase (COX) and lipooxygenase (LOX) synthesis in the digestive tract. Because it damages the cell wall and membrane of bacteria, quercetin can fight both positive and negative gram-positive bacteria. As part of its anti-oxidant abilities, quercetin is also capable of transferring hydrogen atoms, a single electron followed by proteins, and sequential proton loss electron transfers. As an antiviral medication, quercetin also helps to prevent the early stages of hepatitis C, rhinovirus, and influenza virus reproduction. Quercetin has also been found effective against fungi by preventing the growth of biofilms [42].

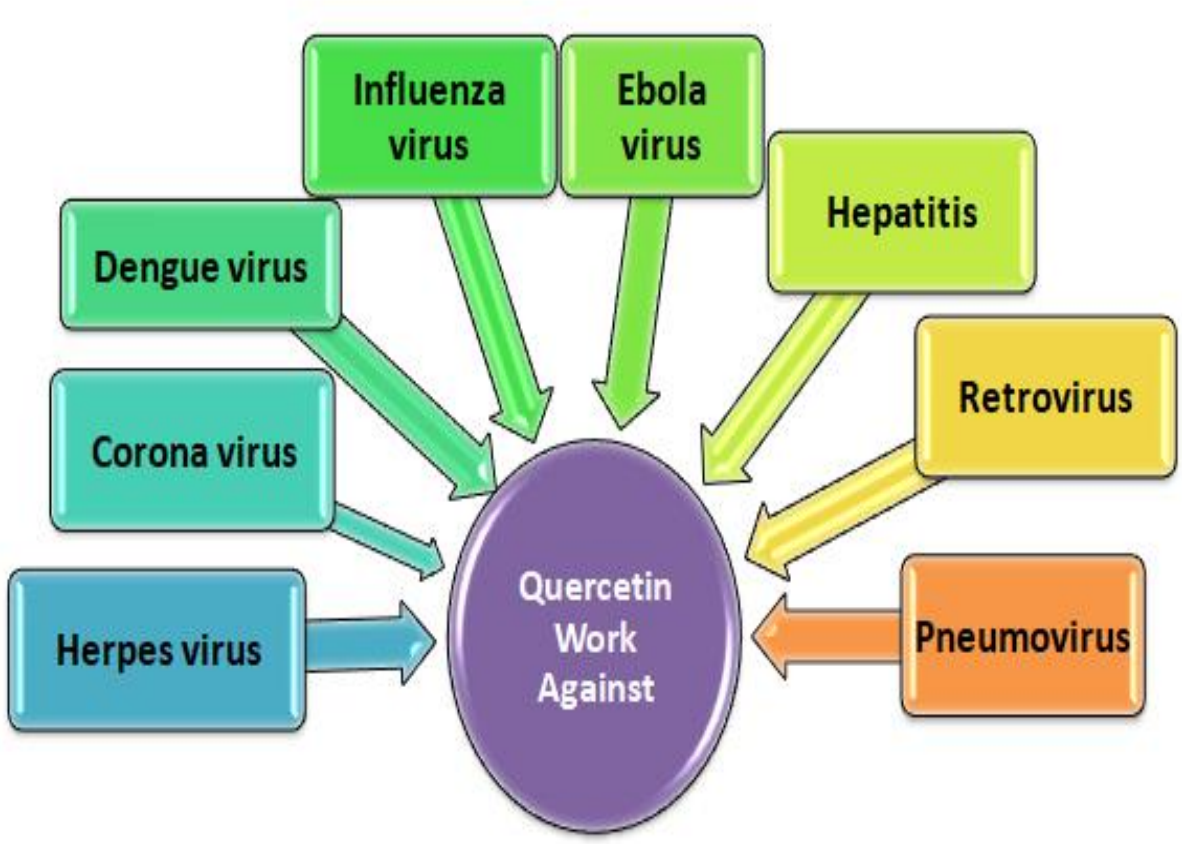

Figure 5 Quercetin work against many viral diseases

2.1.1. Antioxidant potential of quercetin

Antioxidants are the substances or the supplements that work against the radicals formed by oxidation reactions in the body. Generally speaking, antioxidants can be primary, secondary, or multifunctional. Primary antioxidants have the ability to directly transform free radicals into stable molecules by contributing hydrogen or electrons, such as phenolic substances having several hydroxyl groups (-OH). Secondary antioxidants, on the other hand, work indirectly through various processes. Chelation of transition metals, quenching of singlet oxygen, and restoration of primary antioxidants' antioxidant activity are a few of the mechanisms that have been reported. Antioxidants with several functions can exhibit both primary and secondary antioxidant effects. Numerous studies have shown that some topical antioxidants used in sunscreen formulations have photoprotective qualities, including a decrease in erythema, the formation of sunburn cells, and immunosuppression [43].

Quercetin plays a protective role against the free radical caused by the environmental factors such as smoking. The tar present in the cigarette is a potential source of free radicals. The compound present in tar has the ability to damage the membranes of red blood cells. Quercetin as an antioxidant protects the red blood cells from this damage caused by smoking. The targets for Quercetin to act upon as antioxidant are; reactive oxygen species, glutathione enzymatic activity and signal transduction pathways that are actually activated due to some toxicological and ecological elements. So this flavanol explicitly retain the oxidative balance in the body [44]. Due to quercetin neuro-protective impact performing its antioxidant activity to combat toxicity in brain through modulating apoptotic gears, Quercetin is employed in the production medication against Alzheimer's disease [45]. The flavonoid, quercetin, suppresses the production of free radicals in a process of oxidation where hydrogen is eliminated from unsaturated fatty acids. This makes quercetin an effective component against fats production. This process further causes production of peroxy radicals of lipids by the removal of hydrogen that results in more free radicals [46]. The oxidation process of unsaturated fatty acids continues resulting in elimination of hydrogen which ultimately increases the number of free radicals. The driving force behind this cascade of reaction is presence

of metal ions. Excess of free radicals can cause serious health issues like neurodegenerative problems and heart diseases. So, in order to control excess production of free radicals, Quercetin plays vital role. This pigment is present in many ingredients that are commonly used in household kitchen like onions etc. Thus, this pigment plays the role of inhibitor of free radicals by blocking unnecessary oxidation and acting as antioxidant [47].

2.1.2. Anti-inflammatory effect

Inflammation occurs in response to a variety of pathogens and injury to the tissue, and persistent inflammation and the activation of immune system may play a major role in the metabolic abnormalities such as diabetes and obesity [48]. The synthesis of lipooxygenase and cyclooxygenase, the production of which is induced by inflammation, has been found to be inhibited by quercetin. In vivo investigations have also confirmed the anti-inflammatory activity. The considerable inhibition of pro-inflammatory cytokines in cultured fibroblasts is an example of quercetin's inhibitory properties [49]. The protein's phosphorylations that are involved in the inhibition of growth of cells would be inhibited by quercetin. These proteins include p38 MAPK and stress activated protein kinases. A research suggests that quercetin can be used as an effective to combat the infections caused by inflammation. Cells include in the allergic inflammations can also be benefited by the anti-inflammatory property of quercetin [50].

2.1.3. Anti-cancerous activity

The ELAVL1 gene in humans encodes the RNA-binding protein known as HuR (human antigen R), or LAV-like protein 1, which is well known for stabilizing mRNAs and controlling gene expression. Over-expression of the HuR protein has unquestionably been linked with enhanced risk of tumorprogression, metastasis and growth, making it as viable cancer therapeutic target option. Both in vitro and in vivo tests of novel drugs that inhibit HuR expression have yielded encouraging results [51].

Various in vitro and in vivo models have shown that quercetin has some activity against the tumor cells by adopting different mechanisms. This can either be done by initiating

apoptosis or by preventing the cell cycles of cell. Quercetin activity against cancerous cells was examined in cancerous cells of liver. The cell viability was measured using the MTT test with quercetin and in combination with 5-fluorouracil. The findings revealed quercetin and 5-FU's synergistic effect in cycle arrest via apoptosis [52]. In another study, quercetin was found to have anticancer properties when combined with cisplatin. A cell line of breast cancer (EMT6,) was administered subcutaneously into mice to generate tumors [53]. Ovarian cancer has been intensively researched as the major causes of death among women. Quercetin is well-known for its anti-cancer properties as a natural bioflavonoid with potential impacts. However, quercetin's limited water solubility, instability in physiological conditions, and consequently low bioavailability are important obstacles. To maximize the benefits of quercetin, it is vital to optimize the best drug administration strategies [54].

Researchers investigated the utilization of a mixture of medications that functions together so that to combat the resistance in drugs to produce treatments for cancer chemotherapy. Medicines such as oxaliplatin and cisplatin are combined with quercetin for the treatment of many cancers, including ovarian cancer [55]. Researchers have looked at the expression of Bcl-2 family proteins as well as regulatory proteins of the cell cycle in the cells of human cervical cancer. The findings show that quercetin lowered the survival of human immortal cell line (HeLa) by inducing apoptosis and by stopping the cell cycle in G2 phase of mitosis. The de polarization of mitochondrial membrane and the changes in the morphology of nucleus were involved in this manifestation [56]. In various malignant cell lines, including breast cancer it was also reported that quercetin inhibits the formation of heat shock proteins [57]. Heat shock proteins bind to mutant p53 and form a complex, allowing cancerous cells to circumvent usual cell cycle seize mechanisms. Cancerous cells can survive under various physiological conditions (poor circulation, fever, etc.) with the help of heat shock proteinsand are linked to a shorter disease-free survival time [58]. Furthermore, quercetin inhibits the MCF7 and MDAMB231 which are cell lines of human breast cancer by adopting different pathways, including regulation of miR146a expression, initiating apoptosis, down-regulation of receptors of epidermal growth factor and by the initiation of mitochondrial pathways [59].

2.1.4. Antibacterial potential

Bacteria are capable of directly absorbing DNA from their surroundings as well as indirectly through the use of vectors like bacteriophages, conjugative plasmids, and conjugative integrative elements. These DNA transfer processes may take place within microbiomes between various bacteria. Human microbiomes, which are made up of more than 1013 bacterial cells from hundreds of different species and include all the microorganisms (and their genomes) present in human tissues, are intricate systems. In the human body, the skin, mucosa, and gastrointestinal tract have particularly high concentrations and diversity of microorganisms, which may include both pathogenic and non-pathogenic bacteria. A microbiome's whole gene pool, comprising chromosomal genes and extra-chromosomal genetic components including bacteriophages, transposons, plasmids, and other mobile genetic elements, is referred to as the metagenome [60]. Methicillin-resistant since its initial description in 1961, Staphylococcus aureus (MRSA) has emerged as the most prevalent resistant type of bacteria in healthcare. The most frequent sites for MRSA infections are the skin and subcutaneous tissue, followed by areas like the meninges, endocardium, and bone, among others [61]. Quercetin was reported to have selective antibacterial action against different bacteria especially Staphylococcus aureus strain that shows resistance against methicillin and also Staphylococcus epidermidis [62]. Some clinical MRSA have been reported to exhibit unusual quercetin susceptibility. Significantly increased antibacterial activity of quercetin have been reported against MRSA when combined with antibiotics such as oxacillin, ampicillin, vancomycin, gentamicin, and erythromycin [63]. Biofilm is a microbial population that is organized, sophisticated, and sessile and can be present in both living and non-living surfaces in the form of polymer matrix [64]. Quercetin activity against these biofilms were demonstrated against a number of infections caused by bacteria such as infections caused by Vibrio harveyi, Proteus mirabilis, Pseudomonas fluorescens [65].

2.1.5. Antiviral potential

Virus is made up of few building units which are present in every living organism, therefore it is very difficult to control disease caused by viral infection. Viruses are easily

invaded into the cells and have perfect strategies for demolition of the cell metabolism. The resemblance between constituent unit of viruses and that of biological cells make the evolution antiviral drugs tough as these drugs will enter into impotent cell and destroy them [66]. Antiviral drugs are more damaging to forbearer than to the infectious person. The great variations in their genetic material make their control very hard. The continuously changing genome in shielding capsid or membrane makes variations in structure of protein. Due to these variations it is useless to use particular antibodies against surface epitopes [67]. Nucleic acid of a virus is its contagious matter. Nucleic acid includes DNA or RNA. The nucleic acid contains genes while in RNA viral genomes are overlapping. This viral overlapping makes space and destruct the enemy. Nucleic acid of virus is made up of one or two replicas. In RNA complementary strands are present. So the nucleic acids are packed into spherical bundle and are safeguarded by protein capsid. Capsid consists of nucleic acid and simple proteins. An outer lipid membrane is also present in some viruses which contain glycoprotein inserted into them. The points on host cells where the virus attack and enters the cell are examined by glycoprotein. In HIV infection, K+ channel of T4 lymphocytes are the point which are linked with chemokine receptor [68].

Enzymes are also present along with viruses which help in their functioning. Plasma membrane of infectious cell has safeguarding structures which are broken down by specific enzymes, for example neuraminidase or lysozyme. Viral pathogenesis necessitates viral implantation, replication, or dissemination to the tissues of interest and after that they replicate and release their progeny viruses to the tissue environment. The viruses release their progeny viruses mainly in the blood, urogenital tract, alimentary tract and respiratory tract [69]. Viruses mainly use the host's bio machinery in order to multiply, limits the synthesis of biomolecules and also inhibits the synthesis of mRNA in the host cell. These are damages that have been done to the cell directly. Immunology responses and mutations in the targeted host cells are the indirect effects of the viruses. Indirect effects of the virus include mutations in the host cell, inflammation, and the immunological response of the host [70].

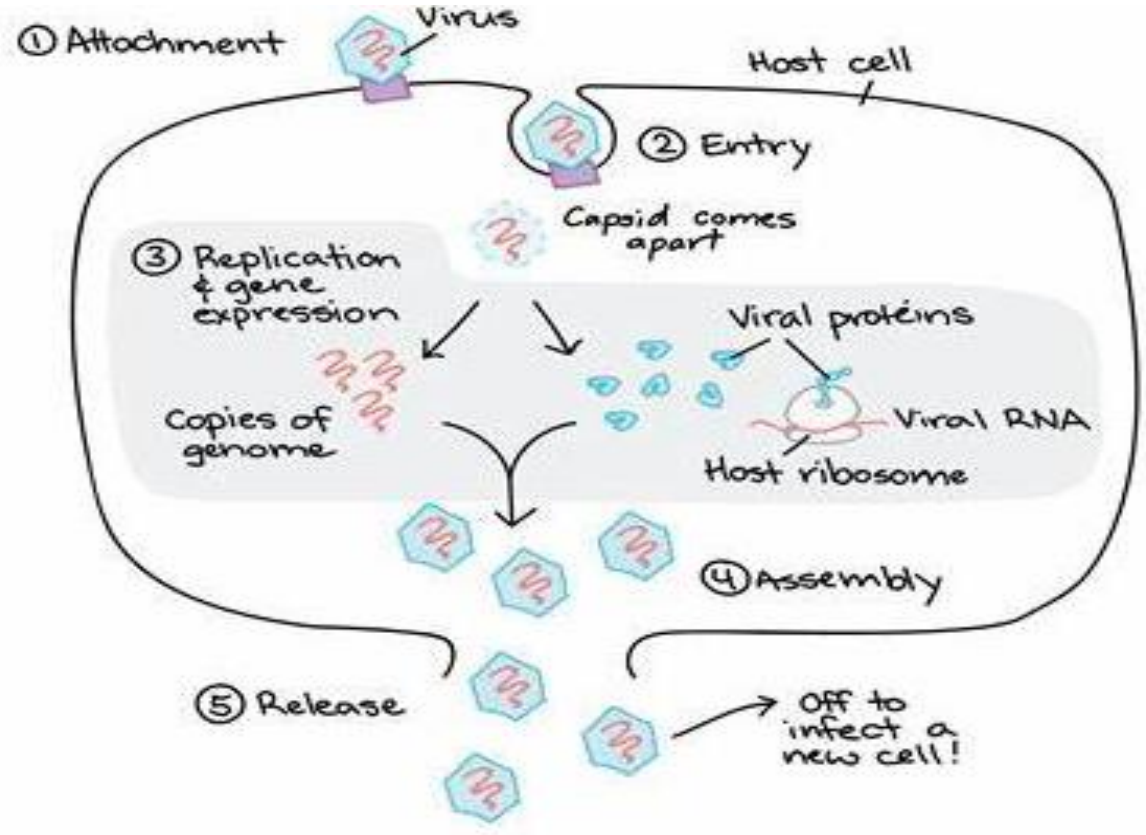

Figure 6 Life cycle of virus [71]

Three variant genes named as polymerase (pol), a gene regulating protein (gag), and envelope are present in genome of each virus. RNA viruses are most fatal as they potentially transforming genes. In RNA viruses, reverse transcriptase is polymerase which can make a DNA chain which is complementary to RNA. It results in destruction of central dogma of genetics that DNA construct RNA and then RNA forms protein. On the entry of virus into target cell through plasma membrane, lipid membrane combines with lysozyme and proteases then hydrolyze the protective protein capsid surrounding the genetic material of virus and small amount of nucleic acid can enter the chromosome through the pores [71]. When the virus infects a cell then reverse transcriptase is released in host cell. When another attacking virus is RNA virus then pol gene provide the previously released reverse transcriptase and make a DNA strand complementary to viral RNA. Viral DNA is then combines with cellular genome. When the attacking virus is viral DNA then it doesn't need reverse transcriptase as they can directly enter their genome into chromosome of the cell with the help of host enzymes [72]. Non-

segregated viral genome then enters into any of these two states, lysogenic or lytic. In the lysogenic state, the virus remains hidden for long duration but become active on second attack of virus or by irradiation and then enters into lytic cycle. In the lytic state, attacking virus takes the control over the cell's metabolism and provides energy as well as commences making new viral particles by using enzymes and substrate present in host cell. In this way, host cell suffer from lack of important substrates and this result death of infected cell and new viral particles escapes the host cell. In the end the infected cell become immortalized and become a source of new viral particles [73].

Flavonoids photochemical inhibit the activity of viruses in different ways. They attack on virus surface and interrupt different phases of viral life cycle i.e. DNA replication, protein translation and poly protein processes and as result they pre-empt the attachment and entrance of virus in the cell. They also pre-empt to release the virus into the healthy host cell. Flavonoids sometimes affect the starting process of replication of viruses such as translation and transcription and sometimes effect the later phases of virus's assembly such as packaging and release. Flavonoids also regulate the immune system [74]. In cultured cells, quercetin suppresses numerous respiratory viruses [37, 41]. The cytopathic effect of the different viruses such as echovirus its different subtypes, rhinovirus, type 1 polio virus are inhibited by the quercetin action at the concentration of 0.03 -0.5 g/ml. This concentration at which the activity of viruses is reduced is known as minimal inhibitory concentrations [75].

In vitro studies on quercetin were also conducted which showed that it has the ability to reduce the activity of enzymes of Human immunodeficiency virus (HIV) such as integrase, protease and reverse transcriptase [76]. The virus's 3-chymotrypsin-like protease (3CLpro), papain-like protease (PLpro), and spike (S) - proteins are all inhibited from binding to Angiotensin converting enzyme 2 (ACE2) in the host cell by quercetin. By the action of quercetin the different proteins of corona virus such as papain and spike proteins are unable to bind to their receptors that are ACE3 on the host cells [77]. Quercetin, exhibit minimal concentration required for viral death values are 116.3, 52.7, and 128.8 M against SARS CoV-3CLpro. The medication concentration necessary to block processes of the body or component by 50% is determined using IC50 values [78].

Humans and animals are both affected by herpes viruses, which cause a variety of illnesses. Latency phase and lytic phase are the two life cycles of herpes virus [79]. There are various compounds in the Ethyl Acetate fraction of Elaeocarpussylvestris, such as isoquercetin, quercetin-3-O-arabinoside, and PGG. PGG is a key component and has been recently investigated as strong VZN inhibitor [80]. Extracts obtained from V. vinifera leaves were prepared in an aqueous methanol solvent, and their chemical profiles were evaluated using High Performance Liquid Chromatography Mass Spectrometry (HPLC-MS). This research aimed to identify and characterize the different flavonoids the majority of which were derived from quercetin. It was also examined that these extracts have inhibitory activity against the corona virus and HSV [81].

2.1.6. Quercitin against SARS COV2

Active viruses are among major health hazard as in recent years, there had emerged many viral outbreaks in the world such as SARS is a severe acute respiratory syndrome discovered in 2003 [82]. In 2009 influenza virus H1N1 discovered. A pneumonia outbreak occurred a few months ago In Wuhan City, Hubei Province, and an unknown aetiology were discovered and it was reported to the office of World Health Organization China [83]. It is enveloped, single stranded, positive sense RNA virus that infects directly the epithelial cells of lungs. The virus can enter into the host cell by attacking to ACE-2 receptor. It infects mostly humans and bats. Researchers have shown that cation selective ion channel are expressed in the infected host cell and then used by the virus to release its progeny from the host cell and infect other host cell [77]. These cation selective channels were created by viral proteins which are coded by ORF-3a of SARS-1 coronavirus.

Knowledge of some major viral proteins such as spike protein, 3 chymotrypsin protease proteins is essential when seeking for novel antiviral drugs. Quercetin inhibits the viral proteins such as papain protease protein and chymotrypsin protease proteins with docking energies 4 and 6 kcal/mol respectively. Quercetin has the potential to interfere with SARS-CoV-2 replication in a theoretical but significant way. Quercetin has been identified as potential COVID-19 mitigating agent using Gene Set Enrichment Analyses. Quercetin affects the expression of 98 out of 332 human genes (30%) encoding SARS-

CoV-2 protein targets, potentially in human cells, interfering with the activities of 23 of 27 (85%) of the SARSCoV-2 viral proteins [84, 85].

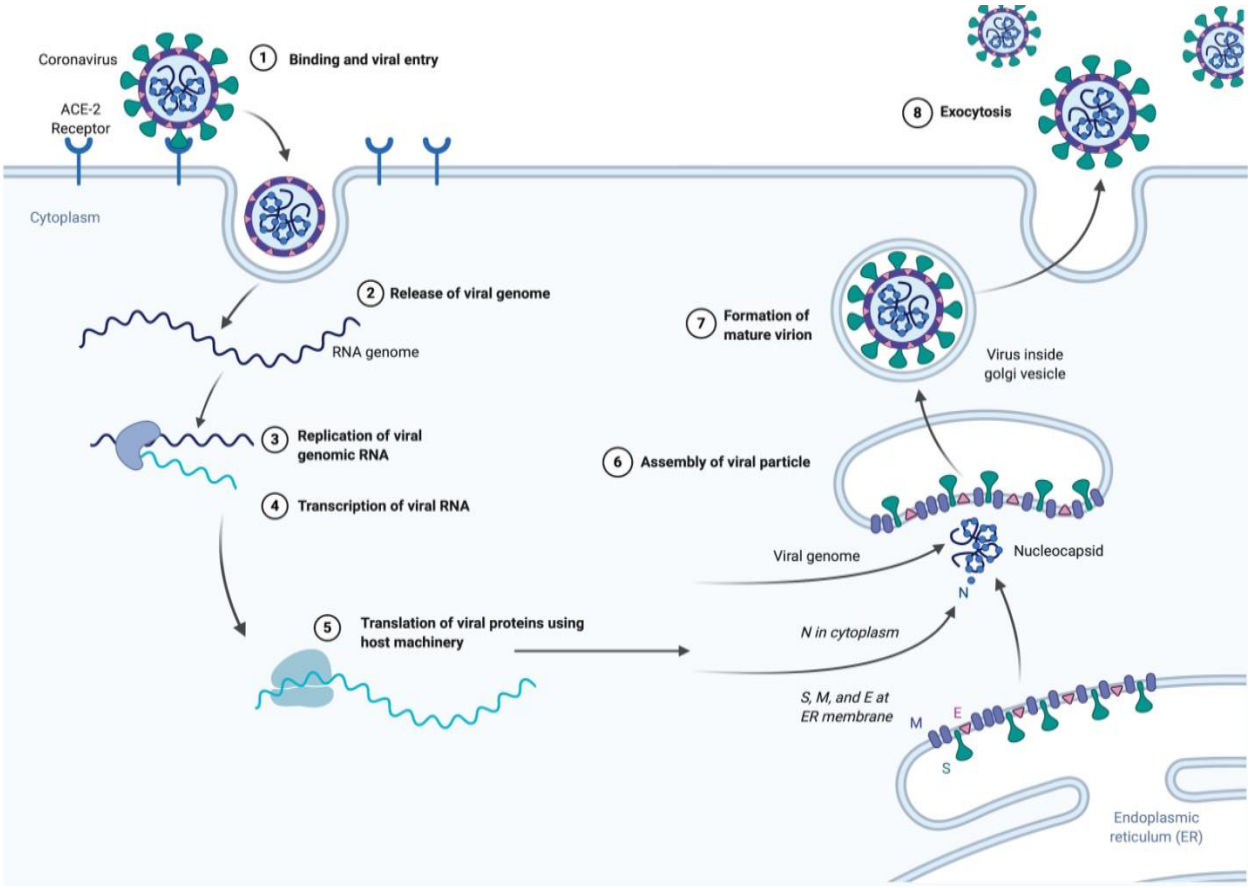

Figure 7 Mechanism of action of corona virus [84]

SARS-COV-2 protease, papain like protease, spike protein, 3-chymotrypin like protease, RNA dependent RNA polymerase, and human angiotensin-converting enzyme 2 are considered to be the most crucial targets for developing effective antiCOVID-19 drugs. Recently, molecular docking studies have proved that strong binding interaction of Quercetin with the papain like protease (PLpro) and 3-chymotrypsin like protease (3CLpro) are possible [86]. According to computer stimulation, Quercetin is the best repressing effect against SARS-COV 2. Mpro main proteases are considered to have significant preference for quercetin. Study revealed that flavonoids have significant potential to interact with transmembrane serine protease2 [87]. Quercetin was considered to be the top scoring ligand for ACE2 receptor interface and for the S

protein. Again docking model identify the small molecules which are able to bind either to S protein-ACE2 receptor interface to disrupt the host virus interaction or isolated viral S protein at its host receptor binding region [88].

Another studies show the relationship between quercetin and two proteins: Spike (S) protein and furin protein. Furin is a host cell enzyme which increases the entanglement of ACE2 receptor with S protein. It is basically responsible for the nonclathoin mediated fusion of membranes. The inhibition of furin could prevent the cleavage of spikes which results the suppressing of virus reproduction [89]. Interaction of quercetin with furin shows a high binding affinity for quercetin. It was proved by the lower number of carbon-hydrogen and hydrogen bonds that reactivity of quercetin on S protein was lower than for the investigated drugs. In Figure, interaction between quercitin-3-β galactoside and the COVID protease which is 3CLpro have been schematized. Target amino acids that are located around the catalytic site of each 3CLpro promoter interact with quercetin as well as flavonoids. Quercitin-3 beta glactoside forms hydrogen bonds with Gln189 and Glu166 amino acids that are located inside particular pocket hallowed in the protein surface [68].

Table 2 Role of quercetin in SARS COV-2 [90]

Quercetin3-β galactoside	It binds to the catalytic pocket of SARS-CoV 3CL protease
Quercetin	ACE2 receptor interface, top scoring ligand for the S protein
Quercetin	It inhibits 3CL protease and PL protease
Quercetin	It interacts with furin with -7.77 kcal/mol binding energy

2.1.7. Quercitin against dengue virus

The Flaviviridae family and genus Flavivirus contain the positive-strand RNA virus known as dengue virus (DENV). Dengue, a common and serious health problem, requires a lot of world's attention because it has affected the tropical countries including Malaysia and more than 900,000 cases were reported from the year 2019 to present [91]. A total of 48,906 dengue cases were reported between 1 January and 25 November 2021 in Pakistan's four provinces, Islamabad, and the autonomous regions of Azad Jammu and

Kashmir, with 183 fatalities (case fatality ratio (CFR): 0.4%). As of November 25, Punjab province had the most cases, with 24,146 cases and 127 fatalities (CFR: 0.5%), accounting for 49.4 percent and 69.4 percent, respectively, of all cases and deaths. Lahore district was recorded due to its majority of deaths [92].

It has four closely related but genetically distinct serotypes (DENV-1, -2, -3, and -4) that are all primarily transmitted by Aedesaegypti mosquitoes, with A. albopictus serving as a secondary vector [93]. The fifth serotypes exerted no influence to human but the main vector for DENV-5 is mosquito Aedesniveus and the female "Aedesaegypti" mosquito, and the female mosquito needs human blood for its nutrition. As the fifth serotype is not common, the WHO started that other four serotypes are main and common cause behind spreading dengue diseases. The virion is made up of a spherical particle with a lipopolysaccharide envelope that is 40–50 nm in diameter. A single open reading frame is present in the roughly 11 kilobyte positive single-strand RNA genome. Three structural proteins and seven structural proteins are encoded by the reading frame. Capsid, membrane, and envelope glycoprotein are structural proteins. NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5 are nonstructural proteins [94]. The E glycoprotein is linked to several crucial biological functions of dengue viruses, such as receptor binding, erythrocyte hemagglutination, the development of neutralizing antibodies, and the protective immune response. The anti-dengue virus activity and papaya leaf extract's potent stimulation of IL-6 and SCF may aid the infected patients' thrombocytopenic conditions. A papain-rich papaya leaf extract has been demonstrated to increase the thrombocyte (platelet) count in dengue patients [95]. The qualitative phytochemical examination shows that every phytochemical, excluding steroids and tannins, is found in papaya leaf material, including glycosides, alkaloids, saponins, flavonoids, and proteins. The anti-oxidant vitamins and minerals included in papaya leaves may aid in raising the levels of total protein, thrombocytes, red blood cells, hemoglobin, and hemotocrit. Carica papaya has been found to have characteristics that help stabilize membranes .In vitro trials showed that leaf extracts, even at low concentrations, effectively prevented heat-induced and hypotonicity-induced hemolysis of erythrocytes collected from both healthy and dengue-infected individuals. As a result, the extracts are probably capable of stabilizing membranes and

guarding against stress-related cell death. This characteristic may be helpful for dengue infection patients since the leaf extracts may be able to stop platelet lysis. The presence of flavonoids and other phenolic chemicals in papaya leaves, according to the theory, may be the cause of this action [96]. Papaya leaf extracts have biological membrane stabilizing characteristics that stop stress from causing the plasma membrane to rupture. The membrane stabilizing function of papaya leaf extracts was caused by flavonoids and other phenolic chemicals, which also assisted to stop internal bleeding in the blood vessels. NS2B-NS3 protease is inhibited by flavonoids found in Carica papaya, which helps to stop the DEN-2 virus [93].

There are two types of dengue infection. One is called primary infection and the other is called secondly infection. If a person gets recover from primary infection then he has the ability to live a protective and health life against the same serotype but the risk of developing secondary infection would be a serious concern to his health. Though DENV become a potentially fatal disease yet there is no advanced medical measurement to be taken. The need of the hour is that the scientist should step forward to develop such a medicine that should be more useful, benefited to the statistical crucial treatment of dengue infection [97]. Dendritic cells (DCs), monocytes/macrophages, B cells, T cells, endothelial cells, hepatocytes, and brain cells of the host are the main targets of DENV. DENV enters the target cell via non-specific receptor-mediated endocytosis in a serotype-specific manner. There are various best-known endocytosis receptors like high-affinity laminin receptor, heparansulphate, HSP-70, HSP-90, GRP-78, DC-SIGN, TAM, TIM-1, caludin-1, AXL, or mannose receptor [98]. To direct viral particles toward the endocytic pathway, envelope proteins on virus surfaces bind to these receptors on the host cell. The decreased pH in the endosome causes a major structural change in the envelope protein. Finally, the viral genome is released into the cytoplasm as a result of the E protein adhering to the endosomal membrane as a result of these alterations. Translation and viral genome replication are the two stages that the released viral RNA goes through in the cell. Virus RNA, like host mRNA, performs similar functions. The most obvious difference between viral RNA and host mRNA is the absence of a poly-A tail. Viral mRNA is translated differently from cellular mRNA [99]. As a result, translation takes place at the ribosome located on the ER, where the genome is converted into

polypeptide chain. Viral serine proteases and cellular proteases break the polypeptide chain down into three structural and seven non-structural proteins. Throughout the transformation process, the host cell goes through a number of alterations. The host cell was compelled by these alterations to encourage viral RNA replication. One of these cell changes is the development of a replication complex (RC), a membrane-bound microenvironment. In RC, viral RNA morphogenesis and amplification have been seen. The tiny dengue viral genome produces proteins that serve a variety of purposes, including genome replication, viral assembly, discharge of fully developed virions, and immunopathogenesis [100].

3. Conclusion and Future Perspectives

Quercetin is a safe dietary supplement with a variety of biological functions in animals as well as in humans. Majority of the literature showed its safety profile in animals as an antimicrobial, antidiabetic, anticancer, antioxidant and anti-inflammatory agent. However, further evaluation in this regard with accurate outcomes is much needed. Poor solubility and oral bioavailability of quercetin were a major problem in its use which was managed by making its complexes with polymers and metal ions in sustained released microspheres, nanospheres and liposomal dosage forms [34]. Synergistic effects of quercetin with anticancer, antimicrobials, antidiabetics and anti-inflammatory agents make it an interesting compound for exploring new treatment modalities for acute and chronic human diseases with lesser side effects and improved efficacy.As a result, additional antiviral techniques will be investigated through the future potential work of isolating the bioactive chemicals that have been found and researching their impact on the function of virally encoded proteins that are essential to the HIV-1 life cycle.

Conflicts of Interest

The authors declared no conflict of interest.

References

[1] Nakhate, Y. D., Talekar, K. S., Giri, S. V., Vasekar, R. D., Mankar, H. C., & Tiwari, P. R. (2019). Pharmacological and chemical composition of carica papaya: On overview. World Journal of Pharmaceutical Research, 8, 811-821.
[2] Ghasemzadeh, A., Azarifar, M., Soroodi, O., & Jaafar, H. Z. (2012). Flavonoid compounds and their antioxidant activity in extract of some tropical plants. Journal of Medicinal Plants Research, 6(13), 2639-2643.
[3] Dotto, J. M., & Abihudi, S. A. (2021). Nutraceutical value of Carica papaya: A review. Scientific African, 13, e00933.
[4] Singh, S. P., Kumar, S., Mathan, S. V., Tomar, M. S., Singh, R. K., Verma, P. K., ... & Acharya, A. (2020). Therapeutic application of carica papaya leaf extract in the management of human diseases. DARU Journal of Pharmaceutical Sciences, 28, 735-744.
[5] Shinde, A., Kolhe, D., Hase, D. P., & Chavan, M. J. (2020). A brief introduction about carica papaya linn. World Journal of Pharmaceutical Research, 9.
[6] Adel, A., Elnaggar, M. S., Al-Sayed, E., & Rabeh, M. A. (2021). Secondary metabolites from carica papaya, and its biological activities: A comprehensive review. Archives of Pharmaceutical Sciences Ain Shams University, 5(2), 331-353.
[7] Patil, P., Alagarasu, K., Chowdhury, D., Kakade, M., Cherian, S., Kaushik, S., ...& Parashar, D. (2022). In-vitro antiviral activity of Carica papaya formulations against dengue virus type 2 and chikungunya virus. Heliyon, 8(12), e11879.
[8] Koul, B., Pudhuvai, B., Sharma, C., Kumar, A., Sharma, V., Yadav, D., & Jin, J. O. (2022). Carica papaya L.: a tropical fruit with benefits beyond the tropics. Diversity, 14(8), 683.
[9] Wadekar, A. B., Nimbalwar, M. G., Panchale, W. A., Gudalwar, B. R., Manwar, J. V., & Bakal, R. L. (2021). Morphology, phytochemistry and pharmacological aspects of carica papaya, an review. GSC Biological and Pharmaceutical Sciences, 14(3), 234-248.
[10] Tomás-Barberán, F. A., & Espín, J. C. (2001). Phenolic compounds and related enzymes as determinants of quality in fruits and vegetables. Journal of the Science of Food and Agriculture, 81(9), 853-876.
[11] Nugroho, A., Heryani, H., Choi, J. S., & Park, H. J. (2017). Identification and quantification of flavonoids in Carica papaya leaf and peroxynitrite-scavenging activity. Asian Pacific Journal of Tropical Biomedicine, 7(3), 208-213.
[12] Bangar, S. P., Chaudhary, V., Sharma, N., Bansal, V., Ozogul, F., & Lorenzo, J. M. (2022). Kaempferol: A flavonoid with wider biological activities and its applications. Critical Reviews in Food Science and Nutrition, 1-25.
[13] Diniz, L. R. L., Souza, M. T. D. S., Duarte, A. B. S., & Sousa, D. P. D. (2020). Mechanistic aspects and therapeutic potential of quercetin against COVID-19-associated acute kidney injury. Molecules, 25(23), 5772.
[14] Lim, X. Y., Chan, J. S. W., Japri, N., Lee, J. C., & Tan, T. Y. C. (2021). Carica papaya L. leaf: a systematic scoping review on biological safety and herb-drug interactions. Evidence-Based Complementary and Alternative Medicine, 2021, 1-21.
[15] Chiow, K. H., Phoon, M. C., Putti, T., Tan, B. K., & Chow, V. T. (2016). Evaluation of antiviral activities of HouttuyniacordataThunb. extract, quercetin, quercetrin and cinanserin on murine coronavirus and dengue virus infection. Asian Pacific Journal of Tropical Medicine, 9(1), 1-7.
[16] Jan, R., Khan, M., Asaf, S., Lubna, Asif, S., & Kim, K. M. (2022). Bioactivity and therapeutic potential of kaempferol and quercetin: new insights for plant and human health. Plants, 11(19), 2623.
[17] Alkandahri, M. Y., Pamungkas, B. T., Oktoba, Z., Shafirany, M. Z., Sulastri, L., Arfania, M., ...& Hamidah, S. Z. (2023). Hepatoprotective effect of kaempferol: a review of the dietary sources, bioavailability, mechanisms of action, and safety. Advances in Pharmacological and Pharmaceutical Sciences, 2023(1), 1387665.

[18] Imran, M., Rauf, A., Shah, Z. A., Saeed, F., Imran, A., Arshad, M. U., ...& Mubarak, M. S. (2019). Chemo-preventive and therapeutic effect of the dietary flavonoid kaempferol: A comprehensive review. Phytotherapy Research, 33(2), 263-275.
[19] Latos-Brozio, M., &Masek, A. (2019). Structure-activity relationships analysis of monomeric and polymeric polyphenols (quercetin, rutin and catechin) obtained by various polymerization methods. Chemistry & Biodiversity, 16(12), e1900426.
[20] Nugrahaningsih, W. H., Latifa, N., & Lisdiana, L. (2022). Absorption of flavonoid rutin after oral treatment of carica papaya leaf extract. Biosaintifika: Journal of Biology & Biology Education, 14(1), 30-35.
[21] Chew, S. K., Teoh, W. H., Hong, S. L., & Yusoff, R. (2022). Extraction of rutin from the leaf of male carica papaya Linn. using microwave-assisted and ultrasound-assisted extractive methods. ASEAN Journal of Chemical Engineering, 22(2), 347-363.
[22] Memar, M. Y., Yekani, M., Sharifi, S., & Dizaj, S. M. (2022). Antibacterial and biofilm inhibitory effects of rutinnanocrystals. Biointerface Research in Applied Chemistry, 13, 132.
[23] Negahdari, R., Bohlouli, S., Sharifi, S., MalekiDizaj, S., RahbarSaadat, Y., Khezri, K., ...& Raeesi, S. (2021). Therapeutic benefits of rutin and its nanoformulations. Phytotherapy Research, 35(4), 1719-1738.
[24] Sultana, B., & Anwar, F. (2008). Flavonols (kaempeferol, quercetin, myricetin) contents of selected fruits, vegetables and medicinal plants. Food Chemistry, 108(3), 879-884.
[25] Kapesova, J., Petrásková, L., Markošová, K., Rebroš, M., Kotik, M., Bojarová, P., & Křen, V. (2019). Bioproduction of quercetin and rutinose catalyzed by rutinosidase: Novel concept of "solid state biocatalysis". International Journal of Molecular Sciences, 20(5), 1112.
[26] Rizaldi, G., Hafid, A. F., & Wahyuni, T. S. (2023). Promising alkaloids and flavonoids compounds as anti-hepatitis c virus agents: a review. Journal of Public Health in Africa, 14(Suppl 1).
[27] Shorobi, F. M., Nisa, F. Y., Saha, S., Chowdhury, M. A. H., Srisuphanunt, M., Hossain, K. H., & Rahman, M. A. (2023). Quercetin: a functional food-flavonoid incredibly attenuates emerging and re-emerging viral infections through immunomodulatory actions. Molecules, 28(3), 938.
[28] Saakre, M., Mathew, D., & Ravisankar, V. (2021). Perspectives on plant flavonoid quercetin-based drugs for novel SARS-CoV-2. Beni-Suef University Journal of Basic and Applied Sciences, 10(1), 1-13.
[29] Chaabi, M. (2020). Antiviral effects of quercetin and related compounds. Naturopathic Currents, 2020, 1-4.
[30] Singh, P., Arif, Y., Bajguz, A., & Hayat, S. (2021). The role of quercetin in plants. Plant Physiology and Biochemistry, 166, 10-19.
[31] Magar, R. T., & Sohng, J. K. (2020). A review on structure, modifications and structure-activity relation of quercetin and its derivatives. Journal of Microbiology and Biotechnology, 30(1), 11.
[32] Ulusoy, H. G., & Sanlier, N. (2020). A mini review of quercetin: from its metabolism to possible mechanisms of its biological activities. Critical Reviews in Food Science and Nutrition, 60(19), 3290-3303.
[33] Bisht, A., Sharma, P., & Agarwal, G. (2023). An insight into physiochemical property, bioavailability and pharmacology of Quercetin: A bioflavonoid, 12(3):1254-1260.
[34] Azeem, M., Hanif, M., Mahmood, K., Ameer, N., Chughtai, F. R. S., & Abid, U. (2023). An insight into anticancer, antioxidant, antimicrobial, antidiabetic and anti-inflammatory effects of quercetin: A review. Polymer Bulletin, 80(1), 241-262.
[35] Magro, V. M. (2023). Use of quercetin for therapeutic purposes in COVID-19 infections: The opinion of the geriatrician doctor. Journal of Modern Biology and Drug Discovery, 2(4).
[36] Carrasco-Pozo, C., Cires, M. J., & Gotteland, M. (2019). Quercetin and epigallocatechingallate in the prevention and treatment of obesity: from molecular to clinical studies. Journal of Medicinal Food, 22(8), 753-770.

[37] Almatroodi, S. A., Alsahli, M. A., Almatroudi, A., Verma, A. K., Aloliqi, A., Allemailem, K. S., ... & Rahmani, A. H. (2021). Potential therapeutic targets of quercetin, a plant flavonol, and its role in the therapy of various types of cancer through the modulation of various cell signaling pathways. Molecules, 26(5), 1315.
[38] Lawson, M. K. (2023). Improvement of therapeutic value of quercetin with chitosan nanoparticle delivery systems and potential applications. International Journal of Molecular Sciences, 24(4), 3293.
[39] Polerà, N., Badolato, M., Perri, F., Carullo, G., & Aiello, F. (2019). Quercetin and its natural sources in wound healing management. Current Medicinal Chemistry, 26(31), 5825-5848.
[40] Di Petrillo, A., Orrù, G., Fais, A., & Fantini, M. C. (2022). Quercetin and its derivates as antiviral potentials: A comprehensive review. Phytotherapy Research, 36(1), 266-278.
[41] Subudhi, B. B., & Swain, R. P. (2023). Quercetin against emerging RNA viral diseases: Potential and challenges for translation. Current Molecular Medicine, 23(9), 849-862.
[42] Thagriki, D. S. (2022). Quercetin and its derivatives are potent inhibitors of the dengue virus. Trends in Phytochemical Research, 6(1), 70-85.
[43] Jesus, A., Mota, S., Torres, A., Cruz, M. T., Sousa, E., Almeida, I. F., & Cidade, H. (2023). Antioxidants in sunscreens: which and what for?. Antioxidants, 12(1), 138.
[44] Xu, D., Hu, M. J., Wang, Y. Q., & Cui, Y. L. (2019). Antioxidant activities of quercetin and its complexes for medicinal application. Molecules, 24(6), 1123.
[45] Salehi, B., Machin, L., Monzote, L., Sharifi-Rad, J., Ezzat, S. M., Salem, M. A., ... & Cho, W. C. (2020). Therapeutic potential of quercetin: new insights and perspectives for human health. ACS Omega, 5(20), 11849-11872.
[46] Al-Ansari, M. M., Al-Humaid, L., Aldawsari, M., Abid, I. F., Jhanani, G. K., & Shanmuganathan, R. (2023). Quercetin extraction from small onion skin (Allium cepa L. var. aggregatum Don.) and its antioxidant activity. Environmental Research, 224, 115497.
[47] Bentz, A. B. (2017). A Review of quercetin: chemistry, antioxident properties, and bioavailability. Journal of young Investigators.
[48] Donath, M. Y., & Shoelson, S. E. (2011). Type 2 diabetes as an inflammatory disease. Nature Reviews Immunology, 11(2), 98-107.
[49] Yoon, J. S., Chae, M. K., Lee, S. Y., & Lee, E. J. (2012). Anti-inflammatory effect of quercetin in a whole orbital tissue culture of Graves' orbitopathy. British Journal of Ophthalmology, 96(8), 1117-1121.
[50] Chen, S., Jiang, H., Wu, X., & Fang, J. (2016). Therapeutic effects of quercetin on inflammation, obesity, and type 2 diabetes. Mediators of Inflammation, 2016(1), 9340637.
[51] Goutas, D., Pergaris, A., Giaginis, C., & Theocharis, S. (2022). HuR as therapeutic target in cancer: what the future holds. Current Medicinal Chemistry, 29(1), 56-65.
[52] Hisaka, T., Sakai, H., Sato, T., Goto, Y., Nomura, Y., Fukutomi, S., ... & Yano, H. (2020). Quercetin suppresses proliferation of liver cancer cell lines in vitro. Anticancer Research, 40(8), 4695-4700.
[53] Liu, H., Lee, J. I., & Ahn, T. G. (2019). Effect of quercetin on the anti-tumor activity of cisplatin in EMT6 breast tumor-bearing mice. Obstetrics & Gynecology Science, 62(4), 242-248.
[54] Xu, G., Li, B., Wang, T., Wan, J., Zhang, Y., Huang, J., & Shen, Y. (2018). Enhancing the anti-ovarian cancer activity of quercetin using a self-assembling micelle and thermosensitive hydrogel drug delivery system. RSC Advances, 8(38), 21229-21242.
[55] Rauf, A., Imran, M., Khan, I. A., ur-Rehman, M., Gilani, S. A., Mehmood, Z., & Mubarak, M. S. (2018). Anticancer potential of quercetin: A comprehensive review. Phytotherapy Research, 32(11), 2109-2130.
[56] Priyadarsini, R. V., Murugan, R. S., Maitreyi, S., Ramalingam, K., Karunagaran, D., & Nagini, S. (2010). The flavonoid quercetin induces cell cycle arrest and mitochondria-mediated apoptosis in human cervical cancer (HeLa) cells through p53 induction and NF-κB inhibition. European Journal of Pharmacology, 649(1-3), 84-91.

[57] Hansen, R. K., Oesterreich, S., Lemieux, P., Sarge, K. D., & Fuqua, S. A. W. (1997). Quercetin inhibits heat shock protein induction but not heat shock factor DNA-binding in human breast carcinoma cells. Biochemical and Biophysical Research Communications, 239(3), 851-856.
[58] Baghel, S. S., Shrivastava, N., Baghel, R. S., Agrawal, P., & Rajput, S. (2012). A review of quercetin: antioxidant and anticancer properties. World Journal of Pharmaceutical Sciences, 1(1), 146-160.
[59] Balakrishnan, S., Bhat, F. A., Raja Singh, P., Mukherjee, S., Elumalai, P., Das, S., ... & Arunakaran, J. (2016). Gold nanoparticle–conjugated quercetin inhibits epithelial–mesenchymal transition, angiogenesis and invasiveness via EGFR/VEGFR-2-mediated pathway in breast cancer. Cell Proliferation, 49(6), 678-697.
[60] Dionisio, F., Domingues, C. P., Rebelo, J. S., Monteiro, F., & Nogueira, T. (2023). The impact of non-pathogenic bacteria on the spread of virulence and resistance genes. International Journal of Molecular Sciences, 24(3), 1967.
[61] Elangovan, S., & Mudgil, P. (2023). Antibacterial properties of eucalyptus globulus essential oil against MRSA: A systematic review. Antibiotics, 12(3), 474.
[62] Veiko, A. G., Olchowik-Grabarek, E., Sekowski, S., Roszkowska, A., Lapshina, E. A., Dobrzynska, I., ... & Zavodnik, I. B. (2023). Antimicrobial activity of quercetin, naringenin and catechin: Flavonoids inhibit Staphylococcus aureus-induced hemolysis and modify membranes of bacteria and erythrocytes. Molecules, 28(3), 1252.
[63] Hirai, I., Okuno, M., Katsuma, R., Arita, N., Tachibana, M., & Yamamoto, Y. (2010). Characterisation of anti-Staphylococcus aureus activity of quercetin. International Journal of Food Science & Technology, 45(6), 1250-1254.
[64] Flemming, H. C., Wingender, J., Szewzyk, U., Steinberg, P., Rice, S. A., & Kjelleberg, S. (2016). Biofilms: an emergent form of bacterial life. Nature Reviews Microbiology, 14(9), 563-575.
[65] Memariani, H., Memariani, M., & Ghasemian, A. (2019). An overview on anti-biofilm properties of quercetin against bacterial pathogens. World Journal of Microbiology and Biotechnology, 35, 1-16.
[66] Krupovic, M., Dolja, V. V., & Koonin, E. V. (2019). Origin of viruses: primordial replicators recruiting capsids from hosts. Nature Reviews Microbiology, 17(7), 449-458.
[67] Ahmad, A., Kaleem, M., Ahmed, Z., & Shafiq, H. (2015). Therapeutic potential of flavonoids and their mechanism of action against microbial and viral infections—A review. Food Research International, 77, 221-235.
[68] Di Petrillo, A., Orrù, G., Fais, A., & Fantini, M. C. (2022). Quercetin and its derivates as antiviral potentials: A comprehensive review. Phytotherapy Research, 36(1), 266-278.
[69] Munafò, F., Donati, E., Brindani, N., Ottonello, G., Armirotti, A., & De Vivo, M. (2022). Quercetin and luteolin are single-digit micromolar inhibitors of the SARS-CoV-2 RNA-dependent RNA polymerase. Scientific Reports, 12(1), 10571.
[70] Sulastri, E., Zubair, M. S., Anas, N. I., Abidin, S., Hardani, R., & Yulianti, R. (2018). Total phenolic, total flavonoid, quercetin content and antioxidant activity of standardized extract of Moringa oleifera leaf from regions with different elevation. Pharmacognosy Journal, 10(6s).
[71] Wu, W., Cheng, Y., Zhou, H., Sun, C., & Zhang, S. (2023). The SARS-CoV-2 nucleocapsid protein: its role in the viral life cycle, structure and functions, and use as a potential target in the development of vaccines and diagnostics. Virology Journal, 20(1), 1-16.
[72] Wilson, V. G. (2022). The Viruses Within–How Human Are We?. In Viruses: Intimate Invaders (pp. 203-226). Cham: Springer International Publishing.
[73] Costa, R., Olea, B., Bracho, M. A., Albert, E., de Michelena, P., Martínez-Costa, C., ...& Navarro, D. (2022). RNA viral loads of SARS-CoV-2 Alpha and Delta variants in nasopharyngeal specimens at diagnosis stratified by age, clinical presentation and vaccination status. Journal of Infection, 84(4), 579-613.
[74] Badshah, S. L., Faisal, S., Muhammad, A., Poulson, B. G., Emwas, A. H., & Jaremko, M. (2021). Antiviral activities of flavonoids. Biomedicine & Pharmacotherapy, 140, 111596.

[75] Ishitsuka, H., Ninomiya, Y. T., Ohsawa, C., Fujiu, M., & Suhara, Y. (1982). Direct and specific inactivation of rhinovirus by chalcone Ro 09-0410. Antimicrobial Agents and Chemotherapy, 22(4), 617-621.
[76] Colunga Biancatelli, R. M. L., Berrill, M., Catravas, J. D., & Marik, P. E. (2020). Quercetin and vitamin C: an experimental, synergistic therapy for the prevention and treatment of SARS-CoV-2 related disease (COVID-19). Frontiers in Immunology, 11, 1451.
[77] Derosa, G., Maffioli, P., D'Angelo, A., & Di Pierro, F. (2021). A role for quercetin in coronavirus disease 2019 (COVID-19). Phytotherapy Research, 35(3), 1230-1236.
[78] Park, J. Y., Yuk, H. J., Ryu, H. W., Lim, S. H., Kim, K. S., Park, K. H., ... & Lee, W. S. (2017). Evaluation of polyphenols from Broussonetia papyrifera as coronavirus protease inhibitors. Journal of Enzyme Inhibition and Medicinal Chemistry, 32(1), 504-512.
[79] Zhu, S., & Viejo-Borbolla, A. (2021). Pathogenesis and virulence of herpes simplex virus. Virulence, 12(1), 2670-2702.
[80] Bae, S., Kim, S. Y., Do, M. H., Lee, C. H., & Song, Y. J. (2017). 1, 2, 3, 4, 6-Penta-O-galloyl-ß-D-glucose, a bioactive compound in Elaeocarpus sylvestris extract, inhibits varicella-zoster virus replication. Antiviral Research, 144, 266-272.
[81] Heleno, S. A., Carocho, M., Reis, F. S., Pires, T. C., Pintado, M., Ferreira, I. C., & Barros, L. (2023). Plant Extracts and SARS-CoV-2: Research and Applications. Life, 13(2), 386.
[82] Noy, I., & Shields, S. (2019). The 2003 severe acute respiratory syndrome epidemic: A retroactive examination of economic costs. Asian Development Bank Economics Working Paper Series, (591).
[83] Sohrabi, C., Alsafi, Z., O'neill, N., Khan, M., Kerwan, A., Al-Jabir, A., ...& Agha, R. (2020). World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). International Journal of Surgery, 76, 71-76.
[84] Shereen, M. A., Khan, S., Kazmi, A., Bashir, N., & Siddique, R. (2020). COVID-19 infection: Emergence, transmission, and characteristics of human coronaviruses. Journal of Advanced Research, 24, 91-98.
[85] Agrawal, P. K., Agrawal, C., & Blunden, G. (2020). Quercetin: antiviral significance and possible COVID-19 integrative considerations. Natural Product Communications, 15(12), 1934578X20976293.
[86] Jo, S., Kim, S., Shin, D. H., & Kim, M. S. (2020). Inhibition of SARS-CoV 3CL protease by flavonoids. Journal of Enzyme Inhibition and Medicinal Chemistry, 35(1), 145-151.
[87] Di Pierro, F., Derosa, G., Maffioli, P., Bertuccioli, A., Togni, S., Riva, A., ...& Ahmed, S. (2021). Possible therapeutic effects of adjuvant quercetin supplementation against early-stage COVID-19 infection: a prospective, randomized, controlled, and open-label study. International Journal of General Medicine, 2359-2366.
[88] Rehman, S. U., Shafqat, F., Fatima, B., Nawaz, M. N., & Niaz, K. (2023). Flavonoids and other polyphenols against SARS-CoV-2. In Application of Natural Products in SARS-CoV-2 (pp. 83-123). Academic Press.
[89] Pregnolato, M., &Zizzi, P. (2023). SARS-CoV-2 spike and ACE2 entanglement-like binding. Quantum Machine Intelligence, 5(1), 8.
[90] Bhati, S., Kaushik, V., & Singh, J. (2021). Rational design of flavonoid based potential inhibitors targeting SARS-CoV 3CL protease for the treatment of COVID-19. Journal of Molecular Structure, 1237, 130380.
[91] Selvarajoo, S., Liew, J. W. K., Tan, W., Lim, X. Y., Refai, W. F., Zaki, R. A., ... & Vythilingam, I. (2020). Knowledge, attitude and practice on dengue prevention and dengue seroprevalence in a dengue hotspot in Malaysia: A cross-sectional study. Scientific Reports, 10(1), 1-13.
[92] Khatri, G., Hasan, M. M., Shaikh, S., Mir, S. L., Sahito, A. M., Rocha, I. C. N., & Elmahi, O. K. O. (2022). The simultaneous crises of dengue and COVID-19 in Pakistan: a double hazard for the country's debilitated healthcare system. Tropical Medicine and Health, 50(1), 1-5.

[93] Sarker, M. M. R., Khan, F., & Mohamed, I. N. (2021). Dengue fever: therapeutic potential of Carica papaya L. Leaves. Frontiers in Pharmacology, 12, 610912.
[94] Sundar, S., Piramanayagam, S., & Natarajan, J. (2022). A review on structural genomics approach applied for drug discovery against three vector-borne viral diseases: Dengue, Chikungunya and Zika. Virus Genes, 58(3), 151-171.
[95] Pambhar, V., Mathur, N., Mehta, A., Mathur, M., Mangalia, R., Verma, A., & Patyal, A. (2022). Effect of doxycycline and doxycycline with carica papaya on thrombocytopenia and leucopenia in acute dengue fever patients. Journal of Family Medicine and Primary Care, 11(6), 3270-3275.
[96] Patil, P., Alagarasu, K., Chowdhury, D., Kakade, M., Cherian, S., Kaushik, S., ...& Parashar, D. (2022). In-vitro antiviral activity of carica papaya formulations against dengue virus type 2 and chikungunya virus. Heliyon, 8(12), e11879.
[97] Teh, B. P., Ahmad, N. B., Mohamad, S. B., Tan, T. Y. C., MohdAbdRazak, M. R. B., Afzan, A. B., & Syed Mohamed, A. F. B. (2022). Carica papaya leaf juice for dengue: A scoping review. Nutrients, 14(8), 1584.
[98] Zerfu, B., Kassa, T., & Legesse, M. (2023). Epidemiology, biology, pathogenesis, clinical manifestations, and diagnosis of dengue virus infection, and its trend in Ethiopia: a comprehensive literature review. Tropical Medicine and Health, 51(1), 11.
[99] Gupta, A., Li, Y., Chen, S. H., Papas, B. N., Martin, N. P., & Morgan, M. (2023). TUT4/7-mediated uridylation of a coronavirus subgenomic RNAs delays viral replication. Communications Biology, 6(1), 438.
[100] Dharmapalan, B. T., Biswas, R., Sankaran, S., Venkidasamy, B., Thiruvengadam, M., George, G., ...& Shariati, M. A. (2022). Inhibitory potential of chromene derivatives on structural and non-structural proteins of dengue virus. Viruses, 14(12), 2656.