A brief overview of flavonoids as antiviral compounds in coronavirus time

Una breve visión de flavonoides como compuestos antivirales en tiempo de coronavirus.

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Abstract

COVID-19 became very early in 2020, as the world's biggest public health problem, becoming the first pandemic of the 21st century. Within this context, and living these quarantine times, the literature was reviewed to find out in-depth what types of natural products have been shown as possible candidates to become antiviral drugs. Flavonoids seem to be the most interesting in their antiviral activity. This review presents the results of an analysis in which the most important structural characteristics that these compounds must possess to show antiviral activity have been observed.

Keywords: antiviral, flavonoids, plants, structure.

Resumen

COVID-19 se convirtió muy temprano en 2020, en el mayor problema de salud pública del mundo, convirtiéndose también en la primera pandemia del siglo XXI. Dentro de este contexto, y viviendo estos tiempos de cuarentena, se revisó la literatura para descubrir en profundidad qué tipos de productos naturales se han mostrado como posibles candidatos para convertirse en medicamentos antivirales. Los flavonoides parecen ser los más interesantes en su actividad antiviral. En esta revisión se presentan los resultados de un análisis en el cual se han observado las características estructurales más importantes que estos compuestos deben poseer para mostrar actividad antiviral.

Palabras claves: antiviral, flavonoides, plantas, estructura.

Introduction

Natural products have been the source of thousands of medicines and treatments to cure, alleviate, and prevent diseases since man exists on earth. Nature has offered to us the most diverse, complex, unique, and unimaginable structures that no chemist could ever dream of. Hundreds of examples could be named and are well recognized that in diseases like cancer, the more important medicines come from plants, and other living organisms (Newman and Cragg, 2020). Plants had been used for viruses' treatments, as well as other diseases by the people in many countries, and several of them showed their potential against specific viruses (Taylor *et al.*, 1996; Lopez *et al.*, 2001; Mukhtar *et al.*, 2008). The literature related to studies where plant extracts are evidenced is extensive (Abad *et al.*, 1999; Vijayan *et al.*, 2004; Müller *et al.*, 2007; Faral-Tello *et al.*, 2012; Zhang *et al.*, 2014; Ordaz-Trinidad *et al.*, 2018, Guo *et al.*, 2019), also, several experimental studies have discovered that a great number of phytochemicals have favorable antiviral activities (Naithani *et al.*, 2008), however, the

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focus of this revision is to show the prospective value of identified flavonoids structure on diverse viruses, due that they look like the best natural secondary metabolites against them.

Diseases caused by a virus infection, are considered to be the most difficult to be treated, due that the virus structures that contain only small building blocks are common in all living organisms. This relationship is the reason it is hard to achieve effective medicines; it is similar to the problem with cancer, the lack of selectivity only on sick cells is the great barrier even to defeat against that disease. Usually, the antiviral drug leaders are more dangerous to the patient than to the virus. On the other hand, the easy mutability of viruses is another hard task to face on viral infections.

In this difficult time of quarantine by the COVID-19, a review of the literature of natural products with antiviral activity showed the flavonoids among natural products most effective in *in-vitro* trials on different types of viruses that attack humans.

Flavonoids are found in different organs of plants; fruit, flowers, leaf, roots, barks, stems, they are well recognized with beneficial properties, between them medical effects on several diseases. Several books and revisions have been showing over the years the diversity of structures, their sources, usefulness, and pharmacology (Tapas *et al.*, 2008; Agrawal, 2011; Kumar and Pandey, 2013; Ahmad *et al.*, 2015; Panche *et al.*, 2016; Xiao *et al.*, 2016; Karack, 2019; Khalid *et al.*, 2019; Rana and Gulliya, 2019).

The purpose of this short review is to present studies on flavonoids isolated from plants, which are assayed to treat different kinds of the virus. From the results showed in this revision, the author makes a series of inferences about the important characteristics existent in the flavonoid structures that result with antiviral activity.

Structure of flavonoids

The flavonoids are a big family of natural compounds that shared a basic skeleton with phenolic rings linked in a few standards structures. Chemically, flavonoids contain a fifteen-carbon skeleton with two benzene rings (A and B) (**Figure 1**) linked by a pyrane ring (C). They have been classified into a variety of substructures such as flavones, flavonols, flavanones, flavanonols, isoflavanones, and miscellaneous. This broad classification is based on the oxidation level of the ring C plus the substitution arrangement in the same ring. The position of the benzene substituent divides the flavonoid class into flavonoids (2-position) and isoflavonoids (3-position) (**Figure 1**). Under the same class, individuals one differ in the pattern of substitution of the A and B rings. Flavonoids also can be classified according to the class of substituent's they can present as, glycosylated, hydroxylated, methylated, acetylated, isoprenylated, and also according to the polymerization degree in biflavonoids, triflavonoids, tetra-flavonoids.

Virus and diseases

The purpose of this revision is to show a series of flavonoids that have been studied against some common viruses diseases; it is not the purpose delve into the mechanisms of action that

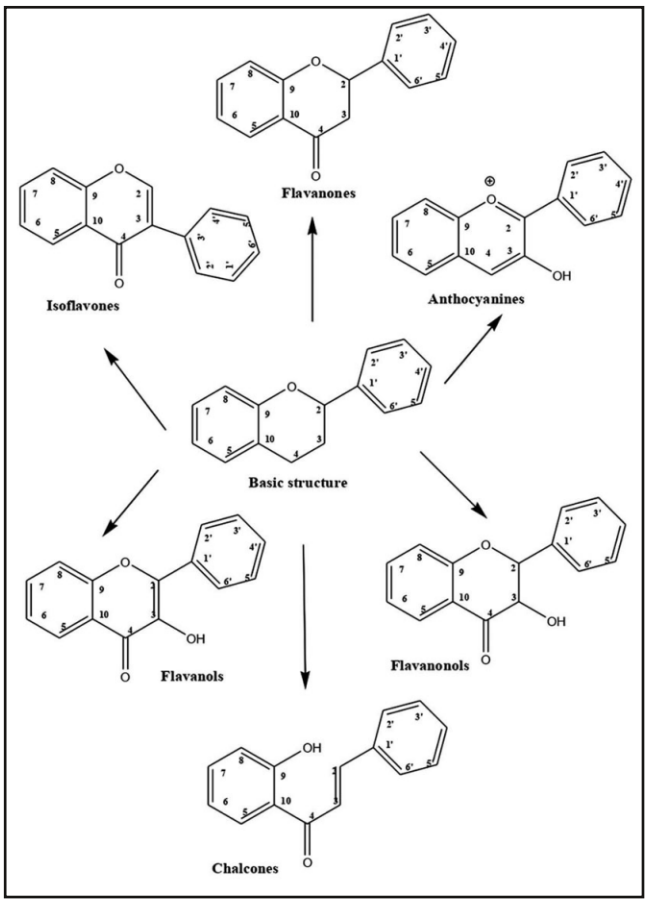

Figure 1. Basic structures of flavonoids.

may occur with different viruses, however, some recent references are included that cite this kind of studies (Anusuya and Gromiha, 2017; Bhargava *et al.*, 2019; Akher *et al.*, 2019; Jo *et al.*, 2019a,b; Lee *et al.*, 2019). It is clear also that the reader has to be aware that in this short review the known viruses or the diseases they cause cannot be named all. This section is intended to show short comments on a series of common diseases produced by viruses and try to give an idea of their importance in the worldwide population.

Dengue

The *dengue* is a worldwide public health problem, is a disease that affects millions of people around the world, especially those that live in tropical area. *Dengue* infection is produced by dengue virus (DENV), transmitted by the *Aedes aegypti* mosquito; there are four DENV genotypes recognized, DENV-1, DENV-2, DENV-3, and DENV-4 (Gibbons and Vaughn *et al.*, 2002).

The disease has several grades of severity, going from its mild form, known as classic *dengue*, to its severe form called hemorrhagic *dengue*, and dengue shock syndrome. So far the trearment is only supportive; analgesics and antipyretics are prescribed to relieve the symptoms. No effective treatments until now exist against the *dengue* virus, and its convalescence may be prolonged especially by the weaknesses that produce (WHO, 2009).

Chikungunya

Chikungunya virus (CHIKV) is an arthropod-borne alphavirus that belongs to the Togaviridae family; it is transmitted by the bite of Aedes mosquitoes. The virus is known for causing an acute febrile illness, rash, and arthralgia known as *Chikungunya* fever; it is followed by potentially chronic and debilitating arthritic symptoms that may last for months or years (Rougueron *et al.*, 2015).

Chikungunya fever is considered a tropical illness; however, millions of cases had been reported around the world including the USA, and many countries of Europe (Morens and Fauci, 2014).

Symptomatic relief is the mainstay treatment for *Chikungunya* fever, including adequate hydration, rest, and pain/fever relief preferably with acetaminophen. WHO (2009) discourages the use of aspirin and most

non steroidal anti-inflammatory drugs (NSAIDs) during the first 48 hours due to the risk of aggravating platelet dysfunction, especially in cases of possible DENV co-infection. Ocular manifestations including anterior and posterior uveitis have been treated with topical steroids and cycloplegics (Subudhi *et al.*, 2018).

Herpes

Herpes is the name of a group of viruses that cause painful blisters and sores. Under this general name they are classified depending on viruses that produce the disease: *Herpes simplex* virus type 1 (HSV-1) and type 2 (HSV- 2) are common pathogens that cause localized skin infections of the mucosal epithelia of the genitals, the oral cavity, the pharynx, the esophagus, and the eye, depending upon the type involved.

Herpes simplex virus type 1 (HSV-1)

Herpes simplex viruses (HSV-1) infect millions of people worldwide, is a highly contagious infection, which is common and endemic throughout the world. HSV-1 is mainly transmitted by oral-to-oral contact to cause oral herpes (which can include symptoms known as "cold sores"), but can also cause genital herpes. Nucleoside analogs have been the support of the clinical treatment of herpes simplex virus 1 (HSV-1). Although HSV infections are rarely life-threatening, they are associated with high morbidity, and the rashes they cause are usually quite painful.

Herpes simplex virus type 2 (HSV-2)

HSV-2 is a sexually transmitted infection. Symptoms of *herpes* include painful blisters or ulcers at the site of infection. HSV-2 infection is widespread throughout the world and is almost exclusively sexually transmitted, causing genital *herpes*, which can also be caused by *Herpes simplex* virus type 1 (HSV-1). Infection with HSV-2 is lifelong and incurable. Nucleoside antivirals, such as acyclovir, famciclovir, and valacyclovir are the most effective medications available for people infected with HSV. These can help to reduce the severity and frequency of symptoms, but cannot cure the disease; they only reduce the viral charge in the organism. Infection with HSV-2 increases the risk of acquiring and transmitting HIV infection (Fatahzadeh and Schwartz, 2007).

HIV and AIDS

HIV is a retrovirus belonging to the subfamily of *lentiviruses*. The study of these classes of viruses has been especially increased after the discovery of HIV (Sharp and Hahn, 2011). *Lentiviruses* are exogenous non-oncogenic retroviruses that cause persistent infections, leading to diseases with long incubation periods. The prefix *lenti* makes mention, exactly, to the ability of these viruses to settle in the infected organism for extended periods. They normally infect cells of the immune system (macrophages, T cells) and cause cytopathic effects in them. An important feature, lacking in other retroviruses, is their ability to infect quiescent cells. Without treatment, the infection might progress to an advanced disease stage called AIDS, one of the most important viral infections affecting humans. Immunodeficiency results in increased susceptibility to a wide range of infections, cancers, and other diseases that people with healthy immune systems can fight off. AIDS is defined by the development of certain cancers,

infections, or other severe clinical manifestations.

The human immunodeficiency virus (HIV) targets the immune system and weakens people's defense systems against infections and some types of cancer. As the virus destroys and impairs the function of immune cells, infected individuals gradually become immunodeficient.

The treatment of HIV/AIDS with medicines is called antiretroviral therapy (ART). It is recommended for everyone who has HIV. The medicines do not cure HIV infection, but they do make it a manageable chronic condition. They also reduce the risk of spreading the virus to others. HIV can be suppressed by combination ART consisting of three or more ARV drugs. ART does not cure HIV infection, but suppresses viral replication within a person's body and allows an individual's immune system to strengthen and regain the capacity to fight off infections. In 2016, WHO recommended that all people living with HIV be provided with lifelong ART, including children, teenagers, adults, pregnant and breastfeeding women, regardless of clinical status or CD4 cell count. By mid-2019, 182 countries had already adopted this recommendation, covering 99% of all people living with HIV globally (Maartens *et al.*, 2014).

Respiratory syncytial virus infection

The human respiratory syncytial virus (RSV) is one of the most common viruses to infect children worldwide and increasingly is recognized as an important pathogen in adults, especially the elderly (Schweitzer and Justice, 2020). RSV is a single-stranded, negative-strand, RNA virus belonging to the Paramyxoviridae family, and is in the genus *Pneumovirus*. RSV was discovered in chimpanzees in 1955 and subsequently confirmed to be a human pathogen shortly after that. The structure of RSV is that of a bilipid-layer-envelope surrounding a ribonucleoprotein core, with several membrane proteins, one of which functions in attachment to host cells, and one of which functions in fusion to host cells. There is only one serotype of RSV, but it is classified into two strains, "A" and "B," with differences consisting of variation in the structure of several structural membrane proteins, most especially the attachment protein influenza viruses (Schweitzer and Justice, 2020).

Treatment for RSV falls into three categories: supportive care, immune prophylaxis, and antiviral medication. The majority of RSV and bronchiolitis cases require no specific medical intervention, and many attempted treatments throughout history are ineffective. Vaccines for RSV and therapeutic interventions in RSV remain a target of intense scientific interest (Ali *et al.*, 2020).

SARS (Severe Acute Respiratory Syndrome)

Viruses that infect animals can jump from one species to another, causing a new, usually severe disease in the new host. For example, in 2003 a virus in the *Coronaviridae* family jumped from an animal reservoir, believed to be horseshoe bats, to humans, causing a highly pathogenic disease in humans called severe acute respiratory syndrome (SARS). The ability of the SARS corona virus to jump from horseshoe bats to humans undoubtedly required genetic changes in the virus. The

changes are suspected to have occurred in the palm civet since the SARS virus present in horseshoe bats is unable to infect humans directly (Vijayanand *et al.*, 2004; Sharma *et al.*, 2020).

Such newly emerged viruses often are highly infectious in humans since they have not been previously encountered by the human immune system and thus humans have no immunity against them. The corona virus that caused SARS, for example, spread quickly among humans, becoming a significant disease threat. The virus was quickly brought under control, owing to prohibitions on travel and quarantine measures. In late 2019 another type of corona virus, called SARS-CoV-2, emerged in China and spread rapidly worldwide, giving rise to a pandemic. SARS-CoV-2 caused an illness known as corona virus disease 2019 (COVID-19), which was very similar to SARS but caused significantly greater mortality, particularly among people over age 65 (Cherry and Krogstad, 2004; Yuki *et al.*, 2020).

Viruses and plants

Several studies have reported the antiviral action of medicinal plants on diverse viruses, between them *Herpes simplex* virus type 2 (HSV-2), *hepatitis B*, (HBV), HIV, *dengue*, *chikungunya*, and inclusive severe acute respiratory syndrome (SARS) (Mukhtar *et al.*, 2008). The extracts of these plants are composed of a wide diversity of secondary metabolites present in the studied species, being the flavonoids the more pervasive structures in a different genus and in general in family plants. The studies to screening flavonoids on virus come from a few years ago, but the more productive years have been the two decades of this century, Quercetin (**1**)(**Figure 2**) is a ubiquitous flavonoid present in many plants, it belongs to subclass known as flavonols; it has been studied from years ago in different diseases and pathologies, resulting very active in several health problems. Researches in 1985, assayed this compound and other flavonoids such as naringin (**2**), hesperitin (**3**), and catechin (**4**) (**Figure 2**), to see the antiviral effect *in vitro* on the infectivity and replication of *herpes simplex* virus type 1 (HSV-I), polio-virus type 1, parainfluenza virus type 3 (Pf- 3), and respiratory syncytial virus (RSV). The experiments were made in cell culture monolayers employing the technique of viral plaque reduction. Quercetin (**1**), gave the best results obtaining a concentration-dependent reduction in the infectivity of each virus (Kaul *et al.*, 1985).

From the plant *Waldsteinia fragarioides* (Michx.) Tratt., belonging to the Rosaceae, was isolated by bioassay-guided fractionation activity, against herpes simplex type 1 (HSV-1), isoquercitrin (**5**) (**Figure 2**) which caused complete suppression of plaque formation by HSV-1 virus at a concentration of 40 g/ml (Abou-Karam and Shier, 1992).

Alkanna orientalis (L.) Boiss. (Boraginaceae), is an herb used in the Sinai Peninsula to treat sore throat, a series of flavones were isolated from this species. These compounds were identified as kumatakenin (**6**), ermanin (**7**), penduletin (**8**), jaceidin (**9**), 6-methoxy-kaempferol 3-methyl ether (**10**), and isokaempferide (**11**) (**Figure 2**); all compounds were tested using a Vero cell infected with the Coxsackievirus B3. The antiviral activity expressed as IC_{50} g/ml for compounds was between 6 - 094 g/ml from 6 to 11, respectively. Chloroquine

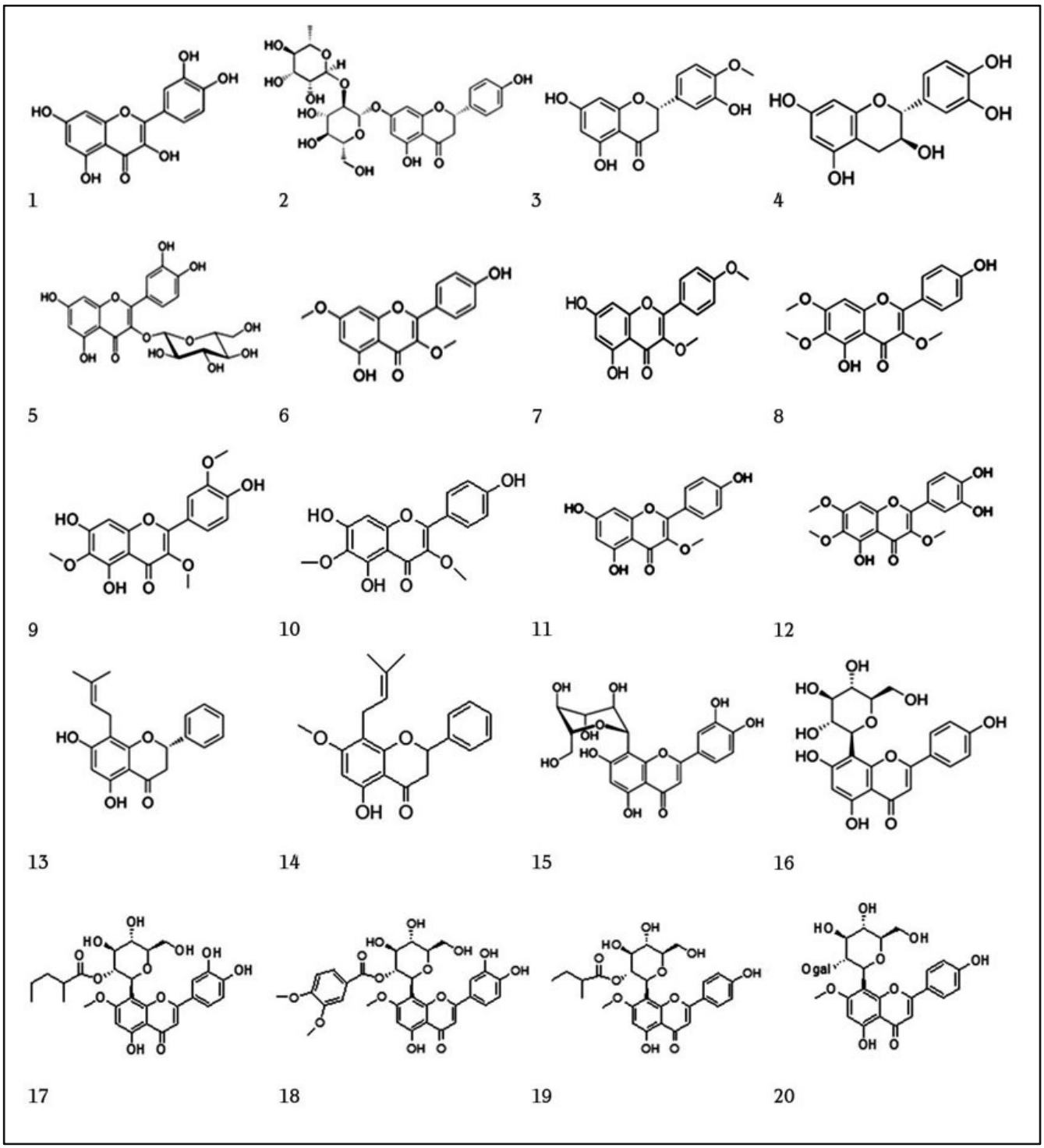

Figure 2. Flavonoid structures 1-20.

was used as a positive control (IC_{50} = 10 g/ml) (El Sohly *et al.*, 1997).

From the ancestral medicine of Australia was reported, by antiviral activity-guided fractionation, the isolation of the flavonechrysosplenol (**12**) from *Pterocaulon sphacelatum* (Labill.) Benth & Hook.f. ex F. Muell. (Asteraceae), the compound was active against poliovirus with an EC_{50} of 0.27 mg/ml (Semple *et al.*, 1999).

Over the *dengue* virus, plants and natural products have been screened, few plants of the *Tephrosia* genus, belonging to the Fabaceae family, *Tephrosia madrensis* Seem., *Tephrosia viridiflora* O.Téllez, and *Tephrosia crassifolia* Benth. were considered good candidates to test antiviral activity. From these plants, two compounds, glabranine (**13**), and 7-O-methyl-glabranine (**14**) (**Figure 2**) were isolated and tested, the results show that glabranine and 7-O-methyl-glabranine isolated from *Tephrosia* spp. had strong inhibitory effects with a dose-dependent inhibitory effect *in vitro* on the *dengue* virus replication (Sanchez *et al.*, 2000).

Chinese culture is one of the richest in medicinal plants, one of these used to treat upper respiratory infections, pharyngitis, tonsillitis, and bronchitis is *Trollius chinensis* Bunge (Ranunculaceae), the flavonoids orientin (**15**), and vitexin (**16**), were considered to evaluate the antiviral activity over the influenza type 3 (Para 3) virus. The results demonstrated that orientin and vitexin possess strong antiviral activities against Para 3 (Li *et al.*, 2002). A later study of the same plant identified two new c-glycosides flavonoids, trollisin I (**17**), trollisin II (**18**), together with two known compounds, 2-O-(2-methylbutanoyl)-isoswertisin (**19**), and vitexin galactoside (**20**) which were screened against antiviral activity on influenza virus A; only compound 19 (**Figure 2**) showed a weak activity (Cai *et al.*, 2006).

The Chinese pharmacopeia included several species of *Morus* genus from the Moraceae family as a series of plants used for the treatment of inflammatory and respiratory diseases. Numerous species of them are rich in flavonoids, one of them is *Morus alba* L. from which were isolated seven prenylated flavones, moralbanone (**21**), kuwanon S (**22**), eudraflavone B (**23**) cyclomorusin A (**24**), hydroperoxide-oxydihydromorusin (**25**), and leachianone G (**26**) (**Figure 3**); all these compounds were tested against *herpes simplex* virus type 1 (HSV-1). The results showed strong antiviral activity of leachianone G with an IC_{50}=1.6 g/ml, while the weak activity was found with mulberroside C (IC_{50}=75.4 g/ml) (Du *et al.*, 2003).

Caesalpinia pulcherrima (L.) Sw. (Leguminosae) is a common medicinal herb from the traditional medicine of Taiwan used to treat different disorders health, including bronchitis and malaria. The major flavonoid isolated from this plant was quercetin (**1**), this was tested in a series of herpes viruses (HSV-1, HSV-2), and adenoviruses (ADV-3, ADV-8, ADV-11), quercetin exhibited a broad antiviral activity, the strongest value was against ADV-3 activity (EC_{50} = 24.3 g/L) (Chiang *et al.*, 2003, Lyu *et al.*, 2005).

Another plant of the vast Chinese medicinal plants is *Elsholtzia rugulosa* Hemsl. (Lamiaceae), this plant is rich in flavonoids, the following ones, apigenin (**27**), luteolin (**28**), apiin (**29**), galuteolin (**30**) and luteolin 3'-glucuronyl acid methyl ester (**31**) (**Figure 3**), were isolated and submitted to *in vitro* assays to test their activity against anti-influenza virus NAs. Results of these experiments show that all tested compounds display anti-influenza virus activity *in vitro*, being the best one apigenin with IC_{50} = 1.43 g/ml (Liu *et al.*, 2008).

Stellera chamaejasme L. (Thymelaeaceae), is considered a toxic plant,

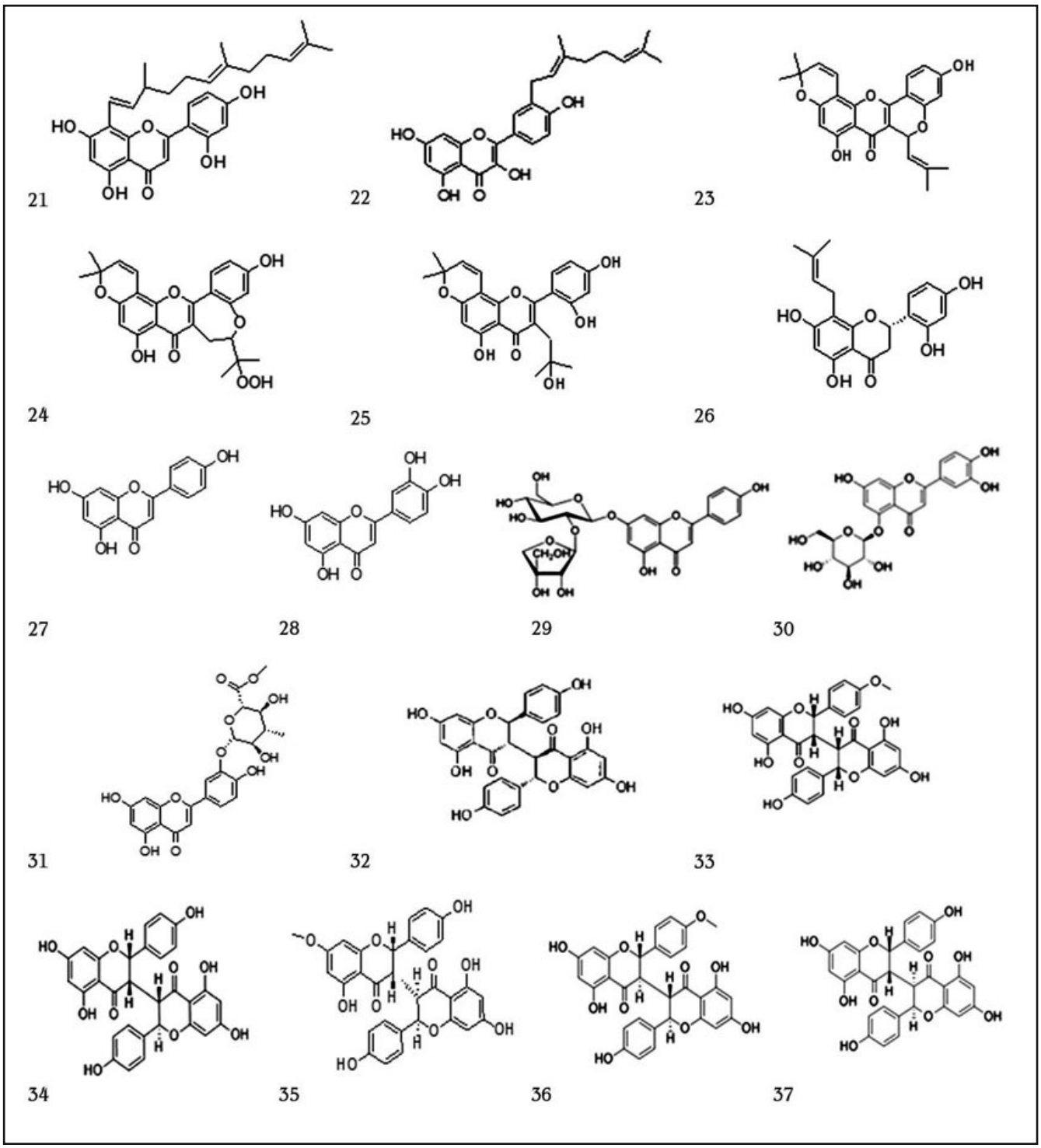

Figure 3. Flavonoid structures 21-37.

however, is used with many medical purposes between them to treat skin ulcers and tuberculosis. The phytochemical study of it led to the isolation of biflavonoids and flavonoids, isosikokianin A (**32**), sikokianin A (**33**), ruixianglangdusu A (**34**), 7-methoxyl-neochamaejasmin A (**35**), sikokianin C (**36**), isoneochamaejasmin A (**37**), chamaechromone (**38**), apigenin (**27**),

quercetin (**1**), rutin (**39**) (**Figures 3 and 4**). All these compounds were assayed to verify anti-HBV activities *in vitro*, resulting in that iskokianin A, chamaechromone, and quercetin, at 0.2 mmol/ml, exhibited potent antiviral activities inhibiting HBsAg secretion by 71.9, 34.0, and 64.3%, respectively (Yang and Chen, 2008).

Ficus benjamina L. (Moraceae), a species of wide distribution in Asia, is considered an ornamental plant very resistant to several plant viruses. A group of researches decided to investigate the secondary metabolites for antiviral activity present in the leaves of *F. benjamina*, due to this resistant. A series of compounds were isolated, between them, three common flavones, quercetin-3-O-rutinoside (**39**), kaempferol-3-O-rutinoside (**40**), kaempferol-3-O-robinobioside (**41**) (**Figure 4**). The inhibition of *herpes simplex* virus 1 and 2 (HSV-1/2), and varicella-zoster virus (VZV) *in vitro* was assayed, the three flavones showed strong inhibition, the compound 41 gave the highest antiviral efficiency, also with a high selectivity index (SI), compared to the standard antiviral drug acyclovir (Yarmolinsky *et al.*, 2012).

A plant with distribution in the Asiatic continent is *Mosla scabra* (Thunb.) C.Y.Wu & H.W.Li, belonging to Lamiaceae, is used as antipyretic, chronic bronchitis inflammation, an antiviral drug for lung diseases. In a study to verify the antiviral activity, the compounds isolated from the plant were evaluated against influenza viruses; the following flavonoids were screened, 5-hydroxy-6,7-dimethoxyflavone (**42**), 5-hydroxy-7,8-dimethoxyflavone (**43**), apigenin (**27**), and acacetin (**44**) (**Figure 4**). The four flavonoids showed antiviral activity, ribavirin was used as a control drug (Wu *et al.*, 2010).

From the plant *Abelmoschus manihot* (L.) Medik. (Malvaceae) was found as the major secondary metabolite quercetin-3-O-β-D-galactoside (**45**) commonly known as hyperoside; it was evaluated on duck hepatitis B virus (DHBV) infection the experiments were realized *in vitro* and also *in vivo* using the DHBV-DNA-infected duckling model. The results suggested that hyperoside is a strong inhibitor of HBsAg and HBeAg secretion in 2.2.15 cells and DHBV-DNA levels in the HBV-infected duck model. The conclusions obtained after analysis of results indicated that hyperoside is a strong inhibitor of HBsAg and HBeAg secretion in 2.2.15 cells and DHBV-DNA levels in the HBV-infected duck model (Wu *et al.*, 2007).

A series of known flavonoids were selected to investigate their activity on the chikungunya virus (CHIKV), baicalein (**46**), fisetin (**47**), and quercetagetin (**48**). Ribavirin was used as a control compound because it is recognized with anti-CHIKV activity. The three compounds gave good antiviral activity being baicalein the best one with an IC_{50} =3.243 g/ml, quercetagetin gave IC_{50} of 13.53 g/ml, and the researches indicated that however, fisetin showed antiviral activity it was cytotoxic on the assayed cells (Lani *et al.*, 2016).

In a similar work six flavonoids isolated from three medicinal plants used in Turkish folk medicine, *Galium fissurense* Ehrend. & Schönb.-Tem. (Rubiaceae), *Viscum album* L. subsp. *album* (Santalaceae), and *Cirsium hypoleucum* DC. (Asteraceae), were assessment against *Herpes virus* simplex type-1 (HSV-1) and Parainfluenza-3 virus.

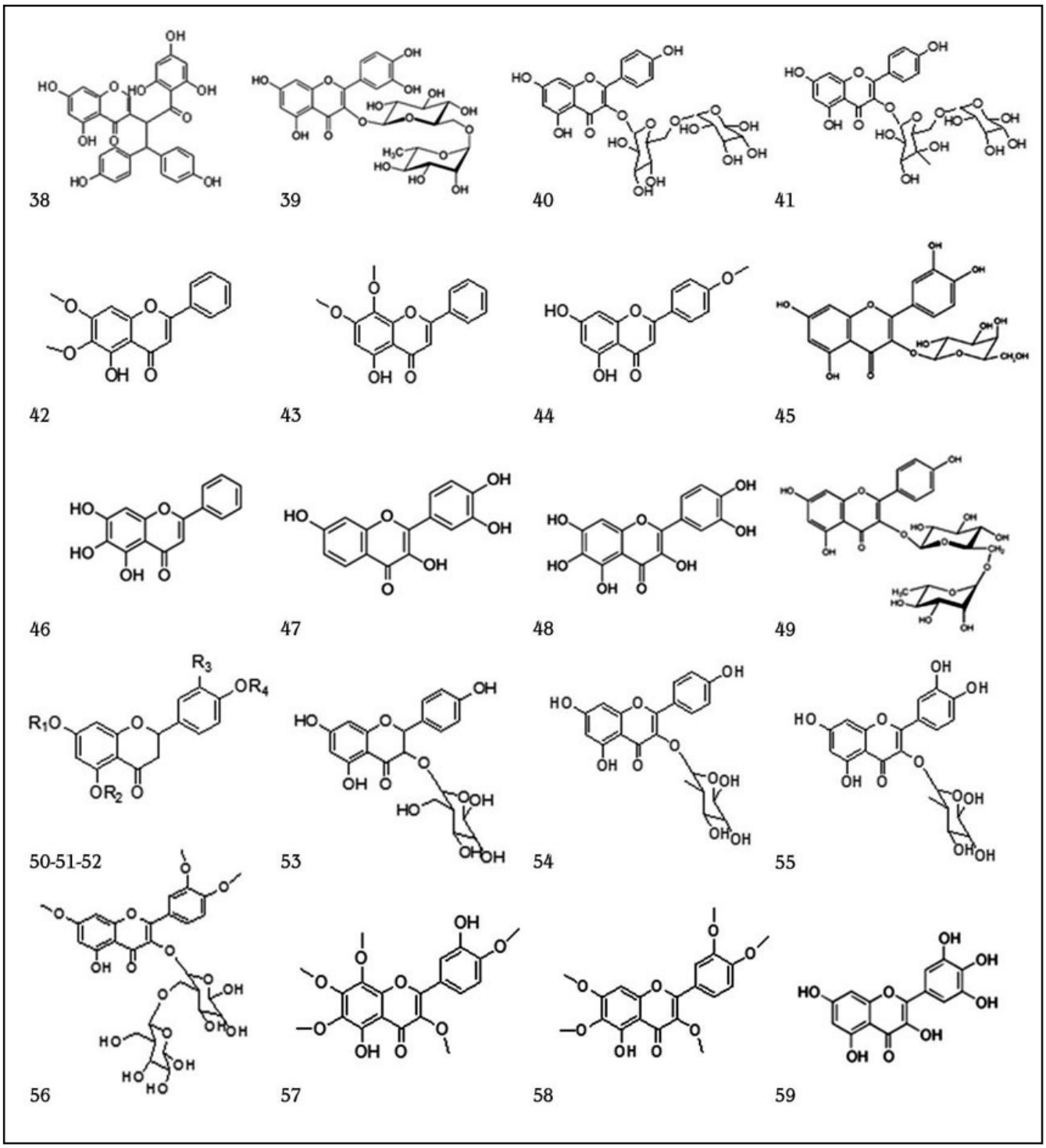

Figure 4. Flavonoid structures 38-59.

50 = R_1= R_2= CH_3, R_3= H, R_4 = Glu
51 = R_1 = R_2 H, R_3 = OH, R_4 =Glu
52 = R_1 = Glu, R_2 = R_3 = R_4 = H

Figure 4 show the following flavonoids: Rutin (**39**), nicotiflorin (**49**), 5,7-dimethoxyflavanone-4'-O-β-*D*-glucopyranoside (**50**), 5,7-dimethoxyflavanone-4'-O-{2''-O-(5'''-O-transcinnamoyl)-β-*D*-apiofuranosyl}- β-*D*-glucopyranoside (**51**), 5,7,

3'-trihidroxyflavanone-4'-O-β-D-glucopyranoside (**52**) and naringenin-3-O-β-D-glucopy ranoside (**53**). These six flavonoids showed significant antiviral activity; the compound 52 offered a remarkable result against HSV-1 with values in the order of acyclovir. On the other hand, rutin (**39**), and 52 gave the best values on RNA-virus PI-3, which were comparable to oseltamivir (Orhan *et al.*, 2010).

Scutellaria baicalensis Georgi (Lamiaceae), named "the golden herbs of the Chinese medicinal plants", it is known by the name *huáng-qín*. The dried roots of *S. baicalensis* constitute as one of the most important Chinese herbal medicines has been used for thousands of years, to treat many diseases (mainly the roots) ranging from the common cold and respiratory infections to dysentery, hypertension, hemorrhages, insomnia, and inflammation. The plant is already used as a supplement for its claimed anti-diabetic and anti-obesity effects (Zhao *et al.*, 2019). This plant is rich in flavonoids being baicalein (**46**) the major metabolite; this compound was evaluated against different stages of the *dengue* virus type 2 (DENV-2) replication, on Vero cells. The results demonstrated that baicalein exhibited potent anti-dengue activity *in vitro* with an IC_{50} =5.39 g/ml, and high selectivity (Zandi *et al.*, 2012).

Eucalyptus is a large genus of Myrtaceae family, include more of 900 species, many of these species have been reported with medicinal properties to treat numerous diseases. From a polar extract of *Eucalyptus citriodora* Hook., were isolated three known flavonoid glycosides, kaempferol-3-O-β-D-glucopyranosyl (1-2)-α-L-rhamnoside (**40**), kaempferol-3-O-α-L-rhamnoside (**54**), quercetin-3-O-α-L-rhamnoside (**55**), and the new citrioside C (**56**) (**Figure 4**). The antiviral activity of these compounds was evaluated against the respiratory syncytial virus (RSV). From all of them, 56 showed significant antiviral activity with an IC_{50} value of 1.9 g/mL and selectivity index (SI) value of 9.8, comparable to that of ribavirin, the other compounds exhibited weak activity (Zhou *et al.*, 2014).

Marcetia taxifolia (A.St.-Hil.) DC. (Melastomataceae), is a plant from the Venezuelan Amazonas, used for dysentery, leucorrhea, diarrheas and to treat skin diseases. In a phytochemical study of this species were isolated a series of metabolites, being the majors one triterpenes and flavonoids (Baptista *et al.*, 2016). These flavonoids were evaluated against the *Hepatitis B* virus (HBV), *Herpes simplex* virus type 1 (HSV-1), and Poliovirus type 1 (PV-1). The compounds 5,3'-dihydroxy-3,6,7,8,4'-pentamethoxyflavone (**57**), 5-hydroxy-3,6,7,3',4' pentametho xyflavone (**58**), myricetine (**59**), and myricetin-3-α-O-rhamnosil (1→6)-α-galactoside (**60**) (**Figures 4 and 5**) were evaluated. The methoxyflavones 57 and 58 exhibited activity with an EC_{50} near to 1 M against PV-1. An inhibitory effect of 90% of 57 and 60% of 58 against HSV-1 was observed at a concentration of 10 μM (Ortega *et al.*, 2019). Previous reports of the antiviral activity of all the flavonoids obtained from this species also showed by computational studies the essential parts of the myricetin derivatives to have antiviral activity (Ortega *et al.*, 2017a,b).

Some flavonoids from different sources are usually taken to explore their potential against viral diseases. Zandi *et al.* (2012) were interested to examine the anti-dengue virus properties

of quercetin (**1**), hesperetin (**3**), naringin (**2**), and daidzein (**61**). The effects of each compound were evaluated against different stages of dengue virus replication DENV-2, the results obtained demonstrated that only quercetin exhibited significant anti DENV replication properties (Zandi *et al.*, 2011a, 2011b).

Pistacia chinensis Bunge (Anacardiaceae), the common pistachio, is a plant from the Chinese ethnomedicinal plants, it is considered with anti-hepatitis effects. From the aerial parts were isolated eight flavonoids, apigenin (**27**), diosmetin (**62**), myricetin (**59**), apigenin-7-O-β-glucoside (**63**), quercetin-3-O-β-glucoside (**64**), myricetin-3-O-α-rhamnoside (**65**), myricetin-3-O-β-glucuronide (**66**), and quercetin 3-O-β-glucoside-7-O-α-rhamnoside (**67**) (**Figure 5**). These compounds were screened against *Hepatitis C* Virus (HCV). The results indicated that apigenin and diosmetin reduced significantly HCV infection, whereas myricetin 3-O-α-rhamnoside and myricetin 3-O-β-glucuronide did not affect HCV infection (Rashed *et al.*, 2014).

In a different study, several flavonoids were investigated to compare their antiviral activity, these compounds have variations in structure regarding hydroxylation and methylation patterns at the 3, 3′, and 4′ position in the flavonoid skeleton. Quercetin (**1**), 3′-methoxyquercetin (**68**), eryodictiol (**69**), diosmetin (**62**), and kaempferol (**70**) (**Figure 5**). Isorhamnetin (3′-methoxyquercetin) showed the best results, suggesting that the methyl group on the B ring of isorhamnetin made a big difference in the strong antiviral activity that it gave compared with the other assayed flavonoids (Dayem *et al.*, 2015); this result agrees with anticancer assays with methylated flavonoid (Walle *et al.*, 2007). These results suggest that the methyl group on the B ring of the carbon skeleton of isorhamnetin could be the reason that it showed the best antiviral activity among the tested flavonoids against the influenza virus.

A mixture of two derivatives of quercetin (**1**), avicularin (**71**), and guajaverin (**72**) was obtained from the species *Psidium guineense* Sw. (Myrtaceae) collected in Venezuela. The mixture exhibited activity against HIV-1 *in vitro* with an IC_{50} of 8.5 g/mL, and compared with quercetin (**1**) (IC_{50}= 53 g/mL), the combination gave best results (Ortega *et al.*, 2017c).

Chalcones are a class of very active flavonoids under the flavonoids family. A study directed to observe the antiviral capacity of eight different structures, flavones, flavanones, flavonols, and chalcones included four of them, 2′,3′,4′-trihidroxychalcone (**73**), 2,2′,4′-trihydroxychalcone (**74**), butein (**75**), and naringenin chalcone (**76**) (**Figure 5**). The results indicated that these structures have low activity on the assayed cytomegalovirus (HCMV), compared with the compounds baicalein (**46**), quercetin (**1**), quercetagetin (**48**), and naringenin (**2**) (Evers *et al.*, 2005; Cotin *et al.*, 2012).

A group of unique flavonoids was isolated from *Houttuynia cordata* Thunb., belonging to the family Saururaceae, used in China to treat fever, reduce swelling, drain pus, and to promote urination. The compounds named as Houttuynoids A-E (**77-81**) (**Figure 5**) was assayed against *Herpes simplex* virus (HSV) and showed potent antiviral action. The results showed those 77-81

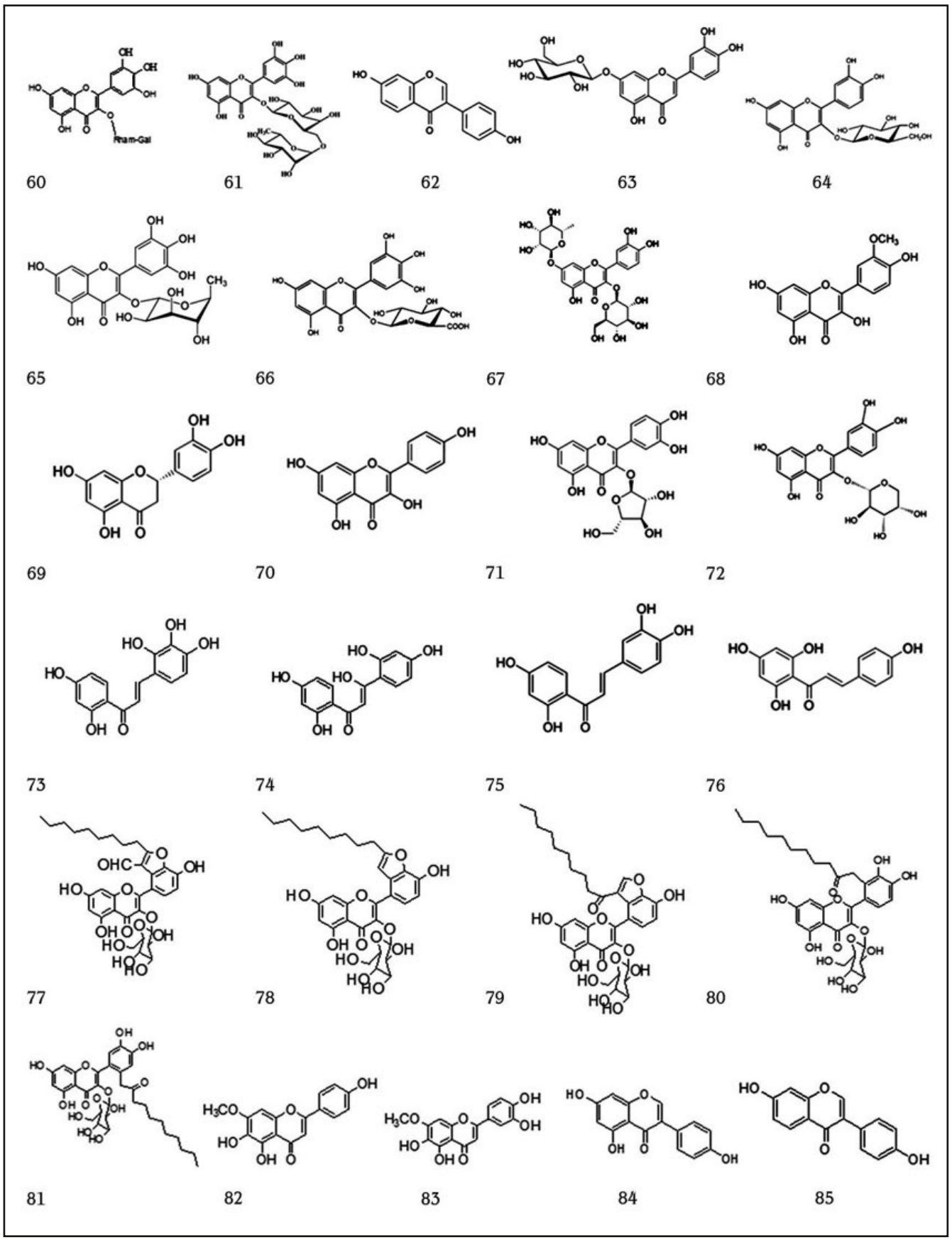

Figure 5. Flavonoid structures 60-85.

exhibited potent inhibitory activities against HSV, with respective IC_{50} values of 23.50, 57.71, 50.75, 59.89, and 42.03 μM (Chen *et al.*, 2012).

Two flavones sorbifolin (**82**) and pedalitin (**83**) isolated from *Pterogyne nitens* Tul., a unique species of this genus belonging to Fabaceae, is a medicinal plant used in Argentina for the treatment of helminthic infestations. These two flavonoids showed inhibition of the *Hepatitis C* virus (HCV) with values of 45.0% and 78.7% respectively at non-cytotoxic concentrations (Shimizu *et al.*, 2017). Genistein (**84**) a common isoflavone found in many plants of Fabaceae showed antiviral activity against *herpes* B virus (LeCher *et al.*, 2019).

Several flavonoids, apigenin (**27**), luteolin (**28**), kaempferol (**71**), formononetin (**85**), isorhamnetin (**68**), and penduletin (**8**), assayed against the enterovirus 71 (EV71) infection, gave promising results (Dai *et al.*, 2019). A review concern to the antiviral mechanisms of flavonoids, mainly against enterovirus A-71 (EV-A71), showed interesting results (Lalani and Poh, 2020).

Conclusions

Natural products remain an invaluable source of new drugs. In the case of antiviral drugs, the most interesting ones considered in this review are the flavonoids; they are presented as important candidates to be considered due to their availability, and they claimed low side-effects. The biological activity of any chemical compound is inherent in its structure; features such as configuration, number and class of substituent, and the metabolism of this compound are without a doubt important to reveal pharmacological effects. In the case of flavonoids is evident that their activities, like other chemical types, are structure-dependent; is necessary to observe the number and position of hydroxyl groups, the class of flavonoid, especially the aglycone state oxidation, for example, if is flavonol, flavone, flavanone; also, is important to look the glycosyl units, the pattern of substitution, and the nature of substituent. The analysis of the results offered in the different works shown above indicates that the antiviral activity of the specific structures depend considerably on the virus class. For example, in many viruses the non-glycosidic flavonoids showed the best results; however, in the HIV looks important the glycosyl units present in the compounds to show antiviral activity. Some authors had been inferred these characteristics in previous reports, and several of them suggest that this fact is due to the difference of mechanisms inhibition on each virus; specific inhibition of certain enzymes should be involucrate and the linkage with glycosyl units results important. Related to the class of flavonoids structure, flavones and flavonols are the more active. From the 85 flavonoid structures, exposed in this review (**Figures 2-5**), 30% of them belonging to the flavones, and 22% to flavonols. In summary, from this 52%, half of them are glycosylated. The sugar present in the flavonoids are diverse, arabinose, galactose, rhamnose, and polysaccharides of them are found in many compounds, but it is evident that glucose is the more common, and also the combination glucose-rhamnose knows like rutinoside; the name rutinoside is because it is the saccharide present in rutin (**39**), one of the ubiquitous flavonols in nature.

Concerning this point, the results showed here indicate that C-glycosylated flavones are not very active, unlike O-glycosylated flavones. The active flavanones are also the glycosylates one. In general, all classes of flavonoids with methoxy groups in their structures present good antiviral activity. Few isoprenylated compounds result actives. As a final point, the biflavonoids tested in these experiments showed no activity, although some biflavones are known to be active in certain types of viruses. Finally, this short review is intended to be a motivation for researchers that continue to consider flavonoids as interesting antiviral drugs that can be tested, hopefully with success, on this new COVID-19 coronavirus.

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