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Review Article

Antiviral Activity of Various Glycoside Compounds

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Abstract
Glycoside compounds consist of several groups of important compounds, such as flavonoids and alkaloids. Sometimes the glycosidic residues in glycoside compounds have an important role in their activity, but some can only increase their pharmacokinetic parameters. However, recent developments in molecular glycobiology have gained a greater understanding of the activity of aglycones vs. glycosides. We use data from 50 articles that discuss the activity of flavonoid glycoside compounds against the herpes simplex virus, influenza virus, and Human Immunodeficiency Virus, the activity of cardiac glycoside compounds against herpes simplex virus, influenza virus, and Human Immunodeficiency Virus. Several glycoside compounds, such as flavonoid glycosides and Cardiac glycosides, have been known to have antiviral activity, including against Herpes Simplex Virus, Influenza, and Human Immunodeficiency Virus. Still, until now, the potential for various Glycoside compounds as antivirals has yet to be widely studied, although many biologically active compounds are in the form of glycosides. Further studies regarding the antiviral activity of this glycoside compound are needed to determine the possibility of this compound as an alternative for treating diseases caused by viruses.
Keywords: Cardiac glycosides, Flavonoid glycosides, HIV, HSV, Influenza

Aktivitas Antivirus Berbagai Senyawa Glikosida

Abstrak
Senyawa glikosida terdiri dari beberapa kelompok senyawa penting, seperti flavonoid dan alkaloid. Terkadang residu glikosidik dalam senyawa glikosida mempunyai peran penting dalam aktivitasnya, namun ada pula yang hanya dapat meningkatkan parameter farmakokinetiknya. Namun, perkembangan terkini dalam glikobiologi molekuler telah memperoleh pemahaman yang lebih baik tentang aktivitas aglikon vs. glikosida. Kami menggunakan data dari 50 artikel yang membahas mengenai aktivitas senyawa flavonoid glikosida terhadap virus herpes simplex, virus influenza, dan Human Immunodeficiency Virus, aktivitas senyawa glikosida jantung terhadap virus herpes simplex, virus influenza, dan Human Immunodeficiency Virus. Beberapa senyawa glikosida, seperti flavonoid glikosida dan glikosida jantung, telah diketahui memiliki aktivitas antivirus, termasuk melawan Virus Herpes Simplex, Influenza, dan Human Immunodeficiency Virus. Namun hingga saat ini potensi berbagai senyawa Glikosida sebagai antivirus belum banyak diteliti, meskipun banyak senyawa aktif biologis yang berbentuk glikosida. Penelitian lebih lanjut mengenai aktivitas antivirus dari senyawa glikosida ini diperlukan untuk mengetahui kemungkinan senyawa ini sebagai alternatif pengobatan penyakit yang disebabkan oleh virus.
Kata Kunci: Flavonoid glikosida, Glikosida jantung, HIV, HSV, Influenza

1. Introduction

Diseases caused by viruses are one of the major threats to the human population, and viruses are also a major cause of respiratory tract infections in children. The existence of disease outbreaks caused by viruses has grown rapidly in recent years and has caused a significant impact on human life, including the sudden increase in the death rate. Over the past two decades, there have been seven epidemics of disease caused by viruses and caused enormous economic losses in the world.[1,2,3] Diseases caused by viruses include Herpes Simplex Virus (HSV) infection, Influenza, and Human Immunodeficiency Virus (HIV).

Herpes simplex virus (HSV) is a global infection.[4] There are two HSV types: HSV type 1 and HSV type 2. HSV type 1 can be transmitted orally and usually causes keratitis and encephalitis. HSV type 1 can also become a genital infection through oral-to-genital contact, but reactivation is lower than HSV type 2.[5,6,7,8] More than 90% of people have one or both of these viruses. HSV-1 is the more common virus, with 65% of people in the United States having antibodies to HSV-1. HSV-2 infection is much rarer than HSV-1 infection, with 15%–80% of people in various populations infected.[9]

Influenza is characterized by highly contagious acute respiratory syndrome because it causes significant morbidity and mortality worldwide by various types of influenza viruses. Seasonal influenza is a mild but severe illness and a significant cause of death in susceptible individuals. It is a common cause of respiratory infections during winter in the Northern and Southern Hemispheres. Still, it can also occur year-round in tropical and subtropical areas and causes 3 million up to 5 million cases of severe disease and 250,000 to 500,000 deaths worldwide each year.[10,11,12] In addition, many strains of influenza cause pharmacological resistance to available antiviral drugs, and new anti-influenza treatments have become a substantial concern in recent years.[13]

HIV is a virus that attacks cells that help the body fight infection, especially white blood cells called CD4 cells, so a person is more susceptible to infections and other diseases leading to the AIDS stage. This virus spreads through contact with certain bodily fluids of humans with HIV[14] by around 15 million people, including 14 million adolescents and adults infected with HIV and 1 million babies born to infected mothers. Every day as many as 5000 people are infected with HIV.[15,16,17]

Traditionally, viral infection control has relied on personal protection with infection control measures, mass vaccination, case isolation, and quarantine of individual contacts because specialized antiviral treatment is generally unavailable for most viral infections.[18] However, antiviral drugs play a crucial role in today's life by suppressing virus transmission and helping the host to survive. Furthermore, understanding the kinetics and dynamics of antiviral drugs helps control the virus during a pandemic, as the host can be exposed to infection again. In addition, Antivirus is effective in cases where no vaccine is available such as the Influenza virus.[19]

Traditional medicine using natural ingredients has proven to contain antiviral activity. Thus screening plants as antivirals and ethnopharmacological approaches can increase the possibility of identifying new bioactive compounds that can be used as antiviral drugs.[2,20,21,22,23] Until now, the potential of various glycoside compounds as antivirals have not been studied, even though many bioactive compounds are in the form of glycosides.[24,25,26,27] A glycoside is any molecule wherein a sugar group is bonded employing its anomeric carbon to another group via a glycosidic bond, and glycosides may also be linked by an O-glycosidic bond. The glycone can consist of a single sugar group (monosaccharide) or some sugar companies (oligosaccharide). The aglycone consists of several important compounds, such as hormones, flavonoids, alkaloids, etc. Sometimes glycosidic residues play an important role in their activity but sometimes only increase their pharmacokinetic parameters. Due to recent developments in molecular glycobiology,

a greater understanding has been gained of aglycone vs glycoside activity and it becomes possible to develop new glycol drugs that are more active or more effective.[17]

2. Method

The literature used as a source of scientific data is 52 articles, with 20 main articles and 32 supporting articles from google scholar, MDPI journal, and ScienceDirect journal. The inclusion criteria used were articles discussing the activity of flavonoid glycoside compounds against herpes simplex virus, influenza virus, and Human Immunodeficiency Virus, and the activity of cardiac glycoside compounds against herpes simplex virus, influenza virus, and Human Immunodeficiency Virus. A literature search using the keywords "antiviral activity of flavonoid glycosides" and "antiviral activity of cardiac glycosides". The internet was used to look for facts and reference materials supporting the data. The scheme of article selection is shown in Figure 1.

3. Result and Discussion

3.1. Flavonoid Glycoside

Generally, the OH groups in phenolic compounds are good targets for biological glycosylation. Many phenolic compounds are present in the glycosylated form. One of the polyphenolic glycoside compounds is the flavonoid glycosides, the largest group. The main structure of flavonoid glycosides is shown in Figure 2. Until 1986, flavone and flavonol glycoside with 900 types of compounds were known. From January 1995 to December 1997, more than 160 new glycoside compounds were known as functional components of traditional medicine. In 2020, more than 8000 flavonoids were reported, including the class of flavonoid glycosides.[28] Several flavonoid glycoside compounds have been tested for their antiviral activity.[29,30,31]

3.2. Anti Herpes Activity of Flavonoid Glycoside

Quercetin 3-O-rutinoside, kaempferol 3-O-rutinoside, and kaempferol 3-O-robinobioside from the Ficus benjamina plant are known to have anti-HSV with EC_{50} 1.5 µM for Quercetin 3-O-rutinoside, EC_{50} 3.0 µM for kaempferol 3-O-rutinoside and EC_{50} 0.9 µM for kaempferol 3-O-robinobioside. Still, the mechanism of action of these three types of flavone glycosides is under investigation. However, preliminary results indicate a different mechanism than with acyclovir.[33] Furthermore, quercetin can interfere with the transcription and translation of viral proteins.[33] Besides having influenza antiviral activity, the compounds *p*-alkylphenyl-6-halogeno-6-deoxy-*β*-D-glucopyranoside and 2-deoxy-D-glucose (2-deoxy-D-arabino-hexose) are

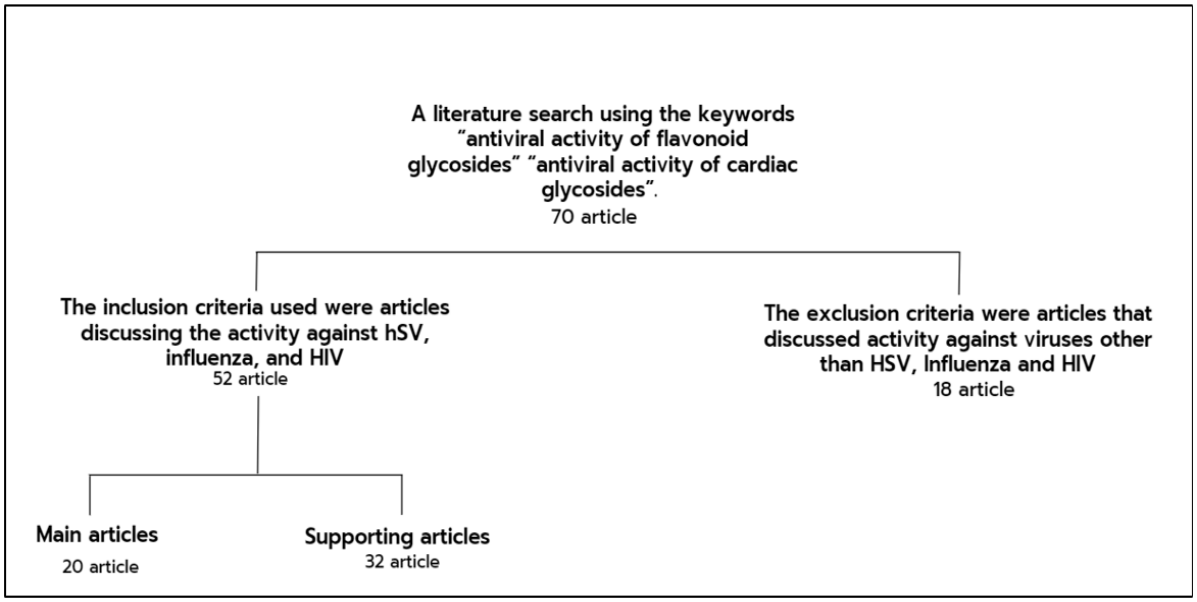

Figure 1. The article selection diagram

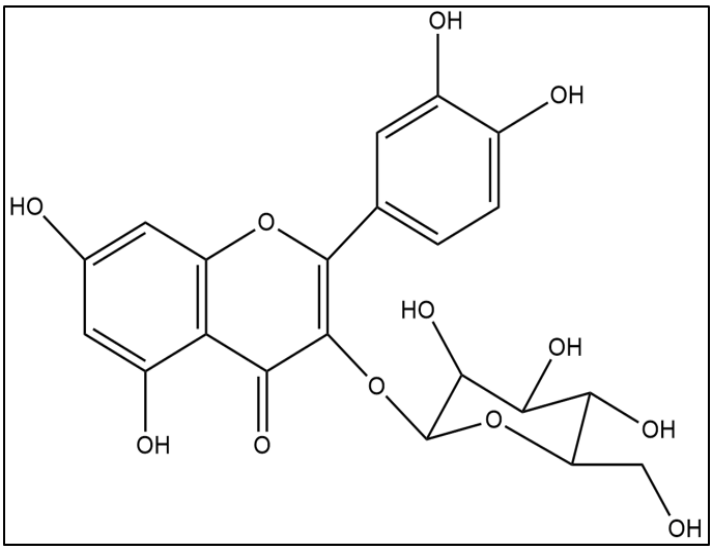

Figure 2. Main structure of flavonoid glycosides.[32]

also known to have anti-HSV activity with inhibit the biosynthesis of glycoprotein.[34,35] Three flavone glycosides derived from *Ficus benjamina* leaves, namely quercetin 3-O-rutinoside, kaempferol 3-O-rutinoside, and kaempferol 3-O-robinobioside, showed antiviral efficiency. They were flavonoid glycosides that were very effective against HSV-1 with a selectivity index (SI) of 266, 100, and 666, respectively. They were more selective than their aglycones, and kaempferol 3-O-robinobioside showed SI similar to that of acyclovir (ACV), the standard anti-HSV drug.[33]

3.3. Anti Influenza Virus of Flavonoid Glycoside

Flavonoid glycoside has two compound types, 2-O-(2 –methylbutanoyl)isoswertisin and vitexin galactoside, isolated from *Trollius chinensis*. In the antivirus test, 2 -O-(2 -methylbutanoyl)isoswertisin compound was known to be quite active against the influenza A virus with an IC_{50} value of 74.3 µg/mL.[36] Three flavonol glycosides have been isolated from *Z. piperitum* leaf fraction. The isolated compound structures were identified as quercetin 3-O-β-D-galactopyranoside, quercetin 3-O-α-L-rhamnopyranoside, and kaempferol 3-O-α-L-rhamnopyranoside. The anti-influenza virus activity of these isolates was evaluated using the plaque reduction test against the influenza A/NWS/33 (H1N1) virus.[37] Then a neuraminidase inhibition test was also performed on the influenza A/NWS/33 virus. The three isolated compounds showed antiviral activity against the influenza A virus *in vitro.* The compound has an inhibitory activity against neuraminidase.[37] This enzyme was thought to play a role in releasing new virus particles from infected cells by cleavage of sialic acid moieties on target cell receptors. However, the neuraminidase inhibitory activity of the isolated compound was weaker than the oseltamivir phosphate (a drug with a specific neuraminidase inhibitor). Therefore, it indicated that the flavonol glycosides of *Z. piperitum* do not have potent anti-influenza activity. However, it can be regarded as a neuraminidase inhibitor and antiviral agent against the influenza A virus.[37] The study of the relationship between structure and activity revealed that phenyl glucoside compounds exhibit potent antiviral effects. The *p*-alkylphenyl-6-halogeno-6-deoxy-*β*-D-giucopyranoside is the most potent antiviral agent against enveloped viruses like the influenza virus,[34] and the 2-deoxy-D-glucose (2-deoxy-D- arabino-hexose) compound is an inhibitor biosynthesis of glycoprotein, reported to have antiviral activity against viral envelopes such as influenza.[35]

3.4. Anti HIV of Flavonoid Glicoside

A compound from the leaves and twigs of *Ochna integerrima*, namely 6-γ,γ-

dimethylal-lyltaxifolin 7-O-beta-d-glucoside is known to show anti-HIV-1 activity in the syncytium assay with EC_{50} 44,2 µg/mL.[38] Herbacitrin is a compound belonging to the flavonoid 7-O-glycoside class derived from *Gossypium hirsutum*. It can inhibit HIV-1 replication dominantly by targeting the HIV-1 integrase enzyme.[39] The glycosylated metabolites obtained from Marcetia taxifolia, namely myricetin 3-rhamnoside and myricetin 3-(6-rhamnosylgalactoside), were reported that have HIV antiviral activity. In vitro study showed the EC_{50} values of 120 µM and 45 µM, respectively. The glycosylated part can increase the anti-HIV-1 activity of myricetin compounds by supporting the internalization of flavonoids into cells. Inhibition of HIV-1 reverse transcriptase is a possible mechanism of action of this compound.[40,41] In addition, the compound quercetin 3-O-(6≤-feruloyl)-β-D-galactopyranoside isolated from Viscosum polygonum is known to show anti-HIV-1 activity with an IC_{50} of 25.61 mg/mL.[42] A list of all flavonoid glycosides with antiviral activities was reported in Table 1. The chemical structure of flavonoid glycoside shown in Figure 3.

3.5. Cardiac Glycoside

Cardiac glycosides (CGs) are one of the natural compounds consisting of the five-ring cardenolide aglycone called genin. The structure is shown in Figure 4, with the monosaccharide numbers attached in Table 2.[43]

These steroid compounds are usually from isolated plant material (digitoxin, strophanthidin), but they are also found in higher mammals as adrenal cortical hormones. Ouabain is the primary function of CGs to inhibit the activity of Na^+/K^+ ATPase (sodium-potassium pump), the enzyme responsible for transversely translocating Na^+ and K^+ ions in cell membranes using ATP as its energy force. To maintain intracellular ion homeostasis and to create a positive inotropic effect in heart failure disease.[43] Subsequently, CGs began to be developed as potential antiviral agents by targeting host cell proteins to reduce resistance to antiviral therapy and became an auspicious approach to the treatment of human viral infections.[13]

3.6. Anti Herpes Simplex Virus of Cardiac Glycoside

Apart from the primary function of CGs as cardiac drugs, some CGs are also known to have antiviral activity. CGs such as G-strophanthidin are known to inhibit herpes simplex virus by inhibiting viral gene expression.[13,44] Ouabain reversibly decreases viral yield by up to 100-fold

Table 1. Antiviral activities of Flavonoid Glycoside Compound and Antiviral activities of Cardiac Glycosides Compound

Virus	Flavonoid Glycoside			Cardiac Glycosides		
		Mechanism of action	Reference		Mechanism of action	Reference
Herpes Simplex Virus	Quercetin 3-O-rutinoside Kaempferol 3-O-rutinoside Kaempferol 3-O-robinobioside	Interfere the processes of transcription and translation of viral protein	33	G-strophanthidin	Inhibition of viral gene expression	44
	Compounds p-alkylphenyl-6-halogeno-6-deoxy-β-D-glucopyranoside	inhibitor of biosynthesis of glycoprotein	34,35	Ouabain	Reduces viral protein synthesis	45

Virus	Flavonoid Glycoside			Cardiac Glycosides		
		Mechanism of action	Reference		Mechanism of action	Reference
Herpes Simplex Virus	2-deoxy-D-glucose (2-deoxy-D-arabino-hexose)	-	33	Digoxin	Inhibition of viral gene expression	13,46
	Quercetin 3-O-rutinoside Kaempferol 3-O-rutinoside Kaempferol 3-O-robinobioside			Digitoxin	Interfere viral DNA synthesis and virus release from host cells	47
Influenza	2 -O-(2 -methylbutanoyl) isoswertisin	-	36			
	quercetin 3-O-β-D-galactopyranoside quercetin 3-O-α-L-rhamnopyranoside kaempferol 3-O-α-L-rhamnopyranoside	neuraminidase inhibitor	37	Digoxin, ouabain and cinobufagin	Inhibition of protein translation	51
	p-alkylphenyl-6-halogeno-6-deoxy-β-D-glucopyranoside	inhibitor biosynthesis of glycoprotein	34	Lanatoside C	Inhibited influenza virus replication	49
	2-deoxy-D-glucose (2-deoxy-D-arabino-hexose)		35			
HIV	6-γ,γ-dimethylal-lyltaxifolin 7-O-beta-d-glucoside	-	38	Digitoxin, lanatoside C, digoxin, ouabain	Alteration of viral pre-RNA splicing	51
	Herbacitrin	inhibit HIV-1 replication	39	convallatoxin, periplocymarin, strophanthidin, gitoxigenin diacetate digoxigenin, cymarin, sarmentogenin gitoxin gitoxigenin, strophanthidinic acid lactone acetate, strophanthidin semicarbazide	Inhibit HIV-1 gene expression by attenuating MEK1/2-ERK1/2 signaling	52
	myricetin rhamnoside myricetin 3-(6-rhamnosylgalactoside)	Inhibition of HIV-1 reverse transcriptase	40			
	quercetin 3-O-(6≤-feruloyl)-b-D-galactopyranoside	-	42			

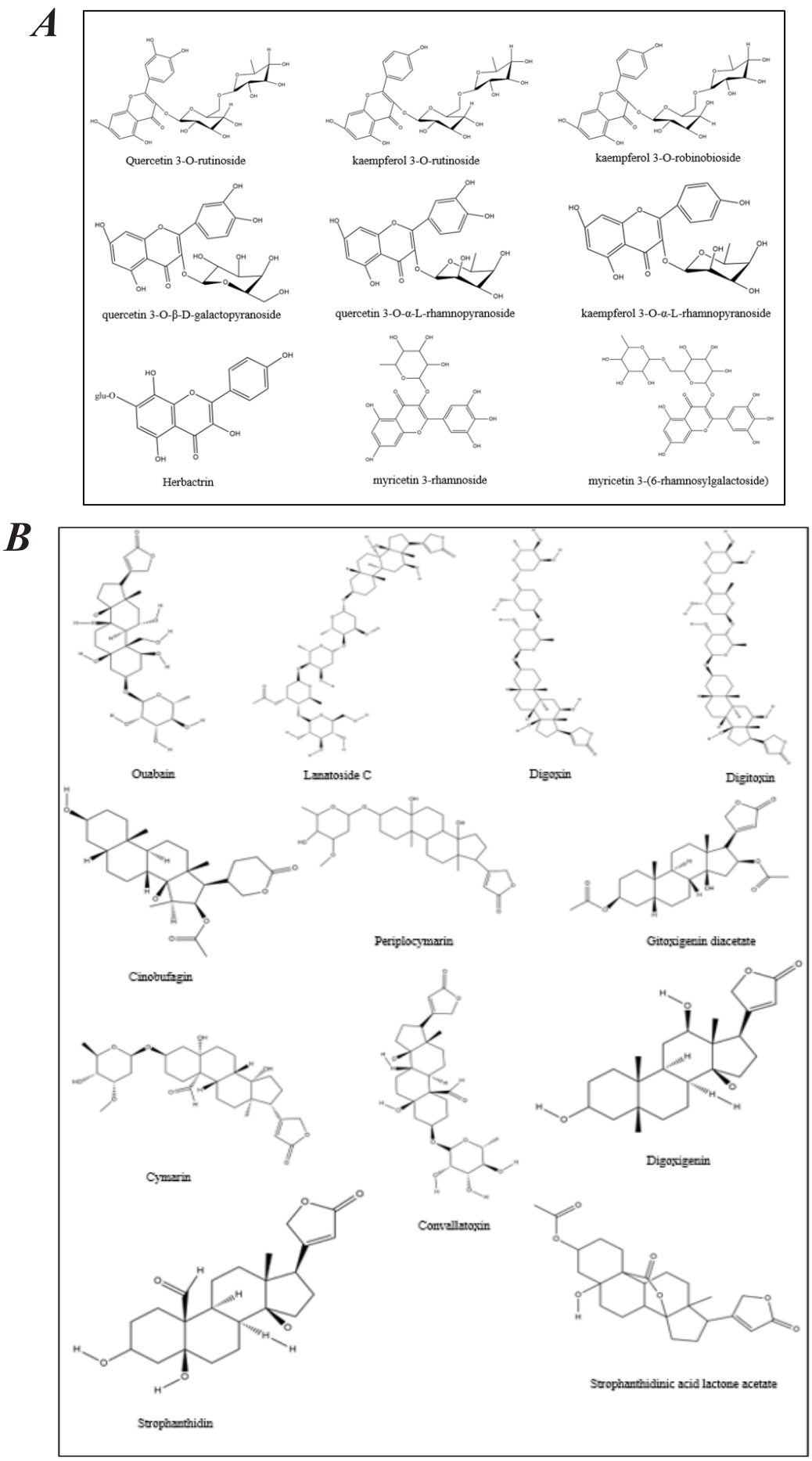

Figure 3. (A) Chemical structure of flavonoid glycoside; (B) Chemical structure of cardiac glycoside

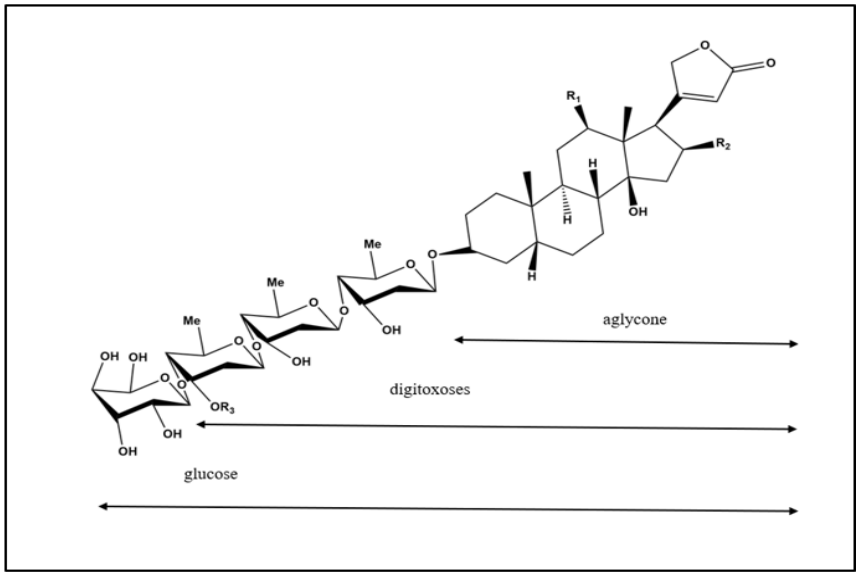

Figure 4. Structure of cardiac glycosides consists five-ring of cardenolides as aglycone with the monosaccharide[43]

without affecting cellular metabolic activity. Ouabain disrupts the capsid transport to the nucleus after fusion with plasma.[45] Digoxin is known as an antiherpes viral by inhibiting viral gene expression.[13,46] Digitoxin is also reported to inhibit HSV replication with an effective concentration of 50% (EC_{50}) 0.05 M. Digitoxin can interfere with the HSV virus life cycle in two different steps, namely viral DNA synthesis and virus release from host cells.[47]

3.7. Antiinfluenza Virus of Cardiac Glycoside

CGs such as digoxin, ouabain, and Cinobufagin can inhibit influenza virus replication in alveolar epithelial cells by lowering intracellular potassium, leading to inhibition of protein translation, independent of viral entry, mRNA transcription and protein degradation. We found that short-term treatment with ouabain prevented IAV replication without cytotoxicity.[48]

High-throughput screens found that Na-,K-ATPase inhibitors, such as ouabain and lanatoside C, inhibited influenza virus replication *in vitro* at nanomolar doses.[49] In addition, influenza virus replication can be reduced by the interaction between the β1 subunit of Na, K-ATPase, and influenza A M2

Table 2. Number of Monosaccharides of Cardiac Glycosides

Structures part	Description	R_1	R_2	R_3
Part A (aglycon)	Digitoxigenin	H	H	-
	Gitoxigenin	H	OH	-
	Digoxigenin	OH	H	-
Part B (trioxide)	Digitoxin	H	H	H
	Gitoxin	H	OH	H
	Digoxin	OH	H	H
Part C (tetraoxide)	Purpurea glycoside A	H	H	H
	Purpurea glycoside B	H	OH	H
Acetylated tetraoxide	Lanatosid A	H	H	CH_3CO
	Lanatosid B	H	OH	CH_3CO
	Lanatosid C	OH	H	CH_3CO

and BM2 proteins.[50]

3.8. Anti-HIV of Cardiac Glycoside

Digitoxin, lanatoside C, digoxin, and ouabain have been known to have inhibitory activity against the HIV-1 virus by targeting viral RNA, namely by alteration of viral pre-RNA splicing.[51] The studies about other glycoside groups, such as convallatoxin, periplocymarin, strophanthidin, gitoxigenin diacetate digoxigenin, cymarin, sarmentogenin gitoxin gitoxigenin, strophanthidinic acid lactone acetate, strophanthidin, semicarbazid, were carried out. The result showed that they could inhibit HIV-1 gene expression by attenuating MEK1/2-ERK1/2 signaling.[50] The list of all CGs with antiviral activities was reported in Table 1. The chemical structure of cardiac glycoside shown in Figure 3.

4. Conclusion and Future Perspectives

Many glycoside compounds exist, especially for the flavonoid and cardiac glycoside groups. They have antiviral activity against HSV, Influenza, and HIV in vitro regarding the mechanism of action and structural information that plays a role in antiviral activity, whether the glycan or aglycan needs further research. We hope that this research can help researchers to evaluate the potential antiviral activity of glycoside compounds in preclinical studies so that they can be developed as effective antiviral drugs.

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