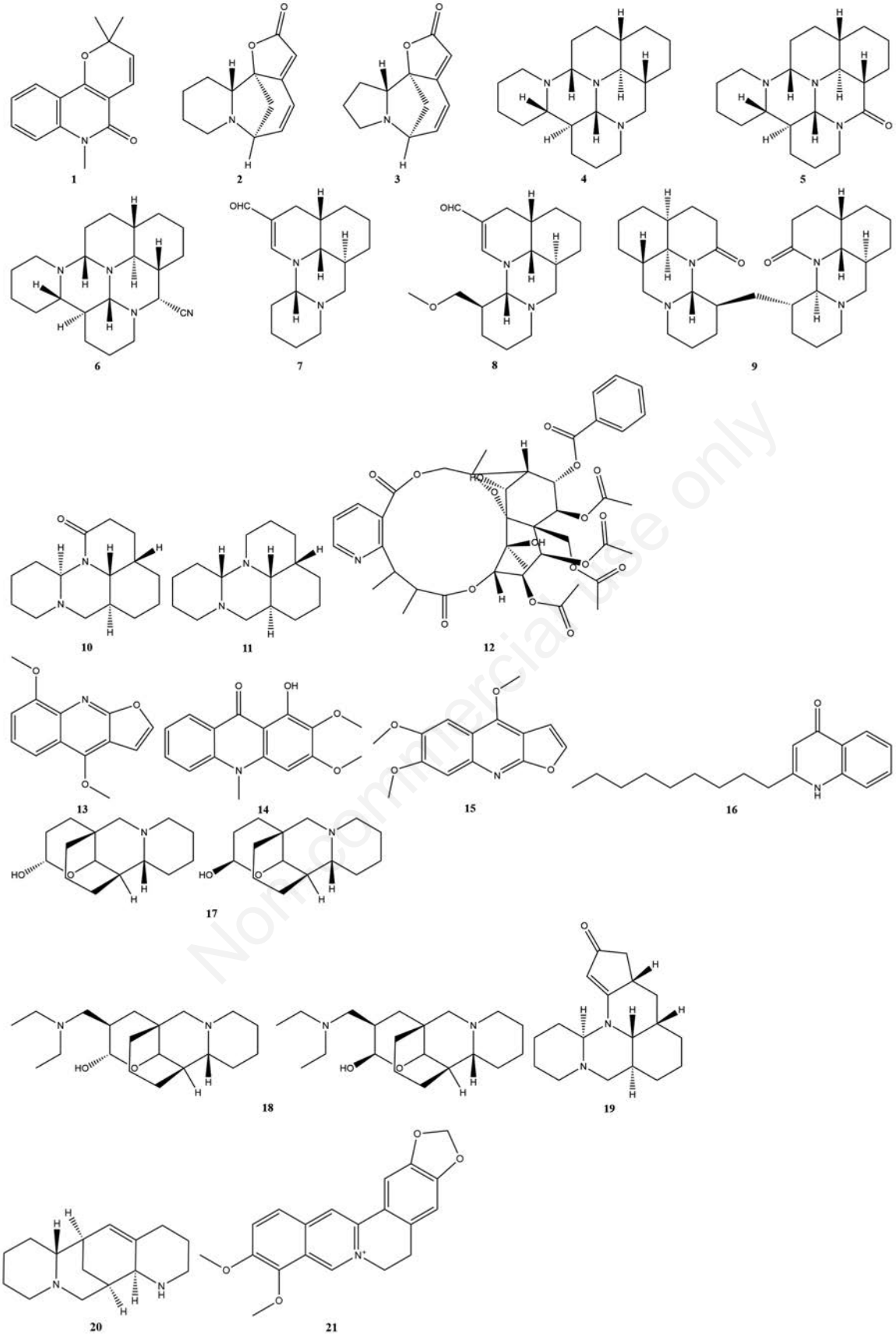

Figure 1. Molecular structure of alkaloids that possess anti-hepatitis C virus activity.

and numbers of functional radical groups present in the chemical structures of various molecules.[34] Various flavonoid compounds and its molecular structure were demonstrated to possess anti-HCV activities (Table 2 and Figure 2).

Flavanones

Hesperidin (22), was identified as the main flavonoid of Citrus extract inhibit NS3-NS4A protease with IC50 value of 11.34±3.83 ng/ml. Molecular docking study found, it inhibit NS3 protease by establishing hydrogen bonds with active site residues (His57, Asp81 and Ser139).[35] Isolation from Taxillus sutchuenensis herba identified isosakuranetin (23), homoeriodictyol-7-O-β-D-glucopyranoside (24) and viscumneoside I (25). These compounds inhibit NS3 protease with IC50 values of 234.4±2.2 mM, 68.9±0.4 mM

Table 1. Alkaloid compounds demonstrated anti-hepatitis C virus activities.

Subclass	Compound	Source	IC_{50}	Target	Ref
Quinoline	N-methylflindersine (1)	*Melicope latifolia* (Fruits)	3.8±2.7 µg/ml	HCV replication and supressed NS3 expression	(23)
	(-)-securinine (2)	*Flueggea virosa* (Twigs and Leaves)	7.7 µM	HCV replication	(24)
	(-)-norsecurinine (3)		27.6 µM		
	Myritonine A (4)	*Myrioneuron tonkinensis* (Leaves and Stems)	16.27±1.49 µM	HCV replication	(25)
	Myritonine B (5)		17.72±4.20 µM		
	Myritonine C (6)		>66.70 µM		
	Myrifamine A (7)		3.27±2.21 µM		(26)
	Myrifamine B (8)	*Myrioneuron faberi* (Leaves and Stems)	0.92±0.26 µM		
	Myrifamine C (9)		10.53±3.14 µM		
	Myrionamide (10)		30.61±2.44 µM		
	Schoberine (11)		7.35±0.56 µM		
	APS (12)	*Maytrenus ilcilifolia* (Root bark)	2.3 µg/ml	HCV replication	(27)
	γ-Fagarine (13)	*Ruta angustifolia* (Leaves)	20.4±0.4 µg/ml		(28)
	Arborinine (14)		6.4±0.7 µg/ml		
	Kokusaginine (15)		6.4±1.6 µg/ml		
	Pseudane IX (16)		1.4±0.2 µg/ml	HCV replication and NS3 protein synthesis	
Quinolizidine	(±)-β-Myrifabral A & (±)-α-Myrifabral A (cluster A) (17)	*Myrineuron faberi* (Leaves and Stems)	4.7 µM	HCV replication	(29)
	(±)-β-Myrifabral B & (±)-α-Myrifabral B (cluster B) (18)		2.2 µM		
	Myriberine A (19)	*Myrineuron faberi* (Twigs and Leaves)	8.49±0.2 µg/ml	HCV replication	(30)
	Aloperine (20)	*Commercial*	7.06±2.17 µM	HCV entry, replication and cell-to-cell transmission through disturbing internalisation from endocytosis to the membrane fusion process	(31)
Isoquinoline	Berberine (21)	*Commercial*	0.49±0.07 µM	HCV attachment, entry/fusion and E1/E2 Glycoprotein	(32)

Table 2. Flavonoids compounds demonstrated anti-hepatitis C virus activity.

Subclass	Compound	Source	IC_{50}	Target	Ref
Flavanone	Hesperidin (22)	Commercial	11.34±3.83 µg/ml	NS3-NS4A Protease	(35)
	Isosakuranetin (23)	*Taxillus sutchuenensis* (Herba)	234.4±2.2 µM	NS3 Protease	(36)
	Homoeriodictyol-7-O-β-D-glucopyranoside (24)		68.9±0.4 µM		
	Viscumneoside I (25)		62.3±2.0 µM		
	Eriodictyol 7-*O*-(6″-caffeoyl)-*β*-*D*-glucopyranoside (26)	*Elsholtzia bodinieri* (Aerial)	0.041 nM	HCV Replication	(37)
Flavonol	Rhamnazin 3-*O*-di-rhamnosyl-glucoside (27)	*Sarcocornia fruticosa* (Leaves)	8.9±2.6 µM	NS3 Protease	(38)
	Rhamnazin 3-*O*-rutinoside (28)		14.3±3.7 µM		
	Rhamnazin 3-*O*-rhamnosyl-galactoside (29)		77.2±5.5 µM		
	Isorhamnetin 3-*O*-rhamnosyl-galactoside (30)		67.6±4.8 µM		
	Isorhamnetin 3-*O*-di-rhamnosyl-galactoside (31)		47.5±6.2 µM		
	Kaempferol-3,7-bisrhamnoside (32)	*Taxillus sutchuenensis* (Herba)	19.4±0.5 µM		(36)
Flavone	Sorbifolin (33)	*Pterogyne nitens* (*Leaves*)	37.93 µM	HCV Entry by direct action on virus particles	(39)
	Pedalitin (34)		51.97 µM	HCV entry by direct action on virus particles and interference on the host cells	
	Diosmetin 7-*O*-β-glucoside-2″-sulphate (35)	*Thalassia hemprichii*	16 µM	NS3-NS4A Protease	(40)
	Diosmetin 7-*O*-β-glucoside (36)		37 µM		
	Quercetin 3,3',4'-trimethyl ether (37)	*Taxillus sutchuenensis* (Herba)	154.6±1.9 µM	NS3 Protease	(36)
	Luteolin (38)	*Elsholtzia bodinieri* (Aerial)	0.56 nM	HCV Replication	(37)
	Ladanein (39)	*Marrubium peregrinum* (Aerial)	2.79 µmol/L	HCV entry at post-binding	(41)
Flavan-3-ol	EGCG (40)	*Commercial*	10.6±2.9 µM	HCV entry, modify the morphology of HCVpp	(43)
Flavonolignan	Silibinin (Silibinin A & Silibinin B) (41)	*Silybum marianum* (Seeds)	34±3 µM	HCV fusion and entry by slowing down trafficking through clathrin-coated pits and vesicles	(47)
	Silibinin A (42)		25±3 µM	HCV fusion	
	Silibinin B (43)		29±4 µM		
	Isosilibinin A (44)		15±3 µM		
	Isosilibinin B (45)		31±4 µM		
	Silicristin (46)		53±3 µM		
	Isosilicristin (47)		81±2 µM		
	Silidianin (48)		100±3 µM		
	Taxifolin (49)		60±3 µM		
	Silibinin A (50)	*Commercial*	96.4±15.9 µM	NS5B polymerase	(45)
	Silibinin B (51)		97.2±24.1 µM		
	Silibinin (Silibinin A & Silibinin B) (52)		82.0±22.3 µM		
	Isosilibinin A (53)		211.6±34.9 µM		
	Isosilibinin B (54)		165.5±17.4 µM		
	Silicristin (55)		> 500 µM		
	Silidianin (56)		> 500 µM		
Anthocyanidin	Delphinidin (57)		3.7±0,8 µM	HCV entry at the binding step, modify the morphology of HCVpp	(43)
Proanthocyanidin	Procyanidin A (58)	*Cinnamomum zeylanicum* (Bark)	2.06 µM	HCV Entry at post-binding	(46)

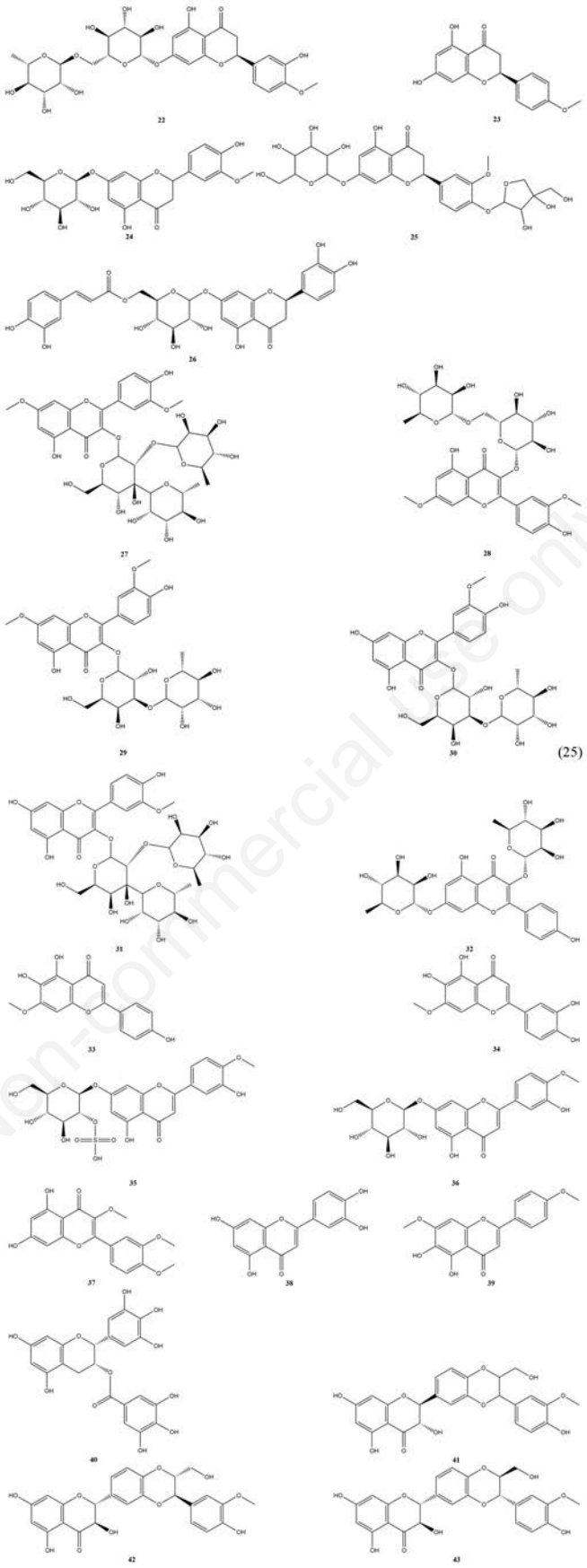

Figure 2. Structure of flavonoids compounds with anti-hepatitis C virus activities

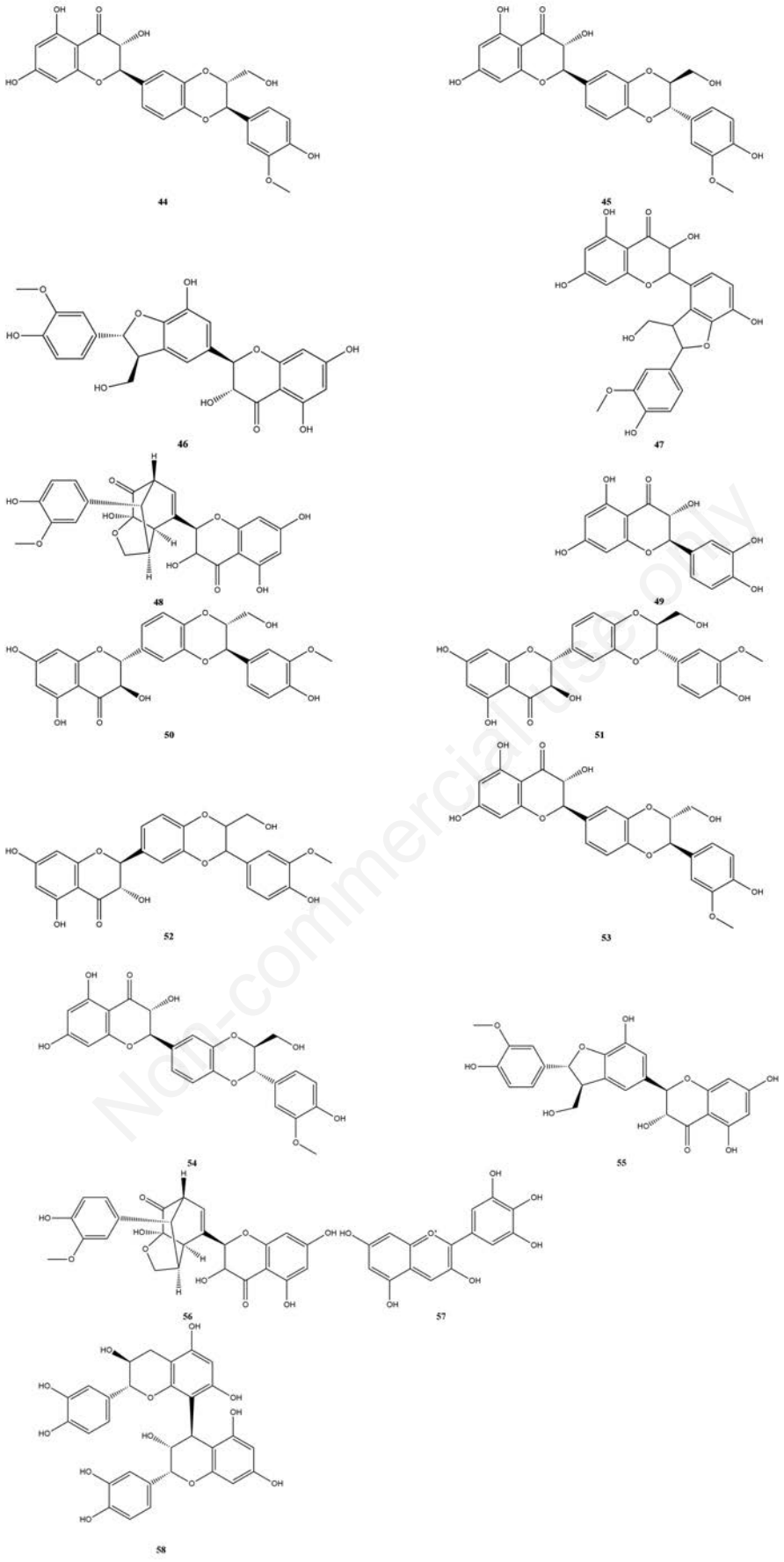

Figure 2. Structure of flavonoids compounds with anti-hepatitis C virus activities

and 62.3±2.0 mM, respectively.[36] Isolation of aerial parts of Elsholtzia bodinieri yielded flavonoid glycoside, eriodictyol 7-O-(6″-caffeoyl)-β-D-glucopyranoside that inhibit HCV replication with IC50 values of 0.041 nM.[37]

Flavonols

Rhamnazin 3-*O*-di-rhamnosyl-glucoside (27), rhamnazin 3-*O*-rutinoside (28), rhamnazin 3-*O*-rhamnosyl-galactoside (29), isorhamnetin 3-*O*-rhamnosyl-galactoside (30) and isorhamnetin 3-*O*-di-rhamnosyl-galactoside (31) were isolated from leaves of *Sarcocornia fruticosa* inhibit NS3 protease with IC_{50} values of 8.9±2.6 mM to 67.6±4.8 mM.[38] *Taxillus sutchuenensis* herba not only contains flavanones, but also contains flavonol kaempferol-3,7-bisrhamnoside (32) that inhibit HCV NS3 protease with IC_{50} value of 19.4 ± 0.5 mM.[36]

Flavones

Sorbifolin (33) and pedalitin (34) isolated from *Pterogyene nitens* leaves has virucidal activity. Nevertheless, pedalitin (34) inhibits interference on the host cells and direct on viral particles. IC_{50} values of these compounds of 37.93 mM and 51.97 mM, respectively.[39] A flavonoid compound diosmetin 7-*O*-β-glucoside-2″-sulphate (35) and Diosmetin 7-*O*-β-glucoside (36) has been isolated from *Thalassia hempricii* inhibit HCV NS3-4A protease with IC_{50} values of 16 and 37 mM, respectively.[40] Quercetin 3,3',4'-trimethyl ether (37) isolated from *Taxillus sutchuenensis* herba inhibit HCV NS3 protease with IC_{50} value of 154.6±1.9 mM.[36] Isolation of aerial parts of *Elsholtzia bodinieri* yielded luteolin (38). It inhibit HCV replication with IC_{50} value of 0.56 nM.[37] Ladanein (39) was identified from aerial parts *of Marrubium peregrinum*. Ladanein was synthetized to compare the activity between ladanein form natural source and synthetic ladanein. These compounds suppress HCV genotype 2a infection with IC_{50} value and 2.54 mmol/L. It also active against the most prevalent HCV genotypes with IC_{50} values of 0.74-4.14 mM. Moreover, it acted synergizstically with cyclosporine A to suppress HCV infection.[41]

Flavan-3-ols

The major component of green tea extract, EGCG (40) inhibit HCV entry[42] acting directly on viral particles and inhibiting their adhesion to the cell surface with IC_{50} value of 10.6±2.9 mM.[43] Additionally, EGCG has pangenotypic activities and antiviral properties against a range of unrelated viruses.[44]

Flavonolignans

HCV fusion is inhibited by silibinin (41), silibinin A (42), silibinin B (43), isosilibinin A (44), isosilibinin B (45), silicristin (46), isosilicristin (47), silidianin (48) and taxifolin (49) with IC_{50} values of 15±3 mM to 100±3 mM. In addition, silibinin (41) inhibit HCV entry by reducing trafficking through clathrin-coated pits and vesicles. High doses of commercially available silibinin A (50), silibinin B (51), silibinin (52), isosilibilin A (53), isosilibinin B (54), silicristin (55) and silidianin (56) decrease NS5B polymerase activity of HCV with IC_{50} values of these compounds of 82.0±22.3 mM to >500 mM.[45]

Anthocyanidins

A plant pigment contains anthocyanidin, delphinidin (57), as a novel HCV entry inhibitor at the binding step that modifies the morphology of HCVpp. The infection more efficiently than 40 does with IC_{50} values of 3.7±0.8 mM and 10.6±2.9 mM.[43]

Proanthocyanidins

Procyanidin A (58) isolated from *Cinnamomum zeylanicum* bark showed anti-HCV activity against different HCV strains and genotypes without considerable cellular toxicity and the mechanism were inhibit HCV entry at post-binding with IC_{50} value of 2.06 mM.[46,47]

Strength and limitations

This review provides information on alkaloids and flavonoids active against the hepatitis C virus. In addition, this review serves as a basis for further research for discovering and developing alternative and complementary therapies for the hepatitis C virus. The data of compounds mechanism against hepatitis C virus are limited so more studies were needed and provided incomplete information.

Conclusions

Alkaloid and flavonoid compounds isolated from medicinal plants are recently explored for their anti-HCV activity. Alkaloids include quinoline, quinolizidine and isoquinoline, and flavonoids include flavanone, flavonol, flavone, flavan-3-ol, flavonolignan, anthocyanidin and proanthocyanidin were reported to possess anti-HCV activity by various mechanism. The berberine alkaloids and eriodictyol 7-*O*-(6″-caffeoyl)-*β*-*D*-glucopyranoside flavonoids had the lowest IC_{50} with values of 0.49 mM and 0.041 nM. Our results provide information of alkaloids and flavonoids to the researcher for the development of alternative and complementary medicine of hepatitis C.

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