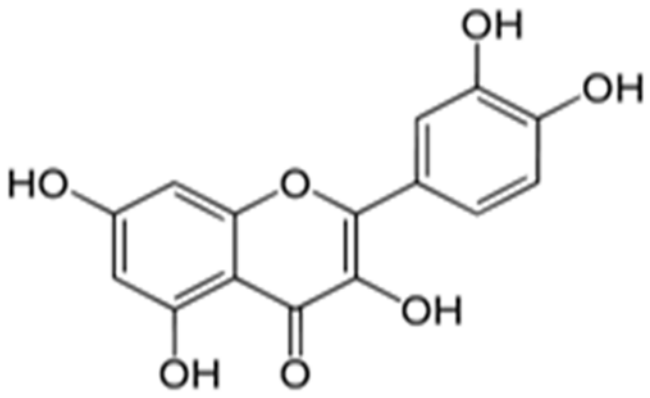
3.0. Bioenhancers Profile

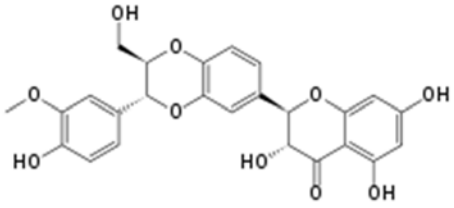
3.0.1. Quercetin

Parameter	Properties
Source	Quercetin is a reddish pigment obtained from foods like black and green tea, apples, onion, grapes, citrus fruit, tomato, broccoli and other leafy green vegetables, and a number of berries.
Description	It is a yellow crystalline powder
IUPAC name	2-(3,4-dihydroxyphenyl)- 3,5,7-trihydroxy-4H-chromen-4-one
Molecular structure	
Molecular formula	$C_{15}H_{10}O_7$
MW	302.23
MP	316 °C
Solubility	Practically insoluble in water; soluble in aqueous alkaline solutions
Mechanism of Action	Modulators of P-gp efflux pump and also has CYP3A4 activity

3.0.1.1. Role of Quercetin as bioenhancer

Quercetin has been shown to increase bioavailability, blood levels and efficacy of a number of drugs including diltiazem (1), digoxin (2, 3) and epigallocatechingallate (4). The plasma concentrations, the area under the plasma concentration-time curve (AUC) and peak concentration (Cmax) of diltiazem in the rabbits pre-treated with Quercetin were significantly higher than those obtained from untreated group. It was reported that diltiazem is metabolized by CYP3A4 both in the liver and small intestine (5, 6) and the absorption of diltiazem in the intestinal mucosa was inhibited by P-gp efflux pump (7, 8) . The increased AUCs and Cmax of diltiazem by pre-treatment of Quercetin might have been resulted from the inhibition of the P-gp efflux pump and the metabolizing enzyme, CYP3A4 in the intestinal mucosa. There were reports on its inhibition ability of the P-gp efflux pump and restraint of the metabolizing enzyme, CYP3A4 (9, 10). The absorption of epigallocatechingallate was also reported to be enhanced with red onion supplementation, abundant source of Quercetin. The AUC of epigallocatechingallate determined over a period of 6 h increased from 1323 to 1814 ng.h/ml, when co-administered with quercetin. Moreover, it was demonstrated that increased amount of quercetin administered along with epigallocatechingallate could increase absorption of epigallocatechingallate from the intestine.

3.0.2. Silibinin (11)

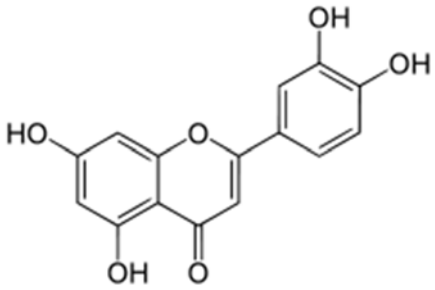
Parameter	Properties
Source	Milk thistle (Silybum marianum) major active constituent is silibinin
Description	It is a white crystalline powder
IUPAC name	(2R,3R)-3,5,7-trihydroxy-2-[(2R,3R)-3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-2,3-dihydrobenzo[b][1,4]dioxin-6-yl]chroman-4-one
Molecular structure	
Molecular formula	$C_{25}H_{22}O_{10}$
MW	482.44
MP	316 °C
Solubility	Practically insoluble in water; soluble in aqueous alkaline solutions
Mechanism of Action	Inhibit Pgp efflux pump

3.0.2.1. Role of Silibinin as bioenhancer

Silymarin is the compound of the interest. Silymarin is composed of mainly silybinin (50–80%), with small amounts of other flavonolignans such as silychristin and silydianin. Silymarin directly interact with P-gp substrate binding. The findings indicated that

silymarin and its metabolites inhibited P-gp mediated cellular efflux, raising a potential for significant drug interactions with P-gp substrates. Silibinin potentiated doxorubicin-induced growth inhibition and apoptosis in human prostate carcinoma DU145 cells (12).

3.0.3. Luteolin (13)

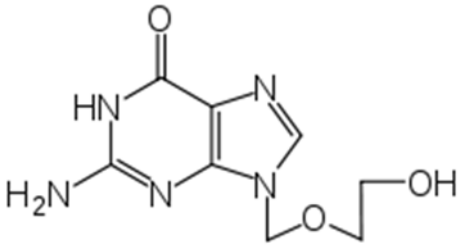
Parameter	Properties
Source	Luteolin is most often found in leaves, but it is also seen in rinds, barks, clover blossom, and ragweed pollen. It has also been isolated from the aromatic flowering plant, Salvia tomentosa in the mint family, Lamiaceae.
Description	It is a yellow crystalline powder
IUPAC name	2-(3,4-Dihydroxyphenyl)- 5,7-dihydroxy-4-chromenone
Molecular structure	
Molecular formula	$C_{15}H_{10}O_6$
MW	286.24
MP	330 °C
Solubility	Soluble in aqueous alkaline solutions, ethanol, water, and methanol.
Mechanism of Action	P-gp efflux pump inhibitor

3.0.3.1. Role of Luteolin as bioenhancer:

Luteolin was seemed to contributing in the enhancement of bioavailability/bioefficacy of drugs. It has been demonstrated as a potent P-glycoprotein inhibitor in the literature reported (14).

3.1. Drug Profile

3.1.1. Acyclovir (15)

Parameter	Acyclovir
Category	Antiviral Drug
Molecular formula	$C_8H_{11}N_5O_3$
Molecular weight	225.21
Molecular Structure	
Chemical name	2-Amino-1, 9-dihydro-9-((2-hydroxyethoxy) methyl)-6*H*-Purin-6-one
Appearance	A white to almost white crystalline powder
Solubility	slightly soluble in water, Very slightly soluble in ethanol; freely soluble in dimethyl sulfoxide
Oral bioavailability	20%
Protein binding	9-33%
Half life	3hrs
BCS Class	Class III
Metabolism	Viral thymidine kinase
Excretion	Renal
Dose	up to 4 g daily

3.1.1.1. Mechanism of Action

Acyclovir inhibits viral DNA synthesis as shown in Figure 3.1.1. Its selectivity of action depends on interaction with two distinct viral proteins: HSV thymidine kinase and DNA polymerase. Cellular uptake and initial phosphorylation are facilitated by HSV thymidine kinase. The affinity of acyclovir for HSV thymidine kinase is about 200 times greater than for the mammalian enzyme. Cellular enzymes convert the monophosphate to acyclovir triphosphate, which is present in forty- to one hundred fold higher concentrations in HSV-infected than in uninfected cells and competes for endogenous deoxyguanosine triphosphate (dGTP). The immunosuppressive agent *mycophenolate mofetil* potentiates the antiherpes activity of acyclovir and related agents by depleting intracellular dGTP pools. Acyclovir triphosphate competitively inhibits viral DNA polymerases and, to a much smaller extent, cellular DNA polymerases. Acyclovir triphosphate also is incorporated into viral DNA, where it acts as a chain terminator because of the lack of a 3¢-hydroxyl group. By a mechanism termed *suicide inactivation,* the terminated DNA template containing acyclovir binds the viral DNA polymerase and leads to its irreversible inactivation.

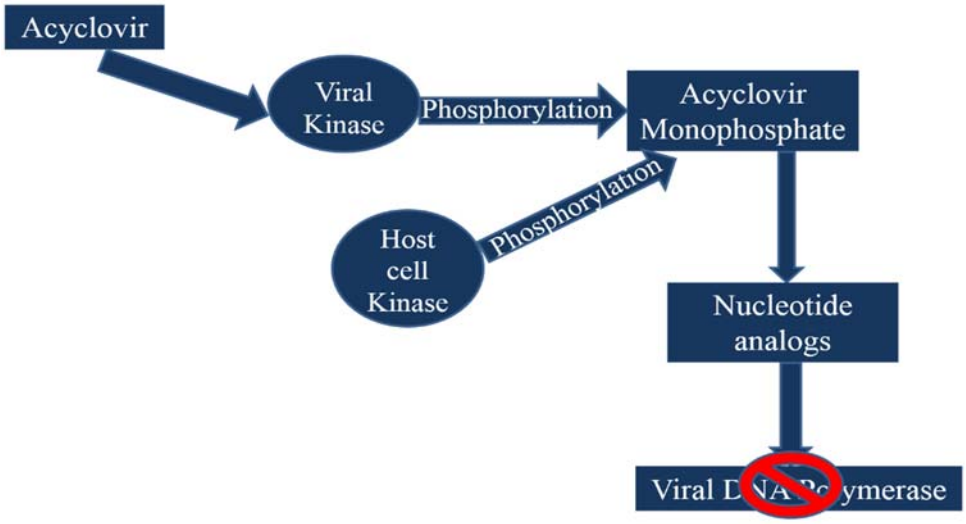


Figure 3.1 Mechanism of action of acyclovir

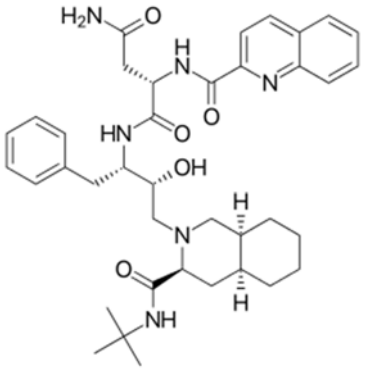
3.1.1.2. Pharmacokinetic profile/Dispositions in the body

Acyclovir is poorly absorbed after oral administration. Peak plasma concentrations occur about 1.5 to 2.5 h after administration. It is excreted mostly unchanged through the kidney both by glomerular filtration and tubular secretion. 30 to 70% of an administered dose can be detected in urine. About 14% is excreted as the inactive metabolite 9–carboxymethoxymethylguanine (the main metabolite), and also 8–hydroxy–9-(2–hydroxyethoxymethyl)guanine has been detected (<0.2% of the dose). Faecal excretion accounts for about 2% of a dose. It is widely distributed into various tissues, including CSF where concentrations reach about 50% those of plasma. It crosses the placenta and is distributed into breast milk. Aciclovir is removed by haemodialysis but not by peritoneal dialysis.

3.1.1.2.1. Pharmacokinetic parameters

The oral bioavailability is approx 20% with a Half–life of Plasma, 2 to 3 h. Volume of distribution is 4L to 55 L/1.73 m^2 With Protein binding in plasma is 9 to 33%. It is administred in the dose of Up to 30 mg/kg body weight daily intravenously; up to 4 g daily by mouth.

3.1.2. Saquinavir (16)

Parameter	Saquinavir
Category	Antiretroviral drug
Molecular formula	$C_{38}H_{50}N_6O_5$
Molecular weight	670.84
Molecular Structure	
Chemical name	2(2*S*)-*N*-[(2*S*, 3*R*)-4-[(3*S*)-3-(*tert*-butylcarbamoyl)-decahydroisoquinolin-2-yl]-3-hydroxy-1-phenylbutan-2-yl]-2-(quinolin-2-ylformamido) butanediamide
Appearance	A white crystalline solid
Solubility	slightly soluble in water
Oral bioavailability	4%
Protein binding	98%
Half life	12hrs
BCS Class	Class III
Metabolism	cytochrome P450 system (CYP3A4)
Excretion	Mainly in faeces (88%) with only 1% in urine.
Dose	1800 mg daily as 600 mg three times a day

3.1.2.1. Mechanism of action

Saquinavir is selectively toxic by potently inhibiting the HIV-encoded protease but not host-encoded aspartyl proteases shown in Figure 3.1.2. Saquinavir reversibly binds to the active site of HIV protease, preventing polypeptide processing and subsequent virus maturation. Virus particles are produced in the presence of Saquinavir but are non-infectious. Virus replication in the presence of Saquinavir selects for drug-resistant virus. The primary Saquinavir resistance mutation occurs at HIV protease codon 90 (a leucine-to-methionine substitution), although primary resistance also has been reported with a glycine-to-valine substitution at codon 48. Secondary resistance mutations occur at codons 36, 46, 82, 84, and others and these are associated with clinical Saquinavir resistance as well as cross-resistance to other HIV protease inhibitors. As is typical of HIV protease inhibitors, high-level resistance requires accumulation of multiple resistance mutations.

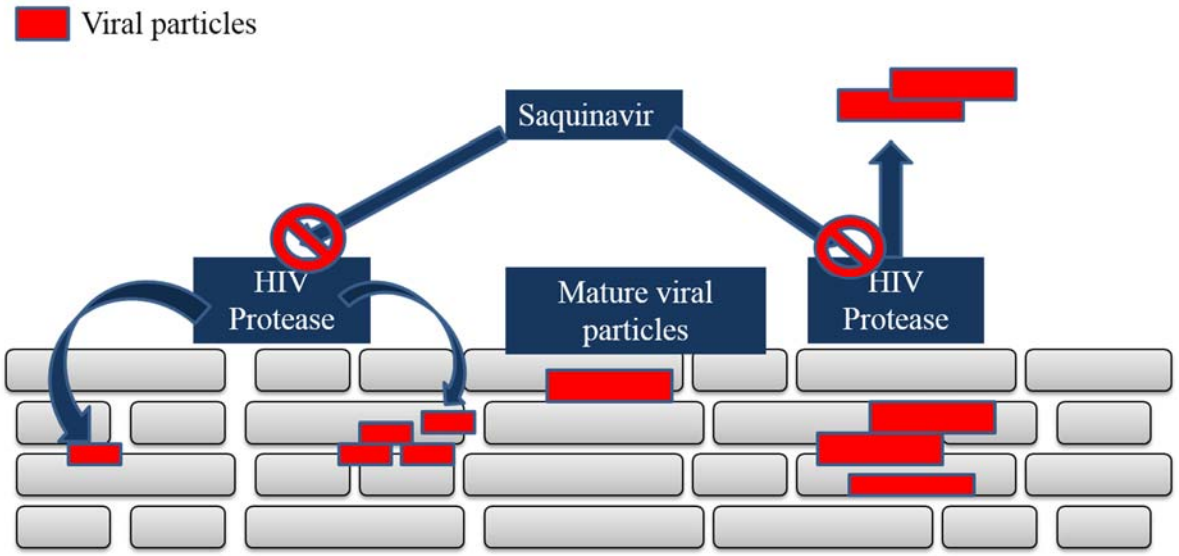


Figure 3.2 Mechanism of action of Saquinavir

3.1.2.2. Pharmacokinetic profile/Disposition in the Body

Saquinavir is absorbed but to a limited extent (30%) following oral administration and undergoes extensive first–pass metabolism in the liver. Peak plasma concentrations are observed approximately 0.77 h after administration of a suspension formulation and 3 to 4 h after capsules. It is extensively distributed into tissues but CNS concentrations are minimal. Metabolism is rapid by the cytochrome P450 system (CYP3A4) and a number of inactive monohydroxylated and dihydroxylated metabolites are formed. The drug is excreted mainly in faeces (88%) with only 1% in urine.

3.1.2.2.1. Pharmacokinetic parameters

The oral bioavailability of saquinavir is low and is affected by the presence of food. In healthy volunteers receiving a single 600 mg dose after a heavy breakfast the bioavailability was found to be around 4%. SQU having half-life 13.2 h, volume of distribution 700 L following an intravenous dose of 12 mg. Clearance is 1.14 L/h/kg while protein binding is approx. 98%. It is given 800 mg daily as 600 mg three times a day.

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