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- **OMICS Group is an amalgamation of Open Access Publications and worldwide international science conferences and events. Established in the year 2007 with the sole aim of making the information on Sciences and technology 'Open Access', OMICS Group publishes 500 online open access scholarly journals in all aspects of Science, Engineering, Management and Technology journals. OMICS Group has been instrumental in taking the knowledge on Science & technology to the doorsteps of ordinary men and women. Research Scholars, Students, Libraries, Educational Institutions, Research centers and the industry are main stakeholders that benefitted greatly from this knowledge dissemination. OMICS Group also organizes 500 International conferences annually across the globe, where knowledge transfer takes place through debates, round table discussions, poster presentations, workshops, symposia and exhibitions.**

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OMICS International is a pioneer and leading science event organizer, which publishes around 500 open access journals and conducts over 500 Medical, Clinical, Engineering, Life Sciences, Pharma scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

Hepatoprotective activity of silymarin against acetaminophen involves an enhancement of the glutathione-dependent detoxification capacity

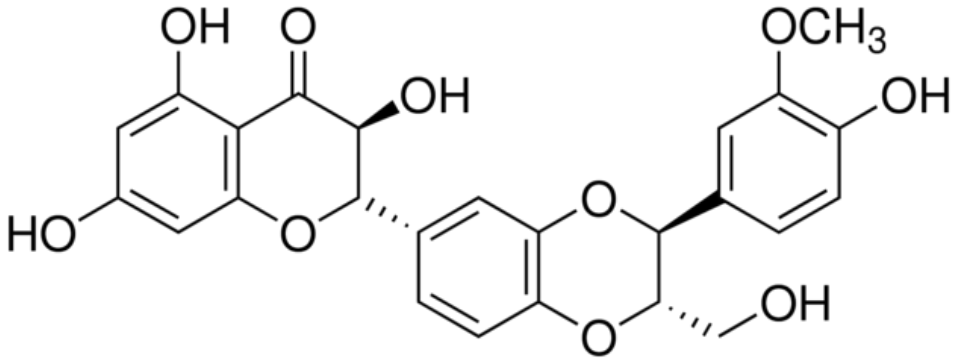
Young Chul Kim

College of Pharmacy
Seoul National University

Enhancement of GSH Detoxicifcation Capacity by Silymarin

Silymarin:

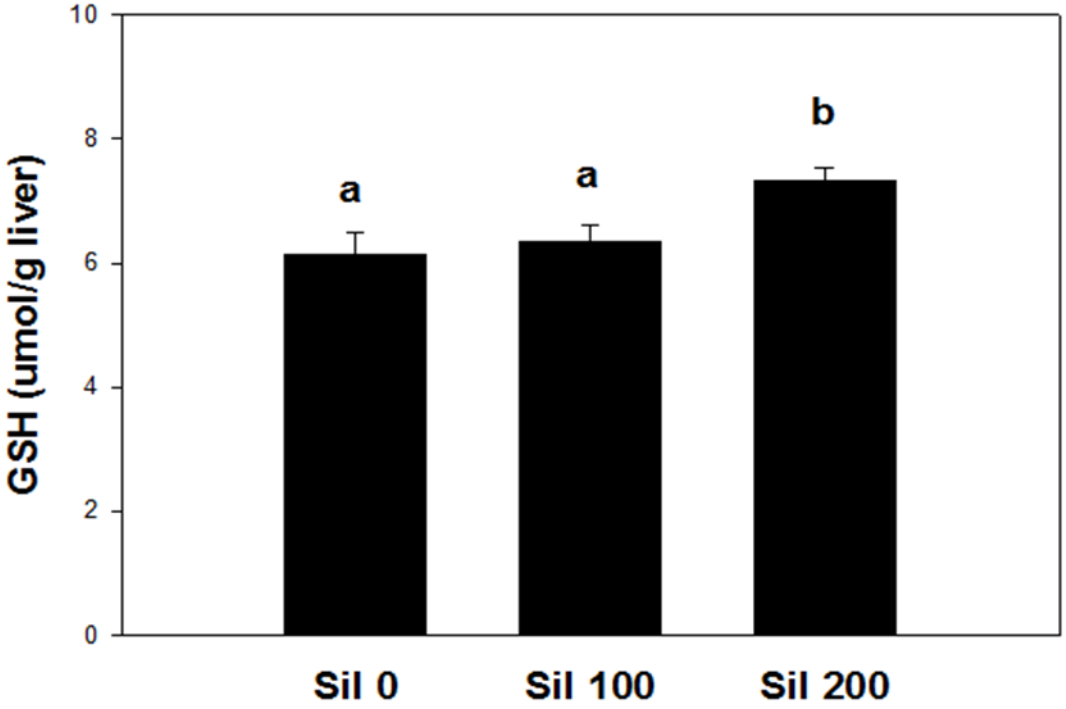
- ✓ **Extract from seeds of milk thistle (*silybum marianum*).**
- ✓ **Mixture of flavonolignans mostly consisting of silybin, silychristin, silydianin, and isosilybin.**



Enhancement of GSH Detoxicifcation Capacity by Silymarin

- ✓ **Has been used as a remedy for the treatment of chronic liver diseases in traditional medicine (ALD, viral hepatitis, liver cirrhosis, etc.).**
- ✓ **Experimental evidence showed that silymarin protects the liver against various toxicants including CCl_4, ethanol, acetaminophen and galactosamine.**
- ✓ **The mechanism of hepatoprotective action provided by silymarin is frequently attributed to its antioxidant effect.**
- ✓ **Silymarin prevents GSH depletion induced by those toxicants, which seems to be a secondary effect resulting from GSH conservation due to its direct radical scavenging activity.**

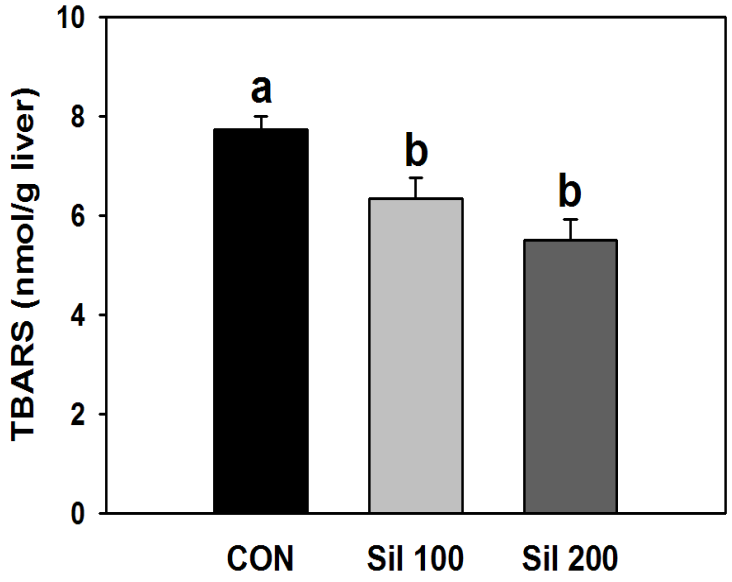
Enhancement of GSH Detoxicifcation Capacity by Silymarin

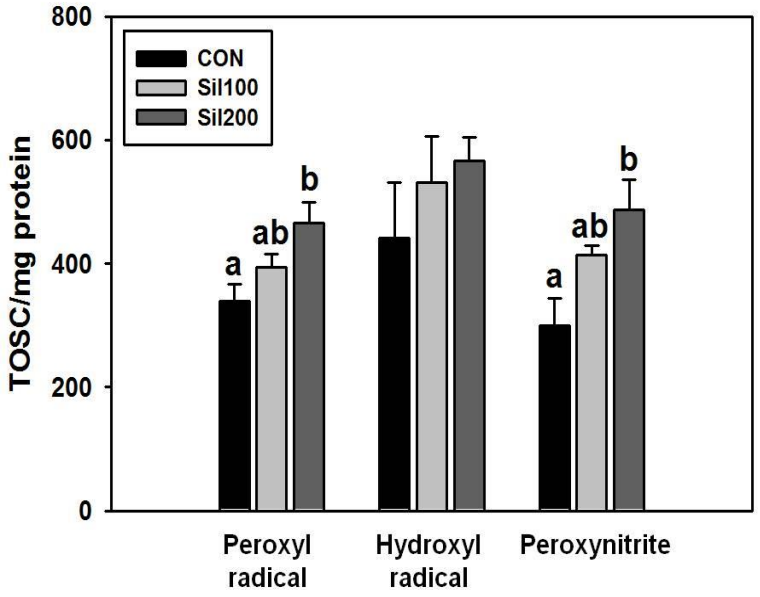


GSH levels in liver of mice treated with silymarin (100 mg/kg or 200 mg/kg) every 12 hr for 3 times. (Kwon et al., BK21 Report to Bukwang Pharmaceuticals, 2008, SNU)

Enhancement of GSH Detoxicifcation Capacity by Silymarin

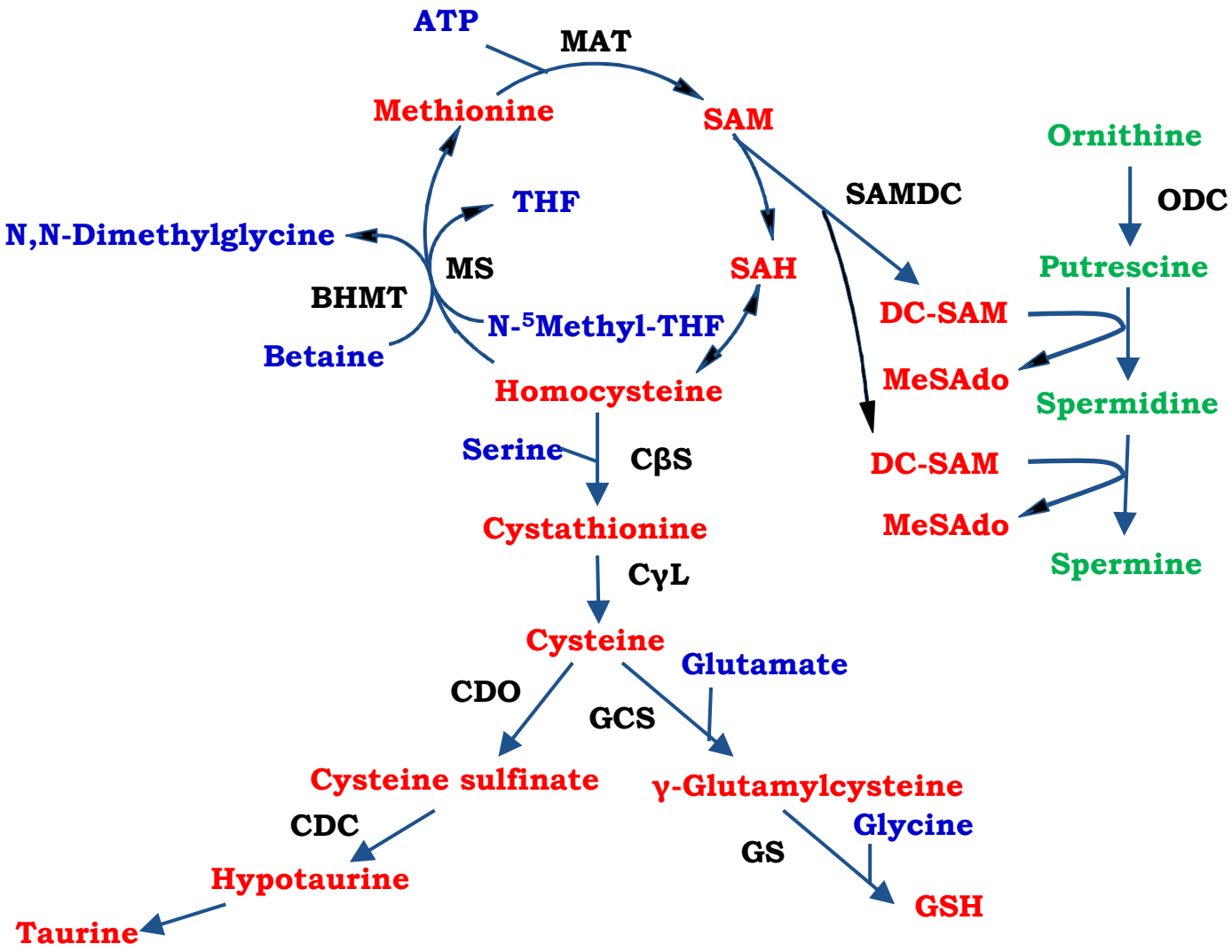
Lipid peroxidation and total oxyradical scavenging capacity (TOSC)





Part I :

Alterations in hepatic transsulfuration reactions in mice treated with silymarin



Metabolic pathway for sulfur amino acids

(Adapted from Kim and Kim, J. Hepatol. 2005)

Enhancement of GSH Detoxicifcation Capacity by Silymarin

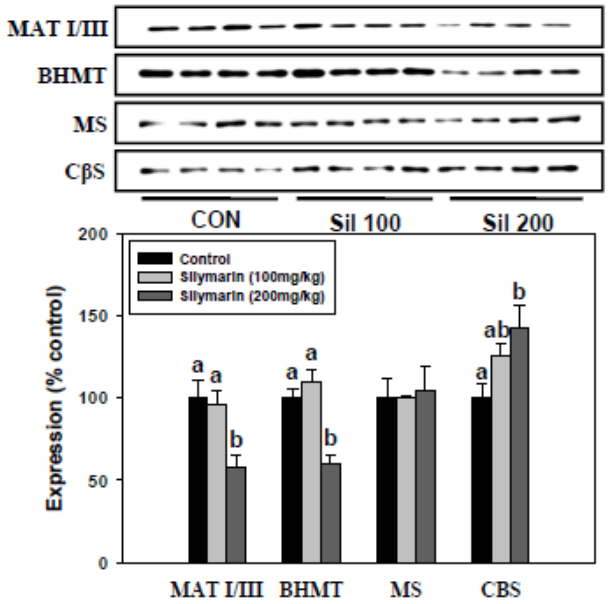
Changes in major sulfur-containing metabolites (I)

	Control	Silymarin (100 mg/kg)	Silymarin (200 mg/kg)
Methionine (nmol/g liver)	38.2 ± 1.4a	46.7 ± 2.5a,b	51.1 ± 6.2b
SAM (nmol/g liver)	99.3 ± 5.2	95.5 ± 4.4	108.8 ± 8.6
SAH (nmol/g liver)	46.0 ± 2.4	49.1 ± 4.4	53.1 ± 4.6
Homocysteine (nmol/g liver)	6.8 ± 0.5	6.8 ± 0.2	6.4 ± 0.3
Cystathionine (nmol/g liver)	9.9 ± 1.4a	13.5 ± 1.6a,b	16.7 ± 1.2b
Cysteine (nmol/g liver)	89.3 ± 9.3a	84.4 ± 3.2a	149.1 ± 10.3b

Changes in enzyme activities involved in the metabolism of sulfur amino acids (I)

	Control	Silymarin (100 mg/kg)	Silymarin (200 mg/kg)
MAT (pmol/mg/min)	41.3 ± 3.2a	38.5 ± 1.4a,b	32.5 ± 1.8b
BHMT (nmol/mg/min)	1.55 ± 0.14a	1.34 ± 0.10a,b	1.14 ± 0.10b
CβS (nmol/mg/min)	7.1± 0.6a	8.7 ± 0.8a,b	10.1 ± 0.8b
CγL (nmol/mg/min)	10.1 ± 0.1	10.4 ± 0.4	10.7 ± 0.5

Changes in enzyme protein expressions involved in the metabolism of sulfur amino acids (I)



Value with different letters are significantly different from one another (ANOVA followed by Newman-Keuls test, $P < 0.05$).

Enhancement of GSH Detoxicifcation Capacity by Silymarin

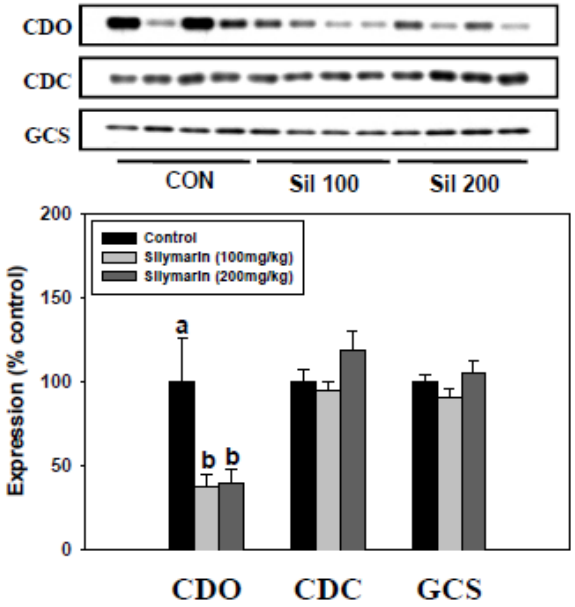
Changes in major sulfur-containing metabolites (II)

	Control	Silymarin (100 mg/kg)	Silymarin (200 mg/kg)
Cysteine (nmol/g liver)	89.3 ± 9.3a	84.4 ± 3.2a	149.1 ± 10.3b
Hypotaurine (μmol/g liver)	0.13 ± 0.02	0.14 ± 0.03	0.16 ± 0.02
Taurine (μmol/g liver)	13.0 ± 0.7	13.4 ± 0.7	14.7 ± 0.4
GSH (μmol/g liver)	5.7 ± 0.3a	5.9 ± 0.3a	6.9 ± 0.2b
GSSG (μmol/g liver)	0.22 ± 0.01	0.20 ± 0.01	0.22 ± 0.01
GSH/GSSG ratio	25.4 ± 0.6a	29.9 ± 0.9b	31.7 ± 1.2b

Changes in enzyme activities involved in the metabolism of sulfur amino acids (II)

	Control	Silymarin (100 mg/kg)	Silymarin (200 mg/kg)
CDO (nmol/mg/min)	0.62 ± 0.07a	0.40 ± 0.02b	0.32± 0.02b
CDC (nmol/mg/min)	16.3 ± 0.8	16.1 ± 0.3	17.3 ± 1.1
GCS (nmol/mg/min)	3.8 ± 0.4	3.3 ± 0.1	3.2 ± 0.5

Changes in enzymes involved in the metabolism of sulfur amino acids (II)



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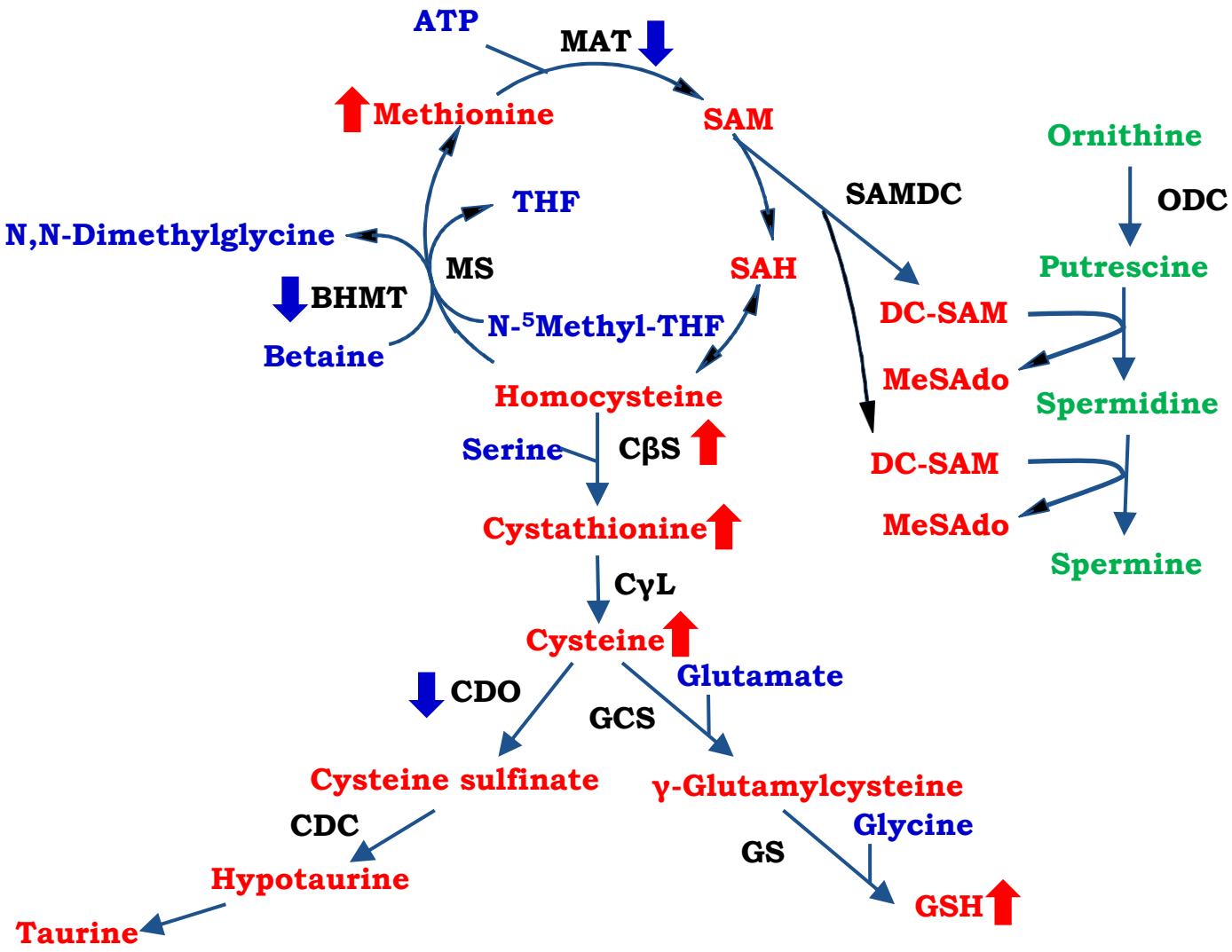


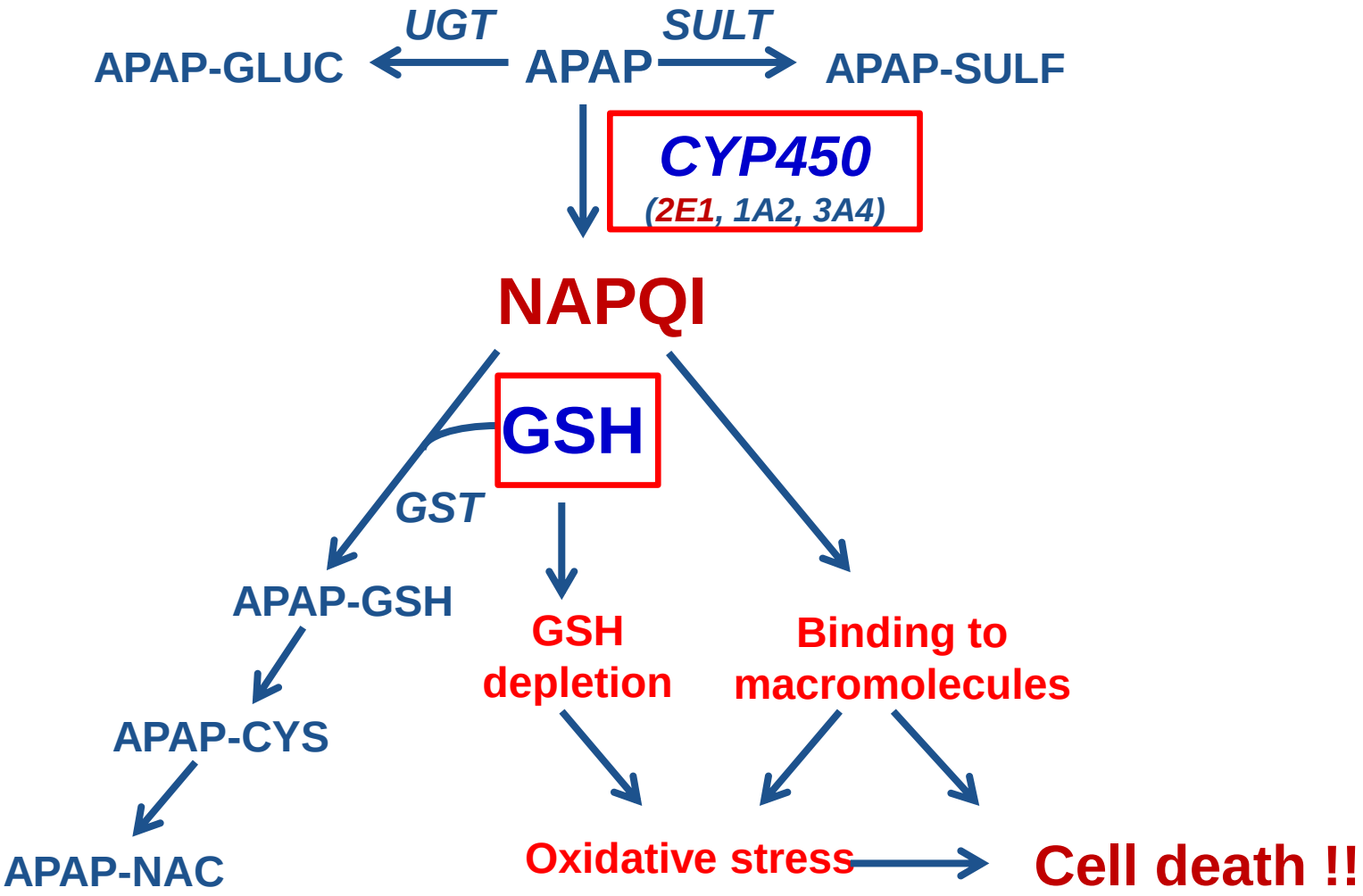
Alterations in the metabolism for sulfur amino acids in mice treated with silymarin

SUMMARY – 1ST PART

- ✓ **Acute silymarin treatment increases hepatic methionine level which is accompanied with inhibition of MAT without a significant change in SAM or SAH.**
- ✓ **BHMT is inhibited, but homocysteine is not accumulated. Instead, the generation of cystathionine is enhanced, probably due to induction of CβS.**
- ✓ **Also cysteine catabolism to taurine is depressed significantly by silymarin as evidenced by down-regulation of CDO.**
- ✓ **The increase in cysteine generation and the inhibition of its catabolism to taurine lead to an elevation of cysteine availability which accounts for the enhancement of GSH synthesis in liver.**

Part II :

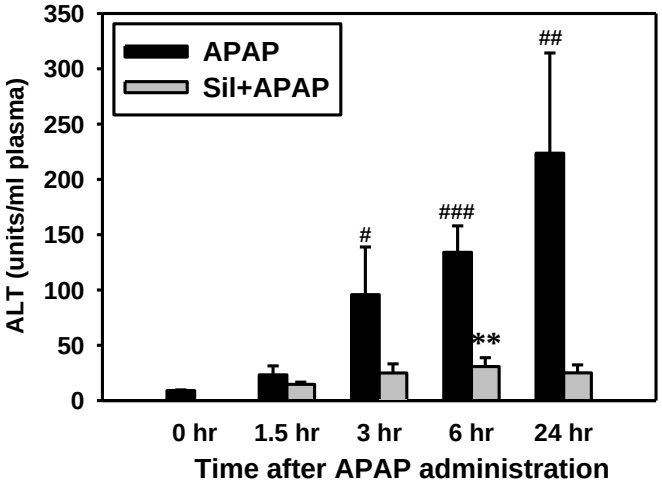
Significance of the enhancement of GSH synthesis by silymarin on acetaminophen hepatotoxicity

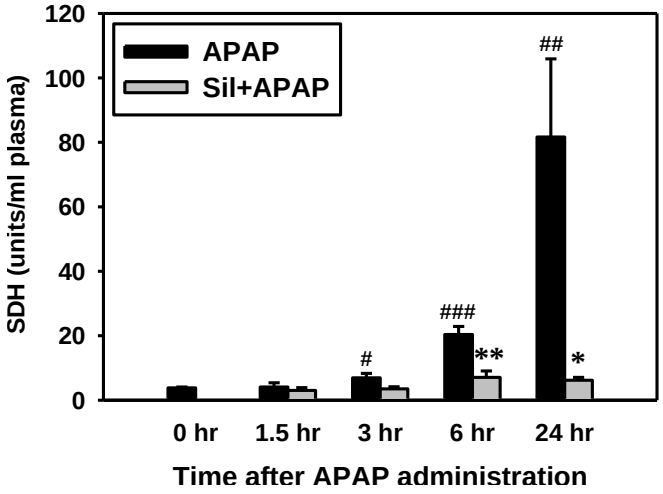


Metabolic fate of acetaminophen

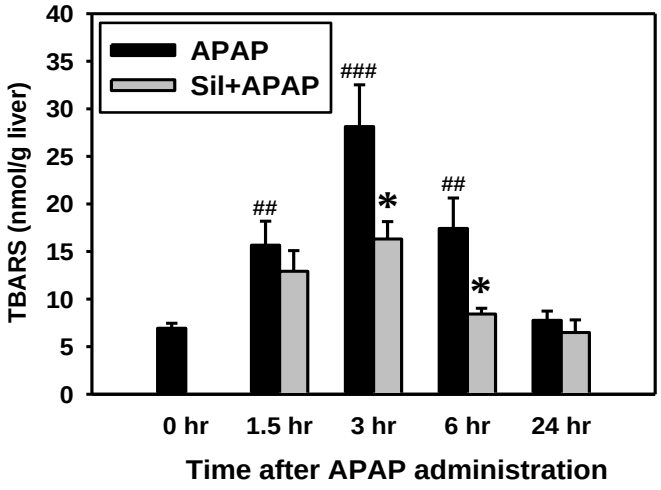
Enhancement of GSH Detoxicifcation Capacity by Silymarin

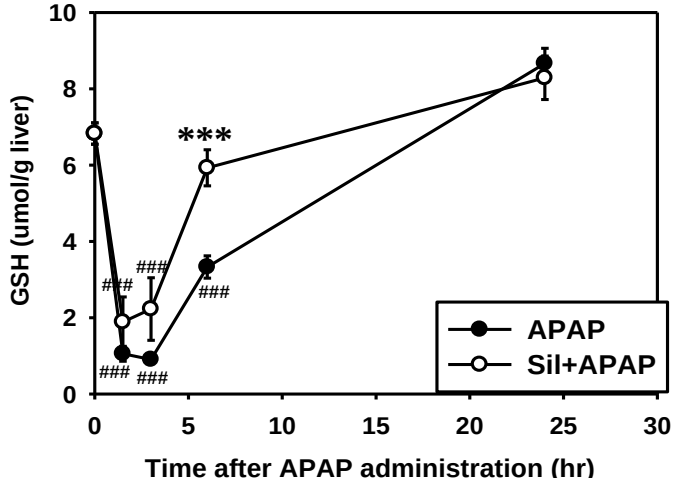
Elevation of enzyme activities in plasma of mice treated with APAP



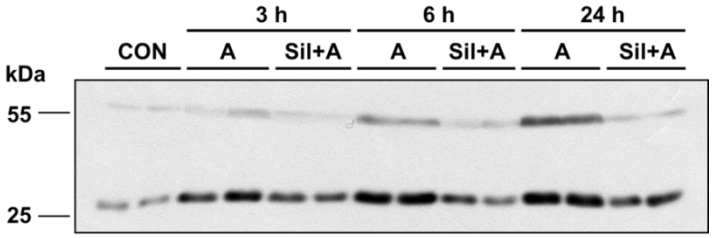


Lipid peroxidation and GSH content in liver

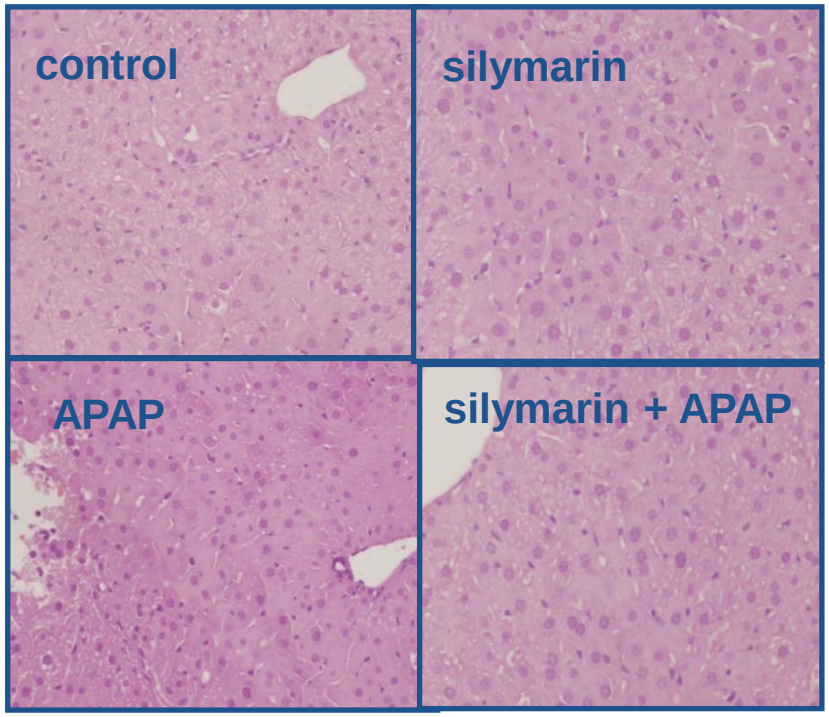




Enhancement of GSH Detoxicifcation Capacity by Silymarin



Formation of nitrotyrosine protein adducts in liver

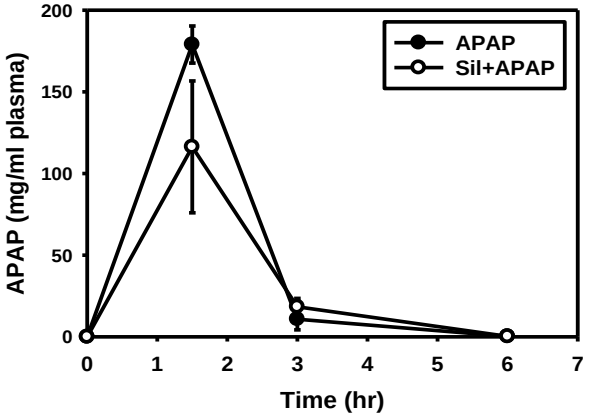


H & E staining

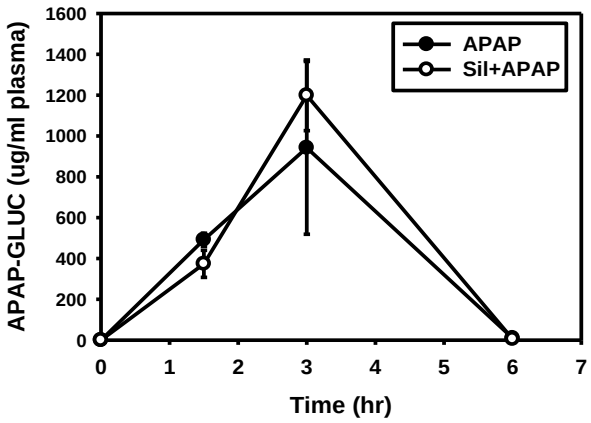
Enhancement of GSH Detoxicifcation Capacity by Silymarin

APAP metabolites in plasma

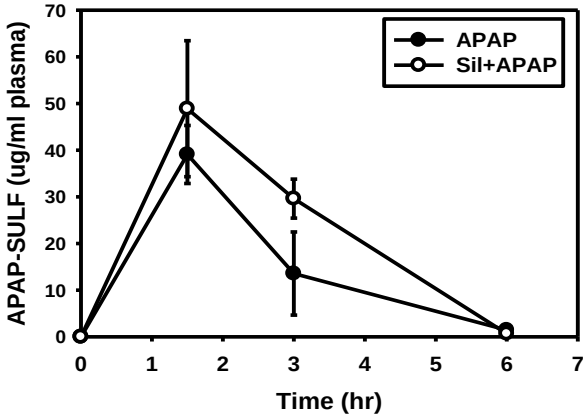
APAP



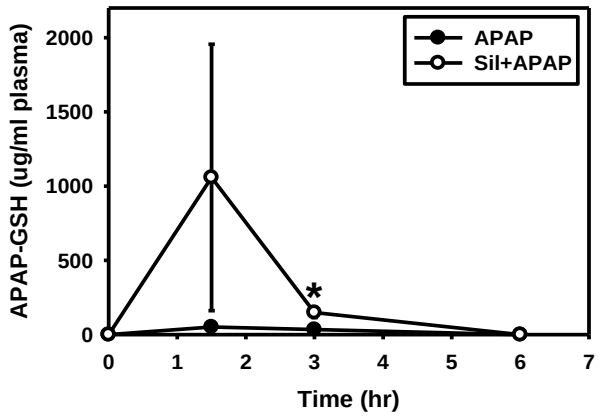
APAP-GLUC



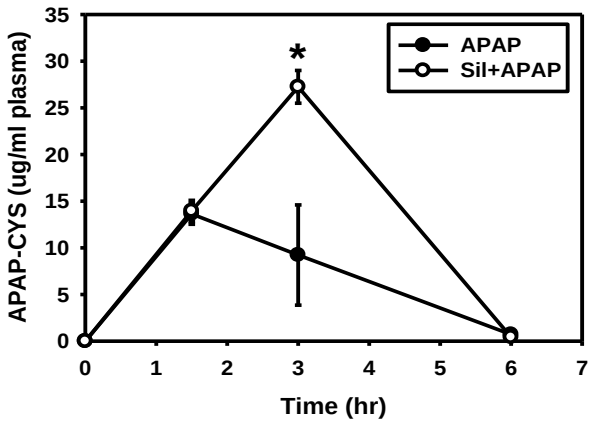
APAP-SULF



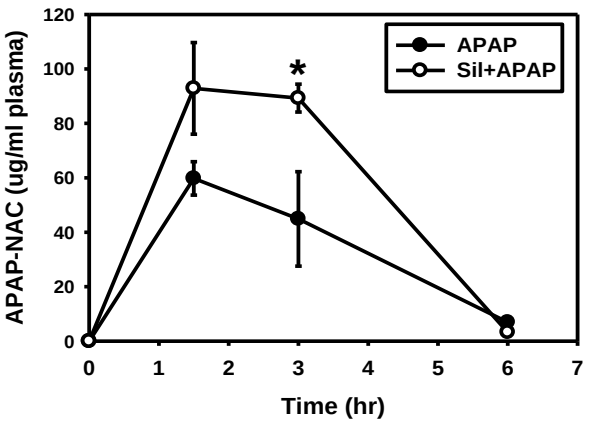
APAP-GSH



APAP-CYS

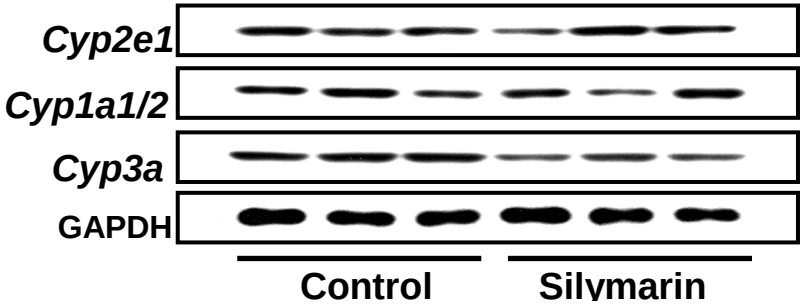


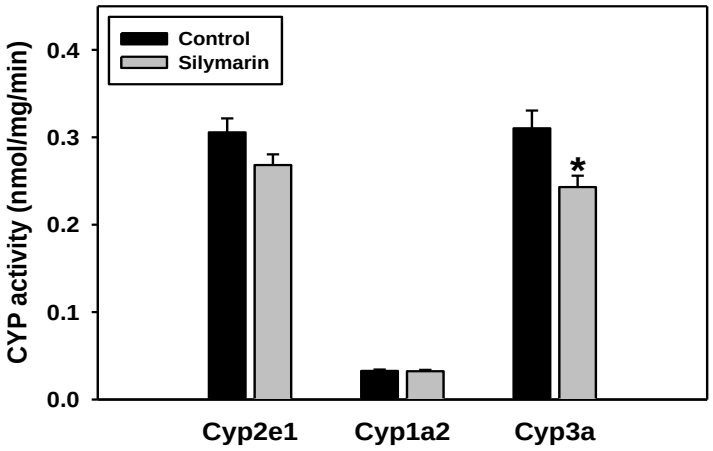
APAP-NAC

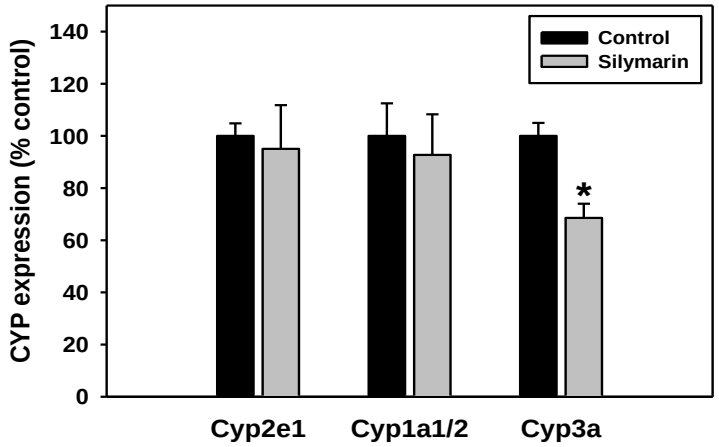


Enhancement of GSH Detoxicifcation Capacity by Silymarin

Changes in CYP enzymes in liver of mice treated with silymarin only







SUMMARY – 2nd PART

- ✓ **Silymarin pretreatment inhibits the hepatotoxicity and lipid peroxidation induced by an acute dose of APAP. GSH depletion is also alleviated.**
- ✓ **Plasma levels of thiol conjugates of APAP are elevated while APAP, APAP-glucuronide and APAP-sulfate are unchanged, indicating GSH conjugation with NAPQI is enhanced.**
- ✓ **Hepatic CYP activity responsible for the metabolic activation of APAP is not induced by silymarin. Therefore, the increased detoxification of APAP via GSH conjugation should be attributed to the elevation of GSH availability in liver.**

CONCLUSIONS

- ✓ The antioxidant activity of silymarin should be, at least in part, attributed to the increase in GSH biosynthesis.
- ✓ The induction of GSH synthesis by silymarin has a physiological significance as shown by the reduction of lipid peroxidation and the improvement of antioxidant defense in the naïve mice.
- ✓ The elevation of hepatic GSH by silymarin may increase the detoxification potential of liver against various toxicants and their electrophilic metabolites.

Thank You !

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Jae Hak Park, D.V.M., Ph.D.
Ms. Ji Hyun Kim

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