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Full Paper

Pattern of co-prescription of silymarin and antidiabetics in outpatient, a population based study

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The aim of this study was to analyze the trend of combined use of silymarin and hypoglycemic drugs (anti-diabetics) by elderly outpatient in 7-year period in Taiwan and assess whether the trends may be in line with the preliminary positive outcome. A systematic review analysis was performed to identify the correlation of silymarin to hypoglycemic drugs. A retrospective and descriptive population based study was then performed by using claim database of the National Health Insurance Research Database, which contains all inpatient and outpatient medical claims of approximately 23 million patients in Taiwan between January 2000 and December 2006. Adult patients aged from 18 years to ≧60 years, who had concurrently prescribed silymarin and antidiabetic drugs at outpatient visit were identified. The prescribing trends were described in terms of prescribing patterns of silymarin monotherapy or combination therapy in each study year. The extents to which the co-prescription of two drugs and the association with patients' characteristics, types of hospitals and co-morbid chronic diseases were assessed and statistically analyzed by SPSS for Windows as well as Many-faceted Rasch Model. A total of 3193049 prescriptions, which included silymarin monotherapy and silymarin-antidiabetics combination therapy, were identified over the 7-year period from 2000 to 2006. The total number of prescription of silymarin monotherapy and silymarin-antidiabetics combination therapy increased from 0.17% (860/515765) in 2000 to 0.76% (2335/ 309053) in 2006 and from 0.01% in 2000 to 0.11% in 2006, respectively. Silymarin combined with antidiabetics were mostly prescribed to patients aged 60 years or older. The proportion of prescriptions with silymarin alone increased about 4 folds from 245 in 2000 to 1022 in 2006, among patients over 60 years old. The number of co-prescriptions prescribed to the same aged patients also increased from 15.49% to 58.8 %. Most prescriptions were prescribed for 28 days. Forty-two percent of the co- prescriptions were prescribed at the same visit. The correlation of co-prescription of silymarin-antidiabetics with patients' characteristics, specialty of prescribing physicians, types of antidiabetics and other co-founders showed statistical significance. Silymarin is widely used in Taiwan and Europe as a hepato-protective drug. As it is able to reduce plasma glucose and pancreatic lipid peroxidation reported by some studies, the increased trends of co-prescription of silymarin and hypoglycemic drugs in elderly population found in this study may imply that some physicians management of diabetic cirrhotic patients had a positive

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trends towards the positive preliminary outcome that silymarin reduces insulin resistance. Therefore, patients who want to use silymarin may need to be informed about the possibility of drug interaction in order to reduce therapeutic failure or increased toxicity of conventional drug therapy.

Keywords: Silymarin, hypoglycemic drugs, Diabetes mellitus, co-prescription, retrospective population study

Introduction

Silymarin is a popular herbal preparation and a general name for several flavonolignans extracted from the seed of milk thistle (*Silybum marianum* L) [1]. Fruit and seeds of the milk thistle are a major source of silymarin which consist of silibinin, isosilybinin, silydianin and silychristin [2, 3]. Preparations of milk thistle seeds have been used as a natural medication for diseases of the liver and biliary tract for over 2000 years. The pharmacological profile of silymarin has been well defined and included hepatoprotective properties, anti-inflammatory, immunomodulating activities and powerful antioxidant that has been used to treat various hepatic disorders, including hepatotoxicity secondary to acute and chronic viral hepatitis [4, 5]. The improvement of the antioxidative defense was performed by preventing glutathione depletion and antifibrotic activity [6]. To date, it is widespread use of silymarin by patients with chronic liver disease in western countries because of substantial clinical trials and a meta-analysis reporting that silymarin is effective for acute and chronic liver diseases [7-9]. Despite its popularity, there is still limited data available on the safety and drug interactions. Since silymarin is usually ingested on a long-term basis, the long term effect on the silymarin-drug interaction needs to be investigated [3].

General public believe that herbal preparations are good for health because they are a natural products. However, potential herbal-drug interaction is a major safety concern, especially for drugs with narrow therapeutic indices and used by the elderly, it may cause severe adverse drug reactions. Recently, few studies indicated that silymarin may reduce HbA1C, plasma glucose and lipid peroxidation [3, 10-15]. Some studies suggested a potential for drug interaction due to inhibitory effects of silymarin on cytochromes P450 [10, 16-18].

In Taiwan, people are usually used Traditional Chinese Medicines (TCM, herbal medicine or complementary or alternative medicine in western countries, TCM) in combination with chemical drugs [19]. There is also an increasing trend worldwide in the use of TCMs or alternative medicines alone or combined with other prescribed medicines [20]. Approximately 16% of prescription-drug users consumed TCM simultaneously [21]. More than 60% of patients do not disclose their use of herbal medicine on their own when physicians took medical history and also many physicians are unaware of the potential herb-drug interactions which might possibly caused severe adverse drug reactions [21].

The aim of this study was to analyze the trend of combined use of silymarin and hypoglycemic drugs by elderly outpatient over a 7-year period in Taiwan and to assess if the trends may be in line with clinical trial outcomes.

Methods

Literature search

A systematic review methodology was used to identify literatures on the correlation of silymarin to hypoglycemic drugs. The terms 'silymarin', 'hypoglycemic or anti-diabetics', 'drug -interaction', were searched in Medline, Pub-med from 1990

to June 2008. Only English language was eligible. Review article, comments and letters were excluded from this review.

Data source

Data were retrieved from the Longitudinal Health Insurance Database (LHID) between January 1, 2000 and December 31, 2006. LHID, which is constructed and managed by the National Health Research Institute, contains comprehensive health care utilization and enrollment information of National Health Insurance (NHI) beneficiaries. LHID comprises the following files: inpatient expenditures by admissions (DD), details of inpatient orders (DO), ambulatory care expenditures by visit (CD), details of ambulatory care orders (OO), expenditures for prescriptions dispensed at contracted pharmacies (GD), and details of prescriptions dispensed at contracted pharmacies (GO).

Patient Selection

The inclusion criteria in the study were adult patients aged 18 years to ≧60 years and used at least one antidiabetic agent and any brand of silymarin prescribed concurrently in one prescription associated with the visit. Silymarin and antidiabetic agents were identified by using the Bureau of National health Insurance Drug Codes [22] and classified by using Anatomic Therapeutic Chemical (ATC) code, which is an internationally accepted classification system of drugs coordinated by the WHO Collaborating Center for Drug Statistics Methodology [23]. Classes of antidiabetic agents were categorized into two pharmacological subgroups: insulins (ATC code: A10A) and oral blood glucose lowering drugs (ATC code: A10B); silymarin (ATC code: A05BA03). Any brand of silymarin and any one of hypoglycemic drugs reimbursed by BNHI prescribed at the same visit were defined as the combination of two drugs.

Silymarin prescribed alone or in combination with antidiabetic drugs for patients with ICD-9 codes, 070.0-070.9 (1. other diseases due to viruses); 155.0-155.2 (2. malignant neoplasm); 270.6-270.9 (3. other metabolic disorders and immunity disorders); 291.0-291.9; 305.0-305.3 (5. mental disorders); 320-389 (6. diseases of the nervous system and sense organs); 390-459 (7. diseases of the circulatory system); 460-519 (8. diseases of the respiratory system); 570.1-576.1 (9. other diseases of digestive system); 580-629 (10. diseases of the genitourinary system); 680-709 (12. diseases of the skin and subcutaneous tissue); 710-739 (13. diseases of the musculoskeletal system and connective tissue); 740-759 (14. congenital anomalies); 760-779 (15. certain conditions originating in the perinatal period); 780-799 (16. symptoms, signs, and ill-defined conditions); 800-799 (17. injury and poisoning); E800-E999 (19. supplementary classification of external causes of injury and poisoning) were also retrieved from the claim database.

Many-faceted Rasch Model (MFRM)

The many-faceted Rasch Model is usually used to analyze multi-level data sets [24]. Each response is associated with probability. Therefore, MFRM was used to analyze the aberrant correlation of different kinds of anti-diabetic drugs with the diseases, physicians specialty, and the studied years. Additionally, it also predicts the future trends and frequency of co-prescribing through the use of item-fit and person-fit statistics in the model [25-27].

The MFRM model is,

$$\log it_{mhkl} \equiv \ln\left(\frac{p_{nijkl}}{p_{ni(j-1)kl}}\right) = \vartheta_n - \left(\delta_i - \tau_j\right) - \gamma_k - \lambda_l$$

where P_{nijkl} and $P_{ni(j\text{-}1)kl}$ are the probability of scoring *j* and *j-1* in item *i* at year occasion *k* for person *n* of medicine department *l,* respectively; γ_k and λ_l is the threshold of year occasion *k* and medicine department *l*, and the others are defined as above MFRM model. The primary advantages of the many-faceted Rasch calibration are (a) that all facets involved in the calibration can be taken into account, (b) that the calibrated facets share the same

metric, and (c) that the measurement scales are additive [28].

Data analysis

The trends of prescribing were described as patterns of silymarin and its co-prescription of antidiabetics. For the calculation of the annual prescribing pattern, the annual number of prescription of either silymarin monotherapy or combination therapy with anti-diabetics were divided by the total number of prescriptions of any pattern. The prescribing patterns in this study were classified into monotherapy or in combination with anti-diabetics. The correlation of prescribing pattern with patient characteristics (age, gender, co-morbid), types of hospitals, specialty of prescribing physicians and other cofounders in the out-patient setting during the study period were evaluated and analyzed.

Chi-square statistics was used to find out the key cofactors correlated to the probability of co-prescription. By using the many-faceted Rasch Model (MFRM) [24, 25, 28], the type of anti-diabetic drugs related to the main cofounders were analyzed (in Rasch model called facets). SPSS for Windows (Version 15) was used to analyze data.

Results and Discussion

From the systematic review, there were 14 published articles, including *in vitro* and *in vivo* studies, indicated that silymarin may be able to reduce insulin resistance and may be used in diabetes mellitus [11, 12, 15, 35-43]. In addition, the silymarin-drug interactions may not be excluded.

A total of 3193049 prescriptions for silymarin monotherapy and silymarin-antidiabetics combination therapy were identified over the 7-year period from 2000 to 2006. The prescribing patterns for monotherapy of silymarin and combination therapy with antidiabetics in each year from 2000 to 2006 were showed in table 1. The total number of prescriptions (included silymarin and silymarin-antidiabetics) for studied drugs declined from 515,765 in 2000 to 309,053 in 2006. The trends of prescribing pattern for silymarin monotherapy and co-prescribed with hypoglycemic drugs increased steadily, the proportion rates showed a significant increase from 0.17% in 2000 to 0.76% in 2006 for silymarin monotherapy and from 0.01% in 2000 to 0.11% in 2006 for co-prescription, respectively ($P<0.01$).

Table 1 shows that no significant change in the use of silymarin monotherapy and silymarin-antidiabetics combination therapy for patients aged <20, but declined significantly for the age of 20-39 and 40-49 years over the studied years. Silymarin either prescribed alone or in combination with hypoglycemic drugs for patients aged 50-59 decreased from 2000 to 2002 but increased from 2002 to 2006 ($P<0.01$); for patients aged $\geqq$ 60 years, both monotherapy or combination therapy increased significantly ($P<0.01$).

The association of co-prescription of silymarin and hypoglycemic drugs with the demographic characteristics showed statistically significant ($P< 0.05$). The trends in association of co-prescription with the years were increased from 2000 to 2003 and then declined from 2003 to 2006 due to the issue of new restricted reimbursement policy. In table 2, the co-prescription of silymarin with anti-diabetics have statistically significant difference between the patients with age $\geqq$ 60 years and other aged groups, the t values are 15.72 for age<20 ; t=8.48 for 20-39; t=3.53 for age 40-49 and t=4.24 for age of 50-59. In addition to the co-prescription prescribed by physicians of internal medicine, there were other specialties co-prescribed silymarin with hypoglycemic drugs, such as obstetrics, pediatrics and surgery (table 2).

Fifteen hypoglycemic drugs were identified to prescribe with silymarin. The first number in the parentheses indicated the sequence and the second number indi-

cated the numbers of generic brands for the same drug. According to the classification of hypoglycemic drugs, oral blood glucose lowering drugs (ATC code: A10B) can be further classified as first generation sulfonulurea agents**:** tolbutamide (1,1), tolazamide (2, 2), chlorpropamide (3, 6); second generation**:** glipizide (4, 25), glyburide (5, 32), glimepiride (6, 14), gliclazide (7, 47), gliquidone (8, 2); Biguanine**:** metformin (11, 75), buformin (12, 1); Meglitinides**:** repaglinide (9, 6), nateglinide (10, 9); Thiazolidinedione**:** rosiglitazone (13, 8), pioglitazone (14, 14) and Alpha-glucosidease inhibitors**:** acarbose (15, 19).

Table 1. Changes in the utilization pattern of Drugs of Anti-diabetic and Silymarin in Taiwan from 2000 to 2006

	2000	2001	2002	2003	2004	2005	2006	P value
Total prescriptions of studied drugs	515765	520628	530733	535558	456,557	324,755	309,053	<.001
Silymarin monotherapy								
A: No. of prescriptions (%)	860(0.17)	1470(0.28)	2164(0.41)	4416(0.82)	3177(0.70)	2925(0.90)	2335(0.76)	<.001
Age (years, %)								
<20	27(3.14)	18(1.22)	17(0.79)	37(0.84)	20(0.63)	26(0.89)	20(0.86)	ns
20-39	159(18.49)	303(20.61)	356(16.45)	695(15.74)	437(13.76)	406(13.90)	318(13.62)	<.001
40-49	229(26.63)	314(21.36)	469(21.67)	883(20.00)	568(17.88)	509(17.40)	404(17.30)	<.001
50-59	200(23.26)	343(23.33)	502(23.19)	949(21.49)	781(24.58)	789(26.97)	632(27.01)	<.001
>=60	245(28.49)	501(34.08)	802(37.06)	1852(41.94)	1371(43.15)	1253(42.84)	1022(43.77)	<.001
Silymarin combination with anti-diabetic drug								
B: No. of prescriptions (%)	71(0.01)	179(0.03)	279(0.05)	2319(0.43)	499(0.11)	373(0.11)	350(0.11)	<.001
Age (years, %)								
<20	0(0.00)	0(0.00)	0(0.00)	15(0.65)	0(0.00)	0(0.00)	0(0.00)	
20-39	0(0.00)	26(14.53)	23(8.24)	337(14.53)	28(5.61)	8(2.14)	17(4.86)	<.001
40-49	32(45.07)	28(15.64)	21(7.53)	412(17.77)	25(5.01)	39(10.46)	52(14.86)	<.001
50-59	28(39.44)	54(30.17)	72(25.81)	517(22.29)	173(34.67)	145(38.87)	136(38.90)	<.001
>=60	11(15.49)	71(39.66)	163(58.42)	1038(44.76)	273(54.71)	181(48.53)	206(58.86)	<.001

Figure 1 shows the results of MFRM analysis in an interval logit scored scale, on which all cofounders are shown separately at the top of the figure within the respective facets. Along the vertical column, the higher the position, the less the probability of co-prescriptions was prescribed. Therefore, hypoglycemic drugs located at the lower bottom of the second vertical column indicated higher prevalence of co-prescribed with silymarin, for example, repaglinide (represented as number 9), which located at the higher position at the bottom of column two as compared to nateglinide, clorpropamide, glipizide, gliquidone, showed less probability of co-prescribed with silymarin. The same results for rosiglitazone, glyburide, gliclazide, metformin Tolbutamide, tolazamide, buformin, pioglitazone and acarbose, co-administered with silymarin, were not be identified in any prescriptions because those did not appeared within the studied facets. The results in other cofounders, such as prescription year, patient's age, comorbid chronic disease and

specialty of prescribing physicians also showed similar results. Furthermore, the co-prescription was most likely prescribed by physicians for treating liver diseases, and then endocrine, nutritional and metabolic diseases and immunity disorders (no.3 in appendix I) and symptoms, signs and ill-defined conditions(no.16 in appendix I) and for patients aged between≧ 60 years (figure 3).

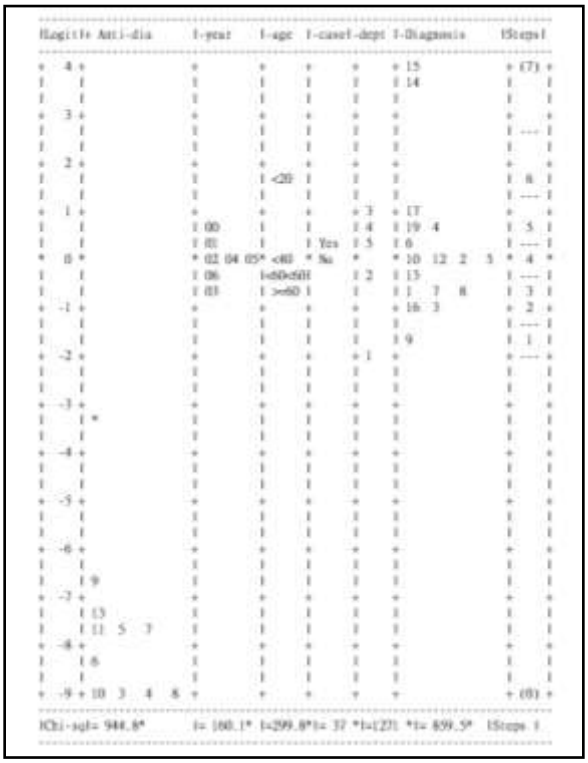

Figure 1. Many-faceted analysis for silymarin-antidiabetics co-prescription

Notes: logit (1st facet); antidiabetics (2nd facet); prescription years (3rd facet) patients' age(4th facet). Specialty of prescribed physicians (6th facet); Diagnosis (7th facet, meaning of number represented in table 3).
**P<0.05*

Figure 2 showed the probability of distribution of studied hypoglycemic drugs co-prescribed with silymarin from the year of 2000 to 2006, which indicated that repaglinide, rosiglitazone, glyburide, gliclazide, metformin were highly co-prescribed with silymarin by physicians as compared to gliquidone,. chlorpropamide.

In this study we found that the number of prescription of silymarin alone was increased dramatically from 2000 to 2003, but declined gradually from 2003 to 2006.

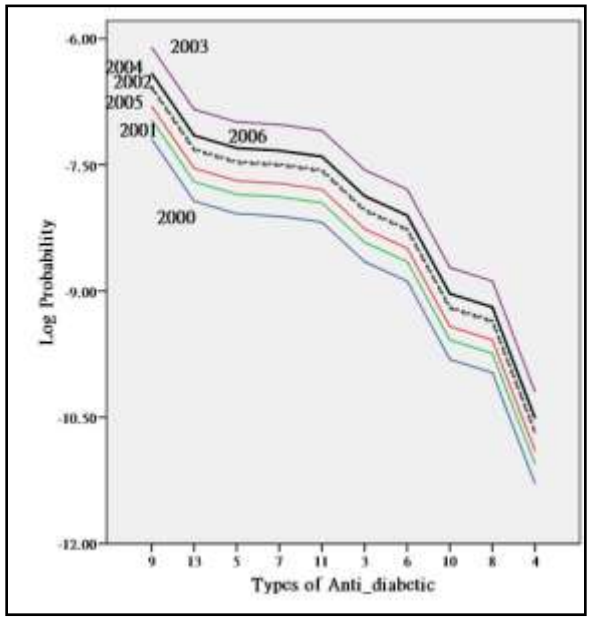

Figure 2. The probability of distribution of studied hypoglycemic drugs co-prescribed with silymarin from the year of 2000 to 2006

Note: 9: repaglinide; 13: rosiglitazone; 5: glyburide; 7: gliclazide; 11: metformin; 3: chlorpropamide; 8:gliquidone; 4: glipizide

Additionally, the trends of association of co-prescription with the years were also declined from year 2003, which showed that year 2003 was a critical year because of the issue of more restricted reimbursement policy by BNHI in order to lower the drug expenditure of silymarin claimed by the medical institutions, which is about US$150602.4 (1US$=NT$33.1) annually [29]. The total number of co-prescription of silymarin with hypoglycemic drugs was increased about 5- folds in 2006 as compared to that in 2000. It may be most likely that the issue of more restricted reimbursement policy for silymarin monotherapy since 2003 and the increased number of diagnosis of patients suffered from both liver diseases and diabetes [30]. Other reasons may be the physicians agreed with the substantial evidences of studies to support the notion

that silymarin has antidiabetic effects by decreasing glycosylated hemoglobin (HbA1c), fasting blood glucose [11-16].

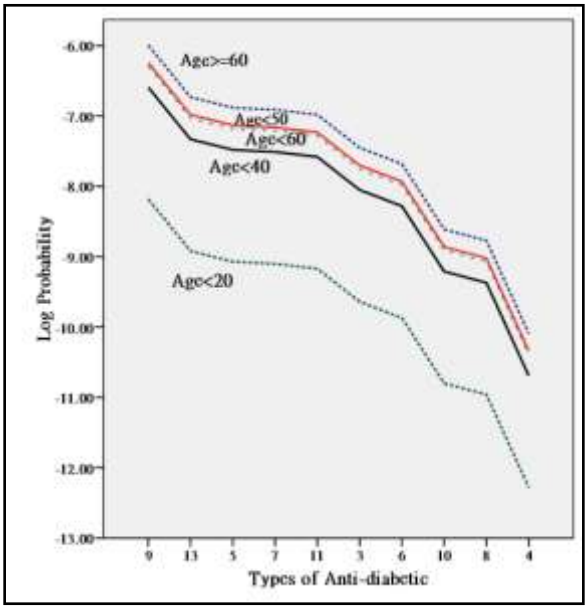

Figure 3. The probability of distribution of studied hypoglycemic drugs co-prescribed with silymarin by patient age

Silymarin has a good safety profile and has been used to treat liver disease since the 16th century and recently widespread used by patients with chronic liver disease in Europe [6]. Few studies to evaluate the potential interaction of silymarin with drugs which may metabolize through cytochrome P 450 2C9 or 3A4 *in vivo* with the conclusion that silymarin may inhibit cytochrome P450 2B6, 2C8, 2C9 and 3A4 with high concentration and reducing P-glycoprotein(P-gp) transport [3, 10-11, 16-17]. Accordingly , the potential risk of drug-drug interactions in co-administration of silymarin and drugs which are metabolized through cytochrome P 2C9 or 3A4 may not be excluded [3], such as hypoglycemic drugs retrieved in this study, for example, repaglinide, rosiglitazone, glyburide, gliclazide, those are metabolized through cytochrome P450 2C8, 2C9, or 3A4 [34]. As silymarin is a popular herbal product in the market and limited information is available on the safety, drug-interactions, we suggest that silymarin preparations should be labeled to alert consumers to potential interactions when co-administration with other drugs. Healthcare professionals (physicians, pharmacists) should give advice to patients, who want to use silymarin, about the possibility of potential drug interactions, especially for patients aged $\geqq$ 60 years.

By using the MFRM model, we found the same results of correlation of key co-factors to co-prescription as chi-square analysis, for example, the prevalence of co-prescription was highly related to digestive disease (represented as symbol 9), then followed by endocrine, nutritional and metabolic diseases and immunity disorders (represented as symbol 3) and symptoms, signs and ill-defined conditions (represented as symbol 16), and infectious, diseases of the circulatory system, diseases of respiratory system (represented as symbol 1,7,8). All these sub-specialty were belongs to internal medicine. However, the correlation of co-prescription to other specialty in addition to the above-mentioned is likely considered as abnormal prescribing pattern or behavior. We assume that the physicians of these specialties may be prescribed as per patients' special request.

The limitation of this study is similar to other studies using administrative databases and need to be illustrated. The claim database used in this study only provide information on the drugs prescribed, it cannot provide any clinical information to evaluate the response of patients on drug therapy, such as patient compliance, laboratory data. The prevalence of co-prescription is just the approximate estimation on healthcare institutions, not including the over-the-counter or self-administered medications which are not covered by BNHI program.

Table 2. Association between demographic characteristics and prescribing pattern of co-prescription of Silymarin and hypoglycemic Drugs from 2000-2006.

	Co-prescribe						
	yes	**%**	**no**	**%**	**Total no. of silymarin alone**	**%**	***p value***
Gender						100.00%	0.075
Female	1775	24.33%	5522	75.67%	7297	42.05%	
Male	2295	22.83%	7755	77.17%	10050	57.95%	
Year						100.00%	<0.001
2000	71	8.26%	789	91.74%	860	4.96%	
2001	179	12.18%	1291	87.82%	1470	8.47%	
2002	279	12.89%	1885	87.11%	2164	12.47%	
2003	2319	52.51%	2097	47.49%	4416	25.46%	
2004	499	15.71%	2678	84.29%	3177	18.31%	
2005	373	12.75%	2552	87.25%	2925	16.86%	
2006	350	14.99%	1985	85.01%	2335	13.46%	
Age						100.00%	<0.001
<20	15	9.09%	150	90.91%	165	0.95%	
20-39	439	16.78%	2177	83.22%	2616	15.08%	
40-49	609	18.04%	2767	81.96%	3376	19.46%	
50-59	1125	27.64%	3080	74.32%	4144	23.89%	
>=60	1943	27.58%	5103	72.42%	7046	40.62%	
Hospital						100.00%	>0.05
public	520	20.54%	2012	79.46%	2532	14.60%	
private	3550	23.96%	11265	76.04%	14815	85.40%	
Specialty						100.00%	<0.001
Internal(1)	3915	23.78%	12545	76.22%	16460	94.89%	
Surgery(2)	77	12.28%	550	87.72%	627	3.61%	
Obstetrics(3)	5	11.11%	40	88.89%	45	0.26%	
Pediatrics(4)	32	59.26%	22	40.74%	54	0.31%	
Others(5)	41	25.47%	120	74.53%	161	0.93%	
Chronic diseases						100.00%	>0.05
No	2967	31.12%	6567	68.88%	9534	54.96%	
Yes	1103	14.12%	6710	85.88%	7813	45.04%	
Total	4070	23.46%	13277	76.54%	17347	100.00%	

In conclusion, silymarin is widely used in Taiwan and Europe as a hepatoprotective drug. As it is able to reduce plasma glucose and pancreatic lipid peroxidation which had been reported by some studies, the increased trends of co-prescription of silymarin and hypoglycemic drugs in elderly population found in this study may need to be concerned. These findings may imply that some physicians

management of diabetic cirrhotic patients had a positive trends towards the positive preliminary outcome that silymarin reduces insulin resistance. However there is still limited information available on the safety, drug-interactions. Patients who want to use silymarin may need to be informed about the possibility of drug interaction in order to reduce therapeutic failure or increased toxicity of conventional drug therapy.

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