Effect of the Single Oral Combination Treatment of Tamoxifen with Gamisoyo-san on the Pharmacokinetics Profiles of Tamoxifen

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The effects of *Gamisoyo-san* (GMSYS) co-administration within 5 min on the pharmacokinetics (PK) of tamoxifen were observed. After 50 mg/kg of tamoxifen oral treatment, GMSYS 100 mg/kg was orally administered within 5 min to 7-wk old male SPF.VAF Outbred Crl:CD [Sprague-Dawley (SD)] rats. The plasma were collected at 30 min before administration, 30 min, 1, 2, 3, 4, 6, 8 and 24 hrs after end of GMSYS treatment, and plasma concentrations of tamoxifen were analyzed using LC-MS/MS methods. Tmax, Cmax, AUC, $t_{1/2}$ and MRT_{inf} of tamoxifen were analysis as compared with tamoxifen single administered rats. Although co-administration with GMSYS did not critically influenced on the pharmacokinetic parameters of oral tamoxifen, they induced increased trends of plasma tamoxifen concentrations, especially significant ($p<0.05$) increases of plasma tamoxifen concentrations were demonstrated at 0.5 hr after end of co-administration with GMSYS as compared with tamoxifen single formula treated rats, at dosage levels of tamoxifen 10 mg/kg and GMSYS 100 mg/kg within 5 min. It is considered that pharmacokinetic studies should be tested like the effects of GMSYS on the pharmacokinetics of tamoxifen, when they were co-administered with prolonger intervals than Tmax of tamoxifen oral administration (about 2.5 hr-intervals), to achieve the optimal dosing regimen of GMSYS and tamoxifen co-administration.

keywords : *Gamisoyo-san*, Pharmacokinetics, Drug-drug interactions, Rat, Tamoxifen

Introduction

Tamoxifen (Nolvadex™) is a nonsteroidal estrogen agonist-antagonist antineoplastic agent has been used for breast cancer[1]. It is the usual endocrine (anti-estrogen) therapy for hormone receptor-positive breast cancer in pre-menopausal women, and is also a standard in post-menopausal women although aromatase inhibitors are also frequently used in that setting[2]. In addition, tamoxifen also used to treat infertility in women with anovulatory disorders[3] and prevention for gynecomastia[4]. Tamoxifen competitively binds to estrogen receptors on tumors and other tissue targets, producing a nuclear complex that decreases DNA synthesis and inhibits estrogen effects. It is a nonsteroidal agent with potent antiestrogenic properties which compete with estrogen for binding sites in breast and other tissues. Tamoxifen causes cells to remain in the G0 and G1 phases of the cell cycle. Because it prevents (pre)cancerous cells from dividing but does not cause cell death, tamoxifen is cytostatic rather than cytocidal[5]. However, various side effects related to tamoxifen treatment also have been arise as bone loss in premenopausal women who continue to menstruate after adjuvant chemotherapy[6], endometrial changes, including cancer, are among tamoxifen's side effects[7], increased risk of thromboembolism[8], cause of fatty liver[9], reduced cognition [10], semantic memory scores[11] and libido[12], and premature growth plate fusion[13]. Tamoxifen also depress the immune response[14], and it also known that hypersensitivity to tamoxifen or any ingredient in the formulation[15]. Tamoxifen is contraindicated, when used in women with ductal carcinoma in situ and women at high risk for breast cancer, concurrent anticoagulant therapy with a warfarin derivative[16], and should be used with caution in patients with leukopenia or thrombocytopenia[17] and pregnant[18].

Gamisoyo-san (GMSYS; *Jiawei-xiao-yao-san* in Chinese, *Kamishoyo-san* in Japanese), one of the commonly prescribed herbal formulas consisted of 10 herbs - Angelicae Gigantis Radix, Paeoniae Radix, Atractylodis Rhizoma Alba, Hoelen, Bupleuri Radix, Gardeniae Fructus,

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Glycyrrhizae Radix et Rhizoma, Moutan Cortex, Menthae Herba and Zingiberis Rhizoma, has routinely been prescribed to relieve irregularity of menstruation, anxiety associated with the menstrual cycle and various menopause-related symptoms occurring in climacteric disturbance[19], Thus, it seems reasonable to suggest that GMSYS should be considered an alternative to hormone-replacement-therapy for patients with climacteric symptoms, especially those who presented psychological symptoms[20]. It is often prescribed for women who complain of general fatigue, hot flushes, stiff shoulders, insomnia, diaphoresis, depression, irritability, etc. It is also applied to treat diverse diseases, including autonomic imbalance, neurosis, eruption, chloasma (melasma), alopecia, constipation[21], functional dyspepsia[22], Parkinson's disease and convulsions[23], and breast cancer[24]. Although many researchers have investigated the pharmacological effects of GMSYS, there has been no study on its possible drug-drug interactions with tamoxifen.

In the present study, the effects of GMSYS co-administration on the pharmacokinetics of tamoxifen were observed as a process of the comprehensive and integrative medicine, combination therapy of tamoxifen with GMSYS to achieve synergic pharmacodynamics and reduce toxicity on the breast cancer patients. After 50 mg/kg of tamoxifen treatment, GMSYS 100 mg/kg was co-administered within 5 min. The plasma were collected at 30min before administration, 30 min, 1, 2, 3, 4, 6, 8 and 24 hrs after end of GMSYS treatment, and plasma concentrations of tamoxifen were analyzed using LC-MS/MS methods. PK parameters of tamoxifen (Tmax, Cmax, AUC, t1/2 and MRTinf) were analysis as compared with tamoxifen single administered rats using noncompartmental pharmacokinetics data analyzer programs.

Materials and Methods

1. Animals and husbandry

A total of twenty-one male SPF.VAF Outbred Crl:CD [Sprague-Dawley (SD)] rats (6-wk old upon receipt; OrientBio, Seungnam, Korea) were used after acclimatization for 12 days. Animals were allocated five per polycarbonate cage in a temperature (20-25℃) and humidity (40-45%) controlled room. Light : dark cycle was 12 hr : 12 hr and feed (Samyang, Korea) and water were supplied free to access. After twelve days of acclimatization, five rats per group were selected based on the body weights, and used further experiments in the present study. All animals were marked by picric acid, and overnight fasted (about 18 hrs; water was not restricted) before treatment, and further fasted during 3 hrs after end of treatment. Animal experiments were conducted according to the national regulations of the usage and welfare of laboratory animals, and approved by the Institutional Animal Care and Use Committee in Daegu Haany University (Gyeongsan, Gyeongbuk, Korea) [Approval No. DHU2013-058].

2. Test articles and formulation

Light brown granules of GMSYS (HANPOONG PHARM & FOODS Co, Ltd., Seoul, Korea), produced according to Korean Good Manufacturing Practice and permitted and regulated by the Korean Food & Drug Administration (Seoul, Korea) were used in this experiment, and tamoxifen (Hangzhou Tacon Co., Ltd, Hangzhou, China) was used as control drug as listed follows. Individual compositions of ten kinds of herbs in GMSYS were listed in Table 1. Tamoxifen and GMSYS were stored in a refrigerator at 4℃ to protect from light and degeneration until use. Both drugs are well dissolved (up to 20 mg/ml solutions in GMSYS and upto 10mg/ml solutions in tamoxifen) in distilled water as vehicle, respectively.

Table 1. Composition of GMSYS Used in This Study

Herbs	Scientific Names	Amounts (g)
Angelicae Gigantis Radix	*Angelica gigas* N.	1.00
Paeoniae Radix	*Paeonia lactiflora* Pall.	1.00
Atractylodis Rhizoma Alba	Atractylodes ovata (Thunb.) DC.	1.00
Hoelen	*Poria cocos* Wolf	1.00
Bupleuri Radix	*Bupleurum falcatum* L.	1.00
Gardeniae Fructus	*Gardenia florida* L.	0.67
Glycyrrhizae Radix et Rhizoma	*Glycyrrhiza uralensis* Fisch	0.67
Moutan Cortex	*Paeonia szechuanica* Fang.	0.67
Menthae Herba	*Mentha arvensis var. piperascens* Makinv.	0.33
Zingiberis Rhizoma	*Zingiber officinale* Roscoe	0.33
Total	10 types	7.67

GMSYS = *Gamisoyo-san* purchase from HANPOONG PHARM & FOODS Co, Ltd. (Seoul, Korea)

3. Groupings and administration

Five rats per group (two groups) were used in this study as follows. The doses of test materials were selected based on their toxicity and pharmacodynamics – 50 mg/kg of tamoxifen with 100 mg/kg of GMSYS. After 50 mg/kg of tamoxifen treatment, GMSYS 100 mg/kg was administered, within 5min. In tamoxifen single treated rats, 50 mg/kg of tamoxifen was orally administered, and then distilled water 5 ml/kg was orally administered, instead of GMSYS solutions, 5min-intervals. Each tamoxifen or GMSYS was single orally administered, in a

volume of 5 m/kg, dissolved in distilled water.

4. Plasma collections

All rats were anesthetized with 2 to 3% isoflurane (Hana Pharm. Co., Hwasung, Korea) in the mixture of 70% N2O and 28.5% O_2, and blood samples (0.5 ml) were collected into 50 IU heparinized tubes via the orbital plexus at 30 min before treatment (as a control), 30 min, 1, 2, 3, 4, 6, 8 and 24 hrs after end of oral administration. Blood samples were immediately centrifuged for 10 min at 13,000 rpm and about 0.3 ml aliquots of plasma were stored in a −150℃ deep freezer until analysis of tamoxifen.

5. Sample preparation and calibrations

Primary stock solution, 1.0 mg/ml of tamoxifen in 100% MeOH (Baker, Phillipsburg, NJ, USA) and internal standard working solution, carbamazepine (Sigma-Aldrich, Sigma, St. Louise, MO, USA) 500 ng/ml in acetonitrile were prepared. Working standard solutions were prepared by dilution with acetonitrile. All standard solutions were stored at -20℃ in the dark when not in use, and calibrated the standard samples as 100 µl of blank plasma; working standard solutions and internal standard working solution were mixed with 200 µl of acetonitrile. In addition, 100 µl of sample plasma and internal standard working solution were mixed with 200 µl of acetonitrile. The mixtures were mixed by vortex-mixing and centrifuged at 12,000 rpm for 10min at 4ºC. The clear supernatants (5.0 µl) were transferred to injection vials and the aliquot was injected into the LC-MS/MS system.

6. LC-MS/MS conditions

Concentrations of tamoxifen in the rat plasma samples were determined LC-MS/MS method. Chromatographic analysis was performed using an Agilent 1100 Series HPLC (Agilent Technologies, Santa Clara, CA, USA) equipped with on-line degasser, binary pump, autosampler and column compartment. Separation of the analyte from potentially interfering material was achieved at ambient temperature using Waters Symmetry™ C18 columns (2.1×50 mm, 3.5 µm) (Waters Corp., Milford, MA, USA) at column oven 30℃. The mobile phase used for the chromatographic separation was composed of 50% distilled water (0.1% formic acid)/50% acetonitrile, and was delivered isocratically at a flow rate of 0.35 ml/min. The column effluent was monitored using an API 2000 triple-quadruple mass-spectometric detector (Applied Biosystems, Foster City, CA, USA). The instrument was equipped with an electrospray interface in positive ion mode, and controlled by the Analyst version 1.4.1 software (Applied Biosystems, Foster City, CA, USA) (Linear ($1/x^2$, no Iterate)). Samples were introduced to the interface through a Turbo IonSpray with the temperature set at 500℃. A high positive voltage of 4.0 kV was applied to the ion spray. Nitrogen was used as the nebulizer gas, curtain gas, and collision gas with the settings of 70, 20, and 7, respectively. The multiple reaction monitoring (MRM) detection method was employed for the detection of tamoxifen; the transitions monitored were carbamazepine (IS): m/z 237>194 (Retention time: 0.63 min), tamoxifen: 372>178 (Retention time: 0.55 min). Calibration curves of tamoxifen were linear over the ranges studied with $r^2 > 0.999$. The lower limit of quantification of the tamoxifen in the rat plasma was 8 ng/ml.

7. Pharmacokinetic analysis

The plasma concentration data were analyzed using a noncompartmental method on commercial pharmacokinetics data analyzer programs (PK solutions 2.0; Summit, Montrose, CO, USA)[25]. The elimination rate constant (K_{el}) was calculated by the log-linear regression of tamoxifen concentration data during the elimination phase, and the terminal half-life ($t_{1/2}$) was calculated by 0.693/Kel. The peak concentration (Cmax) and time to reach the peak concentration (Tmax) of tamoxifen in the plasma were obtained by visual inspection of the data in the concentration-time curve. The area under the plasma concentration-time curve (AUC_{0-t}) from time zero to the time of the last measured concentration (C_{last}) was calculated using the linear trapezoidal rule[26]. The AUC zero to infinity (AUC_{0-inf}) was obtained by adding AUC_{0-t} and the extrapolated area was determined by C_{last}/K_{el}. The mean residence time infinity (MRT_{inf}) was calculated by dividing the first moment of AUC ($AUMC_{0-inf}$) by AUC_{0-inf}.

8. Statistical analyses

All the means are presented with their standard deviation of five rats (Mean ± S.D. of five rat plasma concentrations of tamoxifen). The pharmacokinetic parameters were compared using a non-parametric comparison test, Mann-Whitney U (MW) test, on the SPSS for Windows (Release 14.0K, SPSS Inc., USA). A p-value <0.05 was considered statistically significant. In addition, the percent changes between tamoxifen single treated rats and tamoxifen with GMSYS co-administered rats were calculated to help the understanding of the effects of co-administration: Percentage changes as compared with

tamoxifen 50 mg/kg single treated mice (%) = [((Data of GMSYS co-administrated rats − data of tamoxifen single treated rats)/Data of tamoxifen single treated rats) × 100].

Results

1. Changes on the plasma concentrations of tamoxifen

Tamoxifen was detected from 30 min to 24 hrs after end of administration in the both tamoxifen single or co-administered rats with GMSYS, respectively. Slight increases trends of plasma concentration of tamoxifen were demonstrated throughout all blood collecting points, and especially significant ($p<0.05$) increases of the plasma tamoxifen concentrations were observed at 30 min after co-administration of GMSYS and tamoxifen as compared with tamoxifen single treated rats, in the present study (Fig 1). The plasma tamoxifen concentrations at 30 min, 1, 2, 3, 4, 6, 8 and 24 hrs after end of treatment were changed as 67.93, 23.80, -3.71, 23.93, 20.82, 4.46, -3.38 and -0.05% in tamoxifen + GMSYS treated rats as compared with tamoxifen single treated rats, respectively.

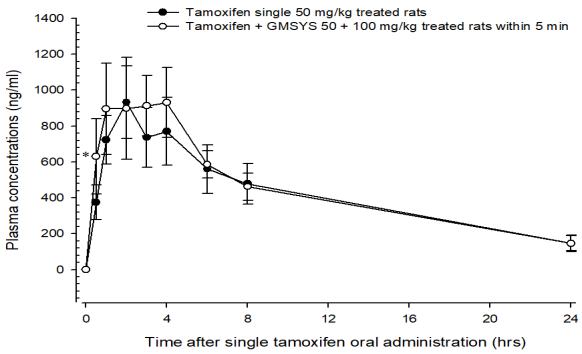

Fig. 1. Plasma Concentrations of Tamoxifen with and without GMSYS Co-administration within 5 min in Male Rats. Values are expressed as mean ± S.D. of five rats (ng/ml). GMSYS = *Gamisoyo-san*. * $p<0.05$ as compared with tamoxifen single treated rats.

2. Changes on the Tmax of tamoxifen

The Tmax of tamoxifen were non-significantly and slightly increased as 9.09% in co-administrated rats with tamoxifen 50 mg/kg and GMSYS 100 mg/kg (2.40±1.14 hr) as compared with tamoxifen single treated rats (2.20±1.10 hr), in the present study(Table 2).

3. Changes on the Cmax of tamoxifen

The Cmax of tamoxifen were non-significantly increased as 4.25% in co-administrated rats with tamoxifen 50 mg/kg and GMSYS 100 mg/kg (1.00±0.21 μg/ml) as compared with tamoxifen single treated rats (0.96±0.19 μg/ml), in the present study (Table 2).

4. Changes on the AUC of tamoxifen

The AUC_{0-t} of tamoxifen were non-significantly increased as 5.34% in co-administrated rats with tamoxifen 50 mg/kg and GMSYS 100 mg/kg (10.07±1.98 hr•μg/ml) as compared with tamoxifen single treated rats (10.16±1.52 hr•μg/ml). In addition, AUC_{0-inf} of tamoxifen were also non-significantly decreased as -5.21% in co-administrated rats with tamoxifen and GMSYS (12.70±2.75 hr•μg/ml) as compared with tamoxifen single treated rats (13.40±2.51 hr•μg/ml), in the present study (Table 2).

5. Changes on the t1/2 of tamoxifen

The t1/2 of tamoxifen were markedly but non-significantly decreased as -28.75% in co-administrated rats with tamoxifen 50 mg/kg and GMSYS 100 mg/kg (9.21±1.30 hr) as compared with tamoxifen single treated rats (12.92±11.13 hr), in the present study (Table 2).

6. Changes on the MRTinf of tamoxifen

The MRTinf of tamoxifen were markedly but non-significantly decreased as -32.00% in co-administrated rats with tamoxifen 50 mg/kg and GMSYS 100 mg/kg (12.03±1.47 hr) as compared with tamoxifen single treated rats (17.69±15.26 hr), in the present study (Table 2).

Table 2. Pharmacokinetic Parameters of Tamoxifen with and without GMSYS Co-administration within 5min in Male Rats

Parameters	Tamoxifen (50 mg/kg)	
	Without GMSYS co-administration (Distill water)	With GMSYS co-administration (100 mg/kg)
Tmax (hrs)	2.20±1.10	2.40±1.14
Cmax (μg/ml)	0.96±0.19	1.00±0.21
AUC_{0-t} (hr•μg/ml)	10.16±1.52	10.70±1.98
AUC_{0-inf} (hr•μg/ml)	13.40±2.51	12.70±2.75
$t_{1/2}$ (hr)	12.92±11.13	9.21±1.30
MRT_{inf} (hr)	17.69±15.26	12.03±1.47

Values are expressed as mean ± S.D. of five rats. GMSYS = *Gamisoyo-san*. Cmax: The peak plasma concentration, Tmax: Time to reach Cmax, AUC_{0-t}: The total area under the plasma concentration-time curve from time zero to time measured, AUC_{0-inf}: The total area under the plasma concentration-time curve from time zero to time infinity, $t_{1/2}$: half life, MRT_{inf}: mean residence to time infinity.

Discussion

In the present study, the effects of GMSYS co-administration on the pharmacokinetics of tamoxifen were observed, combination therapy of tamoxifen with GMSYS to achieve synergic pharmacodynamics and reduce toxicity on the breast cancer patient. Although co-administration with GMSYS did not critically influenced on the pharmacokinetic parameters of oral tamoxifen, they induced increased trends of plasma tamoxifen concentrations, especially significant ($p<0.05$) increases of

plasma tamoxifen concentrations were demonstrated at 0.5 hr after end of co-administration with GMSYS as compared with tamoxifen single formula treated rats, at dosage levels of tamoxifen 50 mg/kg and GMSYS 100 mg/kg within 5 min, in this experiment. These findings are considered as direct evidences that the adverse effects of tamoxifen could be influenced by the enhanced bioavailability of tamoxifen, which might be attributable to the promotion of absorption of tamoxifen by GMSYS. Hence, it is considered that pharmacokinetic studies should be tested like the effects of GMSYS on the pharmacokinetics of tamoxifen, when they were co-administered with prolonger intervals than Tmax of tamoxifen oral administration, about 2.5 hr-intervals, to achieve the optimal dosing regimen of GMSYS and tamoxifen co-administration, as a process of the comprehensive and integrative medicine, the combination therapy of tamoxifen with GMSYS on the breast cancer.

Tamoxifen was absorbed slowly following oral administration and Tmax of tamoxifen occur about 3-6 hrs after a single dose[27] but it rapidly and extensively metabolized in the liver, through a substrate of CYP3A, 2C9, 2D6 including an active major metabolite, N-desmethyltamoxifen has biologic activity similar to that of the parent drug[28]. Steady-state concentrations of tamoxifen are attained after 3-4 weeks and those of N-desmethyltamoxifen, an active metabolite, are attained after 3-8 weeks[29]. Tamoxifen excreted principally in feces as polar conjugates[30] with about 5-7 days of t1/2 in tamoxifen and 9-14 days in N-desmethyltamoxifen[27]. Clearance of tamoxifen is higher in female children 2-10 years of age than in women[31]. In the present study, Tmax of tamoxifen in tamoxifen single oral treated rats was detected as 2.20±1.10 hr, and Cmax, AUC_{0-t}, AUC_{0-inf}, $t_{1/2}$ and MRT_{inf} were detected as 0.96±0.19 μg, 10.16±1.52 hr•μg/ml, 13.40±2.51 hr•μg/ml, 12.92±11.13 hr and 17.69±15.26 hr, respectively. In tamoxifen with GMSYS co-administered rats, Tmax, Cmax, AUC_{0-t}, AUC_{0-inf}, $t_{1/2}$ and MRT_{inf} of tamoxifen were detected as 2.40±1.14 hr, 1.00±0.21 μg, 10.70±1.98 hr•μg/ml, 12.70±2.75 hr•μg/ml, 9.21 ±1.30 hr and 12.03±1.47 hr as changed as 9.09, 4.25, 5.34, -5.21, -28.75 and -32.00% as compared with tamoxifen 50 mg/kg single oral treated rats, respectively. However, no significant changes on the pharmacokinetic parameters of oral tamoxifen were observed after single co-administration with GMSYS as compared with tamoxifen single formula treated rats, at dosage levels of tamoxifen 50 mg/kg and GMSYS 100 mg/kg within 5 min, in this experiment.

As results of combination therapies with other drugs to improve the side effects of tamoxifen or to achieve synergic effects, various drug-drug interactions of tamoxifen have been evaluated; Because tamoxifen was metabolized by a substrate of CYP3A, 2C9, 2D6[32], it interacted with various drugs, namely, combinations containing any of the following medications, depending on the amount present, may also interact with aminoglutethimide - decreased plasma tamoxifen and N-desmethyltamoxifen concentrations[33], anticoagulants - enhanced warfarin effects[34], bromocriptine - increased plasma tamoxifen and N-desmethyltamoxifen concentrations[35], letrozole - decreased plasma letrozole concentrationsa[36], medroxyprogesterone - decreased plasma N-desmethyltamoxifen concentrations but did not reduce plasma tamoxifen concentrations[37], phenobarbital - decreased plasma tamoxifen concentrations[38], rifampin - decreased plasma tamoxifen and N-desmethyltamoxifen concentrations[39], and cyclosporine, erythromycin, diltiazem, erythromycin and nifedipine - competitively inhibited formation of N-desmethyltamoxifen in vitro[40], respectively. However, interactions with herbal products have not been established except for some restricted natural compounds; tamoxifen enhanced warfarin effects, and it is contraindicate that co-administration of tamoxifen and wafarin[34]. In addition, we have been observed the possible interactions with Korean traditional polyherbal formulas; we observed that oral co-administration of *Jaeumkanghwa-tang*, a traditional yin-tonifying herbal medicine has been used for various oriental obstetrical and gynecological fields within 5min did not critically influenced on the pharmacokinetics profiles of tamoxifen after single[41] and repeated[42] co-administration at dosage levels of 50 mg/kg in tamoxifen and 100 mg/kg in *Jaeumkanghwa-tang*, respectively. In this study, single co-administration of GMSYS with tamoxifen within 5min significantly increased the oral absorption of tamoxifen, enough to influence on the toxicity of tamoxifen. Hence, it is considered that pharmacokinetic studies should be tested like the effects of GMSYS on the pharmacokinetics of tamoxifen, when they were co-administered with prolonger intervals than Tmax of tamoxifen oral administration, about 2.5hr-intervals, to achieve the optimal dosing regimen of GMSYS and tamoxifen co-administration, as a process of the comprehensive and integrative medicine, the combination therapy of tamoxifen with GMSYS on the breast cancer.

Conclusion

Although single co-administration with GMSYS within 5

min did not influenced on the pharmacokinetic parameters of oral tamoxifen, GMSYS significantly increased the oral absorption of tamoxifen, when they were single co-administered within 5 min. Therefore, it is considered that pharmacokinetic studies should be tested like the effects of GMSYS on the pharmacokinetics of tamoxifen, when they were co-administered with prolonger intervals than Tmax of tamoxifen oral administration (about 2.5 hr-intervals), to achieve the optimal dosing regimen of GMSYS and tamoxifen co-administration, as a process of the comprehensive and integrative medicine, the combination therapy of tamoxifen with GMSYS on the breast cancer.

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