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Original Article

PREDICTION OF LOG P AND SPECTRUM OF QUERCETINE, GLUCOSAMINE, AND ANDROGRAPHOLIDE AND ITS CORRELATION WITH LABORATORY ANALYSIS

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ABSTRACT

Objective: This study was aimed to confirm the result of computational prediction of log P and spectrum (ultraviolet-visible, ^{1}H-NMR, ^{13}C-NMR) of quercetin, glucosamine and andrographolide with laboratory analysis.

Methods: Quercetine, glucosamine and andrographolide, were downloaded from ChemSpider and were geometry optimised. Log P and spectrum were calculated and predicted and the data obtained were compared with laboratory results. The correlation was calculated by employing mean absolute deviation (MAD), mean square error (MSE), mean forecast error (MFE), and mean absolute percentage error (MAPE) parameters.

Results: The smallest energy value of geometry optimisation was provided by *ab initio* method. Log P prediction showed good accuracy, with r-value 0.995 and p-value 0.05 respectively. The error parameters were: MAD 0.19; MSE 0.06; MFE 0.16, and MAPE 8.62%, respectively. Prediction of λ maximum by *ab initio,* semiempirical, and molecular mechanics were respectively: MAD 2.67, 6.67, and 28.67; MSE 8.67, 45.33, and 830; MFE 2.67, 6.67, and 28.67; and MAPE 1.10%, 2.79%, and 11.99%; r-value 0.997, 0.997, and 0.979; and p-value 0.044, 0.043, and 0.129. ^{1}H-NMR and ^{13}C-NMR spectra prediction were: MAD 0.73 and 1.58; MSE 1.15 and 7.41; MFE 0.27 and 0.69; MAPE 18.35% and 2.68%; r-value 0.942 and 0.986; and p-value 0.001 and 0.001.

Conclusion: There is a positive correlation between computational *ab initio* calculation method with experimental results in predicting log P and spectrum of quercetine, glucosamine, and andrographolide.

Keywords: *Ab initio*, Lipophilicity, Molecular mechanics, Semiempirical, Ultraviolet-visible, ^{1}H-NMR, ^{13}C-NMR

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INTRODUCTION

The rapid development of computational techniques finds its way to be very helpful for related sciences, e. g. for chemistry to predict physicochemical properties of compounds. According to quantum chemistry, a molecular system is described by a wavefunction which can be found by solving the Schrődinger equation:

$$\hat{H}\,\Psi = E\,\Psi$$

In the end, this equation will describe the positions of the nuclei and electrons in the system. Quantum chemistry should be applied for 'small system', which can be treated at a very high level, when electronic properties are sought (electric moments, polarizabilities, shielding constants in NMR, etc) [1].

Energy is one of the most important parameters in science. All computational chemistry techniques define energy such that the system with the lowest energy is the most stable. In formulating a mathematical representation of molecules, it is necessary to define a reference system that is defined as having zero energy. This zero of energy for *ab initio* or density functional theory (DFT) corresponds to having all nuclei and electrons at an infinite distance from one another. Most empirical methods use a valence energy that corresponds to having the valence electrons removed and the resulting ions at an infinite distance. Most molecular mechanics methods use stainless molecule as zero energy [2].

In this work, we confirmed the accuracy of computational technique prediction on physicochemical properties (log P) and spectrum (ultraviolet-visible, ^{1}H-NMR, ^{13}C-NMR) of quercetin (fig. 1a), glucosamine (fig. 1b), and andrographolide (fig. 1c) by comparing it to laboratory analysis. Therefore, computational calculations could be used to simplify and shorten the long process of analytical works in the laboratory. These three compounds were selected to represent molecule with aromatic and carbonyl chromophores which have π → π* and *n* → π* electronic transitions (quercetine), a molecule which lacks of the chromophore (glucosamine), and molecule without aromatic chromophore (andrographolide). These three compounds have been proven to show anti-inflammatory activity in animals [3-8].

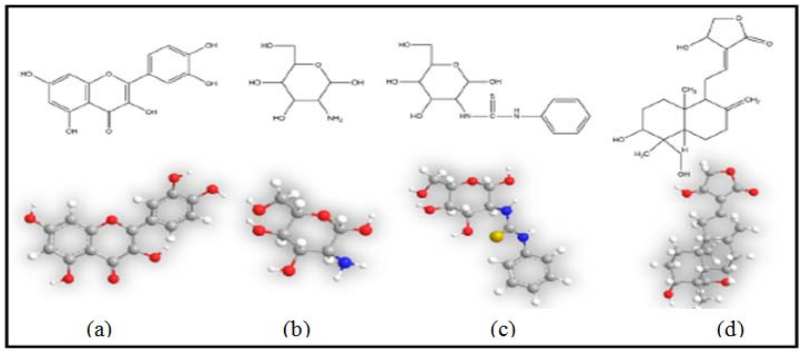


Fig. 1: Chemical structures of quercetine (a), glucosamine (b), PITC-glucosamine (c), and andrographolide (c)

MATERIALS AND METHODS

Methods

Hardware, programs, and instruments

A personal computer equipped with Intel® Core™ i5-450M (2.40 GHz, Cache 3 MB), Intel HM55, 4 GB DDR3 SODIMM PC-8500 of memory, ATI Mobility Radeon HD 5430 512MB, 500 GB Serial ATA 7200 RPM hard drive, was used for computational technique.

Programs used were: Hyper Chem, ChemBio Office®ultra 2010 (trial version) with pre-installed add-on Gamess Client® Pro for *ab initio* calculation, CS MOPAC®Pro for semiempirical calculation, Mechanics®Pro for molecular mechanics calculation.

Instruments used for physicochemical analysis were: ultraviolet-visible spectrophotometer (SPECORD200-Analytic Jena), 1H-NMR spectroscopy (Agilent 500 MHz), 13C-NMR spectroscopy (Agilent 125 MHz).

Chemicals

Standards used were: quercetine (Sigma-Aldrich), glucosamine (DongCheng Biochemical), and andrographolide (Sigma-Aldrich). Chemicals for solvents and reagents were: methanol (Merck), ethanol (Merck), *n*-octanol (Merck), ether (Merck), sodium acetate (Merck), phenylisothiocyanate (PITC) (Merck).

Data Preparations

Structures of quercetin (http://www.chemspider.com/4444051), glucosamine (http://www.chemspider.com/388352), and andrographolide (http://www.chemspider.com/Chemical-Structure. 16735664.html) were downloaded from Chem Spider.

Geometry optimisation for *ab initio* was performed using Hartree-Fock (HF) with central field approximation. The function of coordination used was a linear combination of Slater exp (-x) with STO-3G basis set.

Geometry optimisation for the semiempirical method was performed using neglect of diatomic differential overlap (NDDO) approach with AM1 parameter. Geometry optimisation for molecular mechanics method was performed using MM2 force field.

Log P and spectrum were calculated and predicted using Hyper Chem, ChemBio Office®ultra 2010. Data obtained were compared with laboratory results and calculated their accuracy by employing mean absolute deviation (MAD), mean square error (MSE), mean forecast error (MFE), and mean absolute percentage error (MAPE) parameters.

Laboratory section

Log P was determined by dissolving the compounds in a mixture of *n*-octanol and water and measuring the absorbance of the compounds in each solvent.

NMR spectra of the compounds were determined using 10 ppm of each compound in $CDCl_3$.

RESULTS AND DISCUSSION

Geometry optimisation of quercetin, glucosamine, and andrographolide showed that the lowest energy value waste obtained by *ab initio* method. According to the theory, it could be concluded that in this state the molecules are at their most stable conformations.

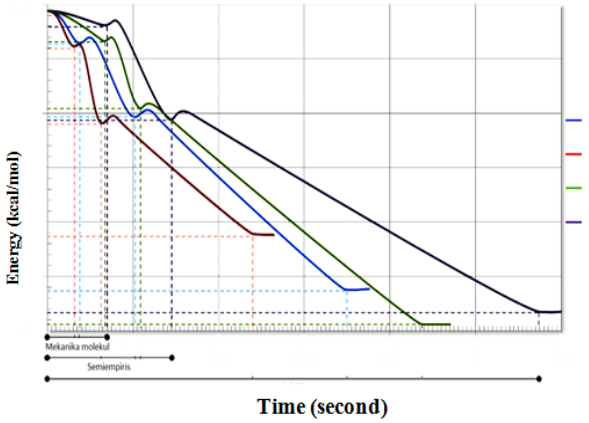


Fig. 2: Potential energy against time during geometry optimisation

UV spectra of the compounds were determined using 10 ppm of each compound in *n*-octanol and water, and log P were determined by measuring the absorbance of the compounds in each solvent. According to Woodward-Fieser, λ_{max} could be predicted by determining the base value of the compound and adding the contribution value of its substituents [9].

For quercetin (fig. 1a), the base structure is 6-membered ring enone (215 nm) with–OH at α-position as the substituent (35 nm), hence its theoretical maximum is 250 nm. fig. 3 shows UV spectra of quercetin in *n*-octanol λ_{max} 255 nm and in water λ_{max} 260 nm. The difference of the maxima is caused by the solvent.

Due to its lack of chromophores, glucosamine (fig. 1b) was reacted with phenylisothiocyanate, prior to be spectrophotometrically measured. The reaction produces a PITC-glucosamine (fig. 1c) which according to the work of Tekko and colleagues gave maximum at 245 nm [10], compared to our work which is 240 nm (fig. 4), whereas the analytical work of Shen for PITC-glucosamine was set at 254 nm [11].

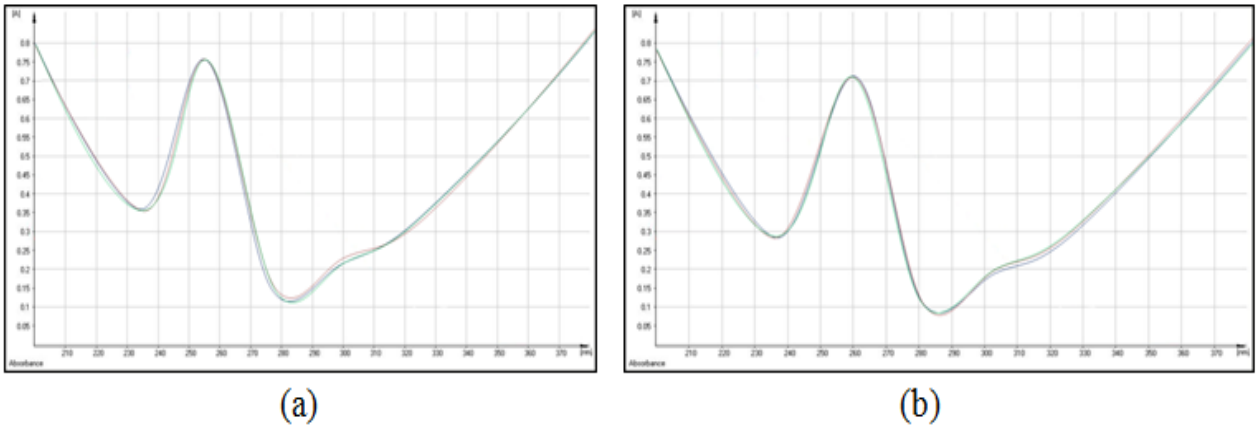


Fig. 3: UV spectra of quercetine in *n*-octanol (a) and in water (b)

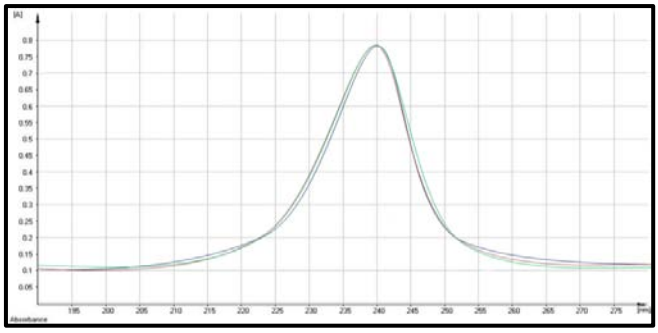
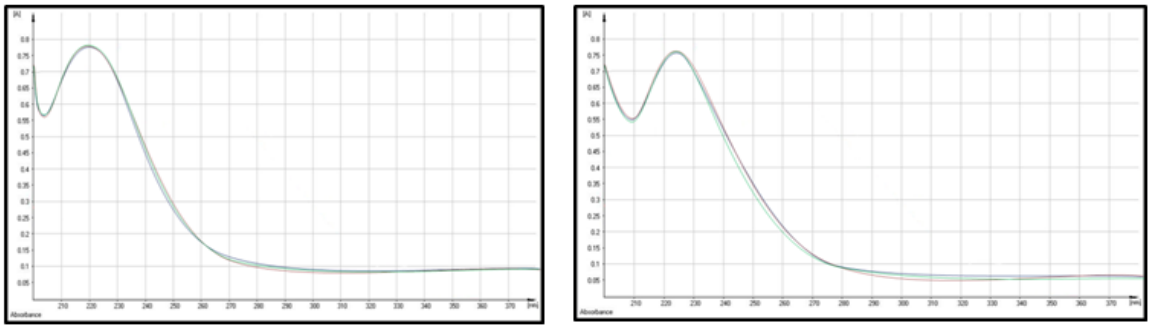


Fig. 4: UV spectrum of derivate of PITC-glucosamine

The base structure of andrographolide (fig. 1d) is 5-membered ring enone (202 nm), with a ring residue at α-position as the substituent (10 nm) and an alkyl substituent at β-position (12 nm), that add up to 230 nm, theoretically.



(a) (b)

Fig. 5: UV spectra of andrographolide in *n*-octanol (a) and in water (b)

Fig. 5 shows UV spectra of andrographolide in *n*-octanol λ_{max} 220 nm and in water λ_{max} 224 nm. The difference of the maxima is caused by the solvent.

Table 1: Determination of Log P

Compounds	Experimental result (A_t)	Prediction (F_t)			Error prediction test				Correlation test	
		I[a]	II[b]	III[c]	MAD	MSE	MFE	MAPE (%)	r-value	p-value
Quercetine	1.45	1.50	1.50	1.50	0.19	0.06	0.16	8.62		
Glucosamine	-2.04	-2.18	-2.18	-2.18					0.995	0.05
Andrographolide	2.51	2.12	2.12	2.12						

[a]: *ab initio*[b]: semiempirical: molecular mechanics

Where:

$$MAD = \sum \left| \frac{A_t - F_t}{n} \right|$$

$$MSE = \sum \frac{(A_t - F_t)^2}{n}$$

$$MFE = \sum \frac{(A_t - F_t)}{n}$$

$$MAPE = \left(\frac{100}{n}\right) \sum \left| A_t - \frac{F_t}{A_t} \right|$$

Determination of log P showed that there is no difference of log P value calculated by the three methods; furthermore, it was proven that there is a good accuracy and correlation between computational calculation and the experimental result (table 1).

Determination of λ_{max} showed there is a good accuracy and correlation between computational calculation (*ab initio* and semiempirical) with experimental results (table 2). NMR spectra predicted, and experiments were showed in fig. 6-8 and table 3, 4.

Table 2: Determination of λ_{max}

Method	Compound	Experimental result (nm)	Computational calculation (nm)	Error prediction test			Correlation test		
				MAD	MSE	MFE	MAPE (%)	r-value	p-value
Ab initio	Quercetine	256	253	2.67	8.67	2.67	1.10	0.997	0.044
	Glucosamine	240	236						
	Andrographolide	222	221						
Semi empirical	Quercetine	256	250	6.67	45.33	6.67	2.79	0.997	0.043
	Glucosamine	240	232						
	Andrographolide	222	216						
Molecular mechanics	Quercetine	256	224	28.67	830	28.67	11.99	0.979	0.129
	Glucosamine	240	215						
	Andrographolide	222	193						

Table 3: ^{1}H-NMR spectra

Compound	Error prediction test				Correlation test	
	MAD[a]	MSE[b]	MFE[c]	MAPE[d]	r-value	p-value
Quercetine	0.86	1.93	-0.35	10.15%	0.940	0.001
Glucosamine	0.79	1.09	0.66	26.71%	0.919	0.001
Andrographolide	0.55	0.43	0.50	18.20%	0.966	0.001

Table 4: ^{13}C-NMR spectra

Compound	Error prediction test				Correlation test	
	MAD[a]	MSE[b]	MFE[c]	MAPE[d]	r-value	p-value
Quercetine	0.63	0.60	0.02	0.48%	0.999	0.001
Glucosamine	3.20	19.32	-1.53	4.32%	0.961	0.002
Andrographolide	0.92	2.31	-0.57	3.23%	0.999	0.001

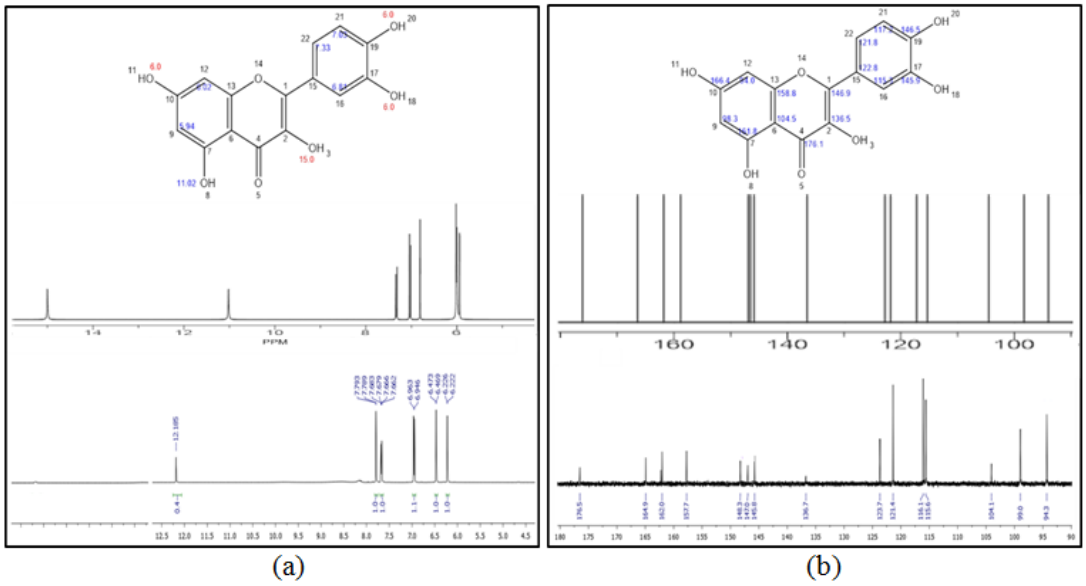


Fig. 6: ^{1}H-NMR (a) and ^{13}C-NMR (b) spectra of quercetin by computational prediction (upper) and laboratory experiment (lower)

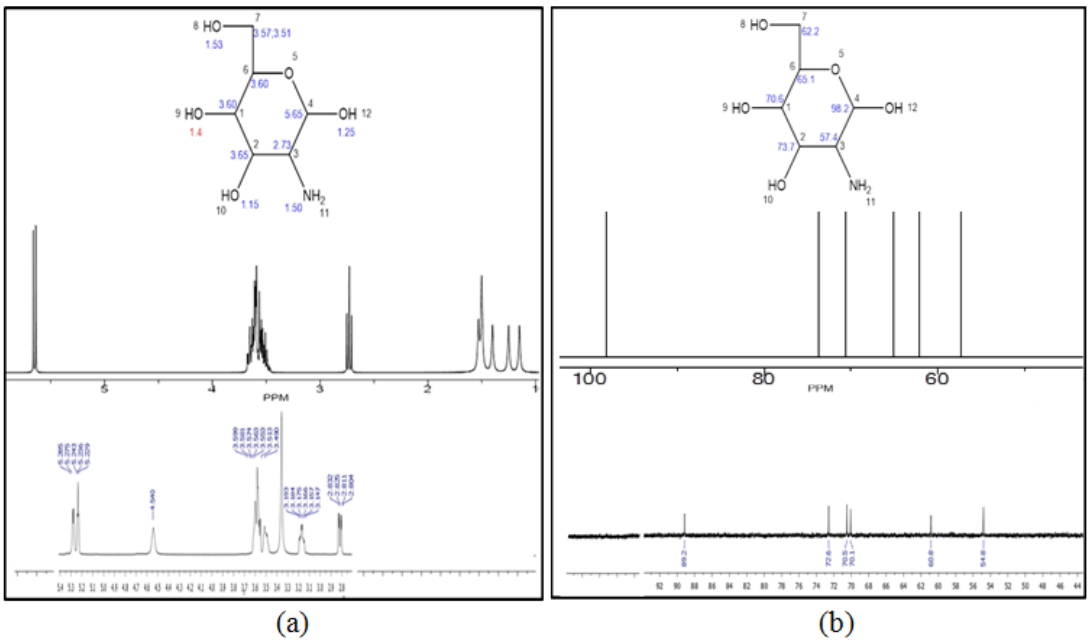
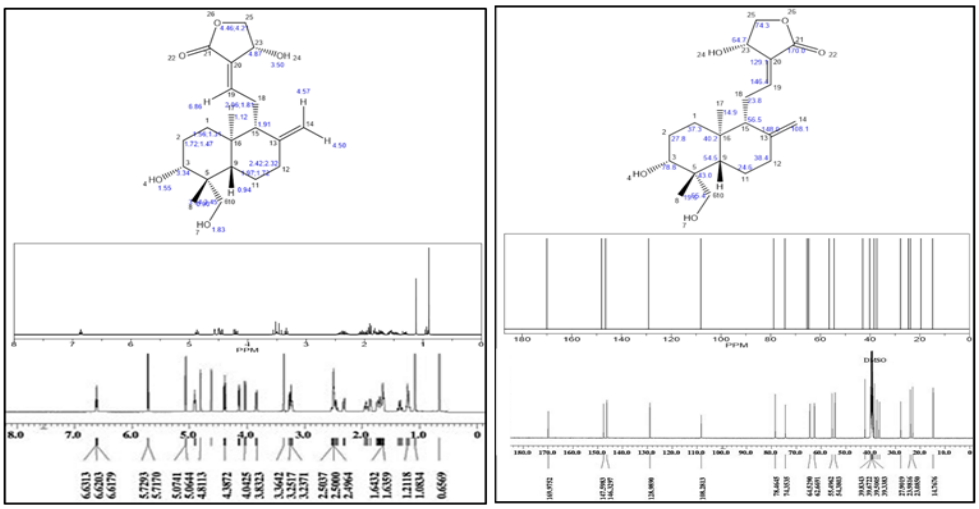


Fig. 7: ^{1}H-NMR (a) and ^{13}C-NMR (b) spectra of glucosamine by computational prediction (upper) and laboratory experiment (lower)



(a) (b)

Fig. 8: ^{1}H-NMR (a) and ^{13}C-NMR (b) spectra of andrographolide by computational prediction (upper) and laboratory experiment (lower)

CONCLUSION

There is a positive correlation between computational *ab initio* calculation method with experimental results in predicting log P and spectrum of quercetin, glucosamine, and andrographolide. This approach can be adapted to a wider range of compounds.

CONFLICTS OF INTERESTS

Declared none

REFERENCES

1. Zeilinski TJ, Swift ML. What every chemist should know about computers II. Chem Educ 1997;2:258-62.
2. Young DC. Computational chemistry: a practical guide for applying the technique to real-world problems. New York: John Wiley and Sons Inc; 2001.
3. Morikawa K, Nonaka M, Narahara M, Torii I, Kawaguchi K, Yoshikawa T, *et al*. Inhibitory effect of quercetin on carrageenan-induced inflammation in rats. Life Sci 2003;74:709-21.
4. Shen YC, Chen CF, Chiou WF. Andrographolide prevents oxygen radical production by human neutrophils: possible mechanism involved in its anti-inflammatory effect. Br J Pharmacol 2002;135:399-406.
5. Xia YF, Ye BQ, Li YD, Wang JG, He XJ, Lin X, *et al*. Andrographolide attenuates inflammation by inhibition of NF-kappaB activation through covalent modification of reduced cysteine62 of p50. J Immunol 2004;173:4207-17.
6. Wiart C. Ethnopharmacology of medicinal plants, Asia and the Pacific. Totowa (New Jersey, USA). Humana Press Inc; 2006.
7. Nagaoka I, Igarashi M, Hua J, Ju Y, Yomogida S, Sakamoto K. Recent aspects of the anti-inflammatory actions of glucosamine. Carbohydr Polym 2011;84:825-30.
8. Petersen SG, Beyer N, Hansen M, Holm L, Aagaard P, Mackey A, *et al*. Nonsteroidal anti-inflammatory drug or glucosamine reduced pain and improved muscle strength with resistance training in a randomised controlled trial of knee osteoarthritis patients. Arch Phys Med Rehabil 2011;92:1185-93.
9. Silverstein RM, Bassler GC, Morril TC. Spectrometric identification of organic compounds, New York: John Wiley and Sons Inc; 1991.
10. Tekko IA, Bonner MC, Williams AC. An optimised reverse-phase high performance liquid chromatographic method for evaluating percutaneous absorption of glucosamine hydrochloride. J Pharm Biomed Anal 2006;41:385-92.
11. Shen X, Yang M, Tomellini SA. Liquid chromatographic analysis of glucosamine in commercial dietary supplements using indirect fluorescent detection. J Chromatogr Sci 2007;45:70-5.

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