Research Paper

Relationship between Effect of Dietary Flavonoid Intake and Risk of Preeclampsia: A Research Study

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The purpose of this research was just to explore the connection between the risk of preeclampsia and the dietary consumption of flavonoids. This research adopted one matched case control study was devised with 1:1 matching by gestational age (±1 w), age (±3 y) as well as presence of gestational diabetes (yes/no). From March 2016 to June 2019, 440 pairs of participators in total were recruited. Information of dietary was attained with one questionnaire of 78 item semi quantitative food frequency. Dietary flavonoid intake was calculated using the residual method. Multivariate conditional logistic regression was adopted with the objective to assessing 95 % confidence intervals and the odds ratios. In comparison to the lowest intake quartiles, passive connections were surveyed between preeclampsia risk and the flavanones consumption (odds ratio=0.506, 95 % confidence interval=0.278-0.920, p=0.024), naringenin (odds ratio=0.477, 95 % confidence interval=0.266-0.853, p=0.02), luteolin (odds ratio=0.597, 95 % confidence interval=0.395-0.902, p<0.007) and quercetin (odds ratio=0.518, 95 % confidence interval=0.286–0.938, p<0.034) after adjustment for potential confounders. Consumption of total anthocyanidins, total flavan-3-ols and eight other specific flavonoids (hesperetin, apigenin, isorhamnetin, kaempferol, myricetin, daidzein, genistein and glycitein) was not associated with preeclampsia risk. The results suggest that increased dietary intake of flavanones (including naringenin), luteolin and quercetin is linked to a decreased preeclampsia risk.

Key words: Preeclampsia, flavonoids, hypertension, etiology, interleukin

Preeclampsia (PE) is just one kind of systemic disease specific to pregnancy and is defined as the onset of new proteinuria and hypertension after 20 w gestation[1]. During the pregnancy, PE is the most ordinary complication, with a prevalence of approximately 2.16 %. Besides, it is an essential factor of fetal, maternal and neonatal death among developing countries[2,3]. Currently, no clear cause is known and the merely efficient therapy for PE is the pregnancy termination after stabilization of the fetus and mother[4]. Therefore, the prevention of PE based on an understanding of its etiology is of great significance for public health.

The lack of a clear etiology of PE remains despite numerous global studies of the associated risk factors. The current theory suggests that maternal endothelial dysfunction and response are interrelated with PE[5,6]. According to this view, the clinical features of PE are rooted in endothelial dysfunction and an imbalance between antigenic and antiangiogenic factors due to abnormal maternal placental function[7,8].

Flavonoids are a class of bioactive polyphenols that have anti-oxidant, anti-tumor, anti-inflammatory and cardiovascular-protective functions. They are widespread in most plants, including vegetables and fruits, and are split into 6 subclasses-anthocyanins, flavan-3-ols, isoflavones, flavonols, flavanones and flavones according to their chemical structure. Many flavonoids exert vasodilatory effects that inhibit endothelial dysfunction by reducing inflammation and oxidative stress[9]. It has been demonstrated that flavonoids reduce levels of inflammatory cytokines, such as Interleukin (IL)-6, Tumor Necrosis Factor-Alpha (TNF-α), IL-8, human IL-1 beta protein (IL-1β) and IL-17, through the Extracellular Regulated Protein Kinases (ERK), Mitogen Activated Protein Kinase (MAPK), Nuclear Factor-kappa B (NF-κB) and Akt pathways[7,8,10]. This implies that there might

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be a connection between PE risk and flavonoids.

A case–control research claimed that the odds of developing PE were reduced by an increase in genistein intake[11]. Overall, however, there have been few studies of the relationship between flavonoids and PE. Therefore, the hospital-based case–control research was implemented to investigate if the dietary intake of flavonoids is linked to the PE risk[12].

MATERIALS AND METHODS

General information:

The total participators came from the First Affiliated Hospital of Zhengzhou University, a multidisciplinary hospital in Zhengzhou, China. The inclusion and exclusion criteria have already been reported among our group's prior researches[13]. According to gestational age (±1 w), age (±3 y) and the Gestational Diabetes Mellitus (GDM) (yes/no), the control group was 1:1 matched to the case group. 1180 pregnant females (648 controls and 532 PE cases) provided baseline data and completed a Food Frequency Questionnaire (FFQ) from March 2016 to June 2019. Participants were excluded if the FFQ was incomplete (n=41) or the value of the whole energy intake was implausible (<800 or >4200 kJ/d) (n=12). The entire participators signed the forms of the written informed consent prior to the research. The research was supported by the Ethics Committee of Scientific Research and Clinical Trials of the First Affiliated Hospital of Zhengzhou University in March 2016 (Scientific research-2016-LW-34; a study on the relationship among PE, vitamin D and dietary in pregnant females).

Data collection:

The participators' sociodemographic characteristics, personal lifestyle information and dietary intakes information were obtained using a structured questionnaire. Their medical history, childbearing history and related medical diagnoses originated in hospital medical documents. The definition of passive smokers and the method of calculating gestational age have been described in previous studies by our group[4].

The total participators were face to face interviewed by the interviewers who had received systematic training. The participants' dietary information during the past 3 mo before the delivery was attained with semi-quantitative FFQ, which included 78 items regarding nutritional status and dietary habits based on foods commonly consumed by Chinese people. The validity and reliability of this questionnaire have been confirmed by studies in Chinese contexts[14,15].

The participators were requested to put down how often on the average they had deplete various foods (never, monthly, weekly or daily) and the intake size every time (ml or g). Daily intakes of dietary flavonoids (mg/d) and energy (kcal/d) (comprising whole anthocyanidins, whole flavan-3-ols, whole flavanones, whole isoflavones and whole flavones) were figured out in the light of Chinese food composition tables[16,17].

Statistical analysis:

The whole dietary intake information was regulated for the entire energy intake with the residual approach. General features of case and control groups were contrasted with the Chi-square (χ^2) assay for variables and the Wilcoxon signed rank-sum test or the paired t-test for quantitative variables. Those quantitative variables are conveyed to be number and mean±Standard Deviation (SD) on condition that normally allocated or to be median and interquartile difference if non-normally allocated. Qualitative variables were compared using the McNemar's test and are expressed as numbers and percentages. According to the values in the control groups, the dietary intakes of flavonoids were categorized into quartiles (Q_1–Q_4). Linear trends were checked through entering the median of every one quartile of flavonoid intake as one continuous variable into multivariate and univariate logistic regression patterns. 95 % Confidence Intervals (CIs) and the Odds Ratios (ORs) for PE risk by each quartile of dietary flavonoid intake were evaluated with models for multivariate conditional logistic regression, with the lowest quartile adopted for the reference team. That model was regulated for age, gestational age, pre-pregnancy Body Mass Index (BMI), daily energy intake, parity, family history of hypertension, gravidity and daily energy expenditure and education level. In sensitivity analyses, participants with GDM were excluded. The whole dissections were implemented with Statistical Package for the Social Sciences (SPSS) 25.0 (SPSS Inc., Chicago, Illinois, United States of America (USA)). One two-tailed $p<0.05$ was thought to be statistically essential. The missing values were excluded; these accounted for less than 10 %.

RESULTS AND DISCUSSION

In the main analysis, 440 eligible cases and 440 matched controls were finally included. The baseline characteristics of the patients with PE and the controls are presented in Table 1. No obvious distinctions were discovered between cases and controls in age, gestational age, income or passive smoking status. Apart from pre-pregnancy BMI and the blood pressure, the rate of family history of hypertension in the case group significantly exceeded that in the control group (all $p<0.001$). In comparison to the control team, the PE case team had more elevated rates of physical activity, lower rates of parity and gravidity, lower total dietary energy intake and lower levels of education (all $p<0.05$).

Table 2 compares the intake of twenty four phytochemicals inside the six subgroups of dietary flavonoids (anthocyanins, isoflavones, flavanones and flavones) between the control and case participants. Contrast to the case team, the control one had higher dietary intakes of catechin, two flavanones (naringenin and hesperetin), two flavones (luteolin and apigenin), four flavonols (quercetin, myricetin, kaempferol and isorhamnetin) and one isoflavone (genistein) (all $p<0.05$). No obvious distinction was discovered between cases and controls in the intake of any other phytochemicals.

These associations between PE risk and certain flavonoids are summarized in Table 3. These consequences of the multivariate conditional logistic regression dissection indicated significant associations between risks of developing PE and the intake of two flavanones (including hesperetin and naringenin), one flavone (including luteolin), kaempferol and one isoflavone (including daidzein) without adjustment for the covariates; all correlations were negative except that for isoflavones, which was positive (all $p<0.05$). After controlling for age, pre-pregnancy BMI, daily energy intake, gestational age, family history of hypertension, parity, gravidity, daily energy expenditure and education level, negative associations were found between PE risk and the intakes of flavanones (Q_4 *vs.* Q_1: OR=0.506, 95 % CI: 0.278–0.920, p=0.024) (including naringenin Q_4 *vs.* Q_1: OR=0.566, 95 % CI: 0.311–1.029, p=0.02), luteolin (Q_4 *vs.* Q_1: OR=0.485, 95 % CI: 0.274–0.859, p=0.008) and quercetin (Q_4 *vs.* Q_1: OR=0.518, 95 % CI: 0.286–0.938, p=0.034). The intakes of hesperetin, flavones, kaempferol and isoflavones (including daidzein, genistein and glycitein) weren`t linked to the PE risk.

Table 4 shows these results of a sensitivity analysis in which the participators blessed with GDM were excluded to delete the impact of the pregnant females with GDM on these consequences. After adjustment for confounders, the above-described associations for flavanones (including hesperetin and naringenin), flavones (including luteolin), kaempferol and quercetin still held, but quercetin intake was no longer correlated with PE risk.

As for the matched case–control research, we

TABLE 1: SOCIODEMOGRAPHIC, LIFESTYLE FEATURES AND CHOSEN PREECLAMPSIA RISK ELEMENTS OF THE PARTICIPATORS (n=440 PAIRS)

	Cases			Controls			p*
	n	Mean/median	SD/IQR	n	Mean/median	SD/IQR	
Age (years)a	440	30.88	5.03	440	31.03	4.85	0.114
Gestational age (weeks)[a]	440	34.17	2.9	440	34.24	2.67	0.066
Systolic pressure (mmHg)[a]	440	153.78	16.71	440	113.17	10.42	<0.001
Diastolic pressure (mmHg)[a]	440	100.21	12.33	440	72.84	8.98	<0.001
Pre-pregnancy BMI (kg/m2)[a]	440	23.67	3.89	440	22.35	3.35	<0.001
Physical activity (MET-h/d)[b]	440	26.17	4.47	440	25.35	5.15	0.034
Total energy intake (kcal/d)[b]	440	1747.21	622.83	440	1866.97	595.38	0.006
Education level, n (%)							0.026
Junior high school or below	207	47		164	37.3		
Senior high school	75	17		83	18.9		
College or above	158	35.9		193	43.9		0.692
Income (Yuan/month), n (%)							

≤2000	61	13.9	46	10.5	
2001-6000	294	66.8	293	66.6	
>6000	59	13.4	81	18.4	
Family history of hypertension, n (%)					<0.001
Yes	159	36.1	82	18.6	
No	281	63.9	358	81.4	
Passive smoker, n (%)					0.488
Yes	67	15.2	59	13.4	
No	373	84.8	381	86.6	
Gravidity, n (%)					0.005
1	116	26.4	79	18	
2	112	25.5	105	23.9	
≥3	212	48.1	256	58.1	
Parity, n (%)					0.001
0	185	42	136	30.9	
1-2	249	56.6	286	65	
≥3	6	1.4	18	4.1	

Note: MET: Metabolic Equivalent Task; ([a]): Indicates mean and SD; ([b]): Indicates median and IQR and *p<0.05

TABLE 2: DISTINCTION BETWEEN RISKS OF DEVELOPING PREECLAMPSIA AND INTAKES OF FLAVONOIDS

Categories	Cases (n=440)	Controls (n=440)	p
Anthocyanins (mg)	53.07 29.61, 94.30	56.69 34.03, 101.71	0.098
Procyanidins (mg)	125.75 74.53, 180.19	138.85 83.13, 194.08	0.224
Anthocyanin (mg)	3.81 2.06, 6.99	3.7 2.23, 6.95	0.707
Delphinidin (mg)	27.87 16.05, 50.57	31.22 18.63, 53.61	0.053
Malvidin (mg)	1.97 0.11, 7.27	1.65 0.19, 7.05	0.588
Pelargonin (mg)	26.4 15.90, 51.15	27.8 16.02, 53.05	0.18
Peonidin (mg)	0.33 0.01, 1.30	0.18 0.02, 1.29	0.755
Petunidin (mg)	0.93 0.15, 2.91	1.07 0.21, 3.18	0.4
flavan-3-ols (mg)	23.72 15.19, 32.70	24.09 16.35, 34.40	0.304
Epicatechin (mg)	11.39 7.08, 16.75	12.07 7.50, 16.91	0.684
Epicatechin gallate (mg)	0.09 0.01, 0.34	0.08 0.01, 0.33	0.737

Epigallocatechin (mg)	3.44 2.11, 5.09	3.35 2.15, 4.94	0.824
Epigallocatechin gallate (mg)	1.38 0.80, 2.07	1.54 0.82, 2.12	0.253
Catechin (mg)	5.76 3.42, 9.14	6.67 4.14, 10.03	0.008
Galloyl catechin (mg)	0.59 0.26, 0.91	0.56 0.26, 0.91	0.715
Flavanones (mg)	7.95 0.85, 30.28	16.89 2.11, 38.09	0.002
Hesperetin (mg)	1.660.14, 6.51	3.69 0.29, 8.59	0.005
Naringenin (mg)	6.17 0.83, 23.55	12.85 1.82, 29.61	0.002
Flavones (mg)	4.56 3.15, 7.03	4.97 3.35, 8.40	0.005
Apigenin (mg)	1.9 1.23, 3.17	2.12 1.23, 4.03	0.04
Luteolin (mg)	2.77 2.03, 4.11	3.06 2.17, 4.76	0.001
Flavonols (mg)	16.04 12.19, 22.20	18.28 14.17, 24.63	0
Isorhamnetin (mg)	1.86 1.08, 3.19	2.02 1.19, 3.50	0.042
Kaempferol (mg)	5.48 3.78, 8.25	6.47 4.77, 9.47	0
Myricetin (mg)	0.89 0.59, 1.34	0.93 0.64, 1.45	0.045
Quercetin (mg)	8.72 6.30, 11.80	10.13 7.35, 13.11	0
Isoflavones (mg)	18.71 10.54-32.15	21.7 13.82-33.29	0.019
Daidzein (mg)	10.2 5.79-17.75	11.47 6.92-17.34	0.141
Genistein (mg)	4.91 1.20-10.42	7.22 3.79-11.92	0
Glycitein (mg)	0.002 0-0.011	0.001 0-0.006	0.748
Total flavonoids (mg)	227.82 154.92, 306.94	237.01 169.60, 327.74	0.048

TABLE 3: HAZARD OF PREECLAMPSIA IN LIGHT OF QUARTILES OF THE DIETARY FLAVONOID INTAKE

Category	Quartiles of dietary flavonoid intake (OR, 95 % CI)				p value
	Q_1	Q_2	Q_3	Q_4	
Flavanones					
Crude	1	0.861 0.581-1.275	0.560** 0.369-0.849	0.581** 0.385-0.876	0.008
Model 1	1	0.885 0.503-1.557	0.406** 0.224-0.736	0.506* 0.278-0.920	0.024
Hesperetin					
Crude	1	0.975 0.658-1.443	0.542** 0.357-0.825	0.684 0.455-1.027	0.04
Model 1	1	0.951** 0.538-1.680	0.406 0.219-0.750	0.605*** 0.330-1.110	0.086
Flavones					
Crude	1	0.936 0.630-1.391	0.594* 0.393-0.896	0.608* 0.403-0.918	0.01
Model 1	1	1.025 0.578-1.817	0.477* 0.266-0.853	0.566 0.311-1.029	0.02
Flavones					
Crude	1	1.036 0.695-1.545	1.011 0.688-1.486	0.603* 0.393-0.924	0.012
Model 1	1	0.786 0.458-1.350	0.646 0.368-1.135	0.470** 0.265-0.834	0.989
Apigenin					
Crude	1	1.316 0.868-1.996	1.082 0.727-1.610	0.774 0.512-1.172	0.067
Model 1	1	0.959 0.543-1.691	0.659 0.370-1.176	0.566 0.318-1.006	0.005
Luteolin					
Crude	1	1.027 0.693-1.522	0.87 0.587-1.289	0.597* 0.395-0.902	0.007
Model 1	1	0.818 0.469-1.428	0.419* 0.275-0.875	0.485* 0.274-0.859	0.008
Flavones					
Crude	1	0.698 0.477-1.022	0.570** 0.375-0.868	0.669* 0.453-0.989	0.059
Model 1	1	0.524* 0.305-0.901	0.685 0.372-1.264	0.537* 0.305-0.945	0.683
Isorhamnetin					
Crude	1	0.999 0.665-1.501	0.99 0.669-1.466	0.011 0.677-1.509	0.953
Model 1	1	0.83 0.485-1.419	0.883 0.514-1.517	0.995 0.535-1.706	0.031

Kaempferol					
Crude	1	0.664* 0.453–0.972	0.475*** 0.316–0.714	0.599* 0.400–0.894	0.007
Model 1	1	0.69 0.407–1.169	0.494* 0.285–0.856	0.577 0.329–1.012	0.297
Myricetin					
Crude	1	0.823 0.540–1.254	0.943 0.630–1.412	0.903 0.616–1.324	0.817
Model 1	1	0.896 0.499–1.610	1.152 0.647–2.051	0.75 0.434–1.294	0.109
Quercetin					
Crude	1	0.794 0.540–1.170	0.691 0.463–1.031	0.679 0.456–1.010	0.056
Model 1	1	0.772 0.448–1.331	0.767 0.438–1.342	0.518* 0.286–0.938	0.034
Isoflavones					
Crude	1	1.11 0.729–1.689	1.408 0.944–2.102	1.787** 1.189–2.685	0.009
Model 1	1	0.95 0.485–1.859	0.962 0.423–2.192	1.163 0.540–2.506	0.397
Daidzein					
Crude	1	0.483*** 0.324–0.720	0.453*** 0.301–0.683	0.664* 0.450–0.979	0.096
Model 1	1	0.464 0.271–0.796	0.596** 0.345–1.028	0.682 0.399–1.167	0.335
Genistein					
Crude	1	0.762 0.505–1.150	0.596** 0.401–0.885	0.946 0.644–1.390	0.885
Model 1	1	1.024 0.593–1.771	0.577* 0.335–0.995	0.977 0.581–1.643	0.681
Glycitein					
Crude	1	0.526** 0.347–0.798	0.541** 0.365–0.861	0.828 0.561–1.223	0.47
Model 1	1	0.602 0.349–1.039	0.684 0.407–1.148	0.808 0.479–1.365	0.541
Total flavonoids					
Crude	1	0.815 0.555–1.195	1.018 0.688–1.506	1.035 0.697–1.538	0.655
Model 1	1	0.508* 0.284–0.908	0.849 0.483–1.489	0.946 0.532–1.682	0.634

Note: Model 1 was adjusted for age, gestational age, daily energy intake, pre-pregnancy BMI, parity, gravidity, family history of hypertension, daily energy expenditure and education level; *p≤0.05 *vs.* Q_1; **p≤0.01 *vs.* Q_1 and ***p≤0.001 *vs.* Q_1

TABLE 4: RISK OF PREECLAMPSIA IN LIGHT OF QUARTILES OF THE DIETARY FLAVONOID INTAKE (WITHOUT THE INCLUSION OF PATIENTS WITH GDM)

Category	Quartiles of dietary flavonoid intake (OR, 95 % CI)				P
	Q_1	Q_2	Q_3	Q_4	
Flavanones					
Crude	1	0.963 0.622–1.490	0.553** 0.355–0.860	0.576* 0.374–0.888	0.007
Model 1	1	1.071 0.573–2.002	0.411** 0.217–0.779	0.527* 0.277–1.000	0.027
Hesperetin					
Crude	1	1.065 0.691–1.641	0.519** 0.333–0.810	0.664 0.429–1.027	0.031
Model 1	1	1.08 0.580–2.012	0.385** 0.199–0.744	0.631 0.327–1.216	0.116
Naringenin					
Crude	1	0.976 0.627–1.520	0.576** 0.371–0.894	0.588** 0.381–0.908	0.008
Model 1	1	1.024 0.543–1.928	0.451* 0.239–0.849	0.546 0.287–1.037	0.033
Flavones					
Crude	1	0.975 0.638–1.489	1.017 0.670–1.542	0.576* 0.361–0.919	0.017
Model 1	1	0.73 0.407–1.307	0.597 0.320–1.115	0.451* 0.240–0.848	0.014
Flavones					
Crude	1	1.357 0.870–2.118	1.111 0.722–1.707	0.756 0.482–1.187	0.073
Model 1	1	0.93 0.503–1.722	0.579 0.303–1.107	0.545 0.289–1.030	0.033
Luteolin					
Crude	1	0.949 0.626–1.438	0.889 0.584–1.353	0.572* 0.362–0.903	0.013
Model 1	1	0.751 0.413–1.367	0.476* 0.253–0.895	0.481* 0.256–0.903	0.013
Flavonols					
Crude	1	0.694 0.464–1.037	0.707 0.453–1.102	0.699 0.455–1.075	0.151
Model 1	1	0.539* 0.301–0.965	0.854 0.438–1.666	0.579 0.304–1.101	0.221
Isorhamnetin					
Crude	1	0.88 0.573–1.354	0.939 0.618–1.426	1.049 0.680–1.619	Crude
Model 1	1	0.753 0.428–1.325	0.863 0.484–1.539	0.969 0.506–1.854	0.915

Kaempferol					
Crude	1	0.668* 0.449–0.994	0.510** 0.330–0.788	0.630* 0.408–0.973	0.021
Model 1	1	0.661 0.379–1.154	0.603 0.335–1.084	0.611 0.328–1.140	0.095
Myricetin					
Crude	1	0.855 0.539–1.355	0.993 0.643–1.531	1.065 0.701–1.618	0.531
Model 1	1	0.884 0.462–1.692	1.114 0.594–2.089	0.795 0.427–1.482	0.483
Quercetin					
Crude	1	0.85 0.563–1.283	0.827 0.539–1.268	0.791 0.514–1.218	0.312
Model 1	1	0.774 0.429–1.395	0.833 0.452–1.538	0.57 0.290–1.121	0.129
Isoflavones					
Crude	1	1.062 0.671–1.682	1.455 0.945–2.240	1.864** 1.201–2.891	0.008
Model 1	1	0.947 0.451–1.989	0.901 0.363–2.237	1.199 0.515–2.787	0.298
Daidzein					
Crude	1	0.489*** 0.322–0.745	0.495** 0.319–0.769	0.721 0.473–1.098	0.254
Model 1	1	0.483* 0.273–0.855	0.613 0.339–1.108	0.671 0.367–1.225	0.377
Daidzein					
Crude	1	0.734 0.473–1.139	0.693 0.455–1.055	1.081 0.716–1.632	0.543
Model 1	1	0.945 0.523–1.708	0.604 0.337–1.082	1.109 0.625–1.970	0.882
Glycitein					
Crude	1	0.587* 0.379–0.908	0.632* 0.417–0.957	0.987 0.651–1.498	0.9
Model 1	1	0.709 0.397–1.265	0.765 0.440–1.332	0.914 0.516–1.616	0.837
Flavonoids					
Crude	1	0.852 0.555–1.307	1.158 0.762–1.762	1.203 0.781–1.854	0.264
Model 1	1	0.486* 0.252–0.937	0.994 0.542–1.823	1.056 0.562–1.983	0.365

Note: Model 1 was adjusted for age, gestational age, daily energy intake, pre-pregnancy BMI, parity, gravidity, family history of hypertension, daily energy expenditure and education level; *p≤0.05 *vs.* Q_1; **p≤0.01 *vs.* Q_1 and ***p≤0.001 *vs.* Q_1

surveyed a passive correlation between PE risk and high dietary intakes of quercetin and luteolin, and moderate consumption of flavanones (naringenin). In my opinion, this is first research to comprehensively investigate the impacts of dietary flavonoid intake upon the PE risk in a Chinese population

Our study found that high intake levels of dietary flavanones (naringenin) and luteolin were associated with more than 40 % reduced risks of PE, with a significant dose–response trend. This corresponds to these consequences of Duan *et al.*[18] that studied mice with gestational hypertension exposed to 50 mg/kg of naringenin during gestation and found that naringenin could markedly attenuate the systemic inflammatory response by lessening serum levels of the pro-inflammatory cytokines IL-2, IL-6 as well as TNF-α. Qin *et al.*[19] found that naringenin reduced endothelial dysfunction induced by high glucose concentrations among the endothelial cells. Perhaps, Naringenin's protective effect against endothelial dysfunction is partly regulated through down-regulating the apoptosis and oxygenated stress by means of Phosphorylation of Protein Kinase C βII (PKCβII)-associated caspase-3 and Nitric Oxide (NO)/Reactive Oxygen Species (ROS) pathway among endothelial cells[18-20]. Previous studies have indicated that hesperetin treatment can significantly lessen these expressions of Matrix Metalloproteinase (MMP) and MMP-9, while MMPs have been shown to be related to angiogenesis and metastasis[21,22]. Notably, endothelial dysfunction is currently believed to be the cause of PE. Yang *et al.*[23] and Queiroz *et al.*[24] found that endothelial dysfunction was significantly improved by luteolin treatment in rats *via* direct promotion of vasodilation. Luteolin is potentially promising for treatment of PE, a condition wherein the endothelium is damaged and dysfunctional. Proof on the correlation between the PE risk and the dietary flavonoid intake is confined as ever, so further studies with larger samples are needed.

After controlling for possible confounding elements, the present study discovered that quercetin intake was negatively associated with PE risk. However, the connection between the PE risk and the quercetin intake did not remain after excluding patients with GDM. Though it isn`t clear how quercetin impacts the advancement of PE, a few researches have supported the potential systems. Li *et al.*[25] found that quercetin treatment in pregnancy significantly decreased the elevated ratio of soluble Fms-like tyrosine kinase-1 (sFlt-1) to placental growth factor and rescued abnormal uteroplacental angiogenic status in a PE rat model. Ebegboni *et al.*[26] indicated that quercetin and the metabolites evidently lessened these levels of the reduced glutathione ($p<0.0001$) in the hypoxia-deoxygenation induced oxygenated stress in one transformed Human First-Trimester Trophoblast Cell Line (HTR-8/SVneo), thereby significantly improving placental function and health against the oxygenated stress. In the present study, these consequences of the multivariate condition logistic regression analysis and sensitivity dissects were inconsistent. There are two possible reasons for this. First, differences in the metabolic profiles of patients with and without GDM may have affected the findings. Second, although the independent and significant associations between GDM and PE have been confirmed, the main mechanistic manifestations are completely different GDM is a proangiogenic state and PE is an antiangiogenic state[27]. This may affect the association between quercetin and these two diseases. Therefore, further studies are needed to elucidate these relationships.

Though it isn`t clear how flavonoids affect the PE, few researches have claimed the potential systems. To begin with, the flavonoids have already been indicated to be effective antioxidants which modulate the oxygenated stress and increase NO bioavailability[28]. Thus, flavonoids may prevent PE by mitigating endothelial dysfunction. Next, flavonoids reduce the levels of sFlt-1, Endothelin-1 (ET-1) and tissue Plasminogen Activator (tPA) in cells and significantly alter several inflammatory pathways, like NF-κB signaling, IL-17 signaling and TNF signaling[29]. Pro-inflammatory cytokines IL-6 and TNF-α impact the function of the endothelial cells through improving the vascular permeability and trigger the trophoblastic cellular apoptosis. They damage and activate the endothelial cells with the aim of initiating maternal inflammatory reactions[30]. Then, the factors of the maternal risk might impact the abnormal cytotrophoblasts of spiral arteries, bringing about the abnormal placentation. The lessened uteroplacental perfusion triggers the placental release of the antiangiogenic markers into maternal circulation, resulting in the mechanical vascular disfunction and endothelial disfunction *via* antiangiogenic markers. Antiangiogenic markers are primarily mediated by soluble Endorphins (sEng) and sFlt-1. The elevated levels of sEng and sFlt-1

trigger the vasoconstriction, endothelial dis function and immune dysregulation, which is able to impact passively fetuses and maternal organ systems. Flavonoids significantly potentiate the vasodilatory effect by means of vascular endothelial growth factor, thereby inhibiting the excessive circulation of sFlt-1[31]. Thus, flavonoids may reduce the emergence of PE through adjusting the maternal oxidative stress, inflammation and the vasodilatory effect.

This research owns some key strengths. To start with, we quantified as many flavonoids as possible, including total flavonoids, six subclasses and 24 specific flavonoid components, to help elucidate the association between PE and dietary flavonoids. Next, we employed 1:1 matching and the multivariate logistic regression with a view to controlling the confounding elements.

However, several limitations must also be noted. First, we distributed the FFQ during the final 3 mo before delivery, which may have affected the accuracy of our results on account of recalling bias. In order to address this, face to face interviews were performed. Food photographs were adopted for the purpose of evaluating the portion sizes to assist the participator in recollecting their daily diets. Second, there may have been several sources of bias in the statistics of dietary flavonoid intake, introduced by factors including the plant storage method, cooking method and growth environment. To eliminate this bias, energy intake (kJ/d) was figured out with the China Food Composition (2nd ed), and each interviewer underwent standardized training. In spite of the restrictions, the discoveries of this research support a protective impact of the flavonoids against the PE advancement among the pregnant female.

To sum up, those consequences suggest that the elevated intake of luteolin and moderate intake of flavanones (naringenin) are linked to a decreased PE risk. Those protective effects of luteolin and naringenin against PE have undoubted public health significance and provide a basis for further research into clinical interventions.

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The study was approved by the Ethics Committee of Scientific Research and Clinical Trials of the First Affiliated Hospital of Zhengzhou University (No. Scientific research-2016-LW-34). All of the participants signed a written informed consent form before the study commenced. All of the procedures in the study were carried out in accordance with the Declaration of Helsinki.

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Author contributions:

Conceptualization by Yanhua Liu; formal analysis was done by Ting Kang, Bingrui Liu; funding acquisition by Yanhua Liu; investigation by Xi Chen, Xianlan Zhao, Yuan Cao, Weifeng Dou, Dandan Duan and Wenjun Fu; methodology by Yanhua Liu; project administration by Quanjun Lyu; resources by Yanhua Liu, Quanjun Lyu; software by Ting Kang, Bingrui Liu; supervision was done by Yanhua Liu; writing original draft by Bingrui Liu; and writing, review and editing by Bingrui Liu and Yanhua Liu.

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The authors declared no conflict of interests.

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