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Effect of nutmeg on glycemic status in rat and mice: a systematic review

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Abstract

Glycemic status depicts a state of individual blood glucose level. Biochemical parameters to identify glycemic status associated with diabetes mellitus include fasting or non-fasting blood glucose, HbA1c, and oral glucose tolerance. Our present work conducted a systematic review aiming to systematically summarize the in vivo experimental results of nutmeg treatments towards the glycemic status of rats and mice. The systematic review followed PRISMA guidelines. PubMed, ProQuest, Wiley Online Library, and Google Scholar were used as databases for searching articles. Twenty-one articles that met the criteria were eventually used in this systematic review. The results of the in vivo studies revealed that the intervention of nutmeg samples in rats and mice had a positive effect. This finding was present in all reviewed articles. Overall, treatment by nutmeg samples was able to attenuate fasting blood glucose, non-fasting blood glucose, and HbA1c in rats and mice, reaching up to 94.52, 60.76, and 48.86%. We also found that nutmeg samples prepared from mace and methanol had the highest effect in reducing blood glucose. Based on this systematic review, it can be concluded that nutmeg has a positive effect on improving glycemic status and reducing the risk of DM in rats and mice.

Keywords: blood glucose; diabetes mellitus; nutmeg; *Myristica*; in vivo.

Practical Application: This review provides systematic and comprehensive information about the potential of nutmeg to improve glycemic status. The findings of this review can be a reference for the use of nutmeg as a diabetes therapy or its development as a functional food.

1 Introduction

Glycemic status means the level of an individual blood glucose which is described by the term hypoglycemia and hyperglycemia. Both terms show abnormality, thus causing health problems. Chronic hyperglycemia accounts for some organ and system dysfunctions such as kidney, nerves, cardiovascular, retina, feet and legs (Amin et al., 2016). To describe glycemic status, some biochemical parameters are used, namely fasting blood glucose (FBG), non-fasting blood glucose (non-FBG), glycated hemoglobin (HbA1c), and oral glucose tolerance (OGT), as many reported by former researchers (Malandrucco et al., 2020; Phillips, 2012a, 2012b; Williamson & Sheedy, 2020; Yu et al., 2012).

In order to improve glycemic status particularly hyperglycemia associated with diabetes mellitus (DM), medication using modern drugs and traditional medicine is used. Several studies have reported the effect of medicinal plants/herbs on glycemic status related to DM. Among these plant sources, nutmeg (*Myristica*) was traditionally approved for treating various diseases such as DM (Simanjuntak, 2018). Ha et al. (2020) mentioned approximately 250 compounds in nutmeg *Myristica fragrans* Houtt, including lignan, neolignan, diphenylalkane, phenylpropanoid, terpenoid, steroid, triterpenoid, saponin, flavonoid, and other chemical substances. Some are reported to exert antidiabetic and anti-obesity effects through various mechanisms, i.e., tetrahydrofuran lignans (nectandrin B, and nectandrin A, tetrahydrofuroguaiacin B), allowing to strongly stimulate adenosine monophosphate-activated protein kinase (AMPK) on differentiated C2C12 cells (Nguyen et al., 2010). In addition, macelignan enables to down-regulate the expression of inflammation-related genes in liver, enhance AMPK activation in skeletal muscle, raise insulin sensitivity, improve the lipid metabolic disorders through by activating peroxisome proliferator–activated receptor (PPAR) α/γ, and reduce endoplasmic reticulum stress (Han et al., 2008). Meanwhile, 3-(3-methyl-5-pentyl-2-furanyl)-2(E)-propenoic acid inhibited α-glucosidase better than acarbose (Sathya et al., 2020). Meso-dihydroguaiaretic acid and otobaphenol could inhibit protein tyrosine phosphatase 1B (PTP1B) as drug target for type 2 DM and obesity through non-competitive mechanism (Ha et al., 2018; Yang et al., 2006). In addition, meso-dihydroguaiaretic acid rose the signaling of intracellular insulin, presumably via inhibition of PTP1B activity (Yang et al., 2006). The scientific evidence on the issue is abundant, but there is no a comprehensive and systematic study summarizing the results of in vivo studies. This present work aimed to provide the summary of in vivo research discussing the effects of nutmeg samples on glycemic status in rats and mice. The output is essential for developing functional ingredients that can be applied to food products to provide various benefits, including helping to relieve DM through various mechanisms (Lin et al., 2022).

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2 Material and methods

2.1 Search strategy

This systematic review followed a guidance of PRISMA (*Preferred Reporting Items for Systematic reviews and Meta-Analyses*) (Page et al., 2021). Literatures were searched on databases namely PubMed, ProQuest, Wiley Online Library and Google Schoolar, regardless publication year until 21 July 2021. The search was based on keywords corresponding to PICO as follows: **(rat OR mice) AND (nutmeg OR "nutmeg seed" OR "nutmeg mace" OR myristica) AND ("blood glucose" OR "blood sugar" OR HbA1c OR "glycated hemoglobin" OR hyperglyc* OR hypoglyc* OR OGT OR OGTT OR "glucose tolerance" OR "fasting blood glucose")**.

The collected articles were then screened. After removing duplicates, we performed a manual review of titles and abstracts, ensuring they complied with research subject (nutmeg and glycemic parameters). Subsequently, the full text version of these relevant records was collected. We excluded articles for any irrelevancy and the article type (e.g. narrative review, book chapter, dissertation, thesis, non-English content, poster, proceeding, supplement, executive summary, forum, symposium, bibliography, abstract, scientific report, news, report, and index).

Full text articles discussing the use of one or more parts of nutmeg plant and measuring one of more glycemic parameters in rats or mice were included for systematic review. The review resulted in the selected studies on glycemic status parameters (FBG, non-FBG, HbA1c, and OGT) using rats or mice treated by nutmeg compared with negative control (without nutmeg treatment), positive control (treated by standard drugs), normal control, and initial condition. The study was eligible when it discussed the effects of nutmeg on glycemic parameters using rats or mice.

2.2 Data extraction

The eligible full text articles were extracted to collect information: authors, year, nutmeg samples (species, parts of plant, form of sample, dose, intervention period), experimental animals used (rat or mice, sex, strain, age or weight as baseline, model, induction method, number of animals, diet), blood sample types, glycemic parameters and their value (Supplementary Material).

2.3 Determination of the nutmeg effects on glycemic parameter changes in rat and mice

To ascertain the effects of nutmeg on glycemic status, the difference of FBG, non-FBG, HbA1c, and area under curve (AUC) in OGT test between treated rats/mice and control groups (negative control, positive control, normal control, and initial condition) was determined, expressed as percentage (% differences). The negative percentage indicated that the values for these parameters in the treated animals were lower than those in the control groups, and vice versa for positive percentage. Percentage of difference was calculated as follows (Equation 1):

$$\%\ Differences = \left[\left(LT\ /\ LC\right) - 1\right] x\ 100 \quad (1)$$

LT is the level of FBG/non-FBG/HbA1c/AUC in treated animals, and LC is the level of FBG/non-FBG/HbA1c/AUC in control groups.

The effect of nutmeg plant parts and solvents for extraction to the reduction of FBG, non-FBG, and HbA1c was also assessed in percentage. The percentage of reduction represented the average % of reduction for FBG, non-FBG, and HbA1c compared with negative control.

3 Results and discussion

3.1 Study selection

The article search resulted in 2338 articles, and we removed 979 articles for duplicates. Furthermore, 1152 articles were excluded due to title irrelevancy, and then 175 of the remaining records were removed after abstract selection. Based on full-text review, 11 articles were discarded, finally resulting in 21 articles that met the eligibility for this systematic review (Figure 1).

3.2 Study characteristics

This present work systematically reviewed 21 articles. Of these records, most nutmeg species used was *Myristica fragrans* Houtt (20 articles), while the remaining was *Myristica malabarica* (1 artiles) and *Myristica cinnamomea* King (1 articles). Nutmeg seed became the most used part (8 articles), while other parts were also discussed, including mace (2 articles), rhizome (1 articles), seed and mace (3 articles), and not specified (7 articles). These nutmeg samples were administered into rats or mice in the form of ethanolic extract (3 articles), methanolic extract (3 articles), petroleum ether extract (2 articles), hydro-alcoholic extract (1 article), diethyl ether extract (1 article), water extract (2 articles), isolate/lignan (3 articles), herbal formula (3 articles), spices mixture (2 articles), and safrole-free extract (1 article).

In terms of experimental animals, we found 14 articles using rats specified as following Sprague-Dawley (1 article), Wistar (11 articles), whereas 2 articles did not specify the stock or strain that were used and only identify them as rats. Eight articles were recorded to use male rats, five articles used male and female ones, and 1 article did not mention it. These rat models were induced at different procedures, hyperglycemia-diabetic induced by alloxan (2 articles), hyperglycemia induced by alloxan (1 article), type 2 DM induced by high fat diet (HFD) (1 article), type 2 DM induced by streptozotocin (2 articles), DM induced by alloxan (1 article), obese induced by HFD (1 article), induced by alloxan without mentioning the model (1 article), induced by streptozotocin without mentioning the model (1 article), induction and model not mentioned specifically (3 articles), and normal rats (3 articles). Meanwhile, seven studies used mice, including C57BL/6J (3 articles), Swiss albino (3 articles), and not specified strain (1 article). The use of male and female mice was reported in two articles, while 3 articles did not mention mice sex. These animal models were induced differently, including obese induced by HFD (1 article), DM induced by alloxan (1 article), hyperglycemia and hypertriglyceridemia induced by chlorpromazine (1 article), obese-DM without specifying induction method (1 article), nonalcoholic fatty liver disease

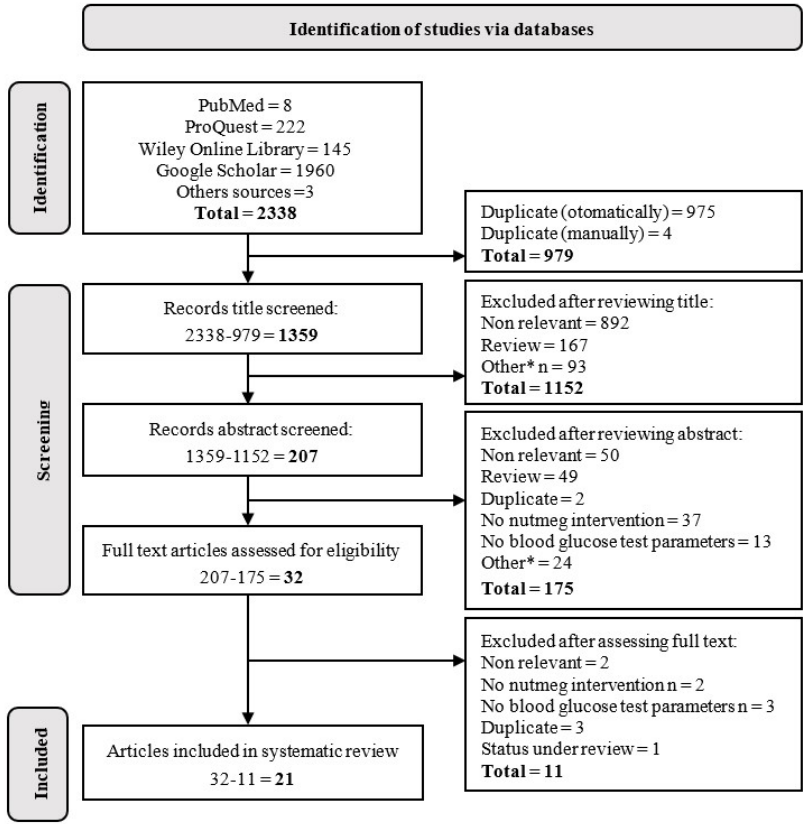

Figure 1. PRISMA Flowchart of the literature search and strategy for the selection of relevant document. *Poster, conference proceding, supplement, executive summary, forum, symposium, bibliography, abstract, scientific report, news, report, index, book.

(NAFLD) (1 article), model not mentioned induced by HFD (1 article), and model not mentioned induced by alloxan (1 article).

Glycemic parameters measured were FBG (9 articles), non-FBG (10 articles), HbA1c (3 articles), and OGT (6 articles).

3.3 Effect of nutmeg on glycemic status in rat and mice

Glycemic status is often evaluated by these parameters, namely FBG, non-FBG, HbA1c, and OGT. The high level of blood plasma glucose (>130 mg/dL) and HbA1c (>7%) indicated poor glycemic control (Lima et al., 2011). Pre-diabetic condition can be observed from FBG (110-125 mg/dL, known as impaired fasting glucose – IFG), 2-hour postprandial glucose (140-198 mg/dL, known as impaired glucose tolerance – IGT) and HbA1c (5.7 – 6.4%) (Phillips, 2012b; American Diabetes Association, 2018; Paprott et al., 2018). Meanwhile, DM can be diagnosed when FBG and/or 2-hour postprandial glucose surpasses 126 mg/dL and 200 mg/dL, respectively, followed with diabetic symptoms (Phillips, 2012b).

HbA1c is a key marker for long-term diabetic complications in type 1 and 2 DM (Malandrucco et al., 2020). HbA1c is a glycated hemoglobin, which serves an indicator for blood plasma glucose level for last 2-3 months. HbA1c test had a lower variability and environmental distractions for on-site glucose test, and became a gold standard of glycemic control (Phillips, 2012a; Yu et al., 2012).

OGT test was also considered as a gold standard for diagnosing DM and impaired glucose regulation – IGR (Phillips, 2012b; Yu et al., 2012). The measurement of vena plasma glucose prior and 2-hour post the 75 g oral glucose ingestion was used to interpret OGT test. This measurement was recommended when FBG test result was unclear (Phillips, 2012b).

In this work, we provided the levels of FBG, non-FBG, HbA1c, and OGT in nutmeg-treated rats, and mice, and compared them with negative control, positive control, normal control, and initial condition. The nutmeg intervention was stated to have a positive effect if the levels of FBG, non-FBG, HbA1c and AUC in the OGT measurement were lower than the control group and initial conditions, or the same as the positive control, normal control and initial conditions. Conversely, it was stated to have a negative effect when the levels of FBG, non-FBG, HbA1c and AUC of the OGT test were higher to that of negative control. The nutmeg intervention resulting in the parameter levels higher than positive control, normal control, initial condition, or similar to negative control was considered as no effect (notation 0). The summary of nutmeg intervention effects on the glycemic status parameters is presented in Table 1.

Most of the nutmeg samples recovered in this work were *Myristica fragrans* Houtt (20 of 21 articles), which were prepared using various plant parts and methods, including solvents for their extraction. Dose and duration used in the intervention

Table 1. Summary of the effects of nutmeg on glycemic status parameters (FBG, non-FBG, HbA1c, and OGT) in mice and rats.

References	Nutmeg sample	Dosage	Duration	Outcome (Compared with NC/PC/N/I)	% Differences	Effects*
(Pashapoor et al., 2020)	Petroleum ether extract from seed of *M. fragrans*	50; 100; and 200 mg/kg bw	21 days	FBG < NC	-55.57	+
				FBG > PC	19.19	0
				FBG > N	130.13	0
				FBG < I	-48.28	+
(Zhao et al., 2020)	Ethanolic 70% extract from seed of *M. fragrans*	250 mg/kg bw	4 weeks	FBG < NC	NS	+
				FBG > N	NS	0
				FBG < I	NS	+
				HbA1c < NC	NS	+
				HbA1c > N	NS	0
				OGT test: AUC < NC	NS	+
				OGT test: AUC > N	NS	0
(Kareem et al., 2009)	Aqueous extract from kernel of *M. fragrans*	100 mg/kg bw	30 days	FBG < NC	-3.9	+
				FBG > PC	23.2	0
		100 mg/kg bw + isoproterenol 85 mg/kg bw	30 days	FBG < NC	-8.8	+
				FBG > PC	NS	0
(Lestari et al., 2019)	Safrole-free nutmeg dry extracts from seed of *M. fragrans* Houtt	5.4 mg/200 g bw	2; 4; and 6 days	FBG < NC	-40	+
				FBG < PC	NS	+
				FBG < I	NS	+
(Eo & Ie, 2020)	Ethanolic extract from *M. fragrans*	273.86; 547.7; and 821.58 mg/kg bw	7; 14; 21; 28; and 35 days	FBG > PC	6.59	0
				FBG < N	-4.71	+
				FBG < I	-72.67	+
		273.86 mg/kg bw + 5mg/kg bw glibenclamide	7; 14; 21; 28; and 35 days	FBG < PC	-0.34	+
				FBG < N	-20.49	+
				FBG < I	-65.17	+
(Lestari et al., 2012)	Methanol extract from seed of *M. fragrans*	125; 250; and 500 mg/kg bw	6 days	FBG < NC	-94.52	+
				FBG < PC	-4.52	+
(Somani & Singhai, 2008)	Petroleum ether extract from seed of *M. fragrans*	200 mg/kg bw	2 weeks	FBG < NC	NS	+
				FBG > PC	40.25	0
				FBG < I	-12.3	+
		50; 100; and 200 mg/kg bw	Administered once at the time of the test	OGT test: AUC < NC	NS	+
				OGT test: AUC = PC	NS	+
(Rajamani et al., 2005)	Kernel and mace of *M. fragrans* in spices mixture	10; 30; 50 mg/kg bw	30 days	FBG < NC	-16.94	+
				FBG < N	-2.56	+
				HbA1c < NC	-48.86	+
				HbA1c = N	0.4	+
(Suganthi et al., 2005)	Kernel and mace of *M. fragrans* in spices mixture	10; 30; 50 mg/kg bw	30 days	FBG < NC	NS	+
				FBG = N	NS	+
(Nasreen et al., 2020)	Water extract of ripe seeds from *M. fragrans*	5 g/kg bw and 5 g/kg bw + glimepiride 1 mg/kg bw)	28 days	Non-FBG < PC	NS	+
		1.5 mg/0.1 mL and 1.5 mg/0.1 mL + glimepiride (0.0004 mg/0.1 mL)	28 days	OGT test: AUC = PC	NS	+
(Vangoori et al., 2019)	Ethyl alcohol extract from mace of *M. fragrans*	200 and 400 mg/kg bw	10 weeks	Non-FBG < NC	-60.76	+
				Non-FBG > PC	26.27	0
				Non-FBG > N	25	0
				Non-FBG < I	-35.02	+
(Nagja et al., 2016)	Polyherbal extract (containing seed of *M. fragrans*)	400 mg/kg bw	7; 14; 21; and 28 days	Non-FBG < NC	-59.44	+
				Non-FBG > PC	6.14	0
				Non-FBG > N	28.52	0
				Non-FBG < I	-53.035	+
	Water-ethanol extract of seed from *M. fragrans*	200 mg/kg bw	Administered once at the time of the test	OGT test: AUC < NC	NS	+
				OGT test: AUC = PC	NS	+
(Nguyen et al., 2010)	Tetrahydrofuran lignans mixture from ethanol extract of *M. fragrans*	200 mg/kg bw	6 weeks	Non-FBG < NC	-14.44	+
(Han et al., 2008)	Macelignan from *M. fragrans* Houtt	10 and 25 mg/kg bw	14 days	Non-FBG < NC	NS	+
				Non-FBG < PC	NS	+
				Non-FBG > N	NS	0
				OGT test: AUC < NC	NS	+
				OGT test: AUC < PC	NS	+
				OGT test: AUC > N	NS	0

Legend: area under curve (AUC); fasting blood glucose (FBG); glycated haemoglobin (HbA1c); initial conditions (I); non-fasting blood glucose (Non-FBG); normal control (N); negative control (NC); the value not showed (NS); oral glucose tolerance (OGT); positive control (PC); 2 hours post-prandial glucose (2h-PPG). *Effects were declared positive (+) if FBG/non-FBG/HbA1c/AUC in OGT test ≤ PC/N/I or < NC; negative (-) if FBG/non-FBG/HbA1c/AUC in OGT test ≥ NC; no effect (0) if FBG/non-FBG/HbA1c/AUC in OGT test > PC/N/I or = NC.

Table 1. Continued...

References	Nutmeg sample	Dosage	Duration	Outcome (Compared with NC/PC/N/I)	% Differences	Effects*
(Peungvicha et al., 2018)	*M. fragrans* in herbal formulae/combined extract	0.5 and 1 g/kg	1 and 30 days	Non-FBG 2h-PPG < NC	-16.9	+
				Non-FBG 2h-PPG < PC	-5	+
		0.5 and 1 g/kg	30 days	HbA1c < NC	-8.79	+
				HbA1c > N	151.51	0
				HbA1c < PC	-3.49	+
(Dayanand et al., 2019)	1 part of *M. fragrans* Houtt in herbal formulation	10; 50; and 100 mg/kg bw	28 days	Non-FBG > NC	23.65	-
(Arulmozhi et al., 2007)	Hydroalcoholic extract from rhizome of *M. fragrans* Houtt	50; 150; and 450 mg/kg bw	7 days	Non-FBG < NC	-41.71	+
				Non-FBG < PC (rosiglitazone)	-1.71	+
				Non-FBG < PC (glimepiride)	-25.71	+
				Non-FBG < PC (fenofibrate)	≥ -41.71	+
				Non-FBG = N	NS	+
(Chowdhury et al., 2017)	Methanol extract from seed and mace of *M. fragrans* Houtt	200 and 400 mg/kg bw	4 days	Non-FBG < NC	-44.78	+
				Non-FBG > PC	17.23	0
(Sailesh & Padmanabha, 2014)	Dry extract diethyl ether of *M. fragrans* Houtt	NS	1; 2; and 3 weeks	Non-FBG < NC	-35.82	+
				Non-FBG > N	16.76	0
				Non-FBG < I	-50.64	+
(Othman et al., 2019)	Malabaricone C from fruits of *Myristica cinnamomea* King	NS	8 weeks	OGT test: AUC < NC	NS	+
				OGT test: AUC > N	NS	0
(Patil et al., 2011)	Methanol extract from mace of *M. fragrans*	100 and 200 mg/kg bw	Administered once at the time of the test	OGT test: AUC < NC	NS	+
				OGT test: AUC > PC	NS	0
				OGT test: AUC > N	NS	0
	Methanol extract from mace of *M. malabarica*	100 and 200 mg/kg bw	Administered once at the time of the test	OGT test: AUC < NC	NS	+
				OGT test: AUC < PC	NS	+
				OGT test: AUC > N	NS	0

Legend: area under curve (AUC); fasting blood glucose (FBG); glycated haemoglobin (HbA1c); initial conditions (I); non-fasting blood glucose (Non-FBG); normal control (N); negative control (NC); the value not showed (NS); oral glucose tolerance (OGT); positive control (PC); 2 hours post-prandial glucose (2h-PPG). *Effects were declared positive (+) if FBG/non-FBG/HbA1c/AUC in OGT test ≤ PC/N/I or < NC; negative (-) if FBG/non-FBG/HbA1c/AUC in OGT test ≥ NC; no effect (0) if FBG/non-FBG/HbA1c/AUC in OGT test > PC/N/I or = NC.

were also various. In the view of experimental animal, rats were more used than mice (14 of 21 articles), and male dominated the experiments. Besides, the experiments differed in animal strain, model, diet, and induction methods. The number of animals used in each article also differed (n = 3–12). Few articles were also found not to provide quantitative values for some parameters; thus, the effects were expressed in qualitative (lower or higher). Standard deviation (SD) for glycemic parameters ranged 0.08–98.73 (12.24% had SD ≥ 30). Nonetheless, all studies reported a consistent result for the effects of nutmeg in experimental animals.

Effect of nutmeg on FBG

In this work, nine articles measured the content of FBG in rats and mice treated with nutmeg samples. The research outputs were then compared with FBG of negative control (8 articles), positive control (7 articles), normal control (5 articles), and their initial FBG level (5 articles). These studies showed positive effects.

The nutmeg sample was able to reduce FBG up to 94.52% when compared to the negative control. The ethanolic extract of *M. fragrans* seed (500 mg/kg bw) administered to male hyperglycemic rats for 6 days was able to dramatically alleviate the level of FBG up to 94.52% (Lestari et al., 2012). This significant alleviation may also depend on other factors such as dose and intervention duration. Meanwhile, the administration of nutmeg seed extract (using petroleum ether) at 50 mg/kg bw for 16 weeks suppressed FBG in male diabetic Wistar rats up to 7.9%, and higher reduction at 45.06% and 55.57% was acquired at 100 mg/kg bw and 200 mg/kg bw, respectively (Pashapoor et al., 2020). Another research reported that FBG in T2DM Wistar rats treated with petroleum ether extract of nutmeg seed was significantly reduced at dose 200 mg/kg bw, but such effect was insignificant at dose of 50 and 100 mg/kg (Somani & Singhai, 2008). The reduction of FBG was also dependent on the length of intervention. The FBG level of T2DM Wistar rats treated with safrole-free extract of *M. fragrans* Houtt seed at dose of 5.4 mg/200 g bw for 2, 4 and 6 weeks was reduced up to 20%, 30%, and 40%, respectively (Lestari et al., 2019).

Furthermore, FBG in rats treated by nutmeg samples was similar to positive control, even lower by 4.25%. The intervention of male tipe 2 DM Wistar rats by safrole-free extract of *M. fragrans* Houtt seed (5.4 mg/200 g bw) for 2, 4, and 6 days could reduce FBG at lower rate than that treated with pioglitazone (0.54 mg/200 g bw) and fenofibrate (3.6 mg/200 g bw) (Lestari et al., 2019). FBG was also lower in male hyperglycemic rats treated with methanolic extract of *M. fragrans* seed at concentration of 125, 250, and 500 mg/kg bw for 6 days than those treated pioglitazone at concentration of 2.7 and 10 mg/kg bw (Lestari et al., 2012). Moreover, FBG in rats administered with nutmeg samples was higher than positive control, showing the difference by <40.25%, even reaching up to <6.59% (Somani & Singhai, 2008; Kareem et al., 2009; Eo & Ie, 2020; Pashapoor et al., 2020). These evidences clearly support the antidiabetic potential of nutmeg, which can be comparable to standard antidiabetic drugs.

FBG in male and female rats induced by alloxan was lower by 4.71% compared with normal groups. Such effect was acquired after administrating the ethanolic extract of *M. fragrans* for 35 days at dose of 821.58 mg/kg bw. Indeed, it could be lower up to 20.49% at dose of 273.86 mg/kg bw when combined with glibenclamide at dose of 5 mg/kg bw (Eo & Ie, 2020). Meanwhile, Wistar albino rats fed with high fructose diet was treated by *M. fragrans* (seed and mace), resulting in FBG level which was comparable with normal group (Rajamani et al., 2005; Suganthi et al., 2005). Alloxan-induced male and female rats had FBG levels 72.67% lower than their initial FBG levels, after being given ethanolic extract of M. fragrans (547.72 mg/kg bw) for 28 days (Eo & Ie, 2020). Intervention of nutmeg samples showed positive effects to FBG when compared with negative control, positive control, normal control, and initial condition.

Effect of nutmeg on non-FBG

We found 10 articles measuring the level of non-FBG in rats and mice treated with nutmeg samples. The results of these studies were compared with negative control (9 articles), positive control (7 articles), normal condition (5 articles), and their initial condition (3 articles).

The level of non-FBG in experimental animals treated with nutmeg samples was lower (14.44%-60,76%) than negative control. The intervention of ethyl alcohol extract of *M. fragrans* mace (400 mg/kg bw) for 10 weeks in obese Wistar rats was able to reduce non-FBG levels up to 60.76% (Vangoori et al., 2019). On the other hand, non-FBG in rats treated with herbal formula containing nutmeg was higher than negative control. Nevertheless, this result was neglectable since the difference was statistically insignificant (Dayanand et al., 2019).

The level of non-FBG in male hyperglycemic and hypertriglyceridemia Swiss albino rats administered with 50 mg/kg bw of hydroalcoholic extract of *M. fragrans* Houtt rhizome for 7 days was lower than those administered with glimepiride (10 mg/kg bw) and fenofibrate (100 mg/kg bw). The treatment at dose of 450 mg/kg bw yielded a lower level of non-FBG compared with rosiglitazone at dose of 10 mg/kg bw (Arulmozhi et al., 2007). In addition, non-FBG levels in rats and mice treated with nutmeg samples were also found to be higher than the positive control, although the difference was not more than 26.27%. (Nagja et al., 2016; Chowdhury et al., 2017; Vangoori et al., 2019).

The level of non-FBG in male and female type 2 DM Wistar rats treated with the polyherbal extract prepared from *M. fragrans* seeds at dose of 400 mg/kg bw for 7, 14, 21 and 28 days was higher, reaching up to 143.76%, 112.66%, 71.54%, and 28.52%, respectively, compared with normal control (Nagja et al., 2016). These findings indicate the possibility of nutmeg sample intervention for reducing non-FBG in tipe 2 DM animals to normal levels when the duration of treatment was extended. Meanwhile, male hyperglycemia and hypertriglyceridemia Swiss albino mice administered with 450 mg/kg bw of hydroalcoholic extract of M. fragrans Houtt rhizome for 7 days showed a level of non-FBG which was relatively comparable with normal groups (Arulmozhi et al., 2007).

In addition, the intervention of nutmeg seed polyherbal extracts to male and female type 2 DM rats at dose of 400 mg/kg bw for 28 days caused lower non-FBG level (53.035%), compared with their initial level (Nagja, et al., 2016). Administration of M. fragrans mace ethyl alcohol extract at a dose of 200 mg/kg bw and 400 mg/kg bw in obese albino Wistar rats for a longer period (70 days) was also able to reduce non-FBG levels by 30.59% and 35.02%, respectively (Vangoori, et al., 2019). In addition, the intervention of *M. fragrans Houtt* extract for 1, 2 and 3 weeks was able to reduce non-FBG levels of hyperglycemic Wistar rats from their initial condition (25.95%, 38.69% and 50.64%, respectively) (Sailesh & Padmanabha, 2014). This underlines the significance of doses and treatment intervals towards the reduction of non-FBG in rats or mice. Overall, nutmeg was evidence able to exert positive effects to non-FBG when compared with negative control, positive control, normal control, and initial level.

Effect of nutmeg on HbA1c

Three articles measuring the levels of HbA1c in rats or mice treated with nutmeg samples. The results of these studies were then compared with negative control (3 articles), positive control (1 article), and normal control (3 articles). Positive effects are shown in the articles.

Nutmeg samples reduced HbA1c by 8.79% - 48.86% when compared with negative control. The greatest reduction of HbA1c (up to 48.86% lower compared with negative control) was acquired when male Wistar albino rats were administered with 50 mg/kg bw of spices mixture containing seed and mace of *M. fragrans* for 30 days (Rajamani et al., 2005). The level of HbA1c in male mice C57BL/6/J NAFLD diminished significantly after a 30-days treatment by ethanolic extracts of *M. fragrans* seed at dose of 250 mg/kg bw (Zhao et al., 2020). This HbA1c-lowering effect could be enhanced by the rise of nutmeg sample dose (Peungvicha et al., 2018; Rajamani et al., 2005).

Furthermore, male type 2 DM Sprague-Dawley rats were treated with 0.5 and 1 g/kg bw of herbal extract containing *M. fragrans* for 30 days, resulting in the reduction of HbA1c by 3.49% compared with those treated with 5 mg/kg bw of glibenclamide (Peungvicha et al., 2018). HbA1c level in male Wistar albino rats treated with nutmeg sample was also found to be comparable to the normal group (Rajamani et al., 2005). Overall, the nutmeg sample intervention had a positive effect on HbA1c when compared to negative controls, positive controls and normal controls.

Effect of nutmeg on OGT

The effect of nutmeg on OGT was discussed by seven articles, and the results were compared with negative control (6 articles), positive control (5 articles), and normal control (4 articles).

This work found that all OGT tests in rats and mice treated with nutmeg showed a positive effect, when compared with negative control. Extracts and isolates derived from nutmeg fruits could improve OGT significantly. Male NAFLD C57BL/6/J mice administered with ethanolic extract of nutmeg seed at dose 250 mg/kg bw for 16 weeks resulted in more satisfied OGT in comparison with negative control (Zhao et al., 2020). Such desirable effect was also observed in several studies using different animal models including streptozotocin-induced male Wistar rats treated with methanolic extract of *M. fragrans* and *M. malabarica* (Patil et al., 2011), male and female normal Wistar rats treated with petroleum ether extract of *M. fragrans* seed (Somani & Singhai, 2008), obese mice treated with 0.1% Malabaricone C from *Myristica cinnamomea* King (Othman et al., 2019), and diabetic-obese C57BL/6J mice treated with macelignan from *M. fragrans Houtt* (Han et al., 2008). The intervention of nutmeg samples in rats and mice also produce remarkable effects on the OGT which is comparable, even much better than those treated with standard antidiabetic (Han et al., 2008; Nagja et al., 2016; Patil et al., 2011; Somani & Singhai, 2008). In general, nutmeg samples had a positive effect on OGT when compared to negative controls and positive controls.

Effect of nutmeg plant parts and extraction solvents on the reduction of FBG, non-FBG, and HbA1c

Discussion on the contribution of plant parts and solvents to the parameters was summarized in Table 2 and Table 3. The reducing effect of blood glucose level in rats and mice differed greatly, depending on the plant parts. The difference could also be caused by the levels of dose and the duration of intervention. This review found that nutmeg seed and mace enabled to cause a more than 50% reduction of blood glucose level. Compared with seed, nutmeg mace showed more powerful reducing effect on blood glucose level. Despite its promising health effect, the research exploring the effects of nutmeg mace on glycemic status of rats and mice are still limited. In this systematic review, only two articles were found to involve nutmeg mace, extracted by methanol and ethanol (Patil et al., 2011; Vangoori et al., 2019).

Nutmeg samples tested on experimental animals are commonly extracted using a solvent. Different solvents are very likely to produce extracts with different yields, chemical substance composition and bioactivity. Our review found that ethanolic and methanolic extracts of the nutmeg exhibited the strongest effects on declining FBG (90.91%) and non-FBG (58.39%) in rats and mice. Conversely, water extracts showed the weakest compared with other organic solvents. It is noteworthy that the organic solvent usage for food production is limited, considering its health risk. Therefore, water extract is regarded the most appreciable regarding its safety. In this systematic review, the use of water as a solvent for nutmeg seed extraction was found in only two articles (Kareem et al., 2009; Nagja et al., 2016).

In summary, our review underscores the substantial assertion that nutmeg mace and methanol extract exhibited the greatest effect for lowering blood glucose. Therefore, the anti-diabetic properties of various fractions of the methanol extract of nutmeg mace are interesting for further study. In addition,

Table 2. Effects of nutmeg part on FBG, non-FBG and HbA1c reduction in rat and mice.

Part of nutmeg	Dosage (mg/kg bw)	Duration (day)	Glycemic parameter	Range of % Reduction*	Average of % Reduction	References
Seed	27–500	2–30	FBG	3.90–94.52	39.31	(Kareem et al., 2009; Lestari et al., 2012, 2019; Pashapoor et al., 2020)
	400	7–28	Non-FBG	16.46–59.44	38.06	(Nagja et al., 2016)
Mace	200–400	70	Non-FBG	56.02–60.76	58.39	(Vangoori et al., 2019)
Kernel and mace	10–50	30	FBG	10.31–16.94	13.97	(Rajamani et al., 2005)
	200–400	4	Non-FBG	22.48–44.78	33.63	(Chowdhury et al., 2017)
	10–50	30	HbA1c	31.47–48.86	40.17	(Rajamani et al., 2005)
Rhizome	50–450	7	Non-FBG	29.03–41.71	35.37	(Arulmozhi et al., 2007)

Legend: fasting blood glucose (FBG); glycated haemoglobin (HbA1c); non-fasting blood glucose (Non-FBG). *Value of % reduction compared with negative control.

Table 3. Effects of extraction solvent on FBG and non-FBG reduction in rat and mice.

Extraction solvent	Dosage (mg/kg bw)	Duration (day)	Glycemic parameter	Range of % Reduction*	Average of % Reduction	References
Petroleum ether	50–200	14–21	FBG	7.90–55.57	36.18	(Pashapoor et al., 2020)
Water	100	30	FBG	3.9–8.8	6.35	(Kareem et al., 2009)
Diethyl ether	NS	21	Non-FBG	24.70–35.82	28.80	(Sailesh & Padmanabha, 2014)
Hydro-alcoholic	50–450	7	Non-FBG	29.03–41.71	35.37	(Arulmozhi et al., 2007)
Ethanolic	200–400	70	Non-FBG	56.02–60.76	58.39	(Vangoori et al., 2019)
Methanol	250–500	6	FBG	87.30–94.52	90.91	(Lestari et al., 2012)
	200–400	4	Non-FBG	22.48–44.78	33.63	(Chowdhury et al., 2017)

Legend: fasting blood glucose (FBG); glycated haemoglobin (HbA1c); non-fasting blood glucose (Non-FBG). *Value of % reduction compared with negative control.

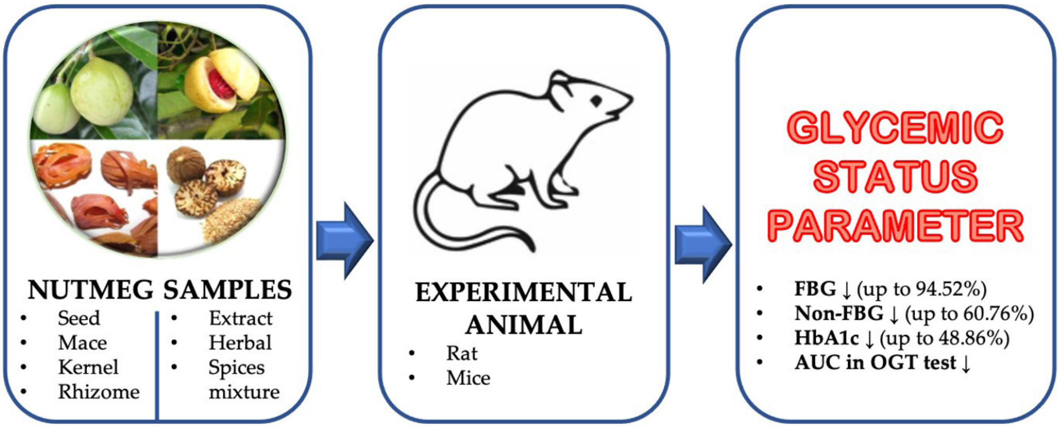

Figure 2. A schematic representation of the effects of nutmeg on glycemic status parameters in mice and rats. The nutmeg sample gave a positive effect by reducing fasting blood glucose (FBG), non-fasting blood glucose (non-FBG), glycated haemoglobin (HbA1c), and area under curve (AUC) on the oral glucose tolerance (OGT) test.

an in vivo study on the effect of mace water extract to reduce blood glucose is also needed to confirm the possibility of mace extract application in safer food products.

4 Conclusion

This systematic review found that the nutmeg intervention had a positive effect on parameters of glycemic status (FBG, non-FBG, HbA1c, and OGT) in rats and mice, especially compared to the negative control and their initial conditions (Figure 2). Surprisingly, such desirable effects also occurred when they were compared with positive control and normal condition. Nutmeg samples (extract, herbal, spices mixture) were reported able to reduce the level of FBG, non-FBG, and HbA1c in rats and mice, reaching 94.52, 60.76 and 48.86%, respectively. Where nutmeg mace and methanol extract showed the highest ability for decreasing blood glucose. Based on these findings, treatment using nutmeg samples in rats and mice showed a positive effect on glycemic status so that it could reduce the risk of DM.

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Supplementary Material

Supplementary material accompanies this paper.

Supplementary 1. Characteristics of included studies in the systematic review.

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