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Review Article

Natural Compounds as Inhibitors of Advanced Glycation End Products Formation: A Systematic Review

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ABSTRACT

Diabetes and related complications are becoming the leading causes of death in the world. In Malaysia, there are around 3.4 million of people affected by diabetes. Long-term diabetes can lead to the development of various complications, such as retinopathy, nephropathy, cardiovascular disease, Alzheimer's disease, and more. This is due to the formation of advanced glycation end-product, AGE in our body. However, the available chemical AGE inhibitors have side effects. Hence, alternative ways such as using natural product derivatives are used to treat diabetic complications. In this systematic review, various medicinal plants are studied to provide an insight of using medicinal plant to treat diabetes complications. Related articles were searched using three databases: PubMed, ScienceDirect, and Scopus. The search strategy was carried out based on PRISMA guidelines. Thirteen articles that fulfilled the inclusion criteria were included for this systematic review. The acetone crude extract of *Seriphium plumosum* leaves and the methanolic crude extract of *Tonna siliata* showed the most potent glycation inhibition, with AGE formation of 2.22% and 2.49%, respectively, compared to Arbutin as the positive control, which had 7.4% AGE formation. *Bacopa monnieri, Canarium album, Lespedeza bicolor, Eucommia ulmoides* and *Spathaolobus suberectus* show inhibition in a dose-dependent manner. The leaves of *Petalostigma banksia* showed the highest IC_{50} value of 56.06±6.10. Meanwhile, *Coptis chinensis* exhibited dose-dependent inhibition in the NBT assay and comparable inhibition in the Girard-T assay. Lastly, the ethanol extract of *Siegesbeckia orientalis* showed the highest inhibition in the NBT assay (24.9%), while the ethyl acetate extract exhibited the highest inhibition in the Girard-T assay (61.9%). The reviewed natural products could be useful in inhibiting AGE formation with fewer side effects.

Keywords: Natural products, Advanced glycation end products, Diabetes, Hyperglycemia, *Seriphium plumosum*, *Tonna siliata*.

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INTRODUCTION

Diabetes is one of the chronic metabolic diseases and it is characterized by increased blood glucose level. Diabetes is noted as one of the leading causes of mortality in the world (Kishore *et al*., 2016). In Malaysia, 17.5% of the total population are affected by this disease (Tee and Yap, 2017). There are various factors which can contribute to development of this disease such as genetic factor or environmental factors (Skyler *et al*., 2016). As blood glucose increase in our body, it will lead to various diabetic complications such as microvascular disease, macrovascular disease as well as neurological diseases (Duh, Sun, and Stitt, 2017). There are macro-vessels and micro-vessels found in our body which has different function (Chawla *et al*., 2016). The macro-vessels mainly supply blood to organs while micro-vessels function as supply nutrient and maintaining the blood pressure (Chawla *et al*., 2016). In diabetic patient, high blood glucose level will affect the vessels' function and cause various complication such as cardiovascular disease, diabetic retinopathy, diabetic nephropathy, Alzheimer's disease, and more (Huang *et al*., 2019).

Due to long term of hyperglycemia, the glucose found in blood tend to form covalent adduct with A protein through glycation while the end-products are known as Advanced Glycation End-product (GE) (Singh, Bali, Singh, and Jaggi, 2014). These abnormal proteins will lose its function and will lead to development of diabetic complications (Borg and Forbes, 2016). Besides, it also will react with other components such as lipid and

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nucleic acid (Singh *et al.*, 2014). In the glycation process, it can be divided into three stages (Singh *et al.*, 2014). The formation of Schiff base is the first step of glycation followed by development of Amadori product (Ho *et al.*, 2024). Finally, AGEs are formed which is the last stage and it is an irreversible process.

The pathogenesis of the diabetic complications is mainly due to interaction between Advanced Glycation End-product (AGE) and Receptor of AGE known as (RAGE) (Yong *et al.*, 2024). RAGE is a multiligand family, when AGE binds to the receptor, it will trigger various pathways such as Janus Kinase-Signal Transduced and Activator of Transcription protein (JAK/STAT), Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase and Mitogen Activated Protein Kinase (MAPK) pathway which lead to release of various components such as Nuclear Factor-kb (NF-κB), Interferon-Stimulated Response Elements (IFN-SRE) that lead to increased oxidative stress and release of inflammatory cytokines and lead to apoptosis (Singh *et al.*, 2014).

There are a lot of drugs developed to inhibit the Advanced Glycation End-product (AGE) which plays an important role in diabetic complication. The example of drugs is aminoguanidine and metformin. The aminoguanidine are the first AGE inhibitor and it can inhibit the dicarbonyl compound formation in the intermediate stage of glycation process and eventually inhibit the formation of AGE (Borg and Forbes, 2016; Ho *et al.*, 2024; Yong, Shirley, Azzani, Anbazhagan, and Ng, 2024; Yong, Wong, Azzani, Mac Guad, and Ng, 2024; Ho, Yong, Lim, and Ng, 2024). For metformin, this drug can activate the 5'AMP-Activated Protein Kinase (AMPK) pathway which can help to reduce the glucose level by reducing the glucose production in liver (Rodrigues *et al.*, 2017; Rhee and Kim, 2018; Ramasamy, Yan, and Schmidt, 2011; Rena, Hardie, and Pearson, 2017). However, these drugs possess different side effects such as increase liver enzyme, formation of autoantibodies, dizziness, muscle pain, and allergic reaction (Nasri and Rafieian-Kopaei, 2014). Hence, an alternative treatment for diabetic complication is needed. Recently, there are many researchers focusing on natural products, as they contain potential Advanced Glycation End-product (AGE) inhibitor (Yang, Li, Yin, Chen, and Gao, 2016). For an example, *Coptis chinensis*, which also known as Huang Lian has the potential to inhibit the formation of AGE (Yang, Li, Yin, Chen, and Gao, 2016; Jiang *et al.*, 2015). Other medicinal plants such as *Eucommia ulmoides*, and *Bacopa monnieri* are shown to be effective in inhibition of Advanced Glycation End-product (AGE) (Kishore *et al.*, 2016; Hussein and Mahfouz, 2016). Furthermore, these medicinal plants can also inhibit the formation of AGEs, the receptor of AGE as well as increase serum insulin level through regeneration of beta pancreatic cells (Kishore, Kaur, and Singh, 2017).

The aim of this systematic review was to provide insights of *in vitro* studies on natural products which inhibited the advanced glycation end-product that causes the diabetic complications.

MATERIALS AND METHODS

Electronic Databases

This systematic review was performed by using three different search engines and databases which were PubMed, ScienceDirect as well as Scopus. Besides, manual searches based on the references found in the reviewed articles was also carried out.

Search Strategy

The search strategy was carried out based on the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher, Liberati, Tetzlaff, Altman, and PRISMA Group, 2009). The flowchart of the searching process, searching criteria as well as selecting of articles was shown in Figure 1. The search strategy included the research papers which evaluated the efficiency of natural product to inhibit the formation of advanced glycation end-product. The search was done by using catalogue descriptors in Medical Subject Heading (MeSH) in English which contained in the title, abstract as well as in text of the studies.

Study Selection

The selection of articles was screened and identified by two authors independently. The full texts that fulfilled the inclusion criteria were obtained. In addition, disagreement between two authors based on the selection was resolved by discussion.

Inclusion Criteria and Exclusion Criteria

Studies that fulfilled the inclusion criteria were included. All the research papers were searched for studies were published between January 2015 and December 2019. Besides, the studies only limited to publications in English. All the *in vivo* and *in vitro* studies on advanced glycation end-product were eligible for inclusion criteria.

For exclusion criteria, review articles, letters, editorials, conference proceeding as well as case reports studies were excluded in the study. In the first screening, those studies that were not relevant were rejected. Besides, those studies that contain only abstracts or incomplete data were also excluded. For the second screening, all the full text articles were screened and those articles that do not fulfilled the inclusion criteria were removed.

Data Extraction

After performing selection of articles based on inclusion and exclusion criteria, extraction of data was performed by the authors. Last name of the first author, publication year as well as country of the study were extracted. Besides, all the important information from the papers such as test model, sample modification, intervention, control vintage, measurement of advanced glycation end-product, assay parameter as well as the outcomes of the studies were extracted. Multiple papers which

contained same measurement will be grouped together and considered as one unique study paper.

RESULTS

Thirteen articles were selected and the important information from each article was summarized in Table 1. Among the 13 articles, different methods were used for the measurement of Advanced Glycation End-product (AGE). Among them, there were eight articles which focused on percentage inhibition of AGE in bovine serum albumin or human serum albumin while three articles were measured based on IC_{50} value of the AGE. There were two articles measuring the different stages of glycation.

As mentioned above, the formation of Advanced Glycation End-product (AGE) can be divided into three stages and these articles were measuring the formation of Amadori product,

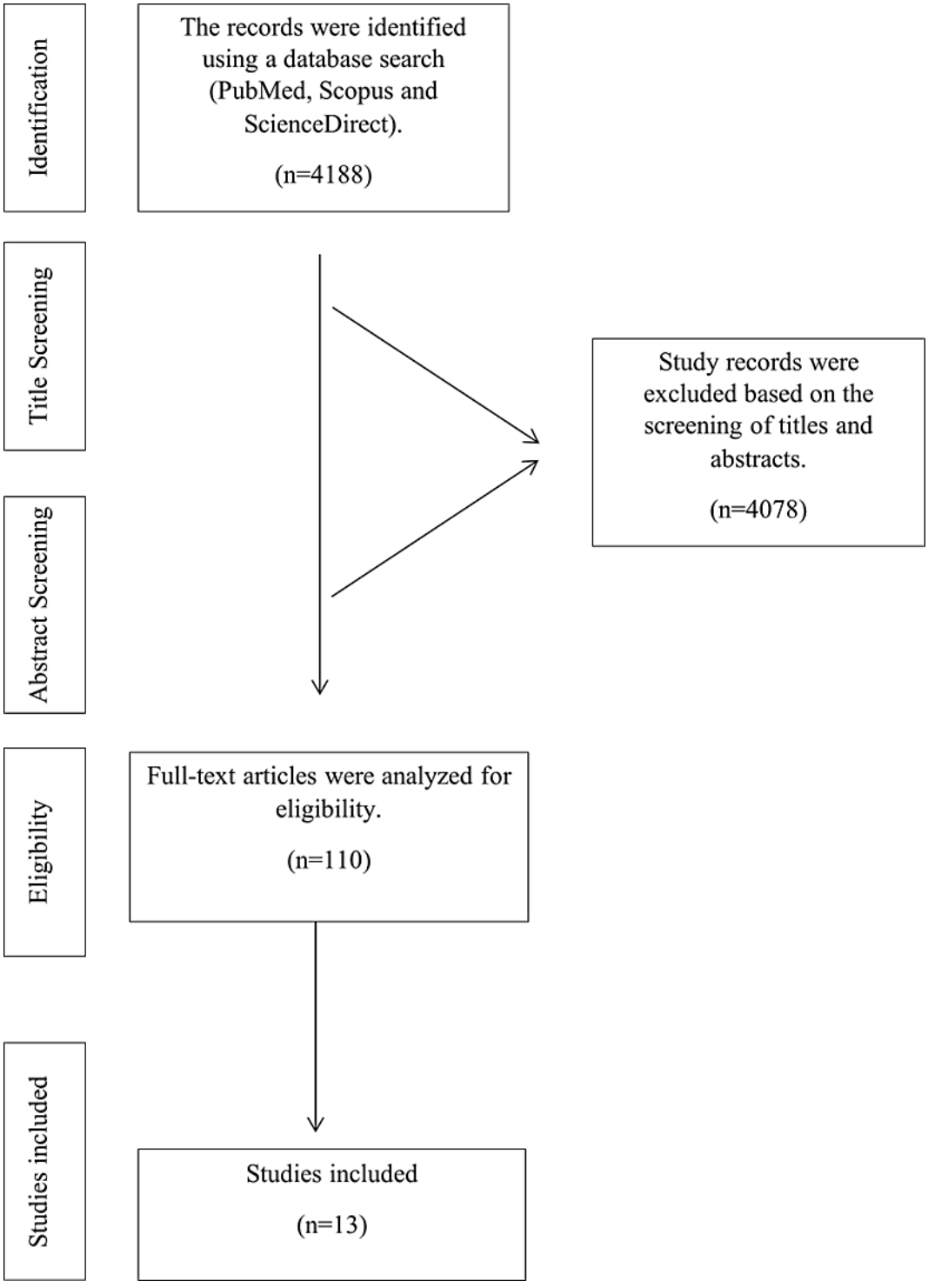

Figure 1: Flowchart of search criteria and study selection.

Table 1: Summary of the selected studies.

Sl. No.	References Place	Experimental Sample	Sample Modification	Intervention	Plant Extract	Control Vintage	Assay	Assay Parameter	Outcome(s) Results	Conclusion
1	Ahmad *et al.*, 2016 Kingdom of Saudi Arabia	BSA (bovine serum albumin)	BSA modified with glucose-Untreated BSA modified with glucose - Treated	Ziziphus oxyphylla- leaves *Cedrela serrata* - leaves Positive control- Aminoguanidine	Crude extract: 80% Methanol Fraction: n-Hexane Chloroform Ethyl acetate n-Butanol Ethyl acetate: Sub-fractions-M1, M2, M3, M4 Ethyl acetate sub-fractions: Compounds - 1,2,3,4,5,6,7	48 hr 60 °C	Glycation inhibition assay	Quantified for relative amount of glycated BSA Based on fluorescence intensity (excitation 360 nm and emission 450 nm) Were analysed in triplicate	IC_{50} values (µg/mL): 1=55920 2=530 19 3 = 556 19 4 = 574 20 5=548 19 6=554 19 7=818 29 M1=586 21 M2=589 21 M3=541 19 M4=593 21 Aminoguanidine= 510 18	The anti-glycation properties of seven pure compounds and four mixtures of flavonoid glycosides indicated that they may have possible applications in the prevention of diabetic complications related to excessive glycation reactions.
2	Beseni *et al.*, 2017 South Africa	BSA (bovine serum albumin)	BSA modified with glucose-Untreated BSA modified with glucose-Treated	*Seriphium plumosum* - leaves Reference standard-Arbutin	Crude extract: Methanol, acetone and hexane	72 hr 60 °C	Glycation inhibition assay	Quantified for relative amount of glycated BSA Based on fluorescence intensity (excitation 370 nm and emission 440 nm) Were analysed in triplicate	Glycation activity (%): Untreated: 100% Treated: Methanol - 7.30% Acetone - 2.22% Hexane - 4.90% Arbutin=7.40%	*Seriphium plumosum* acetone extract showed the highest antiglycation potential. The study reveals the antioxidant, antiglycation and hypoglycaemic potential of crude plant extracts of *S. plumosum*.
3	Beseni *et al.*, 2019 South Africa	BSA (bovine serum albumin)	BSA modified with glucose-Untreated BSA modified with glucose-Treated	*Toona ciliata* - leaves *Schkuhria pinnata* - leaves Reference standard-Arbutin	Crude extract: Methanol, acetone and hexane	72 hr 60 °C	Glycation inhibition assay	Quantified for relative amount of glycated BSA Based on fluorescence intensity (excitation 370 nm and emission 440 nm) Were analysed in triplicate	Glycation activity (%): Untreated: 100% Treated: Toona ciliata: Methanol=2.49%, Acetone=2.79% and Hexane=2.56% Schkuhria pinnata: Methanol=6.62%, Acetone=12.02% and Hexane=15.56% Arbutin=7.40%	*Toona ciliata* methanol extract showed the highest antiglycation potential. The antiglycation activities of all the extracts were significantly higher (p<0.01) than that of Arbutin (positive control).

Sl. No.	References Place	Experimental Sample	Sample Modification	Intervention	Plant Extract	Control Vintage	Assay	Assay Parameter	Outcome(s) Results	Conclusion
4	Deo *et al.*, 2016 Australia	BSA (bovine serum albumin)	BSA modified with glucose-Untreated BSA modified with glucose-Treated	(1) *Petalostigma banksia Britten and S. Moore* - leaves, fruits, roots (2) *Petalostigma pubescens Domin* - leaves, fruits (3) *Memecylon pauciflorum Blume var. pauciflorum*-leaves (4) *Millettia pinnata* (L.) *Panigrahi* - inner bark (5) *Grewia mesomischa Burret* - root bark Positive control: Aminoguanidine *Pre-incubated with plant extracts for 30 min at RT	Crude extracts: Ethanol	3 weeks 37 °C	Glycation inhibition assay	Quantified for relative amount of glycated BSA Based on fluorescence intensity (excitation 370 nm and emission 440 nm) Were analysed in triplicate	IC_{50} values (µg/mL): (1) 56.05 6.10 47.72 1.65 34.49 4.31 (2) 160.74 3.86 83.52 2.02 (3) 76.66 14.50 (4) 71.48 16.40 (5) 50.51 6.77	The antiglycation potential of the selected extracts were compared on the basis of their IC_{50} values and ranged from 34.49 ± 4.31 to 160.74 ± 3.86 µg/mL. Of the selected samples, *P. banksii* fruits and roots had significantly lower ($p<0.05$) levels, whereas *P. pubescens* leaves showed the highest ($p<0.05$) antiglycation IC_{50} value. In *P. pubescens*, different plant components indicated different levels of antiglycation potential. This suggests that the degree of antiglycation activities could vary from plant to plant and in different tissues from the same plant. It is suggested that the ability to reduce the formation of AGEs is closely related to the antioxidant properties of food and medicinal plants.
5	Do *et al.*, 2017 Republic of Korea	BSA (bovine serum albumin)	BSA modified with methylglyoxal - Untreated BSA modified with methylglyoxal - Treated	Lespedeza bicolor - stalks Positive control: Aminoguanidine	Crude extract: 70% Ethanol	7 Days	Glycation inhibition assay	Quantified for relative amount of glycated BSA Based on fluorescence intensity (excitation 355 nm and emission 460 nm) Were analysed in triplicate.	Glycation activity (%): Untreated: 100% Treated: N/A	Addition of *Lespedeza bicolor* (5-10 mg/mL) significantly inhibited the formation of AGEs in a dose-dependent manner.
6	Do *et al.*, 2018 Korea	BSA (bovine serum albumin)	BSA modified with glucose and fructose - Untreated BSA modified with glucose and fructose - Treated	Eucommia ulmoides Oliv-bark	Crude extract: 70% Ethanol	14 Days 37 °C	Glycation inhibition assay	Quantified for relative amount of glycated BSA Based on fluorescence intensity (excitation 350 nm and emission 450 nm) Were analysed in triplicate.	Glycation activity (%): Untreated: 100% Treated: N/A	*Eucommia ulmoides Oliv* inhibit the formation of AGEs in a dose-dependent manner.

Sl. No.	References Place	Experimental Sample	Sample Modification	Intervention	Plant Extract	Control Vintage	Assay	Assay Parameter	Outcome(s) Results	Conclusion
7	Do *et al.*, 2018 Korea	BSA (bovine serum albumin)	BSA modified with glucose and fructose – Untreated. BSA modified with glucose and fructose – Treated.	Spatholobus suberectus-stem	Crude extract: 70% Ethanol	14 Days 37 °C	Glycation inhibition assay	Quantified for relative amount of glycated BSA Based on fluorescence intensity (excitation 350 nm and emission 450 nm) Were analysed in triplicate.	Glycation activity (%): Untreated: 100% Treated: N/A	*Spatholobus suberectus* inhibit the formation of AGEs in a dose-dependent manner.
8	Dzib-Guerra *et al.*, 2016 Mexico	BSA (bovine serum albumin)	BSA modified with D-ribose - Untreated BSA modified with D-ribose-Treated	A-Brosimum alicastrum (BAL) Swartz B-Bunchosia swartziana Griseb C-Ehretia tinifolia (L.) D-Manilkara zapota (L.) P. Royen E-Cassia fistula (L.) F-Cocos nucifera (L.) G-Ocimum campechianum Willdenow H-Piper auritum Kunth I-Rhizophora mangle (L.) Leaves, stems, and roots of each species.	Crude extract: Ethanol Ethyl acetate Except for Cocos nucifera (L.): Traditionally aqueous.	24 hr 37 °C	Glycation inhibition assay	Based on fluorescence intensity. 1 -Vesperlysines-like (exc370 nm; em440 nm) 2-Pentosidine-like (exc335 nm; em385 nm).	IC_{50} values (mg/mL): Root extract of *C. fistula*=0.1 Leaf extract of *P. auritum*=0.35.	
9	Hung *et al.*, 2017 Taiwan	BSA (bovine serum albumin)	BSA modified with glucose-Untreated BSA modified with glucose-Treated	Siegesbeckia orientalis-aerial	Crude extract: 95% Ethanol Fractions: n-Hexane, ethyl acetate and methanol.	7 days 80 °C	NBT reductive assay (absorbance was measured at 530 nm) Girard-T assay (absorbance was monitored at 295 nm against blank - Glyoxal was used as standard).	Based on the formation of Amadori products Based on the formation of dicarbonyl compounds.	NBT reductive assay: Ethanol=24.9% n-Hexane=18.8% Methanol=17.2% Ethyl acetate=15.6% Girard-T assay: Ethyl acetate=61.9% n-Hexane=47.3% Ethanol=46.5% Methanol= 28.2%	*S. orientalis* extracts has slight inhibitory effects on Amadori products formation (from the NBT reduction analysis), but high inhibitory activity on dicarbonyl compound production (from the Girard-T assay). The experimental results of the present study illustrate that S. orientalis extracts can retard the glycation reaction, and its degree of inhibition of the latter stages was higher than the first stage of AGEs formation.

Sl. No.	References Place	Experimental Sample	Sample Modification	Intervention	Plant Extract	Control Vintage	Assay	Assay Parameter	Outcome(s) Results	Conclusion
10	Kishore *et al.*, 2016 India	BSA (bovine serum albumin)	BSA modified with fructose - Untreated BSA modified with fructose – Treated.	*Bacopa monnieri* Linn. - Aerial parts Positive control: Aminoguanidine	Crude extract: Ethanol (BA) Hydro-alcohol (BHA)	4 weeks 37 °C	Glycation inhibition assay	Quantified for relative amount of glycated BSA Based on fluorescence intensity (excitation 355 nm and emission 460 nm) Were analysed in triplicate.	Inhibition of AGEs formation (%): BA (50-500 µg/mL) - 31.34 - 92.29% BHA (50-500 µg/mL) - 31.88 - 93.37% Aminoguanidine=93.37%.	Supplementation with *Bacopa monnieri* might be beneficial via reducing the formation of AGEs.
11	Kuo *et al.*, 2015 Taiwan	BSA (bovine serum albumin)	BSA modified with glucose-Untreated BSA modified with glucose – Treated.	*Canarium album* L. (Core removed) Positive control: Aminoguanidine.	Crude extract: Water Water/Ethanol Ethanol Methanol Acetone Ethyl acetate.	6 weeks 37 °C	Glycation inhibition assay	Quantified for relative amount of glycated BSA Based on fluorescence intensity (excitation 370 nm and emission 440 nm) Were analysed in triplicate.	Inhibition of AGEs formation (%): N/A	Exhibited significant inhibitory effects on AGEs formation in BSA glycation system.
12	Poornima *et al.*, 2015 India	HSA (human serum albumin)	HSA modified with glucose - Untreated HSA modified with glucose – Treated.	Schisandra grandiflora-fruit	Crude extract: Chloroform	One week	Glycation inhibition assay	Quantified for relative amount of glycated BSA Based on fluorescence intensity Were analysed in triplicate.	Glycation activity (%): Untreated: 100% Treated:	

Sl. No.	References Place	Experimental Sample	Sample Modification	Intervention	Plant Extract	Control Vintage	Assay	Assay Parameter	Outcome(s) Results	Conclusion
13	Yang *et al.*, 2016 China	BSA (bovine serum albumin)	BSA modified with glucose-Untreated BSA modified with glucose – Treated.	*Coptis chinensis* Franch - polysaccharides (CCP)	Crude extract: Water	30 days 37 °C	1. Glycation inhibition assay 2. NBT reductive assay 3. Girard-T assay.	1. Quantified for relative amount of glycated BSA Based on fluorescence intensity 2. Based on spectrophotometry intensity Based on the formation of Amadori products-Evaluate the inhibitory rate (%) 3. Based on spectrophotometry intensity Based on the formation of dicarbonyl compounds (mg / mL) Were analysed in triplicate.	1. CCP decreased the fluorescence intensity in dose-dependent manner (p 0.01) 2. CCP dose-dependently inhibited NBT reduction (P 0.01) 3. Comparable inhibitory effects with that of positive control.	CCP can inhibit the AGE formation.

dicarbonyl product as well as AGE. From Hung *et al.*, (2017) it measured Amadori and dicarbonyl product while in Yang *et al.*, (2016) it measured all three stages (Yang *et al.*, 2016; Hung *et al.*, 2017). The measurement of Amadori and dicarbonyl product from these two articles were based on NBT assay and Girard-T assay. Among 13 articles, there were four articles in which the exact value of the inhibition or IC_{50} were unknown. In summary, there were 13 articles measuring the glycation inhibition assay while one article measured both glycation inhibition assay and different stages of AGE. There is only one article that measured based on stages of AGE (Hung *et al.*, 2017). Among these 13 articles reviewed, 12 articles used bovine serum albumin as experimental sample while another one article used human serum (Poornima *et al.*, 2015). For the control vintage, the range were from 24 hr to 42 days while the temperature was kept ranged between 37°C to 80°C.

As mentioned above, there were eight articles measuring the percentage inhibition of Advanced Glycation End-product (AGE). In Baseni *et al.*, (2017) which used *Seriphium plumosum* leaves as model showed the most potent glycation inhibition found in acetone crude extract which was 2.22% AGE formation followed by hexane crude extract and methanol crude extract having value of 4.9% and 7.3% AGE formation (Beseni *et al.*, 2017). In another article from Baseni *et al.*, (2019) which used *Tonna siliata* and *Schkuhria pinnata* leaves as model also showed positive effect on inhibition (Beseni *et al.*, 2019). Among the different crude extracts, methanolic crude extract of *Tonna siliata* showed highest inhibition which gave result of 2.49% followed by acetone extract and hexane crude extract which gave 2.56% and 2.79%, respectively.

In another article from Kishore *et al.*, (2016), the ethanol and hydro-alcohol crude extract from *Bacopa monnieri* with different concentration ranging from 50-500 ug/mL gave glycation inhibition ranging from 36.34-92.91% and 31.88-93.37%, respectively (Kishore *et al.*, 2016). In this article, Aminoguanidine was used as control and gave 93.37% inhibition which have similar effect with 500 ug/mL concentration of *Bacopa Monnieri*. Another article, which used *Canarium album* fruit with the core removed, showed that the water-ethanolic extract had the highest inhibition, followed by methanolic crude extract, water extract, ethanolic extract, acetone extract, and ethyl acetate extract (Kuo *et al.*, 2015). The acetone extract and ethyl acetate crude extract gave similar effects.

Besides, three articles from Do *et al.*, (2017, 2018a, 2018b) which used 70% of ethanolic crude extract from medicinal plants such as *Lespedeza bicolor*, *Eucomnia ulmoides* and *Spatholobus suberectus* showed dose-dependent manner in inhibition of Advanced Glycation End-product (AGE) (Do *et al.*, 2017, 2018a, 2018b).

For the measurement of IC_{50}, three articles were selected. First, in Ahmad *et al.*, (2016) which used 80% methanolic crude extract of both *Ziziphus oxyphylla* and *Cedrela serrata* leaves were tested (Ahmad *et al.*, 2016). From the crude extract, its sub-fractions-n-hexane, chloroform, ethyl acetate and n-butanol were used. However, only the ethyl acetate fraction was sub-fractionated, yielding M1, M2, M3, and M4. In this sub-fraction, there were seven compounds isolated by High Pressure Liquid Chromatography (HPLC). Among the sub-fraction, M3 gave most potent IC~50~ values which was 541±19 followed by M1, M2 and M4 which were 586±21, 589±21 and 593±21, respectively. In this experiment, aminoguanidine was used as positive control which gave value of 510±18. Among the seven compounds, compound 2 had the lowest IC~50~ value (530±19) while compound 7 had the largest IC_{50} value (818±29).

In Deo *et al.*, (2016), five different plants were used as models. There were *Petalostigma pubescens*, *Petalostigma banksia*, *Memecylon pauciflorum*, *Millettia pinnata* and *Grewa nesomischa* (Deo *et al.*, 2016). Different parts of the plant such as leaf, fruit, root, inner bark and bark were used in the experiment. Among them, leaves from *Petalostigma banksia* was significant higher with IC~50~ value of 56.06±6.10. In Dzib-Guerrea *et al.*, (2016), nine different types of medicinal plants were used (Dzib-Guerra *et al.*, 2016). There were *Brosimum alicastrum* (BAL) *Swartz*, *Bunchosia swartziana Griseb*, *Ehretia tinifolia* (L.), *Manilkara zapota* (L.) *P. royen, Cassia fistula* (L.), *Cocos nucifera* (L.), *Ocimum campechianum Willdenow*, *Piper auritum Kunth, Rhizophora mangle* (L.). The leaves, stems, and roots of each plant were tested in the form of ethanol and ethyl acetate extracts, except for *Cocos nucifera*, which was tested as an aqueous extract. However, the results measured vesperlysine-like AGE and pentosidine-like AGE.

In Yang *et al.*, (2016), *Coptis chinensis* polysaccharide was tested in the form of a water extract (Yang *et al.*, 2016). The glycation inhibition assay and NBT assay showed a dose-dependent effect, while the Girard-T assay demonstrated a comparable inhibitory effect. However, the exact inhibition values were not reported in the results.

Lastly, in Hung *et al.*, (2017), the aerial parts of *Siegesbeckia orientalis* were tested (Hung *et al.*, 2017). The 95% ethanol crude extract was fractionated into n-hexane, ethyl acetate, and methanol. In the experiment, this plant exhibited a high inhibitory effect on dicarbonyl compounds and a low inhibitory effect on Amadori products. In the NBT assay, the ethanol extract showed the highest inhibitory effect (24.9%), followed by n-hexane (18.8%), methanol (17.2%), and ethyl acetate (15.6%). In the Girard-T assay, the ethyl acetate extract showed the highest inhibition (61.9%), followed by n-hexane (47.3%), ethanol (46.5%), and methanol (28.2%).

DISCUSSION

Hyperglycemia is the principal cause of diabetic complications. It leads to increased production of Reactive Oxygen Species (ROS), breakdown of starch by α-amylase, α-glucosidase as well as development of Advanced Glycation End-product (AGE) (Deo *et al.*, 2016). As mentioned above, AGEs are the key component in development of diabetic complications. Glycation, a spontaneous reaction of sugars with proteins is one of the sources of developing oxidative stress in our body (Beseni *et al.*, 2019). The reaction forms a stable product known as Amadori product before it turns into dicarbonyl compound such as methylglyoxal and glyoxal. Eventually, AGE is formed from the reaction which then circulate in our body to develop complications (Hung *et al.*, 2017). Nephropathy is one of the diabetic complications developed due to AGEs (Do *et al.*, 2018a). Kidney renal proximal tubule cells are known to absorb the circulating AGEs from glomerular filtrate and detoxify it (Do *et al.*, 2018a). Hence, elevation of AGEs in body can result in accumulation of AGEs, triggering various pathway which lead to increase in ROS and eventually causing permanent damage to renal tubule (Do *et al.*, 2018b). Besides, AGEs also affect the function of the liver. In the study by Yang *et al.*, (2016), diabetes causes liver destruction and decrease the function of the hepatocyte through generation of AGEs (Yang *et al.*, 2016).

Recently, various studies have discussed the pathological pathways of AGEs. The apoptosis mechanism mediated by the p53 protein plays an important role in diabetic complications (Hori, Kuno, Hosoda, and Horio, 2013). When AGE levels increase, oxidative stress in the cell rises, triggering the activation of the B-cell lymphoma 2 (Bcl-2) family and Bcl-2-associated X protein (Bax). This leads to increased mitochondrial permeability, ultimately resulting in cell death (Brunelle and Letai, 2009). Another pathway that induces diabetic complications is the activation of the Receptor for Advanced Glycation End products (RAGE) by AGEs (RAGE-AGE activation) (Do *et al.*, 2018a). RAGE is a multiligand receptor of the immunoglobulin family (Ramasamy *et al.*, 2008). This receptor is normally expressed at low levels but increases in expression when AGE accumulates. When AGE binds to RAGE, it activates various intracellular signaling pathways, such as Mitogen-Activated Protein Kinase (MAPK), which subsequently activates Nuclear Factor-kB (NF-kB). This leads to the release of pro-inflammatory cytokines, including interleukin-6 and tumor necrosis factor-α, ultimately causing cell death (Do *et al.*, 2018a).

Another mechanism by which AGE contributes to diabetic complications is through the polyol pathway (Kishore *et al.*, 2016). Aldose reductase, the first and rate-limiting enzyme in this pathway, is responsible for converting glucose into sorbitol (Reddy *et al.*, 2014). Under euglycemic conditions, glucose is metabolized into pyruvate. However, when in hyperglycemia condition, glucose will then enter polyol pathway and metabolized into sorbitol (Reddy *et al.*, 2014). As a result, increase oxidative stress and over production of sorbitol which increases the osmotic stress in the cell will lead to cell death and causes diabetic complications (Kishore *et al.*, 2016).

To reduce the diabetic complication, compound that can inhibit the AGE could be useful. To date, there are various types of drugs which can inhibit the formation of AGE such as metformin as well as Aminoguanidine. However, the poor development prospects of these drugs and adverse effects are not safe to human (Ramkissoon, Mahomoodally, Subratty, and Ahmed, 2016). Hence, an alternative method needed to be found to reduce the diabetic complication. Recently, many researchers focused on medicinal plants as an alternative way to treat diabetic complications (Kishore *et al.*, 2016). Many studies had shown that there are potential of medicinal plant in inhibiting the formation of AGE (Beseni *et al.*, 2017).

Studies by Ahmad *et al.*, (2016), Deo *et al.*, (2016) and Dzib-Guerra *et al.*, (2016), which measures the IC~50~ values of medicinal plants extracts on fluorescence AGE, it is found that several medicinal plants have similar effect compared to aminoguanidine which is a type of anti-AGE drug (Ahmad *et al.*, 2016; Deo *et al.*, 2016; Dzib-Guerra *et al.*, 2016). In the study by Ahmad *et al.*, (2016), compound 2 exerted a similar effect to aminoguanidine. Also, compound 1, 2, 3, 5, 6 and mixture 3 also showed similar effect (Ahmad *et al.*, 2016). Besides, mixture of compound showed greater effects, and this might be due to synergistic effect of flavonoid glycoside (Ahmad *et al.*, 2016). In Deo *et al.*, (2016), *Petalostigma banksia* showed greatest effect as it possess lowest IC~50~ values (Deo *et al.*, 2016). The antiglycation effect on medicinal plant are closely related to antioxidant properties (Mahomoodally, Subratty, Gurib-Fakim, and Choudhary, 2012; Sadowska-Bartosz and Bartosz, 2015). However, the studies do not show any correlation between antiglycation and antioxidant activities (Deo *et al.*, 2016). This suggested that different medicinal plants may have their independent pathway in inhibition of protein glycation (Deo *et al.*, 2016). In a study by Dzib-Guerra *et al.*, (2016), the root extract of *C. fistula* had greater effect on vesperlysine and pentosidine like AGE compared to aminoguanidine (Dzib-Guerra *et al.*, 2016). It is also shown that there is no correlation between antioxidant and antiglycation in this study (Dzib-Guerra *et al.*, 2016).

Besides, in Baseni *et al.*, (2017 and 2019), methanolic, hexane and acetone extract of *Toona ciliata*, *Seriphium plumosum* and methanolic extract of *Schkuhria pinnata* showed greater AGE inhibition compared to positive control which is Arbutin (Beseni *et al.*, 2017, 2019). It is shown that more polar solvents have better yield compared to less polar solvents as plant contain more polar compounds (Beseni *et al.*, 2019). The lower effect of *Schkuhria pinnata* compared to positive control may be due to highly fibrous nature of its leaves which contain a lot of non-soluble component that reduce the therapeutic function (Kumar, Sinha, Makkar, de

Boeck, and Becker, 2012). In studies by Do *et al.*, (2017, 2018a, 2018b), which used 70% ethanolic extracts of medicinal plants, showed a dose-dependent results (Do *et al.*, 2017, 2018a, 2018b). They showed a similar effect to aminoguanidine as a positive control at higher concentrations (Do *et al.*, 2017, 2018a, 2018b). A similar result was observed in a study (Kishore *et al.*, 2017) that also used aminoguanidine as a positive control. Free radicals were shown to increase the formation of AGE (Rains and Jain, 2011). As a result, phenolic antioxidants found in the medicinal plants gained attention as potent AGE inhibitors (Ramkissoon *et al.*, 2013). As water-ethanolic extract of *Canarium album* contain highest yield of phenolic compounds, it showed greatest AGE inhibition (Kuo *et al.*, 2015). According to Xie and Chen (2013), different flavonoids will have different inhibitory activity against AGE due to structural differences (Xie and Chen, 2013). In High Pressure Liquid Chromatography (HPLC) analysis, it was shown that three of the flavonoid compounds including genistein, quercetin and naringenin significantly inhibit the formation of AGE (Do *et al.*, 2018b). As quercetin and genistein have hydroxyl group at carbon number 5, it can increase the free amines which the latter can breakdown the AGE (Do *et al.*, 2018b). Besides, quercetin and genistein were found to have inhibitory effects in AGE formation (Do *et al.*, 2018b). This is because these compounds have Thiazole ring derivative which can break the Maillard reaction crosslink via thiazolium structure (Gkogkolou and Böhm, 2012). Additionally, these compounds can attach to the pyrrole carbon ring in AGEs, making it susceptible to nucleophilic attacks, which eventually lead to the breakdown of AGEs (Kim, Kim, Moon, and Kim, 2015). In studies by Do *et al.*, (2018a and 2018b), *Spatholobus suberectus* and *Eucommia ulmoides* were able to increase the expression and activation of Glo1 protein which play a significant role in suppressing the formation of AGE (Do *et al.*, 2018a, 2018b). This pathway is important in detoxifying reactive dicarbonyl compound which is converted into D-lactate (Do *et al.*, 2018a). In addition, increased expression of NQO1 and HO-1 by *S. suberectus* also can inhibit formation of AGE (Do *et al.*, 2018b). These molecules are expressed by Nrf2 transcription factor which regulate the Antioxidant Response Elements (AREs) (Spoto, Pisano, and Zoccali, 2016). By upregulating these molecules expression via Nrf2 pathway, it can inhibit the accumulation and formation of AGEs as well as reduce the expression of RAGE (Do *et al.*, 2018a). Moreover, *Bacopa monnieri* extract which contain triterpenoid is able to stimulate release of insulin and reduce oxidative stress (Dewanjee, Das, Sahu, and Gangopadhyay, 2009). Also, this medicinal plant contains various saponins such as bacopasaponin A, B, C, D and pseudojujubogenin which are potent radical scavenger and are found to have renoprotective effect as well as reduce fasting blood glucose level (Kishore *et al.*, 2016). Also, phytosterols found in this medicinal plant having similar effect as stigmasterol in preventing diabetic complications by decreasing the oxidative stress and increase antioxidant levels (Nualkaew, Padee, and Chusri, 2015).

CONCLUSION

In a nutshell, AGE is one of the key components that induce various diabetic complications. The active compounds found in medicinal plants can reduce AGE formation, making them a potential treatment for diabetic complications, as they have fewer side effects compared to synthetic drugs.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AGE: Advanced Glycation End-Product; **IC_{50}:** Half Maximal Inhibitory Concentration; **RAGE:** Receptor of Advanced Glycation End-Product; **JAK/STAT:** Janus Kinase-Signal Transduced and Activator of Transcription; **NADPH:** Nicotinamide Adenine Dinucleotide Phosphate; **MAPK:** Mitogen Activated Protein Kinase; **NF-κB:** Nuclear Factor-kb; **IFN-SRE:** Interferon-Stimulated Response Elements; **AMPK:** 5'AMP-Activated Protein Kinase; **PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **MeSH:** Medical Subject Headings; **HPLC:** High Pressure Liquid Chromatography; **ROS:** Reactive Oxygen Species; **Bcl-2:** B-cell lymphoma 2; **Bax:** Bcl-2-associated X protein.

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