Medicinal Plants
Vol. 14 (3), September 2022, 405-420

doi : 10.5958/0975-6892.2022.00044.2

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Review Article

The ameliorating effects of *Tinospora* species on the formation of advanced glycation end-products (AGEs) and associated oxidative stress

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Received: May 09, 2022; Accepted: June 02, 2022

ABSTRACT

Tinospora is a plant genus widely distributed in Southeast Asia, where it is used as traditional medicine. Extracts from the stem and leaves of *Tinospora crispa* and *Tinospora cordifolia* are rich in phytochemicals like flavonoids, terpenoids, alkaloids etc., which are well known for their hypoglycaemic and/or antioxidant effects. Diabetes-induced hyperglycaemia triggers an increased formation of advanced glycation endproducts (AGE) which are associated with inflammation and oxidative stress causing diabetic complications. Little is known about the effects of *T. crispa* and *T. cordifolia* on AGE formation and prevention of AGE-induced effects like oxidative stress. Therefore, we discussed the updated information on the effects of *Tinospora* extracts on the AGEs formation. Glucose lowering *Tinospora* constituents mainly belonged to the group of terpenoids e.g., borapetoside A and borapetol A, while alkaloids like berberine and palmatine reduced the AGE formation. Flavonoids showed to be protective against AGE-associated oxidative stress. Nonetheless, more in depth studies are further required to understand the protective mechanism of the extracts.

Keywords: Advanced glycation end products, diabetes, oxidative stress, *Tinospora*.

INTRODUCTION

Plants belonging to the genus *Tinospora* (family: Menispermaceae) are woody climbing shrubs with exstipulate alternate roundish leaves and corky barks on its stem. Out of the 34 species known today; *Tinospora cordifolia, T. crispa* and *T. sinensis* are well known for their medicinal plants uses in diabetes, jaundice, rheumatoid arthritis, fever, vomiting, anaemia, polyuria, and other disorders (Khan *et al.*, 2016; Sharma *et al.*, 2019).

Several clinical studies have shown that the *Tinospora* species possess a wide range of biological activities including anti-diabetic (Lokman *et al.*, 2013), antioxidant (Kannadhasan and Venkataraman, 2013, Jayaprakash *et al.*, 2015), anti-inflammatory (Philip *et al.*, 2018, Birla *et al.*, 2019), anti-tumorigenic (Singh *et al.*, 2004, 2005, Ibrahim *et al.*, 2011) and anti-osteoporotic (Kapur *et al.*, 2008) properties. Under prolonged hyperglycaemia, the formation of advanced glycation end products (AGEs) is increased and the products accumulate in the blood and various tissues

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(Chang *et al.*, 2017). New studies have shown a link between AGE accumulation and diabetes related complications such as diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, and diabetic atherosclerosis (Ahmed *et al.*, 2005; Sharma *et al.*, 2012; Singh *et al.*, 2014).

According to the WHO (2021), diabetes affected 422 million people worldwide in 2014, which surged from 108 million in 1980. Developing countries have been experiencing a faster increase in prevalence of diabetes than high-income countries. This trend is worrying as, in 2019, a 1.5 million deaths were attributed to diabetes and another 2.2 million deaths in 2021 were recorded associated with high level of blood glucose (World Health Organization, 2021). Adequate control of the blood sugar level is important for a healthy well-being. Since then, researchers have been an increased interest in utilizing medicinal plants with anti-diabetic or anti-hyperglycaemic properties, which can reduce or even prevent diabetes-associated abnormalities (Surya *et al.*, 2014). In this review we will focus on *Tinospora* concentrate for its' diabetes, diabetes related AGEs formation and oxidative stress ameliorating properties.

Chemical constituents of *Tinospora crispa* and *Tinospora cordifolia*

Tinospora crispa, one of the species in the genus *Tinospora,* is known in Malaysia as *"Akar patawali"* and *"Akar seruntum"* (Noor and Ashcroft, 1989). *T. crispa* is widely distributed in the Southeast Asian region including Malaysia, Indonesia, Thailand, and Philippines. *T. cordifolia* is also widely distributed in South-East Asia but is mainly used in India and neighbouring countries. It has been used as traditional Indian medicine to treat a broad spectrum of illnesses (Chi *et al.*, 2016). The phytochemicals of various *Tinospora* species have been extensively studied and many of them have been isolated and identified for different biological properties. Chi *et al.* (2016) stated that 223 phytochemicals have been isolated from this genus, whereby diterpenoids are the most abundant isolated phytochemicals; others include alkaloids, steroids, terpenoids, polysaccharides and C_6-C_3 derivatives. Ahmad *et al.* (2016) reported a total of 65 compounds isolated from *T. crispa* which are mainly alkaloids, flavonoids, terpenoids, lignans, nucleosides and sterols (Table 1 and Table 2).

Table 1: Classification of compounds found in *T. crispa*

Classification of compounds	Name of the chemical compounds	References
Terpenoids	Borapetol A	Ruan *et al.* (2013)
	Borapetol B	Lokman *et al.* (2013) Ruan et al (2012)
	Borapetol C	Ruan *et al.* (2012)
	Borapetoside D	Choudhary *et al.* (2010)
	Borapetoside H	Koay and Koay (2013)
	Tinocrisposide	Adnan *et al.* (2019)
	(5R,6S,9S,10S,12S)-15,16-Epoxy-2-oxo-6-*O*-(β-Dglucopyranosyl)-cleroda-3,7,13(16),14-tetraen-17,12-olid-18-oic acid methyl ester	Choudhary *et al.* (2010)
	(5R,6R,8S,9R,10S,12S)-15,16-Epoxy-2-oxo-6-*O*- (β-D-glucopyranosyl)-cleroda-3,13(16),14-trien-17,12-olid-18-oic acid methyl ester	Choudhary *et al.* (2010)
	(2R,5R,6R,8S,9S,10S,12S)-15,16-Epoxy-2-hydroxy-6-*O*-{β-D-glucopyranosyl-(1→6)-α-Dxylopyranosyl}-cleroda-3,13(16),14-trien-17,12-olid-18-oic acid methyl ester	Choudhary *et al.* (2010)
	(2R,5R,6R,8R,9S,10S,12S)-15,16-Epoxy-2-hydroxy-6-*O*-(β-D-glucopyranosyl) -cleroda-3,13(16),14-trien-17,12-olid-18-oic acid methyl ester	Choudhary *et al.* (2010)
	(5R,6R,8S,9R,10R,12S)-15,16-Epoxy-2-oxo-6-*O*-(β-D-glucopyranosyl)-cleroda-3, 13(16),14-trien-17,12-olid-18-oic acid methyl Ester	Choudhary *et al.* (2010)

Table 1 contd....

Classification of compounds	Name of the chemical compounds	References
	Tinocrispol A	Lam *et al.* (2012)
	2-*O*-Lactoylborapetoside B	Lam *et al.* (2012)
	6'-*O*-Lactoylborapetoside B	Lam *et al.* (2012)
	(3R,4R,5R,6S,8R,9S,10S,12S)-15,16-Epoxy-3,4-epoxy-6-*O*-(β-D-glucopyranosyl)-cleroda-3,13(16),14-trien-17,12-olid-18-oic acid methylester	Choudhary *et al.* (2010)
	(1R,4S,5R,8S,9R,10S,12S)-15,16-Epoxy-4-*O*-(β-Dglucopyranosyl)-cleroda-2,13(16),14-triene-17(12),18(1)-diolide	Choudhary *et al.* (2010)
	Tinotufolin C	Koay and Koay (2013)
	Tinotufolin F	Koay and Koay (2013)
	Tinotufolin E	Koay and Koay (2013)
	(2*R*,7*S*,8*S*)-8-[(2*S*)-2-(3,4-Dihydroxy-2,5-dimethoxytetrahydro-3-furanyl)-2-hydroxyethyl]-2,8-dimethyl-10-oxo-11-oxatricyclo [7.2.1.02,7] dodec-3-ene-3-carboxylate	Choudhary *et al.* (2010)
	Cycloeucalenol	Kongkathip *et al.* (2002)
	Cycloeucalenone	Kongkathip *et al.* (2002)
	Magnoflorine	Patel and Mishra (2012)
	Palmatine	Patel and Mishra (2012) Neag *et al.* (2018)
	Jatorrhizine	Patel and Mishra (2012
Alkaloids	Berberine	Patel and Mishra (2012 Neag *et al.* (2018) Xia *et al.* (2011) Yin *et al.* (2008a) Yin *et al.* (2008b)
	4,13-Dihydroxy-2,8,9-trimethoxydibenzo [a, g] quinolizinium	Yusoff *et al.* (2014)
	N-Formylasimilobine-2-*O*-β-D-glucopyranoside	Koay and Koay (2013)
	N-Acetyl nornuciferine	Praman *et al.* (2011)
	Higenamine	Praman *et al.* (2012)
	Adenine	Praman *et al.* (2012)
	Adenosine	
	Uridine	Praman *et al.* (2013)
	Salsolinol	Praman *et al.* (2012)
	(")-Litcubinine	Praman *et al.* (2012)
	Tyramine	Praman *et al.* (2012)
	Syringin	Praman *et al.* (2012)
	Tinotuberide	Koay and Koay (2013)
Flavonoids	Isoorientin 2"-*O*-(E)-sinapate	Chang *et al.* (2015)
	2"-(*E*)-*p*-coumarate	Chang *et al.* (2015)
	Cosmosiin 6"-(E)-ferulate	Chang *et al.* (2015)
	Cosmosiin 6"-(E)-cinnamate	Chang *et al.* (2015)

Source: Ahmad *et al.* (2016); Chi *et al.* (2016).

Table 2: Classification of compounds found in *T. cordifolia*

Classification of compounds	Name of the chemical compounds	References
Terpenoids	Tinocordin	Sivasubramanian *et al.* (2013)
	Tinosponone	Iqbal *et al.* (2005)
	Tinosporaside	Ghatpande *et al.* (2019) Choudhary *et al.* (2014)
	Amritoside A	Maurya *et al.* (2004)
	Amritoside B	Maurya *et al.* (2004)
	Amritoside C	Maurya *et al.* (2004)
	Amritoside D	Maurya *et al.* (2004)
	Tinocordioside	Maurya *et al.* (2004)
	Tinocordioside tetraacetate	Maurya *et al.* (2004)
	Tinoscorside C	Van Kiem *et al.* (2010)
	Borapetoside B	Van Kiem *et al.* (2010)
	Borapetoside F	Van Kiem *et al.* (2010)
	Furano diterpene glycoside	Saeed *et al.* (2020) Sharma *et al.* (2018) Pandey *et al.* (2012)
	Cordioside	Pandey *et al.* (2012)
	Tinosporide	Saeed *et al.* (2020)
	(5R,10R)-4R,8R-Dihydroxy-2S,3R:15,16-diepoxycleroda-13(16), 1712S,18,1S-dilactone	Dhanasekaran *et al.* (2009)
	Columbin	Saeed *et al.* (2020)
	Cordifolide A	Tiwari *et al.* (2018) Pan *et al.* (2012)
	Cordifolide B	Tiwari *et al.* (2018)
		Pan *et al.* (2012)
	Cordifolide C	Tiwari *et al.* (2018) Pan *et al.* (2012)
	Cordifolide D	Tiwari *et al.* (2018)
	Cordifolide E	Tiwari *et al.* (2018)
	Tinosporicide	Sharma *et al.* (2020)
	Tinosporaclerodanoid	Ahmad *et al.* (2010)
	Tinosporafuranol	Ahmad *et al.* (2010)
	Tinosporaclerodanol	Ahmad *et al.* (2010)
	Tinocordifolioside	Tiwari *et al.* (2018)
	Tinocordifolin	Tiwari *et al.* (2018)
	Angelicoidenol-2-*O*-β-D-apiofuranosyl-(1→6)-β-D-glucopyranoside	Van Kiem *et al.* (2010)
	Tinosporin	Saeed *et al.* (2020)
Alkaloids	Tinosporic acid	Saeed *et al.* (2020)
	Berberine	Tiwari *et al.* (2018)
	Palmatine	Tiwari *et al.* (2018)
	Jatrorrhizine	Tiwari *et al.* (2018)

Table 2 contd...

Classification of compounds	Name of the chemical compounds	References
	Magnoflorine	Tiwari *et al.* (2018)
	Tembetarine	Tiwari *et al.* (2018)
	N-*trans*-Feruloyl tyramine diacetate	Tiwari *et al.* (2018)
	Choline	Tiwari *et al.* (2018)
	3(a,4-dihydroxy-3-methoxybenzyl)-4-(4-hydroxy-3-methoxybenzyl) tetrahydrofuran	Tiwari *et al.* (2018)
Flavonoids	(–)-Epicatechin	Pushp *et al.* (2013)
	(+)-Catechin	Pushp *et al.* (2013)
Steroids	β-Sitosterol	Tiwari *et al.* (2018) Maurya *et al.* (2009)
	20α-Hydroxy ecdysone	Tiwari *et al.* (2018)
	Polypodine B 20,22-acetonide	Van Kiem *et al.* (2010)

Source: Chi *et al.* (2016).

Advanced glycation endproducts and their role in diabetes-induced complications

Diabetes and its complications have detrimental consequences for human health. Excessive advanced glycation endproducts (AGEs) accumulate in the body during the early stages of diabetes and bind to its receptor RAGE, impairing regulation of glucose. This in turn increased blood glucose levels in the later stages of diabetes which hasten the production of more AGEs (Xiong *et al.*, 2020). The excessive generation of these molecules are crucial in the development of diabetes and its complications.

Advanced glycation end products or in short AGEs are a heterogeneous group of molecules, which were discovered in the early 20th century by the French chemist, Louis Camille Maillard (Maillard, 1912). The formation of AGEs follows the same process that leads to the browning of food during frying. The Maillard reaction is a natural occurring chemical process that takes place between an ε amino group of an exposed amino acid residue of a protein and an aldehyde group of a free monosaccharide such as glucose and fructose.

The reaction of the afore mentioned ε amino group of an exposed amino acid of a protein residue, e.g., lysine, and an aldehyde group of a free monosaccharide, e.g., glucose will cause the formation of glucosyl-lysine which undergoes a supplementary reaction to form a reversible Schiff base (Chaudhuri *et al.*, 2018). The formed Schiff base is an intermediate compound that is unstable and therefore needs to undergo structural rearrangement into a more stable, covalently bound Amadori product (Yamagishi *et al.*, 2015). Over the time, the Amadori products undergo rearrangement once again to form irreversible molecules called AGEs.

The Amadori products could either be: 1) oxidized, resulting in AGE, or 2) dehydrated and deaminated, to assemble highly reactive intermediates called reactive carbonyl compounds or α-dicarbonyl compounds (α-DC), mainly methylglyoxal (MGO), glyoxal (GO) and 3-deoxyglucosone (3DG) (AL-Khateeb *et al.*, 2018). Under long-standing hyperglycaemic conditions, these reactive carbonyl compounds are increasingly formed because they react with proteins, lipids and DNA to produce additional AGEs (Singh *et al.*, 2014). The cells may undergo a stage of intracellular oxidative stress, which is also known as carbonyl stress depending on the amount of AGEs in the cells.

Anaerobic glycolysis, and to a lesser extent, lipid peroxidation produce α-DCs, which undergo unbiased reaction with proteins, lipids, and DNA to produce more AGEs (Rabbani and Thornalley, 2015). MGO, one of the major precursors of AGEs, is produced spontaneously during glycolysis from dihydroxyacetone phosphate and triose phosphate isomers glyceraldehyde-3 phosphate and is primarily linked to the β-elimination of a phosphate group

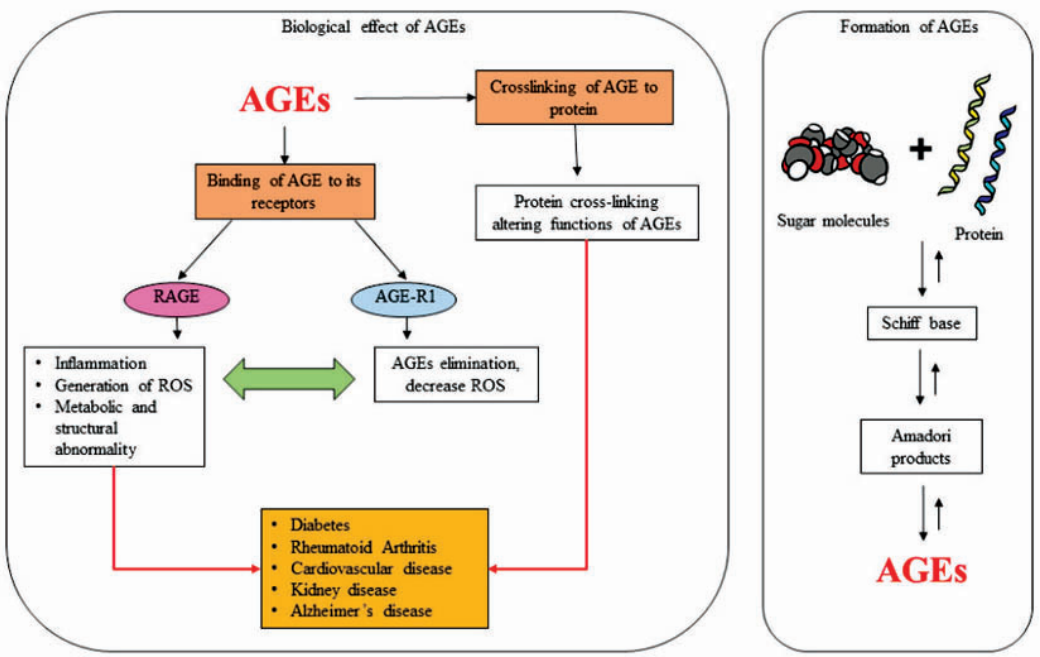


Figure 1: The schematic diagram summarised the biological effects and the formation of AGEs. (*Source:* Abate *et al.*, 2015)

from the enediolate phosphate intermediate (Kieffer *et al.*, 2014).

Receptor for advanced glycation endproducts

AGEs are biomarker molecules that play a significant role in ageing and a multitude of metabolic diseases (Chaudhuri *et al.*, 2018). The accumulation of these heterogeneous molecules is seen in disorders like diabetes, chronic kidney disease, inflammation, neurodegeneration, and ageing (Senatus and Schmidt, 2017). RAGE or the receptor for advanced glycation end products, is a ubiquitous, 55 kDa surface protein (Popa *et al.,* 2014) with three distinct functional structure components; (i) cytosolic, (ii) transmembrane, and (iii) extracellular regions; consisting of two C-type domains and one V-type domain (Lee and Park, 2013). Neeper *et al.* (1992) first characterized the receptor for advanced glycation end products (RAGE) as a type I single-pass membrane protein (receptor) of the immunoglobulin superfamily and is widely known as the signal-transducing receptor for AGEs. Other receptors, in addition to RAGE, are known to bind advanced glycation end products. However, with the exception of RAGE, these receptors may be involved in the elimination of AGE rather than signal transduction.

AGE-RAGE complex

The binding of AGE to RAGE forming an AGE-RAGE complex due to chronic hyperglycaemia evokes oxidative stress, thrombogenic and inflammatory reactions that interfere with various cell's functions, therefore, causing the onset of metabolic diseases (Aragno and Mastrocola, 2017). Once the AGE ligands bind to the RAGE, multiple signalling pathways are activated including reactive oxygen species (ROS) signalling pathway, Rat sarcoma protein 21 (Ras p21) pathway, Ras-extracellular signal-regulated kinase (Erk) pathway, Ras-related C3 botulinum toxin substrate 1 (Rac1)-mitogen activated protein-kinase kinase 6 (Mkk6) pathway, phosphoinositide 3-kinase (PI3K)-caspase 3 (Casp3) dependent pathway, Rac1-Mkk4/7 pathway, Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway, PI3K-protein kinase B (Akt) pathway and mitogen-activated protein kinase (MAPK) mediated pathway. These pathways activate the downstream inflammatory response such as the activation of NF-κB, AP-1 and STAT-3 (Roy, 2013), which are the transcription factors of pro-inflammatory cytokines (IL-1α, IL-6) and tumour necrosis factor (TNF-α). The generation of pro-inflammatory cytokines and TNF-α further increase inflammation (Ahmed, 2005) and oxidative stress resulted

in excessive reactive oxygen species production leading to cell and DNA damage (Nita and Grzybowski, 2016).

AGE-RAGE signalling and oxidative stress

Oxidation stress induced by the AGE-RAGE complex further stimulate the AGEs formation and subsequently the overexpression of RAGE. The activation of RAGE then increases the production of reactive oxygen species (ROS). The protagonist role in oxidative stress and dysfunction of cells is played by the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (D'Agati and Schmidt, 2010). ROS plays an important role in the activation of NFκB signalling via phosphatidylinositol-3 kinase (Pl3K)-protein kinase B (Akt) while the Pl3K-caspase-3 (Csp-3) by activating the protein kinase RNA-activated (PKR) that either induces the NFκB via the p38 MAPK pathway or activate the eukaryotic initiation factor-α (eIFα) which inhibits the synthesis of protein and decrease the rate of translation (Russel *et al.*, 2009). In addition, ROS may also employ Ras (p38 MAPK-Erk1/2 pathway) and Rac1-Mkk6 mediated pathway to activate the NFκB activation, Rac1-Mkk4/7, and JAK-STAT mediated pathway to activate the AP1 and STAT3 respectively (Roy, 2013). The production of ROS can also be directly involved in the Ca^{2+} depended pathway to accelerate the damage of muscle protein.

AGE-MEDIATED PATHWAYS THAT LEAD TO THE COMPLICATIONS OF DIABETES MELLITUS

AGE-RAGE signalling activates the JAK-STAT pathway

Under inflammatory conditions due to the accumulation of AGEs, osteoclastogenesis can occur via other pathways such as MCP-mediated, TNF-α mediated, and IL-6 mediated. As mentioned before, the expression of pro-inflammatory cytokines such as TNF-α, IL-1 and IL-6 are produced. IL-6 is thought to have the highest concentration out of all cytokines because of their involvement in various clinical and physiological conditions (Maeda *et al.*, 2010). In osteoblast, the binding of IL-6 to IL-6R has been known to cut off the ERK pathway (Roy, 2013). Besides, the proinflammatory cytokine IL-6 has been associated as the potential cause of muscle atrophy (Haddad *et al.*, 2005). According to Elkina *et al.* (2011), JAK-STAT pathway is shown to mediate IL-6 in exerting its effects in muscle atrophy or muscle wasting. The JAK-STAT pathway also has been associated with various physiological processes and

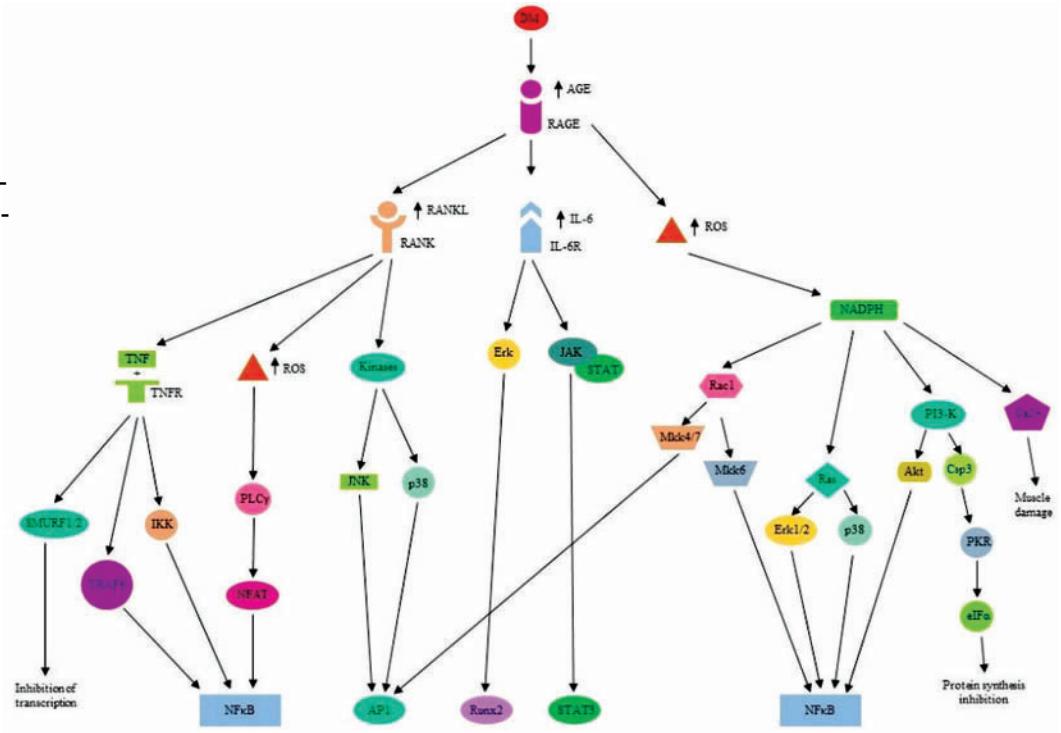


Figure 2: Various possible mechanisms and pathways which could lead to the activation of NF-κB, AP-1 and STAT-3, the transcription factors of pro-inflammatory cytokines (IL-1α, IL-6) and tumour necrosis factor (TNF-α) responsible in the complications of diabetes mellitus. (*Source:* modified from Roy, 2013).

diseases which are employed by many molecules including cytokines, interferons, and growth factors (O'Shea *et al.*, 2015).

AGE-RAGE signalling induces overexpression of RANKL and bone loss

Receptor activator for nuclear kappa-B ligand or RANKL is known as a ligand related to the TNF-related activation-induced of cytokines (TRANCE). Besides binding to RANK, RANKL also binds to osteoprotegerin (OPG), which is considered as a decoy receptor. Therefore, it is necessary to determine the ration of RANKL/OPG. If the ration of RANKL to OPG is > 1, excessive RANKL is available to bind to RANK and initiate differentiation of CD14 monocytes into bone resorbing osteoclasts (osteoclastogenesis (Ono *et al.*, 2020). To balance the formation of bone, it is important that the activities of osteoblastic bone formation and osteoclastic bone resorption are coordinated. The AGE-RAGE signalling may activate NFκB (Peng *et al.*, 2016) which leads to the proinflammatory cytokines and RANKL formation. Under normal condition, RANKL is an important downstream cytokine effector which regulates osteoclastogenesis and modulates osteoclastic bone resorption (Weitzmann, 2013). When RANKL is overexpressed, it may cause rapid bone resorption which causes the imbalance in bone homeostasis, leading to bone loss (Delion *et al.*, 2016).

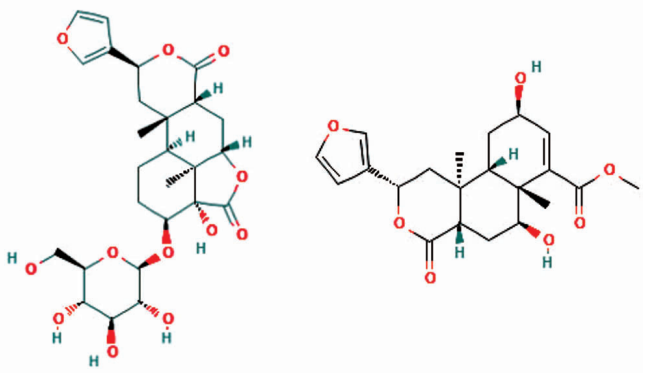
Chronic hyperglycaemia might lead to the over-expression of RANKL due to the accumulation of AGEs. The expression of RANKL through the binding with its receptor, RANK, will activate the signalling pathway for the TNF receptor-associated factor 6 which in turn regulates the osteoclastic differentiation by mediating activation of the NFκB and adapter protein 1 (AP-1). The kinases such as the p38 mitogen-activated protein kinase (MAPK) and JUN N-terminal kinase (JNK)-1 are subsequently activated, which induced transcriptional activation of AP-1 family of proteins (Roy, 2013). AP-1 regulates the proliferation of cells, differentiation, and cell death in diverse cell types (Shaulian and Karin, 2001).

The overexpression of RANKL will also cause the binding of TNFα with its receptor, the TNFα receptor (TNFRα) which in turn activates the NFκB through the IKK pathway and the p38 MAPK pathway subsequently activates the NFκB promoted transcription of inducible nitric oxide synthase (iNOS) and muscle RING-finger protein-1 (MuRF-1) gene that is responsible for the loss of muscle tissues (Hall *et al.*, 2011). ROS-phospholipase Cγ (PLCγ) mediated pathway may also be activated by the TRAF or IKK mediated pathway, and the NFAT induction which activates the NFκB signalling (Roy, 2013).

USAGE OF *TINOSPORA* EXTRACTS AND THEIR ALKALOIDS IN DIABETES TREATMENT

Terpenoids: Borapetoside A and Borapetol B

Borapetoside and borapetol are terpenoid compounds which can be isolated from the *Tinospora* species, mainly from *T. crispa*. No literature was found showing any direct binding of the two compounds to RAGE, although our own docking experiments showed that both compounds bind to RAGE (unpublished data). The effect and therefore inhibition of AGE seems more indirect at the moment. It has been shown that borapetoside A & B (Figure 3) reduce glucose in the circulation and hence there will be less AGEs formation. A study conducted by Ruan *et al.* (2013) has explored the anti-hyperglycaemic effects of the diterpenoids glycoside, borapetoside A, on the insulin-dependent and insulin independent signalling pathway. They have found that peripheral tissues increase their utilization of glucose through the action of borapetoside A, which eventually lowers the hepatic glucogenesis and activates the insulin



Borapetoside A Borapetol B

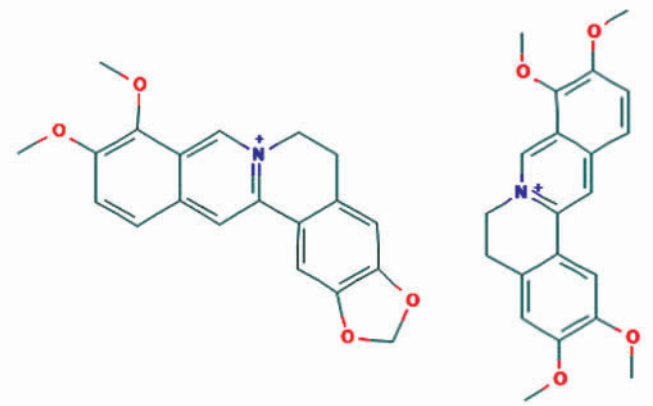
Figure 3: Left to right; the 2D structure of borapetoside A, and borapetol B. (*Source:* National Centre for Biotechnology Information, 2020a; National Centre for Biotechnology Information, 2020b).

signalling pathway that causes increase in the uptake of glucose by insulin, thereafter reduces glucose in the plasma. The anti-diabetic effect of borapetol B compound isolated from *T. crispa* has also been demonstrated. A study carried out by Lokman *et al.* (2013) has provided the evidence that the oral administration of borapetol B by non-glycaemic control Wistar (W) and spontaneously type 2 diabetic Goto-Kakizaki (GK) rats ameliorate the blood glucose levels in treated versus placebo groups.

Alkaloids: Berberine and palmatine

Berberine (Figure 4) has been isolated from various extracts of medicinal plants including *Tinospora* species. It is another well-studied protoberberine alkaloid, which is known for its role in atherosclerosis, glucose metabolism as well as for its nephroprotective and immunomodulatory effects (Neag *et al.*, 2018). In a patient with atherosclerosis, berberine interrupts the process that involves inflammatory changes for the vascular wall by upregulating silent information regulator T1 (SIRT1) expression and through the inhibition of peroxisome proliferator-activated receptor-γ (PPARγ) expression (Chi *et al.*, 2014).

Berberine was also demonstrated to improve glucose metabolism through induction of glycolysis which is likely a consequence of inhibition of glucose oxidation in mitochondria (Yin *et al.*, 2008a). This finding is further supported by Xia *et al.* (2011) who showed that the inhibition of gluconeogenesis might be due to the reduction of ATP level through mitochondrial function inhibition in the liver. Another study by Zhong *et al.* (2020) also reported that berberine impaired hyperglycaemia by regulating gluconeogenesis in diabetic mice through hepatic glucagon pathway. The impact of berberine on HbA1c is comparable with that of metformin (1500mg/day), a drug commonly used to treat hyperglycaemia in studies involving type 2 diabetes mellitus (Yin *et al.*, 2008b). Our own osteoblast cell culture experiments showed a strong reduction of AGEs and reactive oxygen species formation when the cells were incubated with Berberine (unpublished data)



Berberine Palmatine

Figure 4: Left to right; the 2D structure of berberine and palmatine. (*Source:* National Centre for Biotechnology Information, 2020c; National Centre for Biotechnology Information, 2020d).

Patel and Misra (2012) showed that three protoberberine alkaloids isolated from *T. cordifolia*, namely palmatine, magnoflorine, and jatrorrhizine can significantly reduce the plasma glucose level in rats. There have been various studies which demonstrated the potential of palmatine (Figure 4), one of the phytochemicals that can be extracted from *Tinospora* species, in the treatment of hyperglycaemia. In a rat study model conducted by Okechukwu *et al.* (2021) using the diabetes-induced Sprague Dawley rat, the chaperone proteins Calreticulin (CALR) and Glucose Regulatory Protein 78 (GRP78) were downregulated by the administration of palmatine, while peroxidoxin 4 (Prdx4), protein disulfide isomerase (PDIA2/3), Glutathione-S-Transferase (GST), and Serum Albumin (ALB) were upregulated. This indicated that antioxidant proteins in palmatine treated rats may have been activated, protecting cells against endoplasmic stress and reactive oxygen species, which could induce oxidative stress. Furthermore, Mridula *et al.* (2021) has also shown that palmatine may exhibit antioxidant and antiglycation properties.

CONCLUSION

Tinospora crispa and *T. cordifolia* are traditionally used in the treatment of diabetes, as both of them have a glucose lowering effect due to inhibiting gluconeogenesis. In this review, we focused on advanced glycation end-products and their receptor which play an important role in inducing oxidative stress in cells and tissues which in the end leads to cell death and other diabetes associated side effects. After reviewing the known phytochemicals found in *Tinospora*

crispa and *T. cordifolia*, we looked into borapetoside A and B, Berberine and palmatine and if they can be utilized as inhibitor of AGEs-induced cellular stress by blocking the binding of AGEs to its receptor. The development of these beneficial phytochemicals as AGE inhibitors and as treatment of diabetes induced complication seems to be promising. Prevention of excessive AGEs formation and/or prevention of binding of AGEs to its receptor could be added as a potential treatment option for patients with diabetes mellitus. However, more evidence-based animal studies, pre-clinical and clinical trials could be important to support the use of these compounds to treat diabetes and its complications.

ACKNOWLEDGEMENTS

The authors would like to thank the Ministry of Tourism, Arts and Culture Sarawak for supporting the publication under the Regional Conference and Exhibition for Natural Products, Traditional Medicines and Herbs 2021. Many thanks to Tun Zaidi Chair Grant for supporting our on-going work related to the topic that we reviewed.

Conflict of interest

The authors declare no conflict of interest

REFERENCES

Abate G, Delbarba A, Marziano M, Memo M and Uberti D (2015). Advanced glycation end products (AGEs) in food: focusing on Mediterranean pasta. *Nutr. Food Sci.*, 5(6).

Adnan AZ, Armin F, Sudji IR, Novida MD, Roesma DI, Ali HA and Fauzana A (2019). *In vitro* anti-inflammatory activity test of tinocrisposide and freeze-dried aqueous extract of *Tinospora crispa* stems on human red blood cell by increasing membrane stability experiment. *Asian J. Pharm. Clin. Res.*, 12(5): 125-129.

Ahmad F, Ali M and Alam P (2010). New phytoconstituents from the stem bark of *Tinospora cordifolia* Miers. *Nat. Prod. Res.*, 24(10): 926-934.

Ahmad W, Jantan I and Bukhari SN (2016). *Tinospora crispa* (L.) Hook. f. & Thomson: a review of its ethnobotanical, phytochemical, and pharmacological aspects. *Front. Pharmacol.*, 7: 59.

Ahmed N (2005). Advanced glycation endproducts—role in pathology of diabetic complications. *Diabetes Res. Clin. Pract.*, 67(1): 3-21.

AL-Khateeb AR, Shaari NM, Muid SA and Froemming GR (2018). A critical link between advanced glycation end products, osteoporosis and type 2 diabetes mellitus. *Regen. Res.*, 6: 1-9.

Ali SS, Ahmad S and Choudhary MI (1992). A furanoid diterpene from *Tinospora malabarica*. *Phytochemistry*, 31(9): 3155-3157.

American Diabetes Association (2014). Diagnosis and classification of diabetes mellitus. *Diabetes Care*, 37(Supplement 1): S81-S90.

Aragno M and Mastrocola R (2017). Dietary sugars and endogenous formation of advanced glycation endproducts: emerging mechanisms of disease. *Nutrients*, 9(4): 385.

Aranha I and Venkatesh YP (2020). Humoral immune and adjuvant responses of mucosally-administered *Tinospora cordifolia* immunomodulatory protein in BALB/c mice. *J. Ayurveda Integr. Med.*, 11(2): 140-146.

Babu PVA, Sabitha KE and Shyamaladevi CS (2008). Effect of green tea extract on advanced glycation and cross-linking of tail tendon collagen in streptozotocin induced diabetic rats. *Food Chem. Toxicol.*, 46(1): 280-285.

Barraco RA, Marcantonio DR, Phillis JW and Campbell WR. (1987). The effects of parenteral injections of adenosine and its analogs on blood pressure and heart rate in the rat. *Gen. Pharmacol.*, 18(4): 405-416.

Basta G, Lazzerini G, Del Turco S, Ratto GM, Schmidt AM and De Caterina R (2005). At least 2 distinct pathways generating reactive oxygen species mediate vascular cell adhesion molecule-1 induction by advanced glycation end products. *Arterioscler. Thromb. Vasc. Biol.*, 25(7): 1401-1407.

Bhatt RK and Sabata BK (1989). A furanoid diterpene glucoside from *Tinospora cordifolia. Phytochemistry*, 28(9): 2419-2422.

Birla H, Rai SN, Singh SS, Zahra W, Rawat A, Tiwari N, Singh RK, Pathak A and Singh SP (2019). *Tinospora cordifolia* suppresses neuroinflammation in parkinsonian mouse model. *Neuromolecular Med.*, 21(1): 42-53.

Bisset NG and Nwaiwu J (1983). Quaternary alkaloids of *Tinospora* species. *Planta Med.*, 48(8): 275-279.

Bucciarelli LG, Wendt T, Rong L, Lalla E, Hofmann MA, Goova MT, Taguchi A, Yan SF, Yan SD, Stern DM and Schmidt AM (2002). RAGE is a multiligand receptor of the immunoglobulin superfamily: implications for homeostasis and chronic disease. *Cell. Mol. Life Sci.*, 59(7): 1117-1128.

Cavin A, Hostettmann K, Dyatmyko W and Potterat O (1998). Antioxidant and lipophilic constituents of *Tinospora crispa*. *Planta Med.*, 64(5): 393-396.

Chang CC, Chen CY, Chang GD, Chen TH, Chen WL, Wen HC, Huang CY and Chang CH (2017). Hyperglycemia and advanced glycation end products (AGEs) suppress the differentiation of 3T3-L1 preadipocytes. *Oncotarget*, 8(33): 55039.

Chang CC, Ho SL and Lee SS (2015). Acylated glucosylflavones as á-glucosidase inhibitors from *Tinospora crispa* leaf. *Bioorg. Med. Chem.*, 23(13): 3388-3396.

Chang HM, El-Fishawy AM, Slatkin DJ and Schiff PL (1984). Quaternary alkaloids of *Tinospora capillipes*. *Planta Med.*, 50(1): 88-90.

Chaudhuri J, Bains Y, Guha S, Kahn A, Hall D, Bose N, Gugliucci A and Kapahi P (2018). The role of advanced glycation end products in aging and metabolic diseases: bridging association and causality. *Cell Metab.*, 28(3): 337-352.

Chi L, Peng L, Pan N, Hu X and Zhang Y (2014). The anti-atherogenic effects of berberine on foam cell formation are mediated through the upregulation of sirtuin 1. *Int. J. Mol. Med.*, 34(4): 1087-1093.

Chi S, She G, Han D, Wang W, Liu Z and Liu B (2016). Genus *Tinospora*: ethnopharmacology, phytochemistry, and pharmacology. *Evid. Based Complementary Altern. Med.*, 2016.

Choudhari AS, Mandave PC, Deshpande M, Ranjekar P and Prakash O (2020). Phytochemicals in cancer treatment: From preclinical studies to clinical practice. *Front. Pharmacol.*, 10: 1614.

Choudhary MI, Ismail M, Shaari K, Abbaskhan A, Sattar SA and Lajis NH (2010). cis-Clerodane-type furanoditerpenoids from *Tinospora crispa*. *J. Nat. Prod.*, 73(4): 541-547.

Choudhary N, Siddiqui MB and Khatoon S (2014). Pharmacognostic evaluation of *Tinospora cordifolia* (Willd.) Miers and identification of biomarkers. *Indian J. Tradit. Knowl.,*13(3): 543-550.

D'agati V and Schmidt AM (2010). RAGE and the pathogenesis of chronic kidney disease. *Nat. Rev. Nephrol.*, 6(6): 352-360.

Dai P, Wang J, Lin L, Zhang Y and Wang Z (2015). Renoprotective effects of berberine as adjuvant therapy for hypertensive patients with type 2 diabetes mellitus: Evaluation via biochemical markers and color Doppler ultrasonography. *Exp. Ther. Med.*, 10(3): 869-876.

Delion M, Braux J, Jourdain ML, Guillaume C, Bour C, Gangloff S, Pimpec Barthes FL, Sermet Gaudelus I, Jacquot J and Velard F (2016). Overexpression of RANKL in osteoblasts: a possible mechanism of susceptibility to bone disease in cystic fibrosis. *J. Pathol.*, 240(1): 50-60.

Dhanasekaran M, Baskar AA, Ignacimuthu S, Agastian P and Duraipandiyan V (2009). Chemopreventive potential of Epoxy clerodane diterpene from Tinospora cordifolia against diethylnitrosamine-induced hepatocellular carcinoma. *Invest. New Drugs*, 27(4): 347-355.

Domitrovic R, Jakovac H and Blagojevic G (2011). Hepatoprotective activity of berberine is mediated by inhibition of TNF-α, COX-2, and iNOS expression in CCl4-intoxicated mice. *Toxicology*, 280(1-2): 33-43.

Elkina Y, Von Haehling S, Anker SD and Springer J (2011). The role of myostatin in muscle wasting: an overview. *J. Cachexia Sarcopenia Muscle*, 2(3): 143.

Fukuda N, Nakamura M, Yonemitsu M, Kimura T, Isobe R and Komori T (1993). Studies on the constituents of the leaves of *Tinospora tuberculata*, I.–Isolation and structure elucidation of two new furanoid diterpenes, tinotufolin A and B. *Liebigs Ann.*, 1993(3): 325-327.

Fukuda N, Yonemitsu M, Kimura T, Hachiyama S, Miyahara K and Kawasaki T (1985). Studies on the constituents of the stems of *Tinospora tuberculata* Beumee. II. New diterpenoids, borapetoside A and borapetol A. *Chem. Pharm. Bull.*, 33(10): 4438-4444.

Gangan VD, Pradhan P, Sipahimalani AT and Banerji A (1995). Norditerpene furan glycosides from *Tinospora cordifolia*. *Phytochemistry*, 39(5): 1139-1142.

Ghatpande NS, Misar AV, Waghole RJ, Jadhav SH and Kulkarni PP (2019). *Tinospora cordifolia* protects against inflammation associated anaemia by modulating inflammatory cytokines and hepcidin expression in male Wistar rats. *Sci. Rep.*, 9(1): 1-11.

Gillery P and Jaisson S (2014). Post-translational modification derived products (PTMDPs): toxins in chronic diseases? *Clin. Chem. Lab. Med.*, 52(1): 33-38.

Gough PJ, Greaves DR, Suzuki H, Hakkinen T, Hiltunen MO, Turunen M, Herttuala SY, Kodama T and Gordon S (1999). Analysis of macrophage scavenger receptor (SR-A) expression in human aortic atherosclerotic lesions. *Arterioscler. Thromb. Vasc. Biol.*, 19(3): 461-471.

Ha H and Lee HB (2000). Reactive oxygen species as glucose signaling molecules in mesangial cells cultured under high glucose. *Kidney Int.*, 58: S19-S25.

Haddad F, Zaldivar F, Cooper DM and Adams GR (2005). IL-6-induced skeletal muscle atrophy. *J. Appl. Physiol.*, 98(3): 911-917.

Hall DT, Ma JF, Di Marco S and Gallouzi IE (2011). Inducible nitric oxide synthase (iNOS) in muscle wasting syndrome, sarcopenia, and cachexia. *Aging (Albany NY)*, 3(8): 702.

Haneda M, Araki SI, Togawa M, Sugimoto T, Motohide I and Kikkawa R (1997). Mitogen-activated protein kinase cascade is activated in glomeruli of diabetic rats and glomerular mesangial cells cultured under high glucose conditions. *Diabetes*, 46(5): 847-853.

Hundal RS, Krssak M, Dufour S, Laurent D, Lebon V, Chandramouli V, Inzucchi SE, Schumann WC, Petersen KF, Landau BR and Shulman GI (2000). Mechanism by which metformin reduces glucose production in type 2 diabetes. *Diabetes*, 49(12): 2063-2069.

Hungerford NL, Sands DP and Kitching W (1998). Isolation and structure of some constituents of the Australian medicinal plant *Tinospora smilacina* ('snakevine'). *Aust. J. Chem.*, 51(12): 1103-1112.

Ilchmann A, Burgdorf S, Scheurer S, Waibler Z, Nagai R, Wellner A, Yamamoto Y, Yamamoto H, Henle T, Kurts C and Kalinke U (2010). Glycation of a food allergen by the Maillard reaction enhances its T-cell immunogenicity: role of macrophage scavenger receptor class A type I and II. *J. Allergy Clin. Immunol. Pract.*, 125(1): 175-183.

Iqbal J, Husain A and Gupta A (2005). Sensitized photooxygenation of tinosponone, a clerodane diterpene from *Tinospora cordifolia*. *Acta Chim. Slov.,* 52(4): 455.

Ishibashi Y, Matsui T, Takeuchi M and Yamagishi S (2012). Metformin inhibits advanced glycation end products (AGEs)-induced renal tubular cell injury by suppressing reactive oxygen species generation via reducing receptor for AGEs (RAGE) expression. *Horm. Metab. Res.*, 44(12): 891-895.

Islam MS, Alam AHMK, Rahman MAA, Ali Y, Mamun A, Rahman M, Hossain AKMM and Rashid M (2012). Effects of combination of antidiabetic agent and statin on alloxan-induced diabetes with cardiovascular diseases in rats. *J. Sci. Res.*, 4(3): 709-720.

Jayaprakash R, Ramesh V, Sridhar MP and Sasikala C (2015). Antioxidant activity of ethanolic extract of *Tinospora cordifolia* on N-nitrosodiethylamine (diethylnitrosamine) induced liver cancer in male Wister albino rats. *J. Pharm. Bioallied Sci.*, 7(Suppl 1): S40.

Jiang X, Wang X, Tuo M, Ma J and Xie A (2018). RAGE and its emerging role in the pathogenesis of Parkinson's disease. *Neurosci. Lett.*, 672: 65-69.

Kannadhasan R and Venkataraman S (2013). *In vitro* capacity and *in vivo* antioxidant potency of sedimental extract of *Tinospora cordifolia* in streptozotocin induced type 2 diabetes. *Avicenna J. Phytomedicine*, 3(1): 7.

Kapur P, Jarry H, Wuttke W, Pereira BMJ and Seidlova-Wuttke D (2008). Evaluation of the antiosteoporotic potential of *Tinospora cordifolia* in female rats. *Maturitas*, 59(4): 329-338.

Khan MM, dul Haque MS and Chowdhury MSI (2016). Medicinal use of the unique plant *Tinospora cordifolia*: evidence from the traditional medicine and recent research. *Asian J. Med. Biol. Res.*, 2(4): 508-512.

Kiefer AS, Fleming T, Eckert GJ, Poindexter BB, Nawroth, PP and Yoder MC (2014). Methylglyoxal concentrations differ in standard and washed neonatal packed red blood cells. *Pediatr. Res.*, 75(3): 409-414.

Kim MS, Yang YM, Son A, Tian YS, Lee SI, Kang SW, Muallem S and Shin DM (2010). RANKL-mediated reactive oxygen species pathway that induces long lasting Ca^{2+} oscillations essential for osteoclastogenesis. *J. Biol. Chem.*, 285(10): 6913-6921.

Klangjareonchai T and Roongpisuthipong C (2012). The effect of *Tinospora crispa* on serum glucose and insulin levels in patients with type 2 diabetes mellitus. *J. Biotechnol. Biomed.*, 2012.

Koay YC and Koay F (2013). A review of the secondary metabolites and biological activities of *Tinospora crispa* (Menispermaceae). *Trop. J. Pharm. Res.*, 12(4): 641-649.

Kongkathip N, Dhumma-upakorn P, Kongkathip B, Chawananoraset K, Sangchomkaeo P and Hatthakitpanichakul S (2002). Study on cardiac contractility of cycloeucalenol and cycloeucalenone isolated from *Tinospora crispa*. *J. Ethnopharmacol.*, 83(1-2): 95-99.

Lam SH, Ruan CT, Hsieh PH, Su MJ and Lee SS (2012). Hypoglycemic diterpenoids from *Tinospora crispa*. *J. Nat. Prod.*, 75(2): 153-159.

Lange JN, Wood KD, Knight J, Assimos DG and Holmes RP (2012). Glyoxal formation and its role in endogenous oxalate synthesis. *Adv. Urol.*, 2012.

Lee EJ and Park JH (2013). Receptor for advanced glycation endproducts (RAGE), its ligands, and soluble RAGE: potential biomarkers for diagnosis and therapeutic targets for human renal diseases. *Genomics Inform.*, 11(4): 224.

Li X, Guo Y, Yan W, Snyder MP and Li X (2015). Metformin improves diabetic bone health by re-balancing catabolism and nitrogen disposal. *PloS One*, 10(12): e0146152.

Lim AK (2014). Diabetic nephropathy–complications and treatment. *Int. J. Nephrol. Renovasc. Dis.*, 7: 361.

Liu X, Zhang X, Ye L and Yuan H (2016). Protective mechanisms of berberine against experimental autoimmune myocarditis in a rat model. *Biomed. Pharmacother.*, 79: 222-230.

Livesey G and Taylor R (2008). Fructose consumption and consequences for glycation, plasma triacylglycerol, and body weight: meta-analyses and meta-regression models of intervention studies. *Am. J. Clin. Nutr.*, 88(5): 1419-1437.

Lokman FE, Gu HF, Wan Mohamud WN, Yusoff MM, Chia KL and Östenson CG (2013). Antidiabetic effect of oral borapetol B compound, isolated from the plant *Tinospora crispa*, by stimulating insulin release. *Evid. Based Complementary Altern. Med.*, 2013.

López-Díez R, Shekhtman A, Ramasamy R and Schmidt AM (2016). Cellular mechanisms and consequences of glycation in atherosclerosis and obesity. *Biochim. Biophys. Acta Mol. Basis Dis.*, 1862(12): 2244-2252.

Lu L, Zhang RY, Wang XQ, Liu ZH, Shen Y, Ding FH, Meng H, Wang LJ, Yan XX, Yang K and Wang HB (2016). C1q/TNF-related protein-1: an adipokine marking and promoting atherosclerosis. *Eur. Heart J.*, 37(22): 1762-1771.

Madonna R, Pieragostino D, Balistreri CR, Rossi C, Geng YJ, Del Boccio P and De Caterina R (2018). Diabetic macroangiopathy: pathogenetic insights and novel therapeutic approaches with focus on high glucose-mediated vascular damage. *Vascul. Pharmacol.*, 107: 27-34.

Maeda K, Mehta H, Drevets DA and Coggeshall KM (2010). IL-6 increases B-cell IgG production in a feed-forward proinflammatory mechanism to skew hematopoiesis and elevate myeloid production. *Blood*, 115(23): 4699-4706.

Maillard LC (1912). Action des acides amines sur les sucres; formation des melanoidines par voie methodique. *Comptes R. Acad. Sci. (Paris)*, 154: 66-68.

Malik ZA, Singh M and Sharma PL (2011). Neuroprotective effect of *Momordica charantia* in global cerebral ischemia and reperfusion induced neuronal damage in diabetic mice. *J. Ethnopharmacol.*, 133(2): 729-734.

Maurya R, Gupta P, Chand K, Kumar M, Dixit P, Singh N and Dube A (2009). Constituents of *Tinospora sinensis* and their antileishmanial activity against Leishmania donovani. *Nat. Prod. Res.*, 23(12): 1134-1143.

Maurya R, Manhas LR, Gupta P, Mishra PK, Singh G and Yadav PP (2004). Amritosides A, B, C and D: clerodane furano diterpene glucosides from *Tinospora cordifolia*. *Phytochemistry*, 65(14): 2051-2055.

Maurya R and Handa SS (1998). Tinocordifolin, a sesquiterpene from *Tinospora cordifolia. Phytochemistry*, 49(5): 1343-1345.

Maurya R, Dhar KL and Handa SS (1997). A sesquiterpene glucoside from *Tinospora cordifolia*. *Phytochemistry*, 44(4): 749-750.

Maurya R, Wazir V, Tyagi A and Kapil RS (1995). Clerodane diterpenoids from *Tinospora cordifolia*. *Phytochemistry*, 38(3): 659-661.

Maruthur NM, Tseng E, Hutfless S, Wilson LM, Suarez-Cuervo C, Berger Z, Chu Y, Iyoha E, Segal JB and Bolen S (2016). Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: a systematic review and meta-analysis. *Ann. Intern. Med.*, 164(11): 740-751.

Mehreen A, Waheed M, Liaqat I and Arshad N (2016). Phytochemical, antimicrobial, and toxicological evaluation of traditional herbs used to treat sore throat. *Biomed Res. Int.*, 2016.

Miroliaei M, Khazaei S, Moshkelgosha S and Shirvani M (2011). Inhibitory effects of Lemon balm (*Melissa officinalis*, L.) extract on the formation of advanced glycation end products. *Food Chem.*, 129(2): 267-271.

Moin T, Schmittdiel JA, Flory JH, Yeh J, Karter AJ, Kruge LE, Schillinger D, Mangione CM, Herman WH and Walker EA (2018). Review of metformin use for type 2 diabetes prevention. *Am. J. Prev. Med.*, 55(4): 565-574.

Mridula S, Masroor WS, Xavier M, Hui TW, Chan HK, Chirara K and Nwabueze OP (2021). Antioxidant and anti-advanced glycation end products formation properties of palmatine. *J. Pharm. Pharmcogn. Res.*, 9(3): 366-378.

Nadig PD, Revankar RR, Dethe SM, Narayanswamy SB and Aliyar MA (2012). Effect of *Tinospora cordifolia* on experimental diabetic neuropathy. *Indian J. Pharmacol.*, 44(5): 580.

Nathan DM (1993). Long-term complications of diabetes mellitus. *N. Engl. J. Med.*, 328(23): 1676-1685.

National Center for Biotechnology Information (2020a). PubChem Compound Summary for CID 21636215, Borapetoside. Accessed 19 December 2020. https://pubchem.ncbi.nlm.nih.gov/compound/Borapetoside

National Center for Biotechnology Information (2020b). *PubChem Compound Summary for CID 21636044, Borapetol B*. Accessed 19 December 2020. https://pubchem.ncbi.nlm.nih.gov/compound/Borapetol-B

National Center for Biotechnology Information (2020c). *PubChem Compound Summary for CID 2353, Berberine*. Accessed 19 December 2020. https://pubchem.ncbi.nlm.nih.gov/compound/Berberine

National Center for Biotechnology Information (2020d). *PubChem Compound Summary for CID 19009, Palmatine*. Accessed 19 December 2020. https://pubchem.ncbi.nlm.nih.gov/compound/Palmatine

Naziroglu M, Simsek M, Simsek H, Aydilek N, Özcan Z and Atilgan R (2004). The effects of hormone replacement therapy combined with vitamins C and E on antioxidants levels and lipid profiles in postmenopausal women with Type 2 diabetes. *Clin. Chim. Acta*, 344(1-2): 63-71.

Neag MA, Mocan A, Echeverría J, Pop RM, Bocsan CI, Crisan G and Buzoianu AD (2018). Berberine: Botanical occurrence, traditional uses, extraction methods, and relevance in cardiovascular, metabolic, hepatic, and renal disorders. *Front. Pharmacol.*, 9: 557.

Neeper M, Schmidt AM, Brett J, Yan SD, Wang F, Pan YC, Elliston K, Stern D and Shaw A (1992). Cloning and expression of a cell surface receptor for advanced glycosylation end products of proteins. *J. Biol. Chem.*, 267(21): 14998-15004.

Negre-Salvayre A, Salvayre R, Augé N, Pamplona R and Portero-Otin M (2009). Hyperglycemia and glycation in diabetic complications. *Antioxid. Redox. Signal.*, 11(12): 3071-3109.

Ning N, Wang YZ, Zou ZY and Li XG (2015). Pharmacological and safety evaluation of fibrous root of *Rhizoma coptidis*. *Environ. Toxicol. Pharmacol.*, 39(1): 53-69.

Nita M and Grzybowski A (2016). The role of the reactive oxygen species and oxidative stress in the pathomechanism of the age-related ocular diseases and other pathologies of the anterior and posterior eye segments in adults. *Oxid. Med. Cell. Longev.*, 2016.

Noor H and Ashcroft SJ (1989). Antidiabetic effects of *Tinospora crispa* in rats. *J. Ethnopharmacol.*, 27(1-2): 149-161.

O'Shea JJ, Schwartz DM, Villarino AV, Gadina M, McInnes IB and Laurence A (2015). The JAK-STAT pathway: impact on human disease and therapeutic intervention. *Annu. Rev. Med.*, 66: 311-328.

Ohgami N, Nagai R, Ikemoto M, Arai H, Kuniyasu A, Horiuchi S and Nakayama H (2001). Cd36, a member of the class b scavenger receptor family, as a receptor for advanced glycation end products. *J. Biol. Chem.*, 276(5): 3195-3202.

Okechukwu PN, Ekeuku SO, Chan HK, Eluri K and Froemming GR (2021). Palmatine Inhibits Up-Regulation of GRP78 and CALR Protein in an STZ-Induced Diabetic Rat Model. *Curr. Pharm. Biotechnol.*, 22(2): 288-298.

Ono T, Hayashi M, Sasaki F and Nakashima T (2020). RANKL biology: bone metabolism, the immune system, and beyond. *Inflammation and Regeneration*, 40(1), 1-16.

Ott C, Jacobs K, Haucke E, Santos AN, Grune T and Simm A (2014). Role of advanced glycation end products in cellular signaling. *Redox Biol.*, 2: 411-429.

Pan L, Terrazas C, Lezama-Davila CM, Rege N, Gallucci JC, Satoskar AR and Kinghorn AD (2012). Cordifolide A, a sulfur-containing clerodane diterpene glycoside from *Tinospora Cordifolia*. *Org. Lett.*, 14(8): 2118-2121.

Panchabhai TS, Kulkarni UP and Rege NN (2008). Validation of therapeutic claims of *Tinospora cordifolia*: a review. *Phytother. Res.*, 22(4): 425-441.

Pandey M, Chikara SK, Vyas MK, Sharma R, Thakur GS and Bisen PS (2012). *Tinospora cordifolia*: A climbing shrub in health care management. *Int. J. Pharm. Bio. Sci.*, 3(4): 612-628.

Park JS, Svetkauskaite D, He Q, Kim JY, Strassheim D, Ishizaka A and Abraham E (2004). Involvement of toll-like receptors 2 and 4 in cellular activation by high mobility group box 1 protein. *J. Biol. Chem.*, 279(9): 7370-7377.

Patel MB and Mishra SM (2012). Magnoflorine from *Tinospora cordifolia* stem inhibits á-glucosidase and is antiglycemic in rats. *J. Funct, Foods*, 4(1): 79-86.

Peng Y, Kim JM, Park HS, Yang A, Islam C, Lakatta EG and Lin L (2016). AGE-RAGE signal generates a specific NF-êB RelA "barcode" that directs collagen I expression. *Sci. Rep.*, 6(1), 1-10.

Philip S, Tom G and Vasumathi AV (2018). Evaluation of the anti-inflammatory activity of *Tinospora cordifoli*a (Willd.) Miers chloroform extract–a preclinical study. *J. Pharm. Pharmacol.*, 70(8): 1113-1125.

Popa I, Ganea E and Petrescu SM (2014). Expression and subcellular localization of RAGE in melanoma cells. *Biochem. Cell Biol.*, 92(2): 127-136.

Praman S, Mulvany MJ, Williams DE, Andersen RJ and Jansakul C (2012). Hypotensive and cardio-chronotropic constituents of *Tinospora crispa* and mechanisms of action on the cardiovascular system in anesthetized rats. *J. Ethnopharmacol.*, 140(1): 166-178.

Puratchimani V and Jha S (2007). HPTLC standardization of *Tinospora cordifolia* using tinosporaside. *Indian J. Pharm. Sci.*, 69(4): 578.

Pushp P, Sharma N, Joseph GS and Singh RP (2013). Antioxidant activity and detection of (–) epicatechin in the methanolic extract of stem of *Tinospora cordifolia*. *J. Food Sci. Technol.*, 50(3): 567-572.

Quintana FJ, Pitashny M and Cohen IR (2003). Experimental autoimmune myasthenia gravis in naive non obese diabetic (NOD/LtJ) mice: susceptibility associated with natural IgG antibodies to the acetylcholine receptor. *Int. Immunol.*, 15(1): 11-16.

Rabbani N and Thornalley PJ (2015). Dicarbonyl stress in cell and tissue dysfunction contributing to ageing and disease. *Biochem. Biophys. Res. Commun.*, 458(2): 221-226.

Rakib A, Ahmed S, Islam MA, Haye A, Uddin SN, Uddin MMN, Hossain MK, Paul A and Emran TB (2020). Antipyretic and hepatoprotective potential of *Tinospora crispa* and investigation of possible lead compounds through in silico approaches. *Food Sci. Nutri.*, 8(1), 547-556.

Ramasamy R, Yan SF and Schmidt AM (2011). Receptor for AGE (RAGE): signaling mechanisms in the pathogenesis of diabetes and its complications. *Ann, N. Y. Acad. Sci.*, 1243: 88.

Redlich K and Smolen JS (2012). Inflammatory bone loss: pathogenesis and therapeutic intervention. *Nat. Rev. Drug Discov.*, 11(3): 234-250.

Roldi LP, Pereira RV, Tronchini EA, Rizo GV, Scoaris CR, Zanoni JN and Natali MR (2009). Vitamin E (á-tocopherol) supplementation in diabetic rats: effects on the proximal colon. *BMC Gastroenterol.*, 9(1): 1-8.

Roy B (2013). Biomolecular basis of the role of diabetes mellitus in osteoporosis and bone fractures. *World J. Diabetes*, 4(4): 101.

Ruan CT, Lam SH, Lee SS and Su MJ (2013). Hypoglycemic action of borapetoside A from the plant *Tinospora crispa* in mice. *Phytomedicine*, 20(8-9): 667-675.

Ruan CT, Lam SH, Chi TC, Lee SS and Su MJ (2012). Borapetoside C from *Tinospora crispa* improves insulin sensitivity in diabetic mice. *Phytomedicine*, 19(8-9): 719-724.

Rubenstein DA, Maria Z and Yin W (2011). Glycated albumin modulates endothelial cell thrombogenic and inflammatory responses. *J. Diabetes Sci. Technol.*, 5(3): 703-713.

Russell ST, Rajani S, Dhadda RS and Tisdale MJ (2009). Mechanism of induction of muscle protein loss by hyperglycaemia. *Exp. Cell Res.*, 315(1): 16-25.

Saxena M, Saxena J, Nema R, Singh D and Gupta A (2013). Phytochemistry of medicinal plants. *J. Pharmacogn. Phytochem.*, 1(6).

Schäfer G (1983). Biguanides. A review of history, pharmacodynamics and therapy. *Diabete & Metabolisme*, 9(2): 148-163.

Schäffler A and Buechler C (2012). CTRP family: linking immunity to metabolism. *Trends in Endocrinol. Metab*, 23(4): 194-204.

Schmidt AM and Stern DM (2001). Receptor for age (RAGE) is a gene within the major histocompatibility class III region: implications for host response mechanisms in homeostasis and chronic disease. *Front. Biosci*, 6: D1151-D1160.

Senatus LM and Schmidt AM (2017). The AGE-RAGE axis: implications for age-associated arterial diseases. *Front. Genet*, 8: 187.

Shakher J and Stevens MJ (2011). Update on the management of diabetic polyneuropathies. *Diabetes Metab. Syndr. Obes.*, 4: 289.

Sharma A, Kalotra S, Bajaj P, Singh H and Kaur G (2020). Butanol extract of *Tinospora cordifolia* ameliorates cognitive deficits associated with glutamate-induced excitotoxicity: A mechanistic study using hippocampal neurons. *Neuromolecular Med.*, 22(1): 81-99.

Sharma Y, Saxena S, Mishra A, Saxena A and Natu SM (2012). Advanced glycation end products and diabetic retinopathy. *J. Ocul. Biol. Dis. Infor.*, 5(3-4): 63-69.

Shaulian E and Karin M (2001). AP-1 in cell proliferation and survival. *Oncogene*, 20(19): 2390-2400.

Sheetz MJ and King GL (2002). Molecular understanding of hyperglycemia's adverse effects for diabetic complications. *Jama*, 288(20): 2579-2588.

Shiu SW, Wong Y and Tan KC (2012). Effect of advanced glycation end products on lectin-like oxidized low density lipoprotein receptor-1 expression in endothelial cells. *J. Atheroscler. Thromb*, 11742.

Singh N, Singh SM and Shrivastava P (2004). Immunomodulatory and antitumor actions of medicinal plant *Tinospora cordifolia* are mediated through activation of tumor associated macrophages. *Immunopharmacol. Immunotoxicol.*, 26(1): 145-162.

Singh N, Singh SM and Shrivastava P (2005). Effect of *Tinospora cordifolia* on the antitumor activity of tumor-associated macrophages–derived dendritic cells. *Immunopharmacol. Immunotoxicol.*, 27(1): 1-14.

Singh VP, Bali A, Singh N and Jaggi AS (2014). Advanced glycation end products and diabetic complications. *Korean J. Physiol. Pharmacol.*, 18(1): 1-14.

Sivasubramanian A, Gadepalli Narasimha KK, Rathnasamy R and Campos AMO (2013). A new antifeedant clerodane diterpenoid from *Tinospora cordifolia*. *Nat. Prod. Res.*, 27(16): 1431-1436.

Sourris KC and Forbes JM (2009). Interactions between advanced glycation end-products (AGE) and their receptors in the development and progression of diabetic nephropathy-are these receptors valid therapeutic targets. *Curr. Drug Targets*, 10(1): 42-50.

Surya S, Salam AD, Tomy DV, Carla B, Kumar RA and Sunil C (2014.) Diabetes mellitus and medicinal plants-a review. *Asian Pac. J. Trop. Dis.*, 4(5): 337-347.

Takiyama Y, Harumi T, Watanabe J, Fujita Y, Honjo J, Shimizu N, Makino Y and Haneda M (2011). Tubular injury in a rat model of type 2 diabetes is prevented by metformin: a possible role of HIF-1α expression and oxygen metabolism. *Diabetes*, 60(3): 981-992.

Tavakoli M, Mojaddidi M, Fadavi H and Malik RA (2008). Pathophysiology and treatment of painful diabetic neuropathy. *Curr. Pain Headache Rep.*, 12(3): 192-197.

Thériault JR, Palmer HJ and Pittman DD (2011). Inhibition of the Unfolded Protein Response by metformin in renal proximal tubular epithelial cells. *Biochem. Biophys. Res. Commun.*, 409(3): 500-505.

Tiwari P, Nayak P, Prusty SK and Sahu PK (2018). Phytochemistry and pharmacology of *Tinospora cordifolia*: A review. *Syst. Rev. Pharm.*, 9(1): 70-78.

Thornalley PJ (1998). Cell activation by glycated proteins. AGE receptors, receptor recognition factors and functional classification of AGEs. *Cell. Mol. Biol. (Noisy-le-Grand, France)*, *44*(7): 1013-1023.

Uribarri J and He JC (2015). The low AGE diet: a neglected aspect of clinical nephrology practice? *Nephron*, 130(1): 48-53.

van Beijnum JR, Buurman WA and Griffioen AW (2008). Convergence and amplification of toll-like receptor (TLR) and receptor for advanced glycation end products (RAGE) signalling pathways via high mobility group B1 (HMGB1). *Angiogenesis*, 11(1): 91-99.

Van Kiem P, Van Minh C, Dat NT, Hang DT, Nam NH, Cuong NX, Huong HT and Van Lau T (2010). Aporphine alkaloids, clerodane diterpenes, and other constituents from *Tinospora cordifolia*. *Fitoterapia*, 81(6): 485-489.

Vistoli G, De Maddis D, Cipak A, Zarkovic N, Carini M and Aldini G (2013). Advanced glycoxidation and lipoxidation end products (AGEs and ALEs): an overview of their mechanisms of formation. *Free Radic. Res.*, 47(sup1): 3-27.

Vlassara H, Cai W, Crandall J, Goldberg T, Oberstein R, Dardaine V, Peppa M and Rayfield EJ (2002). Inflammatory mediators are induced by dietary glycotoxins, a major risk factor for diabetic angiopathy. *Proc. Natl. Acad. Sci.*, 99(24): 15596-15601.

Vlassara H, Li YM, Imani F, Wojciechowicz D, Yang Z, Liu FT and Cerami A (1995). Identification of galectin-3 as a high-affinity binding protein for advanced glycation end products (AGE): a new member of the AGE-receptor complex. *Mol.*, 1(6): 634-646.

Verzelloni E, Tagliazucchi D, Del Rio D, Calani L and Conte A (2011). Antiglycative and antioxidative properties of coffee fractions. *Food Chem.*, 124(4): 1430-1435.

Wang LJ, Lu L, Zhang FR, Chen QJ, De Caterina R and Shen WF (2011). Increased serum high mobility group box 1 and cleaved receptor for advanced glycation endproducts levels and decreased endogenous secretory receptor for advanced glycation endproducts levels in diabetic and non diabetic patients with heart failure. *Eur. J. Heart Fail.*, 13(4): 440-449.

Wazir V, Maurya R and Kapil RS (1995). Cordioside, a clerodane furano diterpene glucoside from *Tinospora cordifolia*. *Phytochemistry*, 38(2): 447-449.

Weitzmann MN (2013). The role of inflammatory cytokines, the RANKL/OPG axis, and the immunoskeletal interface in physiological bone turnover and osteoporosis. *Scientifica*, 2013.

Wilson JR, Stittsworth Jr JD, Kadir A and Fisher MA (1998). Conduction velocity versus amplitude analysis: evidence for demyelination in diabetic neuropathy. *Muscle Nerve*, 21(9): 1228-1230.

World Health Organization (2021). Diabetes. Accessed 14 October 2021. https://www.who.int/news-room/fact-sheets/detail/diabetes

World Health Organization (2019). World Health Organization model list of essential medicines: 21st list 2019 (No. WHO/MVP/EMP/IAU/2019.06). World Health Organization.

Xia X, Yan J, Shen Y, Tang K, Yin J, Zhang Y, Yang D, Liang H, Ye J and Weng J (2011). Berberine improves glucose metabolism in diabetic rats by inhibition of hepatic gluconeogenesis. *PLoS One*, 6(2): e16556.

Xiong W, Zhou Z and Zhang X (2019). Hypoglycemic Drugs and Advanced Glycation End products. *Atherosclerosis*, 5: 22.

Yamagishi SI, Nakamura N, Suematsu M, Kaseda K and Matsui T (2015). Advanced glycation end products: a molecular target for vascular complications in diabetes. *Mol.*, 21(1): S32-S40.

Yang SZ and Chen PH (2016). Cambial variants in the Family Menispermaceae in Taiwan. *Am. J. Plant Sci.*, 7(6): 841.

Yazdanparast R, Ardestani A and Jamshidi S (2007). Experimental diabetes treated with *Achillea santolina*: effect on pancreatic oxidative parameters. *J. Ethnopharmacol.*, 112(1): 13-18.

Yin J, Gao Z, Liu D, Liu Z and Ye J (2008a). Berberine improves glucose metabolism through induction of glycolysis. *Am. J. Physiol. Endocrinol. Metab*., 294(1): e148-e156.

Yin J, Xing H and Ye J (2008b). Efficacy of berberine in patients with type 2 diabetes mellitus. *Metabolism*, 57(5): 712-717.

Yusoff M, Hamid H and Houghton P (2014). Anticholinesterase inhibitory activity of quaternary alkaloids from *Tinospora crispa*. *Molecules*, 19(1): 1201-1211.

Zeller I and Srivastava S (2014). Macrophage functions in atherosclerosis. *Circ. Res.*, 115(12): e83-e85.

Zhang L, Virgous C and Si H (2019). Synergistic anti-inflammatory effects and mechanisms of combined phytochemicals. *J. Nutr. Biochem.*, 69: 19-30.

Zhang YJ, Gan RY, Li S, Zhou Y, Li AN, Xu DP and Li HB (2015). Antioxidant phytochemicals for the prevention and treatment of chronic diseases. *Molecules*, 20(12): 21138-21156.

Zhao X, Zhang J, Tong N, Chen Y and Luo Y (2012). Protective effects of berberine on doxorubicin-induced hepatotoxicity in mice. *Biol. Pharm. Bull.*, 35(5): 796-800.

Zhou ZE, Tang Y, Jin X, Chen C, Lu Y, Liu L and Shen C (2016). Metformin inhibits advanced glycation end products-induced inflammatory response in murine macrophages partly through AMPK activation and RAGE/NFκB pathway suppression. *J. Diabetes Res.*, 2016.

Zhuang A, Yap FY, McCarthy D, Leung C, Sourris KC, Penfold SA, Thallas-Bonke V, Coughlan MT, Schulz BL and Forbes JM (2019). Globally elevating the AGE clearance receptor, OST48, does not protect against the development of diabetic kidney disease, despite improving insulin secretion. *Sci. Rep.*, 9(1): 1-10.