Biosensors and Bioelectronics 133 (2019) 107–124

Contents lists available at ScienceDirect

Biosensors and Bioelectronics

journal homepage: www.elsevier.com/locate/bios

Methylglyoxal – An emerging biomarker for diabetes mellitus diagnosis and its detection methods

Lakshmishri Ramachandra Bhat[a,b], Srinivasan Vedantham[c], Uma Maheswari Krishnan[b,d], John Bosco Balaguru Rayappan[a,b,*]

[a] School of Electrical & Electronics Engineering, SASTRA Deemed University, Thanjavur 613004, India
[b] Centre for Nanotechnology & Advanced Biomaterials (CeNTAB), SASTRA Deemed University, Thanjavur 613004, India
[c] Disease Program Lead-Diabetes, MedGenome Inc., Narayana Health City, Bangalore 560099, India
[d] School of Chemical & Biotechnology, SASTRA Deemed University, Thanjavur 613004, India

ARTICLE INFO

Keywords:
Diabetes Mellitus
Glucose
Methylglyoxal
Detection methods
Advanced glycation end products (AGEs)

ABSTRACT

Diabetes Mellitus (DM) is one among the supreme metabolic issues observed in history since 3000 BCE and has gained much interest recently due to the increasing number of diabetic cases every year. Glucose is considered as the most iconic biomarker for diabetes detection, and fluctuations in its levels are related to different stages of DM. However, methylglyoxal (MG) is evolving as a diabetes marker since it plays a significant role in biological processes Apart from DM, MG causes several metabolic irregularities like hypertension, neuropathy, nephropathy, oxidative stress. Besides, MG is a predominant precursor of advanced glycation end products (AGEs), which result in protein dysfunction, glycation of vascular tissues and aging. In this background, detection of MG has much importance, and the design of smart models is desirable. MG formation, detoxification, and its glycation effects have paved the way for the development of detection strategies which are described in detail here. The direct and indirect methods of MG measurement have been established in the past. At present, techniques like high-performance liquid chromatography, gas chromatography-mass spectrometry, enzyme-linked immunosorbent assay, capillary electrophoresis, electrochemical biosensors have been used to quantify MG present in the samples. Here, we have tried to correlate the function of MG and detection strategies to explain the major challenges posed towards implementation of easy, efficient and accurate standardization.

1. Introduction

Diabetes is the most iconic issue in the health industry irrespective of age and vegetation. It is a major non-communicative metabolic disorder, having a devastating impact on the healthcare and economy (Dall et al., 2014). DM is broadly classified as type 1 (T1DM), type 2 (T2DM) and gestational diabetes (GDM). The reason behind T1DM and T2DM are lack of insulin production due to β- cell destruction and ability to intake insulin by cells due to insulin resistance, respectively (American Diabetes Association, 2018; Nichols et al., 2013; Zarkogianni et al., 2015). GDM is the condition of glucose intolerance during pregnancy (Goldenberg and Punthakee, 2013). Proper therapeutic intervention through the external supply of insulin and systematic medication can be the remedies of type 1 and 2 diabetes respectively (Ransom et al., 2013). Also, great efforts are taken for the treatment of diabetic complications and the discovery of new biomarkers, which have significant relation with diabetes. Huge rise in the number of diabetes cases reported each year to imply the need for preventive rather than reactive approach (Zarkogianni et al., 2015) along with deployment of point of care devices across the nations. Knowledge about the origin, diagnosis, and treatment of DM must be spread to implement preventive measures to fight this count effectively (Ekoé et al., 2013). In this scenario, the International Diabetes Federation has been trying to draw the attention of countries towards early diagnosis of diabetes to ensure the diabetes-free lifecycle of future generations.

At present, diagnosis of DM and its categorization is mainly based on the identification and quantification of biomarkers like glycated hemoglobin and glucose in blood, urine (Gu et al., 2016; Radhakumary and Sreenivasan, 2011), sweat (Chen et al., 2017; Liu et al., 2018), tears (Park et al., 2018), saliva, etc. Also, parameters like fasting plasma glucose, oral glucose tolerance, postprandial plasma glucose criteria, are executed for DM diagnosis (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2002). Moreover, food and lifestyle highly influence glucose levels, which lead to more

* Corresponding author at: School of Electrical & Electronics Engineering, SASTRA Deemed University, Thanjavur 613004, India.
E-mail address: rjbosco@ece.sastra.edu (J.B.B. Rayappan).

https://doi.org/10.1016/j.bios.2019.03.010
Received 6 December 2018; Received in revised form 7 March 2019; Accepted 7 March 2019
Available online 08 March 2019
0956-5663/

complications in the assessment of diabetic conditions.

In this scenario, new biomarkers (independent of the glucose levels) and techniques for accurate and early diagnosis (prediabetic stage) of diabetes having immense importance. The identification of prediabetes as well as prediction of associated complications has been a field, under keen observation by many researchers and physicians across the globe. Methylglyoxal (MG) is emerging as a biomarker of diabetes mellitus (DM) as it has a close association with protein glycation and insulin resistance. As a biomarker, MG investigated for several other ailments. Now, the identification of the root cause of diabetes and its complications brings MG's potential for diabetes diagnosis into the limelight.

Keeping this as the background, we have presented the major types of diabetes and their causes influenced by glucose levels and insulin resistance. The biomarker MG and its origin, sources, formation, detoxification and a major contribution to the onset of diabetic complications are discussed briefly. Also, deliberately explained the different detection methodologies and the current scenario of MG research and its future perspectives.

2. Types of Diabetes Mellitus

DM is commonly classified as Type 1, Type 2, gestational and others based on specific criteria are shown in Table 1 (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2002). Insulin-dependent diabetes or TIDM occurs primarily due to autoimmune destruction of β-cells caused to lack of insulin secretion which results in ketoacidosis and hyperglycemia. The exogenous insulin injections might help to maintain the level for the routine process. (Epstein et al., 1994). In certain cases, autoimmunity is not observed, and such patients are classified as type 1 idiopathy (American Diabetes Association, 2005). Non-insulin-dependent diabetes or T2DM arises due to insulin resistance or insulin deficiency. The major cause of this type of diabetes is lack of physical activity. Since the function of β-cells and insulin levels have been abnormal, T2DM results in spontaneous ketoacidosis and gradual occurrence of hyperglycemia condition. The other specific types of diabetes associated with several reasons like genetic defects (Bell and Polonsky, 2001; Edghill and Hattersley, 2008; Stekelenburg and Schwitzgebel, 2016), dysfunction of hormones (Fu et al., 2013; Hage et al., 2011), drugs or chemicals (Chan et al., 1996; Izzedine et al., 2005; O'Byrne and Feely, 1990; Pandit et al., 1993), infections, syndromes (Doyle et al., 1982; Schwartz et al., 1978; Soffer et al., 1961; Taylor, 1992) and immunity (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2002) affected the function of β-cells and insulin. GDM is often related to glucose intolerance during pregnancy period. The screening and treatment of GDM are very important; else it may lead to T1DM or T2DM in the future. Overall, the synergic effect of β-cell and insulin against the glucose level cause metabolic abnormality, micro- and macrovascular complications (Ogawa et al., 2010) and casualty (O'Byrne and Feely, 1990). However, brief reports on the types of diabetes and their effects are available in the references (Bell et al., 1991; Bell and Polonsky, 2001; Epstein et al., 1994; Ross et al., 2004; Smushkin and Vella, 2010; The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2002).

Table 1
Types and sub-types of diabetes mellitus (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2002).

Types	Classification
1	Type 1 diabetes
2	Type 2 diabetes
3	Gestational diabetes
4	Other specific types – Genetic defects of β-cell function – Genetic defects in insulin action – Diseases of the exocrine pancreas – Endocrinopathies – Drug- or chemical-induced – Infections – Uncommon forms of immune-mediated diabetes – Other genetic syndromes sometimes associated with diabetes

3. DM diagnosis and biomarkers

The explicit symptoms of the early stages of DM are imperceptible due to many factors like lifestyle, physical condition, food. However, it has led to severe casualties such as vascular complications, chronic disorders, hyperglycemia and so on. The WHO expert committee defined the diagnostic criteria of glucose level in the blood (mg/dL or mmol/L) for normal and diabetic subjects based on epidemiological studies (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2002).

Glucose is considered as the predominant biomarker for hyperglycemia (Dall et al., 2014). From 1962 onwards, there has been extensive research focused on developing methods for the measurement of glucose in various matrices such as blood, urine, and saliva (Liu et al., 2018). Furthermore, the measurement of glucose is classified into different categories for the identification of the exactness of diabetic condition. The tests like Fasting Plasma Glucose (FPG), 2-h Plasma Glucose (2hPG), Oral Glucose Tolerance Test (OGTT), Random Plasma Glucose test (RPG), Glycated Hemoglobin (HbA_{1C}) have been regulated for diagnosis and confirmation of DM. Besides, researchers have tried to establish close relations with alternative biomarkers such as glutamic acid decarboxylase autoantibodies (GADA), insulin autoantibodies (IAA), insulinoma-associated-2-autoantibodies (IA-2A), islet cell cytoplasmic autoantibodies (ICA), C-peptide (Bingley, 2010; Bonifacio, 2015; Regnell and Lernmark, 2017; Wasserfall and Atkinson, 2006), methylglyoxal (MG) (Beisswenger, 2014), amino acids, lipid metabolomics, palmitoleate (Roberts et al., 2014) for the prediction of types of DM.

Identifying a particular type of DM is the major issue due to its specificity and several exogenous and endogenous factors which are interlinked with the onset of DM. Generally, DM is closely associated with autoantibodies (Bingley, 2010). In particular, the T1DM autoimmune disorder can be characterized by the presence of ICA and GADA (Bingley, 2010; Bonifacio, 2015; Regnell and Lernmark, 2017; Wasserfall and Atkinson, 2006). Similarly, these autoantibodies are used to determine T2DM, but C-peptide secretion and age factor may lead to uncertainty (Bingley, 2010). Roberts et al. demonstrated that the branched-chain amino acids could be a screening biomarker for T2DM (Roberts et al., 2014). However, at present HbA_{1C} and FPG are considered for T2DM diagnosis. But, HbA_{1C} levels are dependent on hemoglobin count and in-turn erythrocyte turnover which may vary due to anemia and renal diseases (Bloomgarden, 2017). Moreover, HbA_{1C} is shown to be unreliable recently, as it varies according to age, ethnicity, and is imprecise (Bloomgarden et al., 2008). Thus, identification of biomarkers and their related etymological studies and clinical endpoints are required for standardization.

Nevertheless, screening of prediabetic state and association of biomarkers with a specific type of diabetes is a real challenge. Except for T1DM, all other types of DM take prolonged duration to show hyperglycemia and related problems including severe damage to the internal organs and metabolic dysfunction well before the diabetic state. Subjects have a high risk for the development of DM and cardiovascular diseases within 5–10 years screening of prediabetic state. Besides the risk of prediabetes, various challenges make identification of DM cumbersome. The prediabetic condition is above the average of normal blood glucose level and below diabetic condition and referred to as impaired glucose tolerance (IGT) or impaired fasting glucose (IFG).

Metabolomics is the study of metabolite level related to certain diseases. Rui et al. have successfully displayed a significant variation in the metabolites of prediabetic and T2DM subject. The concentration of

metabolites such as glycine, lysophosphatidylcholine and acetylcarnitine have significantly varied for IGT individuals (Wang-Sattler et al., 2012). Indeed, the prevailing understanding of the biological pathways induced by excess glucose in the blood and other related compounds (fatty acids, amino acids, proteins) might be helpful for the identification of new biomarkers. Furthermore, the credentials of clinical research, analysis time, cost, sampling convenience, stability, reproducibility must satisfy the choice of new biomarkers. Relatively, MG favored all the parameters to be considered as a new biomarker. PJ Beisswenger, in his groundbreaking study, identified that MG (the specific precursor of advanced glycation end products (AGEs)) as a highly stable chemically reactive biomarker for prediabetes, T1DM, and T2DM (Beisswenger, 2014). In this background, the significance of AGEs, research insights of MG on diabetes, sources and formation of MG, detoxification of MG, the relation between MG and insulin resistance, and detection methods of MG have explained in the following sections.

4. AGEs

AGEs are the complex and heterogeneous group of chemical compounds (glycotoxins) (Goldin et al., 2006; Singh et al., 2001) formed non-enzymatically through the interaction of carboxyl group of reducing sugars and amino groups in the biomolecules like proteins, nucleic acids, lipids, peptides (Goh and Cooper, 2008). This reaction called as Maillard reaction produces the intermediate compounds like Schiff bases and Amadori products (Kiho et al., 2005; Singh et al., 2001; Talukdar et al., 2009). Mostly, long-lived and stable proteins are targeted by glycating agents via covalent cross-link formation results in AGEs which, promote hardening and permanent dysfunction of tissues through the process of tissue remodeling (Singh et al., 2001). Briefly, intracellular AGEs interfere with the cytological signaling pathways and their levels, which are dependent on glycolysis process. Endogenous AGEs production and accumulation is naturally a gradual process as glucose is the least reactive sugar residue that promotes glycation. However, both the long-lived and short-lived proteins are involved the glycation reaction during hyperglycemic condition. Also, exogenous AGEs originated from processed food products, smoke, beverages, etc. (Goldberg et al., 2004; Uribarri et al., 2010) also induce an inflammatory response at a higher rate. Dietary exposure to foods containing higher amounts of carbohydrates, proteins, and fat accompanies with greater quantities of AGEs resulting in severe damage to the body tissue. As a result, the insoluble and long-lasting AGEs contribute significantly to the development and progression of aging (Desai et al., 2010; Thornalley, 2008), metabolic disorders like oxidative stress (Chang and Wu, 2006; Desai et al., 2010; Rondeau et al., 2008), cancer (Bellahcène et al., 2018), cardiovascular disorders (Kilhovd et al., 2009), diabetes-related retinopathy (Murata et al., 1997), nephropathy (Goh and Cooper, 2008; Rabbani and Thornalley, 2014; Schmidt, 2018), neuropathy (Krautwald and Münch, 2010), micro and macroangiopathy (Ogawa et al., 2010; Vlassara et al., 2002), Alzheimer's disease (Angeloni et al., 2014) and hypertension (Chang and Wu, 2006). In this scenario, one would imagine that measurement and analysis of AGEs will decipher/unfold the issue and provide direction for therapeutic interventions towards metabolic complexities. But the major issue is the identification of a particular compound (AGEs) towards the pathological cause. Secondly, AGEs are found in free, as well as bound form in the blood and tissues. In a social perspective, there is no standardized/recognized method for AGEs measurement [35] and hence, comparison and follow up of clinical effects of AGEs is challenging.

Indeed, high levels of early glycation products (EGP) and AGEs resulted in the acceleration of diabetic complications (Beisswenger, 2014). The α-oxoaldehydes are formed as EGP during the Maillard reaction (Fig. 1) as a precursor of AGEs (Thornalley, 2005). The α-oxoaldehydes are chemically reactive up to 20,000 times than glucose with amino groups of biomolecules (Beisswenger, 2014; Singh et al., 2001; Thornalley, 2005). Thus, the α- oxoaldehydes compounds mediated glycation is several orders rapid than glucose directed glycation (Brownlee, 2001; Mittelmaier and Pischetsrieder, 2011; Tauer et al., 2001). Fig. 2 depicts the formation of α-oxoaldehydes through the different reaction process including the classical Maillard reaction. These α-oxoaldehydes are highly potent even in the unfavorable conditions and retain the glycating activity (Thornalley, 2005).

Nevertheless, an electrophilic nature of AGEs precursors attract themselves towards nucleophilic biomolecules and lead to condensation reactions (Vistoli et al., 2013). Amongst these dicarbonyl compounds, MG, glyoxal, and 3-DG are found to be playing a significant role (Thornalley et al., 1999) in the development and progression of diabetic angiopathy (Ogawa et al., 2010), chronic kidney and cardiovascular diseases (Nakayama et al., 2008). AGEs derived by different glycating agents cross-react with antibodies designed for MG-derived AGEs, which indicates that MG might be the common mid-way in the AGE formation process (Vander Jagt and Hunsaker, 2003). MG is more reactive than acetol and a much better substrate for aldose reductase (Vander Jagt et al., 1992). Also, MG is found to be an independent risk factor for many metabolic parameter changes including blood pressure, glomerular filtration rate, etc. (Ogawa et al., 2010). Besides, MG is considered as the most dangerous dicarbonyl compound due to its high rate of endogenous flux inside our human body (Moraru et al., 2018). So, identification and removal of such deleterious precursors would help in retardation of AGEs precipitation in body tissues.

In general, AGEs and their precursors have been identified as biomarkers for diabetes-associated complications. Clinical studies have confirmed the presence of AGEs and their precursors in complicated diabetic subjects (Beisswenger, 2014). The detection of AGEs exhibited 5–15-fold enhanced observations between normal and diabetic than other biomarkers (Beisswenger, 2014; Brings et al., 2017). Especially, AGEs formed from certain α-oxoaldehydes (MG and 3-deoxyglucosone (3-DG)) are directly proportional to postprandial glucose fluctuations in T1DM and T2DM whereas, the standard biomarker HbA_{1C} does not match with these variations. The predictive measurement of AGEs related to MG, 3-DG, and glyoxal, which uniquely respond to the level of glycemia than HbA_{1C} towards the development of biomarkers for early prediction of DM (Beisswenger, 2014). However, dicarbonyl stress related issues (Rabbani and Thornalley, 2015), oxidative products, and AGEs precursor (MG) are associated with diabetic complications (Moraru et al., 2018). Hence, detection of AGEs and other precursors could lead to exploring several functions behind the metabolic pathways associated with glucose concentrations.

5. Methylglyoxal

MG is an electrophilic α,β-dicarbonyl compound (Desai et al., 2010), produced as an intermediate in the glycolysis process (Kalapos, 2008; Thornalley, 1996) in living organisms (Vander Jagt and Hunsaker, 2003). The strong interaction of MG with active functional arginine groups in the proteins influences its highly reactive nature during the glycolysis process than glucose whereas, glucose reacts with lysine groups (Thornalley and Rabbani, 2011a). The production pathway of AGEs and formation mechanisms of MG demonstrate the significance of MG detection over AGEs for the diabetes diagnosis (Fig. 2). Simultaneously, the endogenous and exogenous sources could trigger excessive production of MG. This significantly increases the MG concentration inside and outside the cells during hyperglycemia. The studies using incubated human red blood cells with normal and hyperglycemic condition exhibited the characteristic increase in the concentration and metabolic flux of the formation of MG (Thornalley et al., 2001). In specific, MG and AGEs production increase 2–4 folds in hyperglycemic conditions (Rabbani and Thornalley, 2014). Mostly, MG can be detoxified through the glyoxalase system (GLO I and GLO II enzymes) in normal conditions. In hyperglycemic condition, the GLO

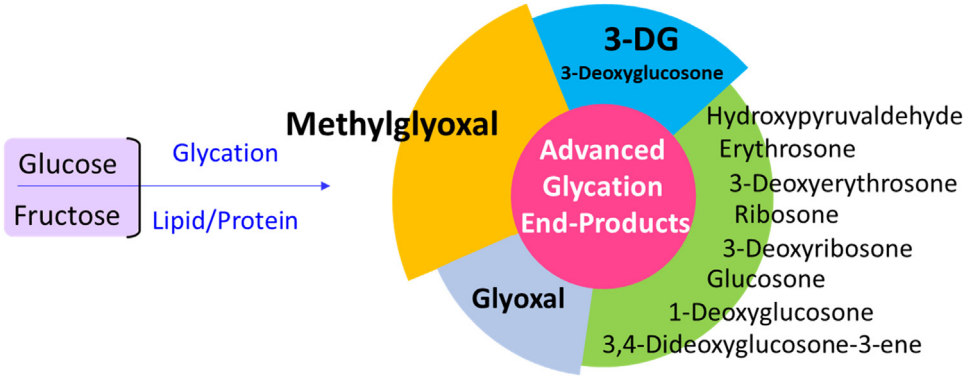

Fig. 1. Formation of 11 α-oxoaldehydes (α-dicarbonyl compounds) - precursors of AGEs (early glycation products) during the glycation reaction.

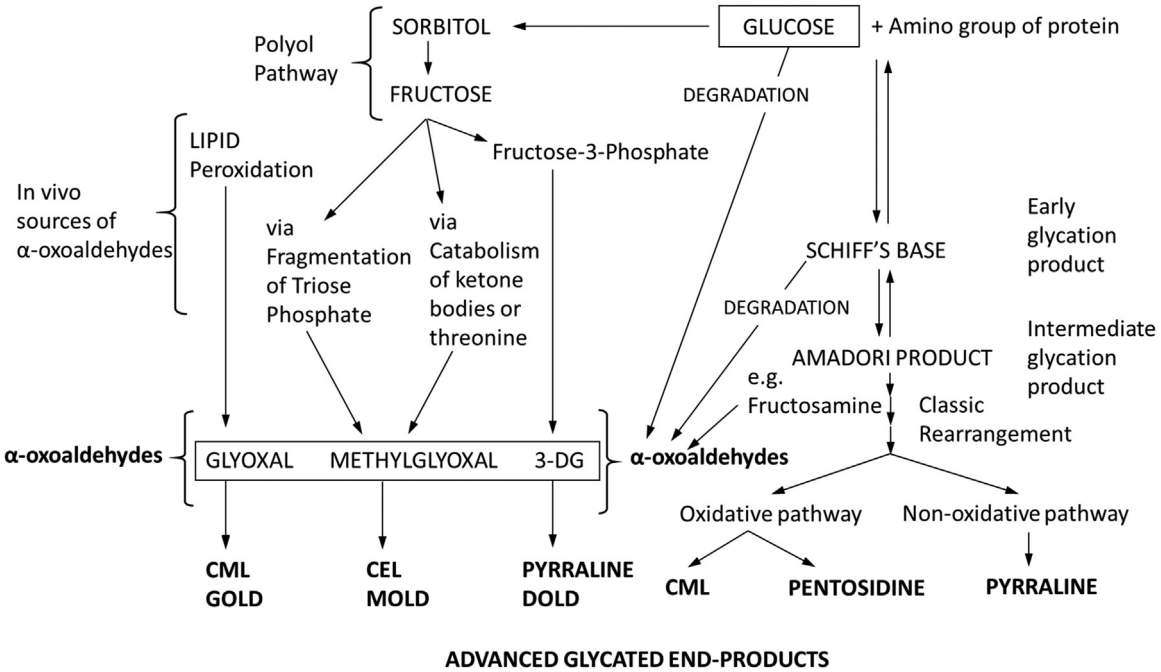

Fig. 2. Glycation reaction and pathways of advanced glycated end-products (redrawn from ref. (Singh et al., 2001)). Reprinted from Singh et al. (2001) with permission of Springer-Verlag © 2001.

enzymes were not elevated corresponding to the increased production of MG (Thornalley, 1988; Thornalley et al., 1989). Type 1 diabetes mellitus (T1DM) subjects exhibited a higher GLO I activity and lower GLO II activity (Thornalley et al., 1989). This might be the reason for the higher threshold of MG in T1DM subjects. MG forms adducts such as hydroimidazolones (MG-H1) which later cross-link and form AGEs (Rabbani and Thornalley, 2014). Moreover, MG-derived AGEs levels vary disproportionately according to the GLO levels. On the other hand, studies revealed that MG could increase the glucose concentration, through direct reduction and conversion of D-lactate from detoxification process (acetone metabolism – MG pathway) (Casazza et al., 1984).

Overall, the production rate of MG and its associated adduct formation or detoxification process is comparatively higher than other precursors and AGEs. In this regard, MG is highlighted as a biomarker for diabetes diagnosis next to AGEs.

5.1. Discovery and follow up

Synthesis, characterization and chemical interactions of MG have been an interest among scientists since the last two decades of the 19th century (Baumann, 1885; Witt et al., 1987). However, MG has driven much attention only after 20–30 years of its discovery. On the complete establishment of the Embden-Meyerhof-Parnas pathway (EMP), MG regained interest in the research community, especially among biologists because of its wide distribution and high reactivity. The detailed timeline of MG related workflow towards diabetes and detection is given in Table 2.

The investigation of MG is widespread in different applications from biology to chemistry such as cell culture, tissue culture, aquaculture, and agriculture. It is noteworthy that, MG is closely associated with internal and external functions of organisms (Kalapos, 1999a; Nemet et al., 2006).

Other areas: MG acts as an inhibitor for cell growth (Egyud and Szent-Gyorgyi, 1966). It is categorized as "retina" substance, as it retarded growth and observed to stop the proliferation of cancer cells in albino mice (Egyuud and Szent-Gyorgyi, 1968), and quahog (Mercenaria mercenaria) (Schmeer, 1964). Various chemical and biological substances such as limonene (Suh et al., 2017), nuclear factor erythroid 2-related factor 2 (Nrf2), carnosic acid with 1-(2-Cyano-3,12,28-trioxolane-1,9(11)-died-28-yl)-1H-imidazole (CDDO-Im) (Nishimoto et al., 2017), honokiol (Suh et al., 2016), fisetin (Maher et al., 2011) are discovered to be alleviating MG accumulation by enhancing its detoxification. Also, CHOP deficiency (Choi et al., 2016; Nam et al., 2015) and the pivotal role of cytochrome c peroxidase (Ccp1) in the enzymatic

Table 2
Significant Milestones in MG evolution in association with DM.

Year	Researcher	Research establishment	Ref.
1885	E. Baumann	Reported the reaction of benzenethiol with pyruvic acid to form hemithioketal	(Baumann, 1885)
1912	L C Maillard	Observed browning of amino acids by sugars and hypothesized its significance in diabetes	(Maillard, 1912)
1913	Neuberg	Explained physiological significance of MG	(Neuberg, 1913)
1913	Dakin & Dudley	Identified MG as a vital intermediate in the glycolysis pathway	(Dakin and Dudley, 1913)
1927	Theodore E. Friedemann	Determination of MG using alkali and hydrogen peroxide	(Friedemann, 1927)
1928	N Ariyama	Colorimetric determination of glyoxals using cyanide	(Ariyama, 1928)
1931	Barrenscheen & M Dregruss	Determination of MG by an alcoholic solution of potassium hydroxide	(Owens and Belcher, 1965)
1932–1939	G Embden, O Meyerhof, and JK Parnas	The complete development of the EMP pathway and identified the MG production from DHAP, the intermediate of the glycolysis pathway	(Racker, 1951)
1932	Lohmann	Identified the importance of reduced GSH in GLO activity	(Lohmann, 1932)
1933	M Jowett & JH Quastel	GLO system: Proposed the formation of an intermediate compound between the reaction of MG and GSH	(Jowett and Quastel, 1933)
1936	K Nagaya, S Yamazoye & S Nakamura	GLO system: Equimolar concentrations of GSH and MG react to form lactic acid, and later GSH is retained concomitantly	(Nagaya, Yamazoye and Nakamura, 1936)
1936	S Yamanote	Described the co-enzyme action of GSH	(Yamazoye, 1936)
1951	E Racker	GLO system: Identified the intermediate compound, S-D-lactoylglutathione (SDL) and two enzymes namely glyoxalase I and glyoxalase II	(Racker, 1951)
1966	LG Egyud & AS Gyorgyi	Described the Retina and Promise nature of MG and GLO	(Egyud and Szent-Gyorgyi, 1966)
1968	S Rahbar	Observed glycation of hemoglobin in red blood cells	(Rahbar, 1968)
1979	Kirk et al.	Found that GLO allele is increased in T1DM patients	(Kirk et al., 1979)
1981	McCann et al.	Emphasized that GLO gene polymorphism is linked with diabetic complications	(McCann et al., 1981)
1984	Brownlee et al.	Reported nonenzymatic glycosylation and AGEs formation through glucose	(Brownlee et al., 1984)
1986	Monnier et al.	Proposed that fluorescence of glycosylated collagen might be due to glucose-derived protein cross-link 2-furoyl − 4(5) -(2-furanyl) imidazole	(Monnier et al., 1986)
1988	PJ Thornalley	Suggested that the glyoxalase pathway is related to diabetic complications during hyperglycemia	(Thornalley, 1988)
1992	Vander Jagt et al.	Proposed an integrative model of diabetic complications, which combines the non-enzymatic glycation and aldose reductase/sorbitol theories	(Vander Jagt et al., 1992)
1992	AC McLellan et al.	Developed D-lactate dehydrogenase enzymatic assay to detect D-lactate levels in diabetic patients	(McLellan et al., 1992)
1993	MR Montoya, MA Zon & JMR Mellado	First electrochemical analysis of MG using linear sweep voltammetry	(Montoya et al., 1993)
2003	Annunziata Lapolla et al.	MG levels correlated with glycated hemoglobin and fasting plasma glucose levels	(Lapolla et al., 2003)
2005	Ina Nemet et al.	MG level variation studied simultaneously in whole blood and plasma of normal and diabetic subjects	(Nemet et al., 2005)
2013	S Chatterjee, J Wen & A Chen	Detection of MG for diabetes diagnosis in human plasma	(Chatterjee et al., 2013)

activity of D-erythroascorbate peroxidase (EAPX1) (Shin et al., 2017) have been investigated to deteriorate MG levels in cells. Although MG was ascribed as growth inhibitor (Egyud and Szent-Gyorgyi, 1966), Lin *et al.* (Lin et al., 2018) have recently reported the cancer-promoting properties of MG and proved that MG-induced oxidative stress leads to colon cancer progression. Similarly, reduction in the cadmium toxicity through stimulation of glutathione reductase and gamma-glutamylcysteine synthetase (γ-ECS) in wheat seedlings by MG has been reported to highlight MG's beneficial roles (Li et al., 2018).

Though the controversy of MG as a beneficial or harmful metabolite is continuing; it is necessary to study the effects of MG through clinical trials for better understanding.

Diabetes: At present, PJ Thornalley (Rabbani et al., 2018; Rabbani and Thornalley, 2018, 2014; Thornalley, 1996, 1995), MP Kalapos (Kalapos, 1999b, 1999a, Kalapos, 2008, 2013), DL Vander Jagt (Vander Jagt, 2008; Vander Jagt et al., 2001, 1992; Vander Jagt and Hunsaker, 2003), and their teams are pioneering in understanding and exploiting the physiological significance of glyoxalase (GLO) system, MG and their roles in metabolic disorders after AS Gyorgyi (Egyud and Szent-Gyorgyi, 1966).

In specific, Thornalley *et al.* have investigated the role of glyoxal and MG in aging (Thornalley, 2008), arginine directed glycation (Thornalley, 2005), the role of MG and AGEs in nephropathy (Rabbani and Thornalley, 2018, 2014). Kalapos has reported the origin of MG (Kalapos, 2013), its implications in living organisms (Kalapos, 1999a) and the role of α-oxoaldehydes in diabetes mellitus (Kalapos, 1992). Beisswenger *et al.* studied the effect of metformin on MG levels in T2DM patients (Beisswenger et al., 1999) and reflection of α-dicarbonyls during hyperglycemia (Beisswenger et al., 2001). In this regard, several approaches have been undertaken to relate MG and its associated products with diabetes.

5.2. Formation and detoxification of MG

Generally, adult human produces ~3 mmol MG per day, which increases depending on the glucose concentration and endo- and exogenous sources (Rabbani and Thornalley, 2014). In specific, the normal level of MG in human blood plasma is 100–120 nM (Beisswenger et al., 1999; Talukdar et al., 2009; Thornalley, 2008). It is evident that higher levels of MG cause accelerated glycation of proteins, which, lead to metabolic irregularities in the human body (Fig. 3). The main sources of MG can be classified as exogenous and endogenous (Frischmann et al., 2005). However, the body cells have an efficient enzymatic system for the detoxification of MG (Fig. 3). The dysfunction of MG detoxification system, due to higher production of MG endogenously or excess intake of MG exogenously may lead to critical situations wherein, MG level increases unconditionally and contribute to faster and severe complications. To reduce and control the MG level, understanding its formation and detoxification pathways is vital.

5.2.1. Formation

The exogenous sources such as food, beverages, smoke contain micromolar concentration of MG and tend to promote the internal reactions towards endogenous productions (Chatterjee and Chen, 2012; Frischmann et al., 2005; Nemet et al., 2006; Uribarri et al., 2010). The endogenous sources like fragmentation of triose phosphates from glycolysis, catabolism of ketone bodies/threonine, lipid peroxidation resulted in the formation of MG (Bellahcène et al., 2018; Kalapos, 1999a; Singh et al., 2001; Vander Jagt, 2008). However, glucose is the major contributor of MG production. Fig. 3 depicts the simplest scheme of

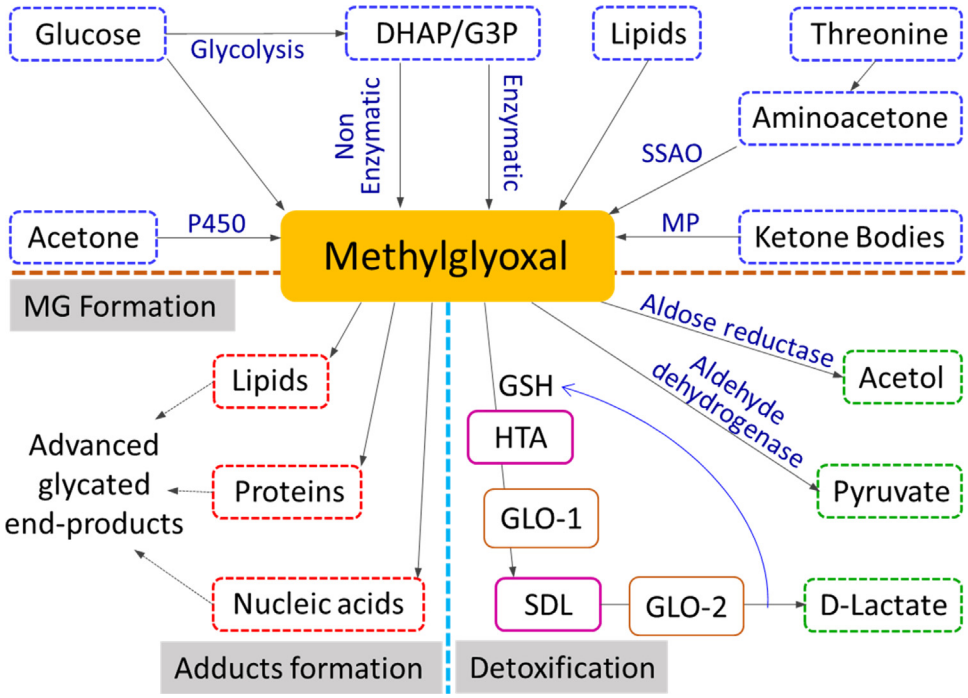

Fig. 3. MG formation, glycation and detoxification pathways. (DHAP – Dihydroxyacetone phosphate; G3P – Glyceraldehyde 3-phosphate; SSAO - Semicarbazide-Sensitive Amine Oxidase; P450 - Cytochrome P4502E1; MP – Myeloperoxidase; ALDH – Aldehyde dehydrogenases; SDL – S-D-Lactoylglutathione; HTA – hemithioacetal; GLO – Glyoxalase; GSH – Glutathione).

formation, glycation and detoxification reaction process of MG.

MG is formed enzymatically and non-enzymatically from different origins, which makes it different from other precursors of AGEs and more suitable for diabetes diagnosis.

Enzymatic: Glycolysis process of glucose resulted in the formation of glyceraldehyde-3- phosphate (G3P) and dihydroxyacetone phosphate (DHAP). MG is produced from G3P by acid-catalyzed reactions and iodoacetate poisoning (Entner and Doudoroff, 1952). Methylglyoxal synthase produces MG along with inorganic phosphate from DHAP (Hopper and Cooper, 1971; Murata et al., 1985b). Catabolic pathway of threonine leads to the formation aminoacetone, which further produces MG by the enzymatic action of monoamine oxidase in *Saccharomyces cerevisiae*, whereas, plasma amine oxidase catalyzes the MG formation in goat plasma. It confirms that, the formation of MG is actively dependent on the sources of enzyme like mitochondrial monoamine oxidase (Katz et al., 1984; Nara et al., 1966), aminoacetone oxidase (Ray and Ray, 1987), plasma amine oxidase (Ray and Ray, 1983) and diamine oxidases (Pegg and McGill, 1978) and their location in organisms (Inoue and Kimura, 1995). MG is tautomerized from enolaldehyde, which is an intermediate of isomerization of DHAP to G3P by triosephosphate isomerase (Iyengar and Rose, 1981; Richard, 1991). Though this reaction is relatively slow, MG formation through triosephosphate isomerase enzyme is considered as the major origin of MG in mammals. Fructose 1,6-bisphosphate aldolase incubation helped in the production of MG and inorganic phosphate (Pi) from DHAP (in rabbit muscles) (Grazi and Trombetta, 1978). Myeloperoxidase catalyzed acetoacetate oxidation in neutrophils (Aleksandrovskii, 1992), metabolic reaction of ketone bodies (Reichard et al., 1986), semicarbazide-sensitive amine oxidase (SSAO) catalysis of acetone (Lyles and Chalmers, 1992) and oxidative decomposition of carbohydrates and lipids (Shamsi et al., 1998) also produce MG. The in-vivo study using rats suggested that enzymes: acetone monooxygenase and acetol monooxygenase converts acetone to acetol and acetol to MG, respectively in the presence of oxygen and nicotinamide adenine dinucleotide phosphate (NADPH) (Casazza et al., 1984). Similarly, other enzymes like cytochrome P-450 monooxygenase (Reichard et al., 1986) and acetol dehydrogenase (Taylor et al., 1980) in the presence of NAD converts acetone and acetol to MG, respectively. Also, autoxidation of glucose (Bellahcène et al., 2018) and the degradation of glycated proteins (Vander Jagt, 2008) are also contributed as a minor source for the production of MG.

Non-enzymatic: The elimination reaction of G3P and DHAP spontaneously through enediolate and enolaldehyde intermediates lead to the formation of MG and inorganic phosphate (Pi) (Richard, 1984). MG formation from DHAP and dihydroxyacetone are favorable in high glycerol environments. Certain biomolecules like glucose 6-phosphate, fructose 6-phosphate and fructose 1,6-bisphosphate were reduced non-enzymatically as MG. Apart from these pathways, MG is suggested to be derived from lipid hydroperoxide. But, it is again linked to the acetone metabolism (Dhar et al., 2008). Alternatively, the non-enzymatic formation of MG confirmed through DHAP and G3P with the chemical reaction of Ringer's bicarbonate buffer (Needham and Lehmann, 1937) or tris and polyvalent anions like tetraborate, phosphate (Riddle and Lorenz, 1968).

5.2.2. Detoxification

MG is mainly degraded by glyoxalase (GLO) system, which has two enzymes namely GLO 1 and GLO 2. In this enzymatic reaction, glutathione (GSH) act as a catalyst which binds with MG to form hemithioacetal (HTA) for the reaction of GLO 1. Here, GLO 1 converts HTA to SDL later GLO 2 converts SDL to D-lactate. Another enzymatic reaction is oxidation of MG to pyruvate through methylglyoxal dehydrogenase with NAD^+ as a cofactor (Taylor et al., 1980) and aldehyde dehydrogenases (Bellahcène et al., 2018). These enzymes independently oxidize MG irrespective of the GLO system. The reductase like α-dicarbonyl/L-xylulose reductase (Odani et al., 2008) and MG reductase (Inoue et al., 1988; Murata et al., 1985a; Ray and Ray, 1984) reduces MG to lactaldehyde. The species *Clostridia* utilizes two enzymes, i.e., aldose reductase and glycerol dehydrogenase to convert MG to acetol and acetol to 1,2-propanediol (Liyanage et al., 2010). However, cofactors like GSH and NADPH are essential for the action of aldose reductase and oxidoreductase, respectively, for the conversion of MG (Aguilera and Prieto, 2001; Ko et al., 2005; Vander Jagt et al., 2001).

5.3. Impact of MG on insulin (resistance/secretion)

Insulin glycation results in insulin resistance, reduces the glucose uptake and insulin clearance in the cells. MG directly modifies the

Table 3
The MG detection methods with their pros and cons and highlighted study reports.

S. No	Method	Major Reagents/Nanomaterials	Advantages	Disadvantages	Linear Range	LOD	Ref
1.	Colorimetric Method	Arsenophosphotungstic acid	● Good results at higher pH ● Other glyoxals also determined	● Interference from solution components ● Not robust method	NA	1 cc of 0.001 M solution	(Ariyama, 1928)
2.	Colorimetric Method	Citrate-capped Gold nanoparticles with OPD	● Specificity ● The chemical reaction to plasmonic signal	● 30 min detection time	0.01–10 μM	0.05 μM	(S.-T. Wang et al., 2015)
3.	Fluorescent method	Methyl diaminobenzene-BODIPY	● Live cell imaging ● Sensitive and selective ● Comparatively faster	● Tedious preparation and optimization	NA	50–100 nM	(Wang et al., 2013)
4.	Capillary Electrophoresis with diode array detection	OPD with solid-phase extraction	● Low sample volume ● Cost-effective	● Extraction required ● Time consumption	0.1 to 3.6 mg L^{-1}	7.2 mg L^{-1}	(Álvaro do Rosário et al., 2005)
5.	Capillary Electrophoresis with amperometric detection	2-thiobarbituric acid (TBA)	● Cost effective	● Derivatization required	1–2000 μg L^{-1}	0.2 μg L^{-1}	(Zhang et al., 2010)
6.	Capillary gas chromatography with flame ionization detection	1,2-diaminopropane	● Short reaction time and elution time	Derivatization required	0.09–1.04 μg mL^{-1}	40 ng mL^{-1}	(Khuhawar et al., 2008)
7.	Gas chromatography with electron capture detection	4,5-dichloro-1,2-phenylenediamine	● Sensitive	● Derivatization required ● Indirect quantification (MQ)	NA	9 fmol	(Ohmori et al., 1987a)
8.	Gas chromatography with thermionic detection	Cysteamine, 2-acetylthiazolidine, dichloromethane	● Precise quantitative data	● Chemical complexity ● Time consumption	0.04–47 ppm	NA	(Hayashi and Shibamoto, 1985)
9.	Gas chromatography with mass spectrometry	PFBOA, MSTFA, 2,3-dimethyl-6,7-dimethoxyquinoxaline	● Simultaneous detection of α -oxoaldehydes	● Complex method ● Derivatization required	31.2–81.2 ng mL^{-1}	31.2 ng mL^{-1}	(Wu et al., 2008)
10.	Gas chromatography with mass spectrometry	PFBHA, BSTFA	● Ambient air measurement	● Huge time consumption	NA	NA	(Ortiz et al., 2006)
11.	Gas chromatography with mass spectrometry	PFBOA	● Small sample volume		NA	NA	(Chen et al., 2013)
12.	Two Static Headspace Gas chromatography with mass spectrometry	PFBHA	● Simple sample treatment ● Simultaneous solid and liquid extraction	● Derivatization required ● Not a reliable method	0.04–100 μg L^{-1}	0.01 μg L^{-1}	(Serrano et al., 2017)
13.	Gas chromatography-mass spectrometry with dispersive liquid-liquid microextraction	2,3-diaminonaphthalene	–	● Tedious sample extraction ● Huge time consumption	1–100 ng mL^{-1}	0.06 ng mL^{-1}	(Pastor-Belda et al., 2017)
14.	High-performance liquid chromatography	OPD, dichloromethane	● Specificity ● Good recovery	● Indirect quantification (MQ) ● Interference by proteins ● Derivatization needed	10–250 nmol	10 nmol	(Ohmori et al., 1987b)
15.	High-performance liquid chromatography	OPD	● Simple and sensitive	● Derivatization needed	NA	NA	(Moree-Testa and Saint-Jalm, 1981)
16.	High-performance liquid chromatography with absorbance detection (fluorimetric detection)	DDB	● Prevention of spontaneous MG formation during the derivatization process	● Expensive technique ● Complex and time-consuming method	NA	45 pmol (10 pmol)	(McLellan et al., 1992)
17.	Reverse-phase high-performance liquid chromatography with UV detection	Trifluoroacetic acid, DDB	● Rapid ● Inexpensive	● Derivatization needed	200–1000 nM	30.6 pmol	(Nemet et al., 2004)
18.	Fluorescence high performance liquid chromatography	1,2-diamino-4,5-methylenedioxybenzene	● Simple ● Large and expensive apparatus not required	● Indirect quantification (DMB) ● Derivatization needed	0.05–1 μM	60 fmol	(Ogasawara et al., 2016)
19.	High-performance liquid chromatography with Fluorescence detection	3,4-diaminopyridine	● Simultaneous determination and quantification of the α-dicarbonyl compounds ● Short separation time ● No clean up required for sample injection	● Derivatization needed ● Complex method	0.02–0.10 mg L^{-1}	0.44 μg L^{-1}	(Rodríguez-Cáceres et al., 2015)
20.	Lucigenin chemiluminescence high-performance liquid chromatography with electron spinResonance detection	TCPO/ANS-CL and Lucigenin-CL assays, SOD and Catalase	● Components with antibacterial activity detected ● Simple and sensitive	● Indirect quantification (ROS) ● The requirement of chemicals and assays	NA	5 mmol L^{-1}	(Karasawa et al., 2017)

(*continued on next page*)

Table 3 (*continued*)

S. No	Method	Major Reagents/Nanomaterials	Advantages	Disadvantages	Linear Range	LOD	Ref
21.	Peroxyoxalate chemiluminescence detection with fluorescence labeling	4-(N, N-dimethylaminosulfonyl)-7-hydrazino-2,1,3-benzoxadiazole,acetonitrile and imidazole–HNO_3 buffer	● High sensitivity	● Fluorescent labeling required	20–420 nM	4.4 to 6.5 nM	(Ali et al., 2014)
22.	ELISA with enhanced chemiluminescence reaction	3-(10′-Phenothiazinyl) propionic acid, TMB	● Lower LOD ● High sensitivity	● Indirect measurement (MG-LDL) ● Requirement of enhancer	0.5–1.6 ng mL^{-1}	0.5 ng mL^{-1}	(Sakharov et al., 2013)
23.	ELISA with gel retardation assay	Immunoglobin G (IgG)	● Specificity of MG-IgG	● Indirect method (MG-IgG)	NA	NA	(Islam et al., 2018)
24.	ELISA	Monoclonal anti-MG-BSA antibody (MG3D11)	● Specificity ● Lower LOD	● Indirect method (sMG)	NA	0.03 nmol mL^{-1}	(Beeri et al., 2011)
25.	Electrochemical method (Non-enzymatic)	SWCNT-Pt	● Robust, portable ● Inexpensive ● Simple and tailorable	● Specificity	0.1–100 μM	2.80 nM	(Chatterjee and Chen, 2012)
26.	Electrochemical method (Non-enzymatic)	SWCNT	● Robust, portable ● Inexpensive ● Simple and tailorable	● Specificity	0.1–100 μM	NA	(Chatterjee et al., 2013)
27.	Electrochemical method (Non-enzymatic)	V_2O_5 nanoplates	● Robust, portable ● Inexpensive ● Simple and tailorable	● Specificity	3–40 μM	0.24 μM	(Ramachandra Bhat et al., 2018)
28.	Electrochemical method (Enzymatic)	ZnO sepals, GSH and GLO 1	● Specificity	● The possibility of enzyme leaching ● Restricted conditions ● Expensive	0.2–100 μM	NA	(Thangavel et al., 2015)
29.	Electrochemical method (Enzymatic)	ZnO flakes, GSH and GLO 1	● Specificity	● The possibility of enzyme leaching ● Restricted conditions ● Expensive	0.2–100 μM	NA	(Ezhilan et al., 2015)
30.	Electrochemical method (Enzymatic)	V_2O_5 and GSH	● Specificity	● The possibility of enzyme leaching ● Restricted conditions ● Expensive	0.1–100 μM	2 nM	(Alagappan et al., 2017)
31.	Electrochemical method (Enzymatic)	CeO_2, GSH and GLO 1	● Specificity	● The possibility of enzyme leaching ● Restricted conditions ● Expensive	5–50 μM	2.14 nM	(Ramachandra et al., 2016)
32.	Electrochemical method (Enzymatic)	ZnO, GSH and GLO 1	● Specificity	● The possibility of enzyme leaching ● Restricted conditions ● Expensive	0.6–2.0 μM	9 nM	(Jayaprakasan et al., 2018)

NA – Not Available; **OPD** – o-phenylenediamine; DDB – 1,2-diamino-4,5-dimethoxybenzene; **BODIPY** – boron-dipyrromethene; **MSTFA** – N-methyl- N-trimethylsilyl-trifluoroacetamide; **BSTFA** – N, O-bis(trimethylsilyl)-trifluoroacetamide **PFBOA** – O- (2,3,4,5,6-pentafluorobenzyl) hydroxylamine; **PFBHA** – O-(2,3,4,5,6-pentafluorobenzyl) hydroxylamine hydrochloride; **2 MQ** – 2-Methylquinoxaline; **ROS** – Reactive Oxygen Species; **SWCNT** – Single Walled Carbon Nanotubes; **DMB** – 1,2-diaminobenzene; **ZnO** – Zinc oxide; **GSH** – Glutathione; **GLO 1** – Glyoxalase 1; **SOD** – Super Oxide Dismutase; **TMB** – 3,3′,5,5′- tetramethylbenzidine;

functions of insulin molecules and affect its signaling pathway. Recently, it has been discovered that MG inhibits the insulin receptor substrate (IRS) – 1 and phosphatidylinositol 4,5- bisphosphate 3-kinase (PI_3K) pathway (Jia, 2010), insulin triggered phosphorylation of protein kinase B (PKB) (Matafome et al., 2017) and extracellular signal-regulated protein kinase ½ (ERK ½) (Cantero et al., 2007; Riboulet-Chavey et al., 2006). The inhibition affects the IRS-1/PI_3K pathway redox independently ending up in decreased insulin secretion (Fiory et al., 2011). In Sprague-Dawley rats, it is demonstrated that MG affects the IRS - 1 phosphorylation and glucose transporter (GLUT4) levels in the adipocytes plasma membrane and results hyperglycemia by the action of insulin resistance (Guo et al., 2009).

Insulin secretion is a function of β-cell towards the response of glucose. The interaction of MG on β-cells and endothelial cells results in swelling and apoptosis towards dysfunction of cell functions (Bo et al., 2016; Vulesevic et al., 2016). Similarly, accumulation of MG on adipose tissue causes severe damage (Guo et al., 2009). In the β-cells, MG promoted the generation of reactive oxygen species and lead to decrease the insulin secretion (Pi et al., 2007). Also, MG reduced the PDX-1 (pancreatic and duodenal homeobox 1) levels, which is the main transcription factor influencing the insulin synthesis (Dhar et al., 2011). MG binds to arginine residues of insulin β-chain adducts and dysfunctions them (Jia et al., 2006). Such MG-insulin adducts disrupt the feedback mechanism of insulin and diminish the hepatic MG release. As a result, autocrine maintenance and removal of insulin are imbalanced (Jia et al., 2006).

Indeed, the external sources of MG could affect insulin secretion/resistance. For instance, Lin et al. and Guo et al. have shown that 1% MG in drinking water resulted in insulin resistance, which was observed in the animal models (Guo et al., 2009; Lin et al., 2018). Similarly, exposure to AGEs and MG rich diet caused for glucose and insulin tolerance (Hofmann et al., 2002).

6. MG detection

In general, detection of MG followed direct and indirect methods based on its high-reactive tendency with chemicals. MG can be measured directly through the reaction with derivatization agents, nanomaterials. In the other case, the MG derived products such as AGEs, D-lactate are quantified and correlated to MG levels indirectly. For example, the interaction of MG with *o*-phenylenediamine (OPD) results in 2-methylquinoxaline (2-MQ), the formation of 2-MQ prevents the aggregation of gold nanoparticles and led to color change which confirms the presence of MG (S.-T. Wang et al., 2015). Similarly, MG was quantified indirectly through the determination of quinoxalines peak from differential pulse polarography method based on the reaction of MG with OPD to form 2-MQ (quinoxalines) (Rodrigues et al., 1999). Colorimetric, capillary electrophoresis, High performance liquid chromatography (HPLC), gas chromatography-mass spectrometry (GCMS), enzyme-linked immunosorbent assay (ELISA), colorimetric, and electrochemical methods were demonstrated successfully as major techniques to detect MG in different samples like food, beverages, biological entities (Chatterjee and Chen, 2012; Hayashi and Shibamoto, 1985; Ohmori et al., 1987a; Serrano et al., 2017).

From literature, one can observe the detection of MG and related studies compared with other biomarkers like HbA_{1C} in the hyperglycemic conditions have gained significant focus. For example, Han et al. (2007) reported that, MG in T1DM and normal subjects as 841.7 ± 237.7 nmol/l and 439.3 ± 90.1 nmol/l, respectively and observed a significant correlation between MG and HbA_{1C} level ($r = 0.635$, $P < 0.001$) in plasma of TIDM subjects. In another study reported that, mean plasma MG level of 65.2 ± 19.2 and 40.1 ± 11.1 ng/mL in newly diagnosed T2DM subjects and controls, respectively, and MG levels correlated positively to FPG ($r = 0.354$, $P < 0.05$) and HbA_{1C} ($r = 0.670$, $P < 0.01$) (Kong et al., 2014). The analyze of MG simultaneously in whole blood and plasma of normal (409 ± 131 and 338 ± 62 nmol/L), and diabetic subjects (742 ± 141 and 520 ± 42 nmol/L) (Nemet et al., 2005) showed that ratio of MG concentration varied between whole blood and plasma. In these reports, MG levels were assessed at different stages of diabetes in the different conditions of diabetic complications (e.g., psoriasis, diabetic nephropathy, etc.). Though the relation between MG and glucose levels is assumed and tested, the exact proportions and standard levels of MG in different stages of diabetes are yet to be established with the help of smart detection technologies. The different MG detection methods and their pros and cons are listed in Table 3.

6.1. Colorimetric

Colorimetric detection of MG using different reagents has gained significant interest among chemists and biologists. In this analytical method, the presence and absence of any chemical compound are identified using a reagent dye or enzyme. Initially, Noboru Ariyama (Ariyama, 1928) used cyanide with arsenophosphotungstic acid under basic conditions whereas, Friedemann's titration (Friedemann, 1927) was carried out by hydrogen peroxide to identify MG. Recently, the surface plasmonic coupling of Au nanoparticles with MG resulted in a visible color change from red to blue due to aggregation and size-dependent optical properties (S.-T. Wang et al., 2015). The Maillard reaction is well-known for the interaction of lysine with reactive MG towards Schiff base (MG-lysine dimers) (Fig. 4**a**). Based on this reaction, the assays were developed with an *ortho*-amine group of OPD to form 2-MQ for MG sensing. (Fig. 4**b**). S.-T. Wang et al. (2015), have showed MG detection using OPD modified Au nanoparticles, where presence of MG results in conversion of OPD to 2-MQ leading to gain its stability by removal of OPD. Fig. 4**c** shows the schematic of OPD-Au aggregation and anti-aggregation characteristics in the absence and presence of MG respectively. MG can interact with OPD to form 2-MQ, which act as an anti-aggregation agent of Au nanoparticles. The selectivity of this assay results in a specific reaction towards MG than the other dicarbonyl compounds. Similar to this method, fluorescent-based MG detection developed by Wang et al. showed unique advantage of mapping MG in living cells as well in plasma medium (Wang et al., 2013). The methyl diaminobenzene-BODIPY (MBo) as a fluorescent molecule selective over other dicarbonyls reacted with MG resulted in faster response even at 50 nM in complex environments. The desired energy transfer between MG and MBo significantly favored stronger fluorescence response for selective detection.

6.2. Capillary electrophoresis

Capillary electrophoresis (CE) is an analytical technique performed in liquids for separation of the constituents. In CE, the analyte liquid passing through the micron-sized capillaries under a constant electric field, where the basic constituents separates according to their electrophoretic mobility. The electrophoretic and electroosmotic forces influences the separation of constituents in the liquid mixture (Yu et al., 2012). CE is advantageous over other chromatographic methods as it requires very less quantity of sample and reagent solutions and provides high separation efficiency. The selection of activity assays is important to quantify the separated MG from the samples. For example, Ma et al. (2008) and Langmaier et al. (2016) showed the separation process of MG in the complex environment and optimization of separation process to avoid the influence of cross reaction between biological molecules like biguaninde drugs, tiopronin. Since MG is non-electroactive and lacks chromophore characteristics, the derivatization step becomes essential to obtain better results using CE or any other optical detection method (Álvaro do Rosário et al., 2005). In this line, OPD was used as derivatizing agent to determine MG in the free-solution mode with diode array detection (Álvaro do Rosário et al., 2005). The 2-thiobarbituric acid (TBA) converts MG and GO for amperometric detection of MG-TBA and GO-TBA adducts in water and urine samples (Fig. 5)

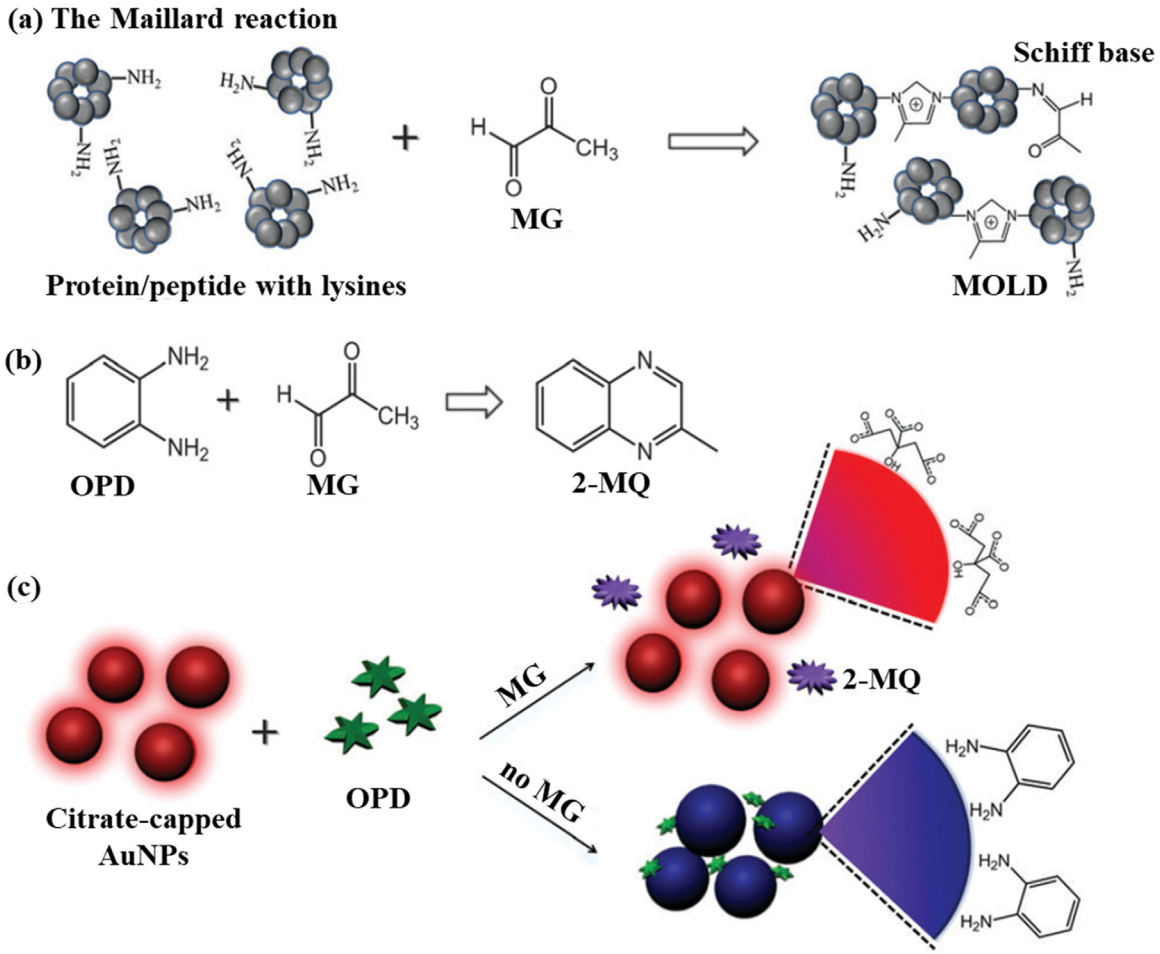

Fig. 4. (a) The formation of MG-lysine dimers (MOLD) from the Maillard reaction of protein lysine residues with MG (b) The chemical reaction of MG and *o*-phenylenediamine (OPD) to form 2-methylquinoxaline (2-MQ). (c) Schematic view of the colorimetric MG sensing based on the anti-aggregation mechanism of citrate-capped Au and OPD. The reaction of MG with OPD results in 2-MQ, which prevents the aggregation. In the absence of MG, OPD favors the aggregation of citrate-capped Au nanoparticles via bidentate binding to gold. (S.-T. Wang et al., 2015). Reprinted from (S.-T. Wang et al., 2015) with permission of the Royal Society of Chemistry © 2015.

(Zhang et al., 2010). The TBA derivatization agent and associated optimized instrumental conditions exhibited low limit of detection 0.2 μg L^{-1} (Zhang et al., 2010) compared with 7.2 μg L^{-1} of OPD based CE (Álvaro do Rosário et al., 2005). Finally, optimization of derivatization agent, working electrode, running buffer, pH, separation voltage, and electrokinetic injection time determines the sensitivity and limit of MG detection.

6.3. HPLC

Identification and separation of components according to their mass or flow rates when passed through a pressurized setup containing adsorbent made of particles describes the high-performance liquid chromatographic (HPLC) operation. The analyte molecules were split and quantified based on the interaction of the compounds present in sample mixture with the solid adsorbent. So, one could assess the amount of a chemical group of interest existing in a mixture. Features to provide a mixture of solvents, specific temperature, detector or to create a composition gradient of the liquids are available in the market nowadays. HPLC of α-oxoaldehydes is carried out using derivatizing agents like 1,2-diamino-4,5-dimethoxybenzene (McLellan et al., 1992), 3,4-diaminopyridine (Rodríguez-Cáceres et al., 2015), dichloro-1,2-

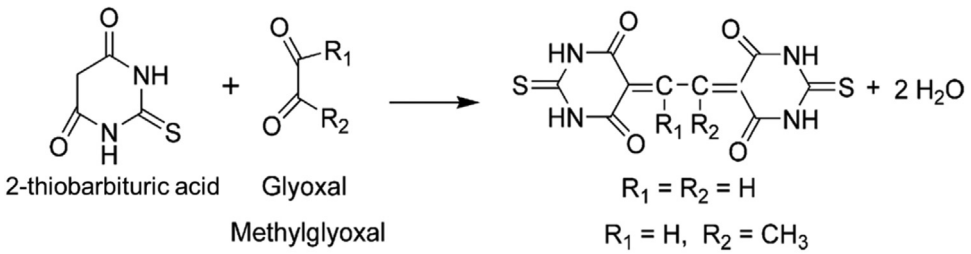

Fig. 5. Structural diagrams of the reaction of MG and GO with 2-thiobarbituric acid (TBA) to form MG-TBA (glyoxal-TBA) (Zhang et al., 2010). Reprinted from (Zhang et al., 2010) with permission of Elsevier © 2010.

phenylenediamine (Ohmori et al., 1987a) and detect the quinoxalines arising out of the reaction (Kalapos, 1999a). In the case of MG, 2-MQ is formed as a result of the reaction between MG and OPD (Moree-Testa and Saint-Jalm, 1981; Ohmori et al., 1987b) (Fig. 4**a**). Derivatization process is mostly performed under acidic conditions to avoid spontaneous production of MG from G3P and DHAP (McLellan et al., 1992). Liquid chromatography combined with mass spectrometry has gained enough momentum in detecting MG. Although, in a recent report, Ogasawara *et al.* have described 1,2 – diaminobenzene (DMB) as fluorescent pre-labeling agent and 1,2-Diamino-4,5-dimethoxybenzene (DDB) as the derivatizing reagent of MG before HPLC determination (Ogasawara et al., 2016). Chemiluminescence property of lucigenin (Karasawa et al., 2017), peroxyoxalate followed by fluorescence labeling with 4-(N, N-dimethylaminosulfonyl)-7-hydrazino-2,1,3-benzoxadiazole (Ali et al., 2014) was employed for MG determination in manuka honey and human blood plasma. Besides, HPLC technique has been utilized to check MG quenching or trapping ability of chemical compounds such as catechin, ethyl acetate, n-butanol (Yang et al., 2018), carnosine derivatives (Vistoli et al., 2017), etc. For this purpose, extracts of different plant species including Blackcurrant (Chen et al., 2014) and Annona muricata Linn. were tried (Justino et al., 2018).

6.4. GCMS

Gas chromatographic detection of MG were carried out using different derivatizing agents like stilbenediamine (Mirza et al., 2007), 2,3-diaminonaphthalene (Pastor-Belda et al., 2017), o-(2,3,4,5,6-pentafluorobenzyl) hydroxylamine (PFBHA) (Saison et al., 2009), O-(2,3,4,5,6-pentafluorobenzyl) hydroxylamine (PFBOA) (Lapolla et al., 2003), N-methyl-N-trimethylsilyl-trifluoroacetamide (MSTFA), 2,3-dimethyl-6,7-dimethoxyquinoxaline (2,3-DAN) (Wu et al., 2008), N,O-bis (trimethylsilyl)-trifluoroacetamide (BSTFA) (Ortiz et al., 2006), 4,5-dichloro-1,2-phenylenediamine (Ohmori et al., 1987a), and 2-acetylthiazolidine (Hayashi and Shibamoto, 1985). These analyses were made to assess MG content in food, beverages, human plasma, tumor extract, mouse brain cells (as diabetes marker), and flavoring agents (Chen et al., 2013; Hayashi and Shibamoto, 1985). In a recent report, two static headspaces GCMS was employed for analysis of 15 aldehydes present in canned vegetables (Serrano et al., 2017). Variation in the derivatizing agent, extraction, and analysis methodologies have influenced the linearity of MG detection. Salting out of the derivatizing agent resulted in improved sensitivities.

Similarly, in-solution or on-fiber derivatization could influence the analyte quantification (Saison et al., 2009). For example, among 41 chemically diverse carbonyl compounds in beer, MG and (*E*)-2-nonenal extracted better from in-solution and on-fiber derivatization. Next, derivatization methodologies like two-step derivatization process (Wu et al., 2008) and overnight derivatization at lower temperatures (Pastor-Belda et al., 2017) have helped the separation of carbonyl compounds and amplify the signals, respectively. However, Chen et al. (2013) have demonstrated the contributing factors like internal standards (synthesis of deuterated MG), reiteration approaches, deproteinization, and chemical derivatization for accurate quantification of MG in complex biological specimens.

6.5. ELISA

Enzyme based detection technique followed the basic principle of attraction between antigen and antibody. The designing of antigen and antibody referred to different types of ELISA namely direct, indirect, sandwich and competitive. The determination of antigen-antibody complex is based on chemiluminescence or fluorescence or colorimetric reaction. Mostly, competitive and sandwich models are used for MG detection. Fig. 6 depicts the schematic of sandwich ELISA for the detection of MG, where MG is bound with low-density protein (Sakharov et al., 2013). In this method, quantification of MG is based on the measurement of MG bound proteins. The antibodies like bovine serum albumin (BSA), histone (Mir et al., 2016), hydroimidazolone (T. Wang et al., 2015) are used for the detection of MG bound proteins. This method provided a platform for the detection of MG in a free or bound state. In a larger group of 267 non-demented people, serum methylglyoxal derivatives were assessed to know their significant relation with diabetes, kidney diseases, age, sex, etc. (Beeri et al., 2011). MG modified human serum albumin (HSA) was detected by using its binding and corresponding immunogenicity assessment through Immunoglobulin G (IgG) levels (Islam et al., 2018, 2017). To analyze the role of oxidative products of lipid peroxidation in alcohol-induced liver diseases, other aldehydes were tested along with MG. However, 4-hydroxynonenal and malondialdehyde showed higher immunogenicity, and in-turn depicted their significance in liver pathogenesis (Mottaran et al., 2002). An AGE N^{ε}– (carboxymethyl lysine) specified antibody (CEL SP) peculiarly reacted with MG modified HSA over glyoxal and 3-DG implying its remarkable association with CEL. It was confirmed by measuring the Horseradish peroxidase (HRP) conjugated anti-mouse IgG antibody (Nagai et al., 2008). The recent studies showed that MG modified low-density lipoprotein (LDL) is fourfold higher in diabetic patients than normal of 5% (Thornalley and Rabbani, 2011b). The immunoassay developed using 3-(10'-phenothiazinyl) propionic acid (PPA) determined MG-LDL with a detection limit of 0.5 ng mL^{-1} through the chemiluminescent sandwich format of ELISA (Sakharov et al., 2013). The detection limit of the developed assay using the conjugate of streptavidin and HRP for colorimetric ELISA was 1.6 ng mL^{-1} (Sakharov et al., 2013). Interestingly, assay developed for chemiluminescent-ELISA (PPA) is sensitive and active than the colorimetric-ELISA detection of MG-LDL (Sakharov et al., 2013).

6.6. Electrochemical

MG detection through electrochemical techniques such as cyclic voltammetry, square wave voltammetry, amperometry have gained momentum from the last decade. The sensitive, portable and user-friendly features of MG detection in different samples like blood plasma, beverages, and food products demonstrated it as an advantageous method. In recent times, electrochemical MG sensors were designed using electrocatalytic nanomaterials as an interface to promote the MG interaction through enzymatic/non-enzymatic manner.

6.6.1. Enzymatic MG detection

The enzyme-based chemical interaction between nanointerface and MG induce a variation in the signal due to condensation, hydrolysis, oxidation or reduction depending upon the functional groups present in the substrate or the enzyme. However, the ultimate change occurs in the number of electrons flow and its direction. As discussed in detoxification of MG (Section 5.2.2), MG decomposed to D-Lactate through the presence of GLO enzyme (Fig. 3). This GLO system mimicked to detect MG in the enzymatic electrochemical approach.

In the electrochemical system, the chemical compounds reduce at their specific reduction potential. Due to the non-electroactive nature of MG, the co-factor (GSH) was used to reduce. The cyclic voltammetry study revealed the MG detection based on GLO 1 enzyme with the co-factor GSH (Ramachandra et al., 2016). The co-factor GSH oxidized to glutathione disulfide (GSSH) at a certain potential. Further, GSSH reacted with MG to form HTA, which is an intermediate product turned to SDL with the reaction of GLO 1 enzyme from the bioelectrode (Eqs. (1)–(4)). The potentials −0.764 and −0.597 V were applied for the reaction of MG to HTA and HTA to SDL, respectively, in the cyclic voltammograms study using platinum (Pt) working electrode modified with GLO 1, ceria nano-interface and chitosan binder (Ramachandra et al., 2016).

In the presence of GSH

$$2\ \mathit{Glutathione} \rightleftharpoons \mathit{Glutathione\ disulfide} + 2H^{+} + 2e^{-} \quad (1)$$

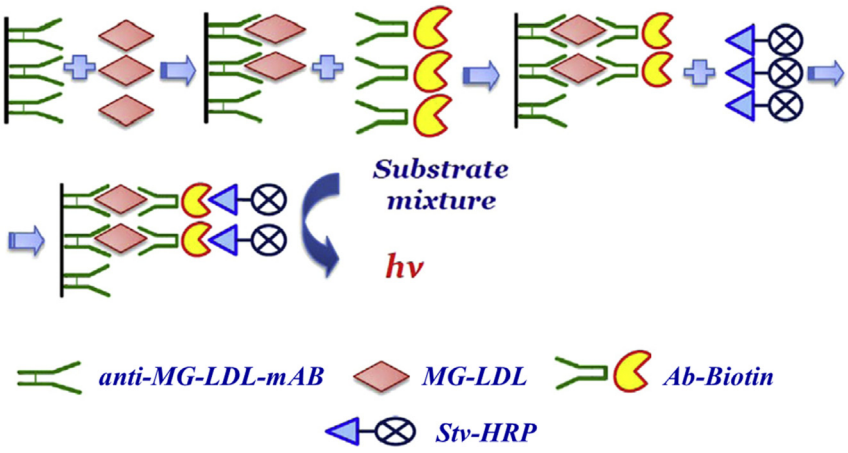

Fig. 6. Schematic representation of sandwich ELISA for the detection of methylglyoxal-modified low-density lipoprotein (MG – Methylglyoxal, LDL – low-density lipoprotein, mAB – monoclonal antibodies, HRP - horseradish peroxidase, Stv – streptavidin) (Sakharov et al., 2013). Reprinted from (Sakharov et al., 2013) with permission of Elsevier © 2013.

In the presence of MG and GSH

$$2\ \textit{Glutathione} \rightarrow \textit{Glutathione disulfide} + 2H^+ + 2e^- \quad (2)$$

$$\textit{Methylglyoxal} + \textit{Glutathione disulfide} + 2H^+ + 2e^- \rightarrow \textit{Hemithioacetal} \quad (3)$$

$$\textit{Hemithioacetal} + \textit{Glyoxalase}\ \ 1 \rightarrow \text{S-D-lactoylglutathione} \quad (4)$$

In enzymatic MG detection, the issues like maintaining the enzyme (GLO 1) stability without leaching and observing reactions of GSH, GLO 1 with MG in a complex environment make this approach cumbersome. However, the different nanointerfaces like zinc oxide (ZnO) flakes [203], and ZnO sepals [204], were reported to enhance the detection characteristics of MG. But still, attention required in the optimization of bioelectrode design, electrolyte, pH, sampling process for the determination of MG.

6.6.2. Non-enzymatic MG detection

In the non-enzymatic approach, the detection of MG is dependent mainly on the properties of nano-interface materials. The nano-interface modified working electrode, electrolyte medium, and sampling process determine the quantification of MG. In comparison with the complex enzymatic system, the parameters of the non-enzymatic system are easy and simple to optimize for better sensing performance and accurate measurement. Also, nano-interface aided decomposition of MG follows the detoxification process. For example, the catalytic property of V_2O_5 induces the decomposition of MG to lactate (Ramachandra Bhat. et al., 2018).

Initially, Montoya *et al.* have shown the possibilities for the reduction of MG on mercury electrodes via linear-sweep voltammetry where, MG undergoes a chemical-electrochemical-chemical (CEC) process with a quasi-reversible electron transfer (Montoya et al., 1993). After a decade, Chatterjee et al. (2013) demonstrated the detection of MG through square wave voltammetric study in human plasma using single-walled carbon nanotubes (SWCNT) modified glassy carbon electrode and correlated as a biomarker for diabetes. Fig. 7**a** shows the cyclic voltammograms with reduction peak at 864 mV for SWNT-GCE, which confirmed the electrocatalytic activity of SWNT. Interestingly, square-wave voltammograms (SWV) exhibited an enhanced reduction of MG at SWNT-GCE electrode (Fig. 7**b**). The well-defined reduction peak for SWNT-GCE in SWV showed the enhanced electrochemical reaction due to the accelerated electron transfer rate. The observed significant improvement in SWV method suggested the importance of the voltammetric characterization. Following that, modification of nano-interface SWNT-GCE with platinum nanoparticles (Pt) (Pt/SWNT/GCE) resulted in a significant sensing performance with the low detection limit of 2.8 nM of MG (Chatterjee and Chen, 2012). The Pt nanoparticles on SWNT facilitates the electroactive surface area, stability, and rapid electron transfer rate towards catalytic activity for electroreduction of MG to acetol. Significantly, we have demonstrated the role of nanointerface and electrode on the internal decomposition reaction of MG (Ramachandra Bhat. et al., 2018). As reported previously, Pt/SWNT/GCE decomposed MG to acetol (Chatterjee and Chen, 2012), but V_2O_5 modified gold working electrode (Au) exhibited the conversion of MG to lactic acid through the intermediate product of pyruvate. In general, MG reduced to lactic acid through the intermolecular Cannizzaro reaction (Chadderdon et al., 2015). Fig. 8 depicted the schematic of the internal reduction of MG via deprotonation and protonation reaction.

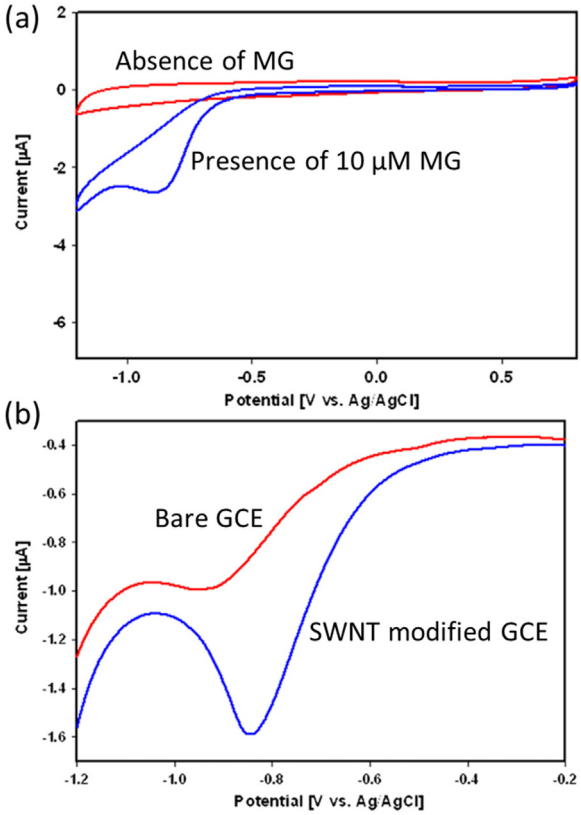

Fig. 7. (a) Cyclic voltammograms graph of SWNT modified GCE in the absence and presence of 10 µM MG (0.1 M PBS (pH 7.4) and 20 mV/s scan rate). (b) Square-wave voltammograms of bare GCE and SWNT modified GCE in the presence of 5 µM MG (in PBS at pH 7.4). (MG – methylglyoxal, SWNT – single-walled carbon nanotube, GCE – glassy carbon electrode, PBS – phosphate buffer solution) (Chatterjee et al., 2013). Reprinted from (Chatterjee et al., 2013) with permission of Elsevier © 2012.

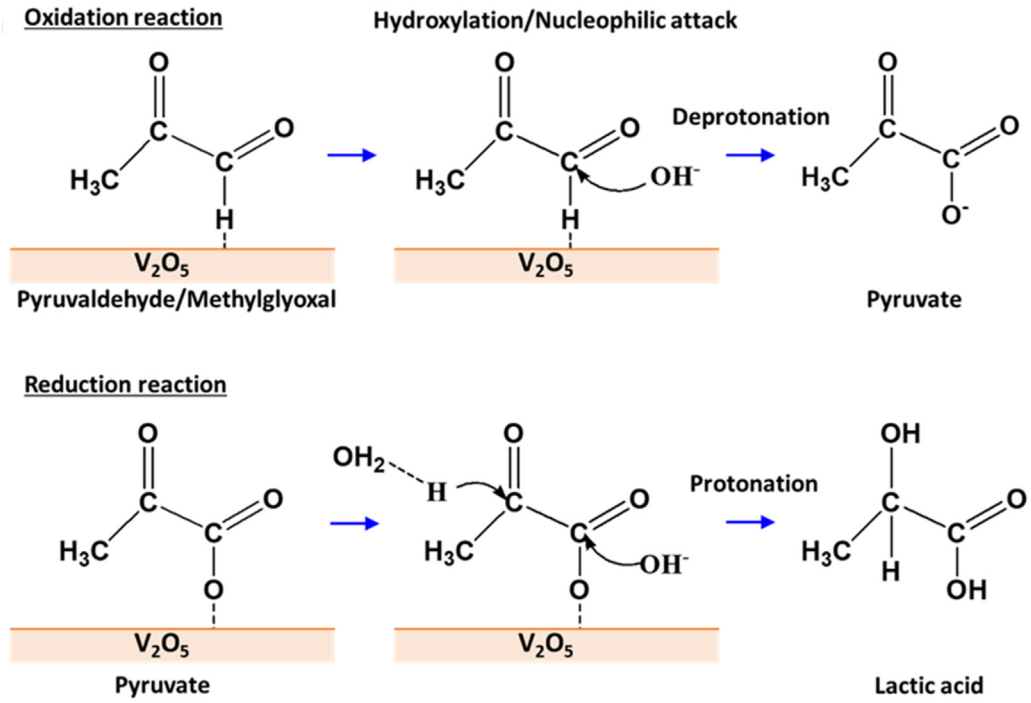

Fig. 8. The two-step electrochemical reaction (oxidation and reduction) of MG turning into lactic acid at V_2O_5 nano-interface immobilized on the Au electrode (Ramachandra Bhat et al., 2018). Reprinted from (Ramachandra Bhat et al., 2018) with permission of Elsevier © 2017.

The two-step reduction reaction of MG is due to the electrocatalytic and electron shuttling property of V_2O_5/Au electrode (Ramachandra Bhat et al., 2018). Similarly, the MG detection using V_2O_5 nanoparticles with GSH in the absence of GLO enzyme, exhibited the catalytic property of V_2O_5 nanoparticles for the oxidation of GSH to GSSG and reduction of MG to HTA (Alagappan et al., 2017). Overall, the parameters such as nano-interface, binder, and the electrode in the non-enzymatic MG detection provide an insight into the possibilities of different pathways of internal reaction. Thus, deep knowledge of nano-interface and their optimization process may lead to the key for the futuristic need in MG determination.

7. Outlook and future perspectives

The stamp of diabetes is hyperglycemia, and hence, the determination of glucose and its effects on either onset and progress of diabetic complications has been the main line of research for years. Extended work has been carried out in establishing glucose as a major cause of diabetes, and the “metabolic memory” concept may also be an important link to diabetes-associated issues (Ceriello et al., 2009). But, the recent reports say that despite maintaining tight glycemic control ($HbA_{1C} < 6.5\%$), diabetic complications arise and make life detrimental (Schalkwijk, 2015). Also, it is suggested that targeting HbA_{1C} to address diabetes would not solve the issues (Hirsch, 2015).

Moreover, the dependency of HbA_{1C} on race and age restricts it from being a reliable marker (Bloomgarden, 2017; Riddle et al., 2017) for DM diagnosis. So, it is very well evident that we need to focus on the fundamental cytological and physiological processes to prevent and rehabilitate people with diabetes. As both endogenous secretions and exogenous food products contribute to the advancement of many metabolic disorders, the predominant chemical moieties should be assessed in detail. In this line, MG is considered as a biomarker for assessment of diabetic complexities because of its close relation with glycation reaction, β-cells dysfunction, obesity, and insulin resistance. However, recent observations obtained of MG related studies have opened a new door for therapeutic and diagnostic interventions. The elevated levels of MG could be linked to an alternate pathway of T2DM initiation (Moraru et al., 2018). Also, dicarbonyls present in food products play a significant role in nucleating tumors and cancers (Hellwig et al., 2018). In short, recent reports insist on understanding the involvement of MG and other dicarbonyls in body metabolism. This knowledge would reveal the vulnerability of humankind towards MG derived metabolic disorders. The detection methods of dicarbonyls must be validated so that MG and AGEs measurement can be standardized for disease confirmation.

The major challenges posed towards the establishment of MG detection strategies and have been focused as a potential trend in the MG research are listed below:

- The in vitro, in vivo and clinical studies to identify MG present in different organs and tissues and correlate to distinguishing the specific type of DM.
- The standardization of AGEs, MG and other oxoaldehydes measurement.
- Distinguishing free and associated MG levels in the blood, plasma, serum towards the diagnosis and development of relation between diabetes and other diseases.
- Overwhelming sampling and methodological complexities for the development of easy, accurate and efficient smart MG measurement devices.
- Specific and selective identification and classification of similar structured dicarbonyl compounds and biomolecules present in body fluids and tissues.
- Establishing close relationship between HbA_{1C} and MG levels and their correlation with DM related associated complications for simple clinical sampling.
- Identification of MG levels during gestation and the related onset of DM would reveal the chances of preventing DM in offspring.

The long-term and systemic investigation of normal and diabetic subjects with measurement of MG levels with other biomarkers such as HbA_{1C}, cholesterol, hormones, antigens to figure out the potential cause and core solution are required. Indeed, due to the significant effect of exogenous AGEs and MG containing food products must be considered

during the clinical samplings to improve the reliability of MG measurement and so on.

8. Conclusion

In this review, we discussed the specific importance of MG as a biomarker among the different DM-related biomarkers and state of the art detection methodologies. The development of detection strategies of MG is based on its highly reactive chemical property and deep understanding of different pathways like formation, adducts formation, detoxification and decomposition mechanisms. The need for derivatization agents for MG detection makes techniques like GCMS, HPLC, etc. cumbersome and expensive. However, the other direct and indirect methods for MG measurement have unfolded deep-lying relations of MG with body metabolism, especially, the influence of MG in LDL glycation. Nevertheless, challenges are existing to achieve specificity in MG assessment concerning various factors, due its close association with other metabolic activities. Also, the influence of MG on DM must be studied and used for therapeutic interventions and rehabilitation. It is noteworthy that MG possesses positive properties, which can be scrutinized by in-depth analysis of real-time clinical studies.

CRediT authorship contribution statement

Lakshmishri Ramachandra Bhat: Conceptualization, Data curation. **Srinivasan Vedantham:** Writing - review & editing. **Uma Maheswari Krishnan:** Supervision. **John Bosco Balaguru Rayappan:** Conceptualization, Funding acquisition, Supervision, Writing - review & editing.

Acknowledgments

The author Lakshmishri sincerely thank the Council of Scientific and Industrial Research for a fellowship under Senior Research Fellowship Scheme (09/1095/0012/2016-EMR-I). Authors extend their sincere gratitude to the Science and Engineering Research Board, Department of Science & Technology (EMR/2016/003724) for financial support. We also acknowledge SASTRA Deemed to be University for providing the infrastructural support.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Aguilera, J., Prieto, J.A., 2001. The Saccharomyces cerevisiae aldose reductase is implied in the metabolism of methylglyoxal in response to stress conditions. Curr. Genet. 39, 273–283. https://doi.org/10.1007/s002940100213.

Alagappan, L.P., Shanmugasundaram, P., Ramachandra, B.L., Gumpu, M.B., Nesakumar, N., Babu, K.J., Vedantham, S., Rayappan, J.B.B., 2017. Fabrication of electrochemical biosensor with vanadium pentoxide nano-interface for the detection of methylglyoxal in rice. Anal. Biochem. 528, 19–25. https://doi.org/10.1016/j.ab.2017.04.010.

Aleksandrovskii, Y.A., 1992. Antithrombin III, C1 inhibitor, methylglyoxal, and polymorphonuclear leukocytes in the development of vascular complications in diabetes mellitus. Thromb. Res. 67, 179–189. https://doi.org/10.1016/0049-3848(92)90137-Y.

Ali, M.F.B., Kishikawa, N., Ohyama, K., Mohamed, H.A.-M., Abdel-Wadood, H.M., Mahmoud, A.M., Imazato, T., Ueki, Y., Wada, M., Kuroda, N., 2014. Chromatographic determination of low-molecular mass unsaturated aliphatic aldehydes with peroxyoxalate chemiluminescence detection after fluorescence labeling with 4-(N,N-dimethylaminosulfonyl)-7-hydrazino-2,1,3-benzoxadiazole. J. Chromatogr. B 953–954, 147–152. https://doi.org/10.1016/j.jchromb.2014.02.009.

Álvaro do Rosário, P.M., Alves Cordeiro, C.A., Freire, A.P., Florêncio Nogueira, J.M., 2005. Analysis of methylglyoxal in water and biological matrices by capillary zone electrophoresis with diode array detection. Electrophoresis 26, 1760–1767. https://doi.org/10.1002/elps.200410216.

American Diabetes Association, 2005. Diagnosis and classification of Diabetes Mellitus. Diabetes Care 28, S37–S42. https://doi.org/10.2337/diacare.28.suppl_1.S37.

American Diabetes Association, 2018. Classification and diagnosis of diabetes: standards of medical care in diabetes—2018. Diabetes Care. https://doi.org/10.2337/dc18-S002.

Angeloni, C., Zambonin, L., Hrelia, S., 2014. Role of methylglyoxal in Alzheimer's disease. Biomed. Res. Int. 2014, 1–12. https://doi.org/10.1155/2014/238485.

Ariyama, N., 1928. Studies on glyoxals. J. Biol. Chem. 77, 359–394.

Baumann, E., 1885. On compounds of aldehydes, ketones, and keto acids with the mercaptans. Eur. J. Inorg. Chem. 18, 883–892.

Beeri, M.S., Moshier, E., Schmeidler, J., Godbold, J., Uribarri, J., Reddy, S., Sano, M., Grossman, H.T., Cai, W., Vlassara, H., Silverman, J.M., 2011. Serum concentration of an inflammatory glycotoxin, methylglyoxal, is associated with increased cognitive decline in elderly individuals. Mech. Ageing Dev. 132, 583–587. https://doi.org/10.1016/j.mad.2011.10.007.

Beisswenger, P.J., Howell, S.K., Touchette, A.D., Lal, S., Szwergold, B.S., 1999. Metformin reduces systemic methylglyoxal levels in type 2 diabetes. Diabetes 48, 198–202. https://doi.org/10.2337/diabetes.48.1.198.

Beisswenger, P.J., Howell, S.K., O'Dell, R.M., Wood, M.E., Touchette, A.D., Szwergold, B.S., 2001. α-Dicarbonyls increase in the postprandial period and reflect the degree of hyperglycemia. Diabetes Care 24, 726–732. https://doi.org/10.2337/diacare.24.4.726.

Beisswenger, P.J., 2014. Methylglyoxal in diabetes: link to treatment, glycaemic control and biomarkers of complications. Biochem. Soc. Trans. 42, 450–456. https://doi.org/10.1042/BST20130275.

Bell, G.I., Xiang, K.S., Newman, M.V., Wu, S.H., Wright, L.G., Fajans, S.S., Spielman, R.S., Cox, N.J., 1991. Gene for non-insulin-dependent diabetes mellitus (maturity-onset diabetes of the young subtype) is linked to DNA polymorphism on human chromosome 20q. Proc. Natl. Acad. Sci. USA 88, 1484–1488. https://doi.org/10.1073/pnas.88.4.1484.

Bell, G.I., Polonsky, K.S., 2001. Diabetes mellitus and genetically programmed defects in β-cell function. Nature 414, 788–791. https://doi.org/10.1038/414788a.

Bellahcène, A., Nokin, M.J., Castronovo, V., Schalkwijk, C., 2018. Methylglyoxal-derived stress: an emerging biological factor involved in the onset and progression of cancer. Semin. Cancer Biol. 49, 64–74. https://doi.org/10.1016/j.semcancer.2017.05.010.

Bingley, P.J., 2010. Clinical applications of diabetes antibody testing. J. Clin. Endocrinol. Metab. 95, 25–33. https://doi.org/10.1210/jc.2009-1365.

Bloomgarden, Z.T., Inzucchi, S.E., Karnieli, E., Le Roith, D., 2008. The proposed terminology "A1c-derived average glucose" is inherently imprecise and should not be adopted. Diabetologia 51, 1111–1114. https://doi.org/10.1007/s00125-008-1027-7.

Bloomgarden, Z., 2017. Beyond HbA1c. J. Diabetes 9, 1052–1053. https://doi.org/10.1111/1753-0407.12590.

Bo, J., Xie, S., Guo, Y., Zhang, C., Guan, Y., Li, C., Lu, J., Meng, Q.H., 2016. Methylglyoxal impairs insulin secretion of pancreatic β -cells through increased production of ROS and mitochondrial dysfunction mediated by upregulation of UCP2 and MAPKs. J. Diabetes Res. 2016, 1–14. https://doi.org/10.1155/2016/2029854.

Bonifacio, E., 2015. Predicting type 1 diabetes using biomarkers. Diabetes Care 38, 989–996. https://doi.org/10.2337/dc15-0101.

Brings, S., Fleming, T., Freichel, M., Muckenthaler, M.U., Herzig, S., Nawroth, P.P., 2017. Dicarbonyls and advanced glycation end-products in the development of diabetic complications and targets for intervention. Int. J. Mol. Sci. https://doi.org/10.3390/ijms18050984.

Brownlee, M., Vlassara, H., Cerami, A., 1984. Nonenzymatic glycosylation: role in the pathogenesis of diabetic complications. Ann. Intern. Med. 101, 527–537. https://doi.org/10.7326/0003-4819-101-4-527.

Brownlee, M., 2001. Biochemistry and molecular cell biology of diabetic complications. Nature 414, 813–820. https://doi.org/10.1038/414813a.

Cantero, A.-V., Portero-Otín, M., Ayala, V., Auge, N., Sanson, M., Elbaz, M., Thiers, J.-C., Pamplona, R., Salvayre, R., Nègre-Salvayre, A., 2007. Methylglyoxal induces advanced glycation end product (AGEs) formation and dysfunction of PDGF receptor-beta: implications for diabetic atherosclerosis. FASEB: J. Fed. Am. Soc. Exp. Biol. 21, 3096–3106. https://doi.org/10.1096/fj.06-7536com.

Casazza, J.P., Felver, M.E., Veech, R.L., 1984. The metabolism of acetone in rat. J. Biol. Chem. 259, 231–236.

Ceriello, A., Ihnat, M.A., Thorpe, J.E., 2009. The "Metabolic memory": is more than just tight glucose control necessary to prevent diabetic complications? J. Clin. Endocrinol. Metab. 94, 410–415. https://doi.org/10.1210/jc.2008-1824.

Chadderdon, D.J., Xin, L., Qi, J., Brady, B., Miller, J.A., Sun, K., Janik, M.J., Li, W., 2015. Selective oxidation of 1,2-propanediol in alkaline anion-exchange membrane electrocatalytic flow reactors: experimental and DFT investigations. ACS Catal. 5, 6926–6936. https://doi.org/10.1021/acscatal.5b01085.

Chan, J.C.N., Cockram, C.S., Critchley, J.A.J.H., 1996. Drug-induced disorders of glucose metabolism mechanisms and management. Drug Saf. 15, 135–157. https://doi.org/10.2165/00002018-199615020-00005.

Chang, T., Wu, L., 2006. Methylglyoxal, oxidative stress, and hypertension. Can. J. Physiol. Pharmacol. 84, 1229–1238. https://doi.org/10.1139/y06-077.

Chatterjee, S., Chen, A., 2012. Voltammetric detection of the α-dicarbonyl compound: methylglyoxal as a flavoring agent in wine and beer. Anal. Chim. Acta 751, 66–70. https://doi.org/10.1016/j.aca.2012.09.011.

Chatterjee, S., Wen, J., Chen, A., 2013. Electrochemical determination of methylglyoxal as a biomarker in human plasma. Biosens. Bioelectron. 42, 349–354. https://doi.org/10.1016/j.bios.2012.10.091.

Chen, B.-G., Lin, C.H., Chen, C., Hambsch, B., Chern, C.-L., 2013. Quantitation by GC–MS of methylglyoxal as a marker in anxiety-related studies. Chromatographia 76, 571–576. https://doi.org/10.1007/s10337-013-2397-7.

Chen, X.Y., Huang, I.M., Hwang, L.S., Ho, C.T., Li, S., Lo, C.Y., 2014. Anthocyanins in blackcurrant effectively prevent the formation of advanced glycation end products by trapping methylglyoxal. J. Funct. Foods 8, 259–268. https://doi.org/10.1016/j.jff.

2014.03.025.
Chen, Y., Lu, S., Zhang, S., Li, Y., Qu, Z., Chen, Y., Lu, B., Wang, X., Feng, X., 2017. Skin-like biosensor system via electrochemical channels for noninvasive blood glucose monitoring. Sci. Adv. 3, e1701629. https://doi.org/10.1126/sciadv.1701629.
Choi, Y.Y., Kim, S., Han, J.H., Nam, D.H., Park, K.M., Kim, S.Y., Woo, C.H., 2016. CHOP deficiency inhibits methylglyoxal-induced endothelial dysfunction. Biochem. Biophys. Res. Commun. 480, 362–368. https://doi.org/10.1016/j.bbrc.2016.10.051.
Dakin, H.D., Dudley, H.W., 1913. On glyoxalase. J. Biol. Chem. 14, 423–431.
Dall, T.M., Yang, W., Halder, P., Pang, B., Massoudi, M., Wintfeld, N., Semilla, A.P., Franz, J., Hogan, P.F., 2014. The economic burden of elevated blood glucose levels in 2012: diagnosed and undiagnosed diabetes, gestational diabetes mellitus, and prediabetes. Diabetes Care 37, 3172–3179. https://doi.org/10.2337/dc14-1036.
Desai, K.M., Chang, T., Wang, H., Banigesh, A., Dhar, A., Liu, J., Untereiner, A., Wu, L., 2010. Oxidative stress and aging: is methylglyoxal the hidden enemy. Can. J. Physiol. Pharmacol. 88, 273–284. https://doi.org/10.1139/Y10-010.
Dhar, A., Desai, K., Kazachmov, M., Yu, P., Wu, L., 2008. Methylglyoxal production in vascular smooth muscle cells from different metabolic precursors. Metabolism 57, 1211–1220. https://doi.org/10.1016/j.metabol.2008.04.014.
Dhar, A., Dhar, I., Jiang, B., Desai, K.M., Wu, L., 2011. Chronic methylglyoxal infusion by minipump causes pancreatic β-cell dysfunction and induces type 2 diabetes in Sprague-Dawley rats. Diabetes 60, 899–908. https://doi.org/10.2337/db10-0627.
Doyle, F.H., Fraser, T.R., Joplin, G.F., 1982. The acromegaly syndrome. Q. J. Med. 202, 189–204.
Edghill, E.L., Hattersley, A.T., 2008. Genetic disorders of the pancreatic beta cell and diabetes (Permanent Neonatal Diabetes and Maturity-Onset Diabetes of the Young). In: Pancreatic Beta Cell in Health and Disease. Springer Japan, Tokyo, pp. 399–430. https://doi.org/10.1007/978-4-431-75452-7_19.
Egyud, L.G., Szent-Gyorgyi, A., 1966. Cell division, SH, ketoaldehydes, and cancer. Proc. Natl. Acad. Sci. USA 55, 388–393. https://doi.org/10.1073/pnas.55.2.388.
Egyuud, L.G., Szent-Gyorgyi, A., 1968. Cancerostatic action of methylglyoxal (1140–1140). Science (80-.) 160. https://doi.org/10.1126/science.160.3832.1140.
Ekoé, J.-M., Punthakee, Z., Ransom, T., Prebtani, A.P.H., Goldenberg, R., 2013. Screening for Type 1 and Type 2 diabetes. Can. J. Diabetes 37, S12–S15. https://doi.org/10.1016/j.jcjd.2013.01.012.
Entner, N., Doudoroff, M., 1952. Glucose and gluconic acid oxidation of Pseudomonas saccharophila. J. Biol. Chem. 196, 853–862.
Epstein, F.H., Atkinson, M.A., Maclaren, N.K., 1994. The pathogenesis of insulin-dependent Diabetes Mellitus. N. Engl. J. Med. 331, 1428–1436. https://doi.org/10.1056/NEJM199411243312107.
Ezhilan, M., Alagesan, S., Ramachandra, B.L., Gumpu, M.B., Nesakumar, N., Vedantham, S., Sethuraman, S., Krishnan, U.M., Rayappan, J.B.B., 2015. Chemometric analysis for the determination of methylglyoxal in grilled chicken using ZnO flakes based glyoxalase 1 biosensor. Sens. Lett. 13, 245–253. https://doi.org/10.1166/sl.2015.3425.
Fiory, F., Lombardi, A., Miele, C., Giudicelli, J., Beguinot, F., Van Obberghen, E., 2011. Methylglyoxal impairs insulin signalling and insulin action on glucose-induced insulin secretion in the pancreatic beta cell line INS-1E. Diabetologia 54, 2941–2952. https://doi.org/10.1007/s00125-011-2280-8.
Friedemann, T.E., 1927. The action of alkali and hydrogen peroxide on glyoxals. J. Biol. Chem. 73, 331–334.
Frischmann, M., Bidmon, C., Angerer, J., Pischetsrieder, M., 2005. Identification of DNA adducts of methylglyoxal. Chem. Res. Toxicol. 18, 1586–1592. https://doi.org/10.1021/tx0501278.
Fu, Z., Gilbert, R., Liu, D, E., 2013. Regulation of insulin synthesis and secretion and pancreatic beta-cell dysfunction in diabetes. Curr. Diabetes Rev. 9, 25–53. https://doi.org/10.2174/1573399811309010025.
Goh, S.-Y., Cooper, M.E., 2008. The role of advanced glycation end products in progression and complications of diabetes. J. Clin. Endocrinol. Metab. 93, 1143–1152. https://doi.org/10.1210/jc.2007-1817.
Goldberg, T., Cai, W., Peppa, M., Dardaine, V., Baliga, B.S., Uribarri, J., Vlassara, H., 2004. Advanced glycoxidation end products in commonly consumed foods. J. Am. Diet. Assoc. 104, 1287–1291. https://doi.org/10.1016/j.jada.2004.05.214.
Goldenberg, R., Punthakee, Z., 2013. Definition, classification and diagnosis of diabetes, prediabetes and metabolic syndrome. Can. J. Diabetes 37, S8–S11. https://doi.org/10.1016/j.jcjd.2013.01.011.
Goldin, A., Beckman, J.A., Schmidt, A.M., Creager, M.A., 2006. Advanced glycation end products. Circulation 114, 597–605. https://doi.org/10.1161/CIRCULATIONAHA.106.621854.
Grazi, E., Trombetta, G., 1978. A new intermediate of the aldolase reaction, the pyruvaldehyde-aldolase-orthophosphate complex. Biochem. J. 175, 361–365. https://doi.org/10.1042/bj1750361.
Gu, X., Wang, H., Schultz, Z.D., Camden, J.P., 2016. Sensing glucose in urine and serum and hydrogen peroxide in living cells by use of a novel boronate nanoprobe based on surface-enhanced raman spectroscopy. Anal. Chem. 88, 7191–7197. https://doi.org/10.1021/acs.analchem.6b01378.
Guo, Q., Mori, T., Jiang, Y., Hu, C., Osaki, Y., Yoneki, Y., Sun, Y., Hosoya, T., Kawamata, A., Ogawa, S., Nakayama, M., Miyata, T., Ito, S., 2009. Methylglyoxal contributes to the development of insulin resistance and salt sensitivity in Sprague–Dawley rats. J. Hypertens. 27, 1664–1671. https://doi.org/10.1097/HJH.0b013e32832c419a.
Hage, M., Zantout, M.S., Azar, S.T., 2011. Thyroid disorders and diabetes mellitus. J. Thyroid Res. 2011, 1–7. https://doi.org/10.4061/2011/439463.
Han, Y., Randell, E., Vasdev, S., Gill, V., Gadag, V., Newhook, L.A., Grant, M., Hagerty, D., 2007. Plasma methylglyoxal and glyoxal are elevated and related to early membrane alteration in young, complication-free patients with Type 1 diabetes. Mol. Cell. Biochem. 305, 123–131. https://doi.org/10.1007/s11010-007-9535-1.
Hayashi, T., Shibamoto, T., 1985. Analysis of methyl glyoxal in foods and beverages. J. Agric. Food Chem. 33, 1090–1093. https://doi.org/10.1021/jf00066a018.
Hellwig, M., Gensberger-reigl, S., Henle, T., Pischetsrieder, M., 2018. Food-derived 1,2-dicarbonyl compounds and their role in diseases. Semin. Cancer Biol. 49, 1–8. https://doi.org/10.1016/j.semcancer.2017.11.014.
Hirsch, I.B., 2015. Glycemic variability and diabetes complications: does it matter? Of course it does!. Diabetes Care 38, 1610–1614. https://doi.org/10.2337/dc14-2898.
Hofmann, S.M., Dong, H.-J., Li, Z., Cai, W., Altomonte, J., Thung, S.N., Zeng, F., Fisher, E.A., Vlassara, H., 2002. Improved insulin sensitivity is associated with restricted intake of dietary glycoxidation products in the db/db mouse. Diabetes 51, 2082–2089. https://doi.org/10.2337/DIABETES.51.7.2082.
Hopper, D.J., Cooper, R.A., 1971. The regulation of Escherichia coli methylglyoxal synthase; a new control site in glycolysis? FEBS Lett. 13, 213–216. https://doi.org/10.1016/0014-5793(71)80538-0.
Inoue, Y., Rhee, H., Watanabe, K., Murata, K., Kimura, A., 1988. Metabolism of 2-oxoaldehyde in mold. Purification and characterization of two methylglyoxal reductases from Aspergillus niger. Eur. J. Biochem. 171, 213–218. https://doi.org/10.1111/j.1432-1033.1988.tb13778.x.
Inoue, Y., Kimura, A., 1995. Methylglyoxal and regulation of its metabolism in microorganisms. Adv. Microb. Physiol. 37, 177–227. https://doi.org/10.1016/S0065-2911(08)60146-0.
Islam, S., Moinuddin, Mir, A.R., Arfat, M.Y., Alam, K., Ali, A., 2017. Studies on glycoxidatively modified human IgG: implications in immuno-pathology of type 2 diabetes mellitus. Int. J. Biol. Macromol. 104, 19–29. https://doi.org/10.1016/j.ijbiomac.2017.05.190.
Islam, S., Mir, A.R., Abidi, M., Talha, M., Zafar, A., Habib, S., Moinuddin, 2018. Methylglyoxal modified IgG generates autoimmune response in rheumatoid arthritis. Int. J. Biol. Macromol. 118, 15–23. https://doi.org/10.1016/j.ijbiomac.2018.06.040.
Iyengar, R., Rose, I.A., 1981. Concentration of activated intermediates of the fructose-1,6-bisphosphate aldolase and triosephosphate isomerase reactions. Biochemistry 20, 1223–1229. https://doi.org/10.1021/bi00508a026.
Izzedine, H., Launay-Vacher, V., Deybach, C., Bourry, E., Barrou, B., Deray, G., 2005. Drug-induced diabetes mellitus. Exp. Opin. Drug Saf. 4, 1097–1109. https://doi.org/10.1517/14740338.4.6.1097.
Jayaprakasan, A., Thangavel, A., Ramachandra Bhat, L., Gumpu, M.B., Nesakumar, N., Jayanth Babu, K., Vedantham, S., Rayappan, J.B.B., 2018. Fabrication of an electrochemical biosensor with ZnO nanoflakes interface for methylglyoxal quantification in food samples. Food Sci. Biotechnol. 27. https://doi.org/10.1007/s10068-017-0193-0.
Jia, X., 2010. Role of Methylglyoxal in the Pathogenesis of Insulin Resistance. University of Saskatchewan.
Jia, X., Olson, D.J.H., Ross, A.R.S., Wu, L., 2006. Structural and functional changes in human insulin induced by methylglyoxal. FASEB J. 20, 1555–1557. https://doi.org/10.1096/fj.05-5478fje.
Jowett, M., Quastel, J.H., 1933. The glyoxalase activity of the red blood cell: the function of glutathione. Biochem. J. 27, 486–498.
Justino, A.B., Miranda, N.C., Franco, R.R., Martins, M.M., Silva, N.M., da, Espindola, F.S., 2018. Annona muricata Linn. leaf as a source of antioxidant compounds with in vitro antidiabetic and inhibitory potential against α-amylase, α-glucosidase, lipase, non-enzymatic glycation and lipid peroxidation. Biomed. Pharmacother. 100, 83–92. https://doi.org/10.1016/j.biopha.2018.01.172.
Kalapos, M.P., 1992. Mechanisms leading to complications in diabetes mellitus: pathological role of α-oxoaldehydes. Biochem. Educ. 20, 27–29. https://doi.org/10.1016/0307-4412(92)90012-B.
Kalapos, M.P., 1999a. Methylglyoxal in living organisms. Toxicol. Lett. 110, 145–175. https://doi.org/10.1016/S0378-4274(99)00160-5.
Kalapos, M.P., 1999b. On the promine/retine theory of cell division: now and then. Biochim. Biophys. Acta - Gen. Subj. 1426, 1–16. https://doi.org/10.1016/S0304-4165(98)00141-X.
Kalapos, M.P., 2008. The tandem of free radicals and methylglyoxal. Chem. Biol. Interact. 171, 251–271. https://doi.org/10.1016/j.cbi.2007.11.009.
Kalapos, M.P., 2013. Where does plasma methylglyoxal originate from? Diabetes Res. Clin. Pract. 99, 260–271. https://doi.org/10.1016/j.diabres.2012.11.003.
Karasawa, K., Haraya, S., Okubo, S., Arakawa, H., 2017. Novel assay of antibacterial components in manuka honey using lucigenin-chemiluminescence-HPLC. Anal. Chim. Acta 954, 151–158. https://doi.org/10.1016/j.aca.2016.12.004.
Katz, I.R., Wittenberg, J.B., Wittenberg, B.A., 1984. Monoamine oxidase, an intracellular probe of oxygen pressure in isolated cardiac myocytes. J. Biol. Chem. 2590, 7504–7509.
Khuhawar, M.Y., Zardari, L.A., Laghari, A.J., 2008. Capillary gas chromatographic determination of methylglyoxal from serum of diabetic patients by precolumn derivatization with 1,2-diamonopropane. J. Chromatogr. B 873, 15–19. https://doi.org/10.1016/j.jchromb.2008.04.048.
Kiho, T., Kato, M., Usui, S., Hirano, K., 2005. Effect of buformin and metformin on formation of advanced glycation end products by methylglyoxal. Clin. Chim. Acta 358, 139–145. https://doi.org/10.1016/j.cccn.2005.02.012.
Kilhovd, B.K., Juutilainen, A., Lehto, S., Rönnemaa, T., Torjesen, P.A., Hanssen, K.F., Laakso, M., 2009. Increased serum levels of methylglyoxal-derived hydroimidazolone-AGE are associated with increased cardiovascular disease mortality in nondiabetic women. Atherosclerosis 205, 590–594. https://doi.org/10.1016/j.atherosclerosis.2008.12.041.
Kirk, R., Theophilus, J., Whitehouse, S., Court, J., Zimmet, P., 1979. Genetic susceptibility to diabetes mellitus the distribution of properdin factor B (Bf) and glyoxalase (GLO) phenotypes. Diabetes 28, 949–951.
Ko, J., Kim, I., Yoo, S., Min, B., Kim, K., Park, C., 2005. Conversion of methylglyoxal to acetol by Escherichia coli aldo-keto reductases. J. Bacteriol. 187, 5782–5789. https://doi.org/10.1128/JB.187.16.5782-5789.2005.

Krautwald, M., Münch, G., 2010. Advanced glycation end products as biomarkers and gerontotoxins – a basis to explore methylglyoxal-lowering agents for Alzheimer's disease? Exp. Gerontol. 45, 744–751. https://doi.org/10.1016/j.exger.2010.03.001.

Langmaier, J., Samec, Z., Samcová, E., Petr, T., 2016. Voltammetric and capillary electrophoretic study of scavenger kinetics of methylglyoxal by antidiabetic biguanide drugs. J. Electroanal. Chem. 777, 26–32. https://doi.org/10.1016/j.jelechem.2016.07.025.

Lapolla, A., Flamini, R., Dalla Vedova, A., Senesi, A., Reitano, R., Fedele, D., Basso, E., Seraglia, R., Traldi, P., 2003. Glyoxal and methylglyoxal levels in diabetic patients: quantitative determination by a new GC/MS method. Clin. Chem. Lab. Med. 41, 1166–1173. https://doi.org/10.1515/CCLM.2003.180.

Li, Z.G., Nie, Q., Yang, C.L., Wang, Y., Zhou, Z.H., 2018. Signaling molecule methylglyoxal ameliorates cadmium injury in wheat (Triticum aestivum L) by a coordinated induction of glutathione pool and glyoxalase system. Ecotoxicol. Environ. Saf. 149, 101–107. https://doi.org/10.1016/j.ecoenv.2017.11.021.

Lin, J.A., Wu, C.H., Yen, G.C., 2018. Methylglyoxal displays colorectal cancer-promoting properties in the murine models of azoxymethane and CT26 isografts. Free Radic. Biol. Med. 115, 436–446. https://doi.org/10.1016/j.freeradbiomed.2017.12.020.

Liu, Q., Liu, Y., Wu, F., Cao, X., Li, Z., Alharbi, M., Abbas, A.N., Amer, M.R., Zhou, C., 2018. Highly sensitive and wearable In_2O_3 nanoribbon transistor biosensors with integrated on-chip gate for glucose monitoring in body fluids. ACS Nano 12, 1170–1178. https://doi.org/10.1021/acsnano.7b06823.

Liyanage, H., Kashket, S., Young, M., 2010. Methylglyoxal by a novel mechanism involving glycerol dehydrogenase. Society 67, 2004–2010. https://doi.org/10.1128/AEM.67.5.2004.

Lohmann, K., 1932. A study of the enzymatic transformation of synthetic methylglyoxal to lactic acid. Biocheniische Z. 254, 332–354.

Lyles, G.A., Chalmers, J., 1992. The metabolism of aminoacetone to methylglyoxal by semicarbazide-sensitive amine oxidase in human umbilical artery. Biochem. Pharmacol. 43, 1409–1414. https://doi.org/10.1016/0006-2952(92)90196-P.

Ma, J., Peng, X., Cheng, K.-W., Chen, F., Yang, D., Chen, B., Wang, M., 2008. Use of capillary electrophoresis to evaluate protective effects of methylglyoxal scavengers on the activity of creatine kinase. J. Sep. Sci. 31, 2846–2851. https://doi.org/10.1002/jssc.200800241.

Maher, P., Dargusch, R., Ehren, J.L., Okada, S., Sharma, K., Schubert, D., 2011. Fisetin lowers methylglyoxal dependent protein glycation and limits the complications of diabetes. PLoS One 6. https://doi.org/10.1371/journal.pone.0021226.

Maillard, L.C., 1912. Action of amino acids on sugars. Formation of melanoidins in a methodical way. Comptes rendus l'Académie Des. Sci. 154, 66–68.

Matafome, P., Rodrigues, T., Sena, C., Seiça, R., 2017. Methylglyoxal in metabolic disorders: facts, myths, and promises. Med. Res. Rev. 37, 368–403. https://doi.org/10.1002/med.21410.

McCann, V.J., Davis, R.E., Welborn, T.A., Constable, I.J., Beale, D.G., 1981. Glyoxalase phenotypes in patients with diabetes mellitus. Aust. N. Z. J. Med. 11, 380–382. https://doi.org/10.1111/j.1445-5994.1981.tb03516.x.

McLellan, A.C., Phillips, S.A., Thornalley, P.J., 1992. The assay of methylglyoxal in biological systems by derivatization with 1,2-diamino-4,5-dimethoxybenzene. Anal. Biochem. 206, 17–23. https://doi.org/10.1016/S0003-2697(05)80005-3.

Mir, A.R., Moinuddin, Islam, S., 2016. Circulating autoantibodies in cancer patients have high specificity for glycoxidation modified histone H2A. Clin. Chim. Acta 453, 48–55. https://doi.org/10.1016/j.cca.2015.12.004.

Mirza, M.A., Kandhro, A.J., Memon, S.Q., Khuhawar, M.Y., Arain, R., 2007. Determination of glyoxal and methylglyoxal in the serum of diabetic patients by MEKC using stilbenediamine as derivatizing reagent. Electrophoresis 28, 3940–3947. https://doi.org/10.1002/elps.200700129.

Mittelmaier, S., Pischetsrieder, M., 2011. Multistep ultrahigh performance liquid chromatography/tandem mass spectrometry analysis for untargeted quantification of glycating activity and identification of most relevant glycation products. Anal. Chem. 83, 9660–9668. https://doi.org/10.1021/ac2025706.

Monnier, V.M., Vishwanath, V., Frank, K.E., Elmets, C.A., Dauchot, P., Kohn, R.R., 1986. Relation between complications of type I diabetes mellitus and collagen-linked fluorescence. N. Engl. J. Med. 314, 403–408. https://doi.org/10.1056/NEJM198602133140702.

Montoya, M.R., Zon, M.A., Mellado, J.M.R., 1993. Investigation of the reduction of 1,2-cyclohexanedione and methylglyoxal on mercury electrodes under pure kinetic conditions by linear-sweep voltammetry. J. Electroanal. Chem. 353, 217–224. https://doi.org/10.1016/0022-0728(93)80298-V.

Moraru, A., Wiederstein, J., Pfaff, D., Fleming, T., Miller, A.K., Nawroth, P., Teleman, A.A., 2018. Elevated levels of the reactive metabolite methylglyoxal recapitulate progression of type 2 diabetes. Cell Metab. 27, 1–9. https://doi.org/10.1016/j.cmet.2018.02.003.

Moree-Testa, P., Saint-Jalm, Y., 1981. Determination of α-dicarbonyl compounds in cigarette smoke. J. Chromatogr. A. https://doi.org/10.1016/S0021-9673(00)88074-7.

Mottaran, E., Stewart, S.F., Rolla, R., Vay, D., Cipriani, V., Moretti, M., Vidali, M., Sartori, M., Rigamonti, C., Day, C.P., Albano, E., 2002. Lipid peroxidation contributes to immune reactions associated with alcoholic liver disease. Free Radic. Biol. Med. 32, 38–45. https://doi.org/10.1016/S0891-5849(01)00757-2.

Murata, K., Fukuda, Y., Simosaka, M., Watanabe, K., Saikusa, T., Kimura, A., 1985a. Metabolism of 2-oxoaldehyde in yeasts: purification and characterization of NADPH-dependent methylglyoxal-reducing enzyme from Saccharomyces cerevisiae. Eur. J. Biochem. 151, 631–636. https://doi.org/10.1111/j.1432-1033.1985.tb09151.x.

Murata, K., Fukuda, Y., Watanabe, K., Saikusa, T., Shimosaka, M., Kimura, A., 1985b. Characterization of methylglyoxal synthase in Saccharomyces cerevisiae. Biochem. Biophys. Res. Commun. 131, 190–198. https://doi.org/10.1016/0006-291X(85)91788-7.

Murata, T., Nagai, R., Ishibashi, T., Inomuta, H., Ikeda, K., Horiuchi, S., 1997. The relationship between accumulation of advanced glycation end products and expression of vascular endothelial growth factor in human diabetic retinas. Diabetologia 40, 764–769.

Nagai, R., Fujiwara, Y., Mera, K., Yamagata, K., Sakashita, N., Takeya, M., 2008. Immunochemical detection of Nε-(carboxyethyl)lysine using a specific antibody. J. Immunol. Methods 332, 112–120. https://doi.org/10.1016/j.jim.2007.12.020.

Nagaya, K., Yamazoye, S., Nakamura, S., 1936. Glyoxalase and its co-enzyme: on kidney glyoxalase. J. Biochem. 23, 41–56.

Nakayama, K., Nakayama, M., Iwabuchi, M., Terawaki, H., Sato, T., Kohno, M., Ito, S., 2008. Plasma α-oxoaldehyde levels in diabetic and nondiabetic chronic kidney disease patients. Am. J. Nephrol. 28, 871–878. https://doi.org/10.1159/000139653.

Nam, D.H., Han, J.H., Lee, T.J., Shishido, T., Lim, J.H., Kim, G.Y., Woo, C.H., 2015. CHOP deficiency prevents methylglyoxal-induced myocyte apoptosis and cardiac dysfunction. J. Mol. Cell. Cardiol. 85, 168–177. https://doi.org/10.1016/j.yjmcc.2015.05.016.

Nara, S., Gomes, B., Yasunobu, K.T., 1966. Amine oxidase: beef liver mitochondrial monoamine oxidase, a copper-containing protein. J. Biol. Chem. 241, 2774–2780.

Needham, J., Lehmann, H., 1937. Intermediary carbohydrate metabolism in embryonic life: glyceraldehyde and glucolysis. Biochem. J. 31, 1913–1925.

Nemet, I., Turk, Z., Duvnjak, L., Car, N., Varga-Defterdarović, L., 2005. Humoral methylglyoxal level reflects glycemic fluctuation. Clin. Biochem. 38, 379–383. https://doi.org/10.1016/j.clinbiochem.2004.12.008.

Nemet, I., Varga-Defterdarović, L., Turk, Z., 2004. Preparation and quantification of methylglyoxal in human plasma using reverse-phase high-performance liquid chromatography. Clin. Biochem. 37, 875–881. https://doi.org/10.1016/j.clinbiochem.2004.05.024.

Nemet, I., Varga-Defterdarović, L., Turk, Z., 2006. Methylglyoxal in food and living organisms. Mol. Nutr. Food Res. 50, 1105–1117. https://doi.org/10.1002/mnfr.200600065.

Neuberg, C., 1913. The destruction of lactic aldehyde and methylglyoxal by animal organs. Biochem Z. 49, 502–506.

Nichols, S.P., Koh, A., Storm, W.L., Shin, J.H., Schoenfisch, M.H., 2013. Biocompatible materials for continuous glucose monitoring devices. Chem. Rev. 113, 2528–2549. https://doi.org/10.1021/cr300387j.

Nishimoto, S., Koike, S., Inoue, N., Suzuki, T., Ogasawara, Y., 2017. Activation of Nrf2 attenuates carbonyl stress induced by methylglyoxal in human neuroblastoma cells: increase in GSH levels is a critical event for the detoxification mechanism. Biochem. Biophys. Res. Commun. 483, 874–879. https://doi.org/10.1016/j.bbrc.2017.01.024.

O'Byrne, S., Feely, J, 1990. Effects of drugs on glucose tolerance in non-insulin-dependent diabetics (Part I). Drugs 40, 6–18. https://doi.org/10.2165/00003495-199040010-00002.

Odani, H., Asami, J., Ishii, A., Oide, K., Sudo, T., Nakamura, A., Miyata, N., Otsuka, N., Maeda, K., Nakagawa, J., 2008. Suppression of renal α-dicarbonyl compounds generated following ureteral obstruction by kidney-specific α-dicarbonyl/L-xylulose reductase. Ann. N.Y. Acad. Sci. USA 1126, 320–324. https://doi.org/10.1196/annals.1433.003.

Ogasawara, Y., Tanaka, R., Koike, S., Horiuchi, Y., Miyashita, M., Arai, M., 2016. Determination of methylglyoxal in human blood plasma using fluorescence high performance liquid chromatography after derivatization with 1,2-diamino-4,5-methylenedioxybenzene. J. Chromatogr. B 1029–1030, 102–105. https://doi.org/10.1016/j.jchromb.2016.07.019.

Ogawa, S., Nakayama, K., Nakayama, M., Mori, T., Matsushima, M., Okamura, M., Senda, M., Nako, K., Miyata, T., Ito, S., 2010. Methylglyoxal is a predictor in type 2 diabetic patients of intima-media thickening and elevation of blood pressure. Hypertension 56, 471–476. https://doi.org/10.1161/HYPERTENSIONAHA.110.156786.

Ohmori, S., Kawase, M., Mori, M., Hirota, T., 1987a. Simple and sensitive determination of methylglyoxal in biological samples by gas chromatography with electron-capture detection. J. Chromatogr. 415, 221–229.

Ohmori, S., Mori, M., Kawase, M., Tsuboi, S., 1987b. Determination of methylglyoxal as 2-methylquinoxaline by high-performance liquid chromatography and its application to biological samples. J. Chromatogr. 414, 149–155.

Ortiz, R., Hagino, H., Sekiguchi, K., Wang, Q., Sakamoto, K., 2006. Ambient air measurements of six bifunctional carbonyls in a suburban area. Atmos. Res. 82, 709–718. https://doi.org/10.1016/j.atmosres.2006.02.025.

Owens, C.W.I., Belcher, R.V., 1965. A colorimetric micro-method for the determination of glutathione. Biochem. J. 94, 705–711. https://doi.org/10.1042/bj0940705.

Pandit, M.K., Burke, J., Gustafson, A.B., Minocha, A., Peiris, A.N., 1993. Drug-induced disorders of glucose tolerance. Ann. Intern. Med. 118, 529. https://doi.org/10.7326/0003-4819-118-7-199304010-00008.

Park, J., Kim, J., Kim, S.-Y., Cheong, W.H., Jang, J., Park, Y.-G., Na, K., Kim, Y.-T., Heo, J.H., Lee, C.Y., Lee, J.H., Bien, F., Park, J.-U., 2018. Soft, smart contact lenses with integrations of wireless circuits, glucose sensors, and displays. Sci. Adv. 4, eaap9841. https://doi.org/10.1126/sciadv.aap9841.

Pastor-Belda, M., Fernández-García, A.J., Campillo, N., Pérez-Cárceles, M.D., Motas, M., Hernández-Córdoba, M., Viñas, P., 2017. Glyoxal and methylglyoxal as urinary markers of diabetes. Determination using a dispersive liquid–liquid microextraction procedure combined with gas chromatography–mass spectrometry. J. Chromatogr. A. https://doi.org/10.1016/j.chroma.2017.06.041.

Pegg, A.E., McGill, S.M., 1978. Inhibition of diamine oxidase by 1,1-[(methylethanediylidene)-dinitrilo]-bis-(3-aminoguanidine) and 1,1′-[(methylethanediylidene)-dinitrilo]-diguanidine. Biochem. Pharmacol. 27, 1625–1629. https://doi.org/10.1016/0006-2952(78)90170-3.

Pi, J., Bai, Y., Zhang, Q., Wong, V., Floering, L.M., Daniel, K., Reece, J.M., Deeney, J.T., Andersen, M.E., Corkey, B.E., Collins, S., 2007. Reactive oxygen species as a signal in glucose-stimulated insulin secretion. Diabetes 56, 1783–1791. https://doi.org/10.

2337/db06-1601.
Rabbani, N., Thornalley, P.J., 2014. The critical role of methylglyoxal and glyoxalase 1 in diabetic nephropathy. Diabetes 63, 50–52. https://doi.org/10.2337/db13-1606.
Rabbani, N., Thornalley, P.J., 2015. Dicarbonyl stress in cell and tissue dysfunction contributing to ageing and disease. Biochem. Biophys. Res. Commun. 458, 221–226. https://doi.org/10.1016/j.bbrc.2015.01.140.
Rabbani, N., Thornalley, P.J., 2018. Advanced glycation end products in the pathogenesis of chronic kidney disease. Kidney Int. 93, 803–813. https://doi.org/10.1016/j.kint.2017.11.034.
Rabbani, N., Xue, M., Weickert, M.O., Thornalley, P.J., 2018. Multiple roles of glyoxalase 1-mediated suppression of methylglyoxal glycation in cancer biology—involvement in tumour suppression, tumour growth, multidrug resistance and target for chemotherapy. Semin. Cancer Biol. 49, 83–93. https://doi.org/10.1016/j.semcancer.2017.05.006.
Racker, E., 1951. The mechanism of action of glyoxalase. J. Biol. Chem. 190, 685–696.
Radhakumary, C., Sreenivasan, K., 2011. Naked eye detection of glucose in urine using glucose oxidase immobilized gold nanoparticles. Anal. Chem. 83, 2829–2833. https://doi.org/10.1021/ac1032879.
Rahbar, S., 1968. An abnormal hemoglobin in red cells of diabetics. Clin. Chim. Acta 22, 296–298. https://doi.org/10.1016/0009-8981(68)90372-0.
Ramachandra Bhat, L., Vedantham, S., Krishnan, U.M., Rayappan, J.B.B., 2018. A non-enzymatic two step catalytic reduction of methylglyoxal by nanostructured V_2O_5 modified electrode. Biosens. Bioelectron. 103, 143–150. https://doi.org/10.1016/j.bios.2017.12.036.
Ramachandra, B.L., Vedantham, S., Krishnan, U.M., Nesakumar, N., Rayappan, J.B.B., 2016. Estimation of methylglyoxal in cow milk – an accurate electrochemical response time based approach. Anal. Methods 8, 2207–2217. https://doi.org/10.1039/C5AY02901E.
Ransom, T., Goldenberg, R., Mikalachki, A., Prebtani, A.P.H., Punthakee, Z., 2013. Reducing the risk of developing diabetes. Can. J. Diabetes 37, S16–S19. https://doi.org/10.1016/j.jcjd.2013.01.013.
Ray, M., Ray, S., 1984. Purification and partial characterization of a methylglyoxal reductase from goat liver. BBA - Gen. Subj. 802, 119–127. https://doi.org/10.1016/0304-4165(84)90041-2.
Ray, M., Ray, S., 1987. Aminoacetone oxidase from goat liver. Formation of methylglyoxal from aminoacetone. J. Biol. Chem. 262, 5974–5977.
Ray, S., Ray, M., 1983. Formation of methylglyoxal from aminoacetone from goat plasma. J. Biol. Chem. 258, 3461–3462.
Regnell, S.E., Lernmark, Å., 2017. Early prediction of autoimmune (type 1) diabetes. Diabetologia 60, 1370–1381. https://doi.org/10.1007/s00125-017-4308-1.
Reichard, G.A., Skutches, C.L., Hoeldtke, R.D., Owen, O.E., 1986. Acetone metabolism in humans during diabetic ketoacidosis. Diabetes 35, 668–674. https://doi.org/10.2337/diab.35.6.668.
Riboulet-Chavey, A., Pierron, A., Durand, I., Murdaca, J., Giudicelli, J., Van Obberghen, E., 2006. Methylglyoxal impairs the insulin signaling pathways independently of the formation of intracellular reactive oxygen species. Diabetes 55, 1289–1299. https://doi.org/10.2337/db05-0857.
Richard, J.P., 1984. Acid-base catalysis of the elimination and isomerization reactions of triose phosphates. J. Am. Chem. Soc. 106, 4926–4936. https://doi.org/10.1021/ja00329a050.
Richard, J.P., 1991. Kinetic parameters for the elimination reaction catalyzed by triosephosphate isomerase and an estimation of the reaction's physiological significance. Biochemistry 30, 4581–4585. https://doi.org/10.1021/bi00232a031.
Riddle, M.C., Gerstein, H.C., Cefalu, W.T., 2017. Maturation of CGM and glycemic measurements beyond HbA1c- a turning point in research and clinical decisions. Diabetes Care 40, 1611–1613. https://doi.org/10.2337/dci17-0049.
Riddle, V., Lorenz, F.W., 1968. Nonenzymic, polyvalent anion-catalyzed formation of methylglyoxal as an explanation of its presence in physiological systems. J. Biol. Chem. 243, 2718–2724.
Roberts, L.D., Koulman, A., Griffin, J.L., 2014. Towards metabolic biomarkers of insulin resistance and type 2 diabetes: progress from the metabolome. Lancet Diabetes Endocrinol. 2, 65–75. https://doi.org/10.1016/S2213-8587(13)70143-8.
Rodrigues, J.A., Barros, A.A., Rodrigues, P.G., 1999. Differential pulse polarographic determination of α-dicarbonyl compounds in foodstuffs after derivatization with o-phenylenediamine. J. Agric. Food Chem. 47, 3219–3222. https://doi.org/10.1021/jf980856b.
Rodríguez-Cáceres, M.I., Palomino-Vasco, M., Mora-Diez, N., Acedo-Valenzuela, M.I., 2015. Novel HPLC - fluorescence methodology for the determination of methylglyoxal and glyoxal. Application to the analysis of monovarietal wines "Ribera del Guadiana". Food Chem. 187, 159–165. https://doi.org/10.1016/j.foodchem.2015.04.103.
Rondeau, P., Singh, N.R., Caillens, H., Tallet, F., Bourdon, E., 2008. Oxidative stresses induced by glycoxidized human or bovine serum albumin on human monocytes. Free Radic. Biol. Med. 45, 799–812. https://doi.org/10.1016/j.freeradbiomed.2008.06.004.
Ross, S.A., Gulve, E.A., Wang, M., 2004. Chemistry and biochemistry of type 2 diabetes. Chem. Rev. 104, 1255–1282. https://doi.org/10.1021/cr0204653.
Saison, D., De Schutter, D.P., Delvaux, F., Delvaux, F.R., 2009. Determination of carbonyl compounds in beer by derivatisation and headspace solid-phase microextraction in combination with gas chromatography and mass spectrometry. J. Chromatogr. A 1216, 5061–5068. https://doi.org/10.1016/j.chroma.2009.04.077.
Sakharov, I.Y., Demiyanova, A.S., Gribas, A.V., Uskova, N.A., Efremov, E.E., Vdovenko, M.M., 2013. 3-(10′-Phenothiazinyl)propionic acid is a potent primary enhancer of peroxidase-induced chemiluminescence and its application in sensitive ELISA of methylglyoxal-modified low density lipoprotein. Talanta 115, 414–417. https://doi.org/10.1016/j.talanta.2013.05.074.
Schalkwijk, C.G., 2015. Vascular AGE-ing by methylglyoxal: the past, the present and the future. Diabetologia 58, 1715–1719. https://doi.org/10.1007/s00125-015-3597-5.
Schmeer, M.R., 1964. Growth-inhibiting agents from mercenaria extracts: chemical and biological properties. Science (80-.) 144, 413–414. https://doi.org/10.1126/science.144.3617.413.
Schmidt, A.M., 2018. Highlighting diabetes mellitus the epidemic continues. Arterioscler. Thromb. Vasc. Biol. 38, e1–e8. https://doi.org/10.1161/ATVBAHA.117.310221.
Schwartz, S.S., Zeidler, A., Moossa, A.R., Kuku, S.F., Rubenstein, A.H., 1978. A prospective study of glucose tolerance, insulin, C-peptide, and glucagon responses in patients with pancreatic carcinoma. Am. J. Dig. Dis. 23, 1107–1114. https://doi.org/10.1007/BF01072886.
Serrano, M., Gallego, M., Silva, M., 2017. Quantitative analysis of aldehydes in canned vegetables using static headspace–gas chromatography–mass spectrometry. J. Chromatogr. A 1524, 21–28. https://doi.org/10.1016/j.chroma.2017.09.067.
Shamsi, F.A., Partal, A., Sady, C., Glomb, M.A., Nagaraj, R.H., 1998. Immunological evidence for methylglyoxal-derived modifications in vivo: determination of antigenic epitopes. J. Biol. Chem. 273, 6928–6936. https://doi.org/10.1074/jbc.273.12.6928.
Shin, Y.H., Lee, S., Ku, M.H., Kwak, M.K., Kang, S.O., 2017. Cytochrome c peroxidase regulates intracellular reactive oxygen species and methylglyoxal via enzyme activities of erythroascorbate peroxidase and glutathione-related enzymes in Candida albicans. Int. J. Biochem. Cell Biol. 92, 183–201. https://doi.org/10.1016/j.biocel.2017.10.004.
Singh, R., Barden, A., Mori, T., Beilin, L., 2001. Advanced glycation end-products: a review. Diabetologia 44, 129–146. https://doi.org/10.1007/s001250051591.
Smushkin, G., Vella, A., 2010. What is type 2 diabetes? Medicine 38, 597–601. https://doi.org/10.1016/j.mpmed.2010.08.008.
Soffer, L.J., Iannaccone, A., Gabrilove, J.L., 1961. Cushing's syndrome. Am. J. Med. 30, 129–146.
Stekelenburg, C.M., Schwitzgebel, V.M., 2016. Genetic defects of the β-Cell that cause diabetes. In: Endocrine Development. Karger Publishers, pp. 179–202. https://doi.org/10.1159/000439417.
Suh, K.S., Chon, S., Choi, E.M., 2016. Protective effects of honokiol against methylglyoxal-induced osteoblast damage. Chem. Biol. Interact. 244, 169–177. https://doi.org/10.1016/j.cbi.2015.12.015.
Suh, K.S., Chon, S., Choi, E.M., 2017. Limonene protects osteoblasts against methylglyoxal-derived adduct formation by regulating glyoxalase, oxidative stress, and mitochondrial function. Chem. Biol. Interact. 278, 15–21. https://doi.org/10.1016/j.cbi.2017.10.001.
Talukdar, D., Chaudhuri, B.S., Ray, M., Ray, S., 2009. Critical evaluation of toxic versus beneficial effects of methylglyoxal. Biochemistry 74, 1059–1069. https://doi.org/10.1134/S0006297909100010.
Tauer, A., Knerr, T., Niwa, T., Schaub, T.P., Lage, C., Passlick-Deetjen, J., Pischetsrieder, M., 2001. In vitro formation of N-epsilon-(carboxymethyl)lysine and imidazolones under conditions similar to continuous ambulatory peritoneal dialysis. Biochem. Biophys. Res. Commun. 280, 1408–1414. https://doi.org/10.1006/bbrc.2001.4294.
Taylor, D.G., Trudgill, P.W., Cripps, R.E., Harris, P.R., 1980. The microbial metabolism of acetone. Microbiology 118, 159–170. https://doi.org/10.1099/00221287-118-1-159.
Taylor, S.I., 1992. Lilly lecture: molecular mechanisms of insulin resistance: lessons from patients with mutations in the insulin-receptor gene. Diabetes 41, 1473–1490. https://doi.org/10.2337/diab.41.11.1473.
Thangavel, A., Alagesan, S., Nesakumar, N., Ramachandra, B.L., Gumpu, M.B., Vedantham, S., Sethuraman, S., Krishnan, U.M., Rayappan, J.B.B., 2015. Optimization of electrochemical parameters for specific blood methylglyoxal determination using ZnO sepals based glyoxalase 1 biosensor. Sens. Lett. 13, 328–337. https://doi.org/10.1166/sl.2015.3439.
The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2002. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 25, S5–S20. https://doi.org/10.2337/diacare.25.2007.S5.
Thornalley, P.J., 1988. Modification of the glyoxalase system in human red blood cells by glucose in vitro. Biochem. J. 254, 751–755.
Thornalley, P.J., 1995. Advances in glyoxalase research. Glyoxalase expression in malignancy, anti-proliferative effects of methylglyoxal, glyoxalase I inhibitor diesters and S-d-lactoylglutathione, and methylglyoxal-modified protein binding and endocytosis by the advanced glyca. Crit. Rev. Oncol. Hematol. 20, 99–128. https://doi.org/10.1016/1040-8428(94)00149-N.
Thornalley, P.J., 1996. Pharmacology of methylglyoxal: formation, modification of proteins and nucleic acids, and enzymatic detoxification - a role in pathogenesis and antiproliferative chemotherapy. Gen. Pharmacol. 27, 565–573. https://doi.org/10.1016/0306-3623(95)02054-3.
Thornalley, P.J., 2005. Dicarbonyl intermediates in the Maillard reaction. Ann. N. Y. Acad. Sci. USA 1043, 111–117. https://doi.org/10.1196/annals.1333.014.
Thornalley, P.J., 2008. Protein and nucleotide damage by glyoxal and methylglyoxal in physiological systems – role in ageing and disease. Drug Metabol. Drug Interact. 23, 125–150. https://doi.org/10.1515/DMDI.2008.23.1-2.125.
Thornalley, P.J., Hooper, N.I., Jennings, P.E., Florkowski, C.M., Jones, A.F., Lunec, J., Barnett, A.H., 1989. The human red blood cell glyoxalase system in diabetes mellitus. Diabetes Res. Clin. Pract. 7, 115–120. https://doi.org/10.1016/0168-8227(89)90101-0.
Thornalley, P.J., Jahan, I., Ng, R., 2001. Suppression of the accumulation of triosephosphates and increased formation of methylglyoxal in human red blood cells during hyperglycaemia by thiamine in vitro. J. Biochem. 129, 543–549.
Thornalley, P.J., Lanborg, A., Minhas, H.S., 1999. Formation of glyoxal, methylglyoxal and 3-deoxyglucosone in the glycation of proteins by glucose. Biochem. J. 344, 109–116. https://doi.org/10.1042/bj3440109.
Thornalley, P.J., Rabbani, N., 2011a. Protein damage in diabetes and uremia—identifying

hotspots of proteome damage where minimal modification is amplified to marked pathophysiological effect. Free Radic. Res. 45, 89–100. https://doi.org/10.3109/10715762.2010.534162.

Thornalley, P.J., Rabbani, N., 2011b. Methylglyoxal modification of LDL: proatherogenicity without oxidation opens new paths to prevent cardiovascular disease. Clin. Lipidol. 6, 631–634. https://doi.org/10.2217/clp.11.53.

Uribarri, J., Woodruff, S., Goodman, S., Cai, W., Chen, X., Pyzik, R., Yong, A., Striker, G.E., Vlassara, H., 2010. Advanced glycation end products in foods and a practical guide to their reduction in the diet (e12). J. Am. Diet. Assoc. 110, 911–916. https://doi.org/10.1016/j.jada.2010.03.018.

Vander Jagt, D.L., 2008. Methylglyoxal, diabetes mellitus and diabetic complications. Drug Metabol. Drug Interact. 23, 93–124. https://doi.org/10.1515/DMDI.2008.23.1-2.93.

Vander Jagt, D.L., Hassebrook, R.K., Hunsaker, L.A., Brown, W.M., Royer, R.E., 2001. Metabolism of the 2-oxoaldehyde methylglyoxal by aldose reductase and by glyoxalase-I: roles for glutathione in both enzymes and implications for diabetic complications. Chem. Biol. Interact. 130–132, 549–562. https://doi.org/10.1016/S0009-2797(00)00298-2.

Vander Jagt, D.L., Hunsaker, L.A., 2003. Methylglyoxal metabolism and diabetic complications: roles of aldose reductase, glyoxalase-I, betaine aldehyde dehydrogenase and 2-oxoaldehyde dehydrogenase. Chem. Biol. Interact. 143–144, 341–351. https://doi.org/10.1016/S0009-2797(02)00212-0.

Vander Jagt, D.L., Robinson, B., Taylor, K.K., Hunsaker, L.A., 1992. Reduction of trioses by NADPH-dependent aldo-keto reductases. Aldose reductase, methylglyoxal, and diabetic complications. J. Biol. Chem. 267, 4364–4369.

Vistoli, G., Colzani, M., Mazzolari, A., Gilardoni, E., Rivaletto, C., Carini, M., Aldini, G., 2017. Quenching activity of carnosine derivatives towards reactive carbonyl species: focus on α−(methylglyoxal) and β−(malondialdehyde) dicarbonyls. Biochem. Biophys. Res. Commun. 492, 487–492. https://doi.org/10.1016/j.bbrc.2017.08.069.

Vistoli, G., De Maddis, D., Cipak, A., Zarkovic, N., Carini, M., Aldini, G., 2013. Advanced glycoxidation and lipoxidation end products (AGEs and ALEs): an overview of their mechanisms of formation. Free Radic. Res. 47, 3–27. https://doi.org/10.3109/10715762.2013.815348.

Vlassara, H., Cai, W., Crandall, J., Goldberg, T., Oberstein, R., Dardaine, V., Peppa, M., Rayfield, E.J., 2002. Inflammatory mediators are induced by dietary glycotoxins, a major risk factor for diabetic angiopathy. Proc. Natl. Acad. Sci. 99, 15596–15601. https://doi.org/10.1073/pnas.242407999.

Vulesevic, B., McNeill, B., Giacco, F., Maeda, K., Blackburn, N.J.R., Brownlee, M., Milne, R.W., Suuronen, E.J., 2016. Methylglyoxal-induced endothelial cell loss and inflammation contribute to the development of diabetic cardiomyopathy. Diabetes 65, 1699–1713. https://doi.org/10.2337/db15-0568.

Wang, S.-T., Lin, Y., Spicer, C.D., Stevens, M.M., 2015. Bio-inspired Maillard-Like reactions enable a simple and sensitive assay for colorimetric detection of methylglyoxal. Chem. Commun. 51, 11026–11029. https://doi.org/10.1039/c5cc02590g.

Wang, T., Douglass, E.F., Fitzgerald, K.J., Spiegel, D.A., 2013. A “turn-on” fluorescent sensor for methylglyoxal. J. Am. Chem. Soc. 135, 12429–12433. https://doi.org/10.1021/ja406077j.

Wang, T., Streeter, M.D., Spiegel, D.A., 2015. Generation and characterization of antibodies against arginine-derived advanced glycation endproducts. Bioorg. Med. Chem. Lett. 25, 4881–4886. https://doi.org/10.1016/j.bmcl.2015.06.013.

Wang-Sattler, R., Yu, Z., Herder, C., Messias, A.C., Floegel, A., He, Y., Heim, K., Campillos, M., Holzapfel, C., Thorand, B., Grallert, H., Xu, T., Bader, E., Huth, C., Mittelstrass, K., Döring, A., Meisinger, C., Gieger, C., Prehn, C., Roemisch-Margl, W., Carstensen, M., Xie, L., Yamanaka-Okumura, H., Xing, G., Ceglarek, U., Thiery, J., Giani, G., Lickert, H., Lin, X., Li, Y., Boeing, H., Joost, H.-G., de Angelis, M.H., Rathmann, W., Suhre, K., Prokisch, H., Peters, A., Meitinger, T., Roden, M., Wichmann, H.-E., Pischon, T., Adamski, J., Illig, T., 2012. Novel biomarkers for pre-diabetes identified by metabolomics. Mol. Syst. Biol. 8 (615), 11. https://doi.org/10.1038/msb.2012.43.

Wasserfall, C.H., Atkinson, M.A., 2006. Autoantibody markers for the diagnosis and prediction of type 1 diabetes. Autoimmun. Rev. 5, 424–428. https://doi.org/10.1016/j.autrev.2005.12.002.

Witt, H.T., Saygin, O., Brettel, K., Schlodder, E., 1987. On the cleavage of water. Prog. Photo. Res. 1 (20), 523–531.

Wu, M.-Y., Chen, B.-G., Chang, C.D., Huang, M.H., Wu, T.-G., Chang, D.-M., Lee, Y.-J., Wang, H.C., Lee, C.-I., Chern, C.-L., Liu, R.H., 2008. A novel derivatization approach for simultaneous determination of glyoxal, methylglyoxal, and 3-deoxyglucosone in plasma by gas chromatography-mass spectrometry. J. Chromatogr. A 1204, 81–86. https://doi.org/10.1016/j.chroma.2008.07.040.

Yamazoye, S., 1936. Glyoxalase and its co-enzyme: III. The mechanism of the action of glutathione as the co-enzyme of glyoxalase. J. Biochem. 23, 319–334. https://doi.org/10.1093/oxfordjournals.jbchem.a125544.

Yang, R., Wang, W.X., Chen, H.J., He, Z.C., Jia, A.Q., 2018. The inhibition of advanced glycation end-products by five fractions and three main flavonoids from Camellia nitidissima Chi flowers. J. Food Drug Anal. 26, 252–259. https://doi.org/10.1016/j.jfda.2017.03.007.

Yu, H., Xu, X., Sun, J., You, T., 2012. Recent progress for capillary electrophoresis with electrochemical detection. Cent. Eur. J. Chem. 10, 639–651. https://doi.org/10.2478/s11532-012-0005-6.

Zarkogianni, K., Litsa, E., Mitsis, K., Wu, P.-Y., Kaddi, C.D., Cheng, C., Wang, M.D., Nikita, K.S., 2015. A review of emerging technologies for the management of diabetes mellitus. IEEE Trans. Biomed. Eng. 62, 2735–2749. https://doi.org/10.1109/TBME.2015.2470521.

Zhang, J., Zhang, H., Li, M., Zhang, D., Chu, Q., Ye, J., 2010. A novel capillary electrophoretic method for determining methylglyoxal and glyoxal in urine and water samples. J. Chromatogr. A 1217, 5124–5129. https://doi.org/10.1016/j.chroma.2010.05.040.