Metformin: a review on its ethnobotanical source and versatile uses

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At present metformin is the core for the management of type-2 diabetes mellitus. The key clue of metformin as a hypoglycemic drug was collected from the traditional utilization of *Galega officinalis* for the management of diabetes. Modern study recommends several valuable activities of Metformin other than the hypoglycemic effect such as type-1 diabetes mellitus, polycystic ovary syndrome, cholesterol-lowering effect, avoidance of heart disease, age, cancer, and neuroprotection. In the present review, we are discussing about the source and versatile utilization of metformin and its outcome.

Keywords:
cancer, diabetes mellitus, metformin, neuroprotective, polycystic ovary syndrome, traditional use, type-1 diabetes mellitus, type-2 diabetes mellitus

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Introduction

Currently, metformin is a biguanide derivative (dimethylbiguanide), which becomes the first-line drug for type-2 diabetes mellitus (T2-DM) treatment. In the modern time, metformin becomes a well-accepted drug due to its low cost, lesser side effects, and multiple benefits in different disease states along with both types of diabetes mellitus (T1-DM and T2-DM). Traditionally, *Galega officinalis* (galega, goat's rue, Italian fitch or professor-weed, French lilac) is recognized to treat diabetes in Europe and found to be well-off in Guanidine. Guanidine analogs (metformin and several non-Metformin drugs) were used for the treatment of diabetes in 1920s–1930s, but those drugs were withdrawn due to its toxicities (mainly lactic acidosis) and the better accessibility of insulin in the market. Metformin was revived in the investigation for antimalarial drugs (proguanil and chloroproguanil) in 1940s and for the duration of clinical trial, it is proved useful to treat influenza infection when it occasionally lowered the blood glucose level. Jean Sterne a French physician was first precisely used and reported metformin as an oral hypoglycemic agent to treat diabetes in 1957. But metformin get less awareness due to its less potency in comparison to other biguanide derivatives, which were progressively discontinued in the late 1970 due to their toxic effects like lactic acidosis. Metformin opposes insulin resistance and tackles hyperglycemia without weight gain or higher risk of hypoglycemia and after concentrated analysis metformin was introduced in 1995 in the USA. The UK Prospective Diabetes Study (UKPDS) in 1998 reported that long use of metformin give cardiovascular benefits, and provided a justification to accept metformin as an initial therapy to treat hyperglycemia in T2-DM [1] (Fig. 1).

Versatile use of metformin

Metformin is mainly used for the cure of T-2DM, but is also used in polycystic ovary syndrome (PCOS). Outcomes emerge to be improved even in those with some extent of kidney disease, heart failure, or liver problems [2].

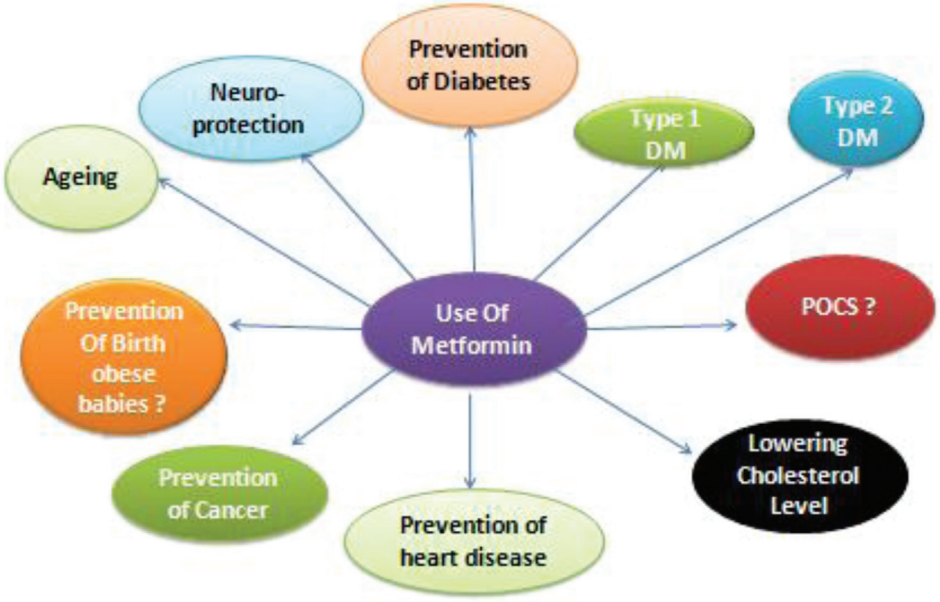
Metformin for the treatment of persons at risk for diabetes

Salpeter *et al*. [3] have reported the use of metformin in persons at risk for diabetes in *The American Journal of Medicine* in 2008, They observed that metformin treatment recovered weight, lipid profiles, and insulin resistance and reduces newer inception of diabetes by 40%.

Metformin for the management of type-1 diabetes mellitus

Beysel *et al*. [4] have reported that beneficial actions of metformin for the treatment of T1-DM in a *BMC Endocrine Disorders Journal* in 2018 reported that metformin reduced glucose level, reduced metabolic syndrome, and insulin dose necessity more than insulin

Figure 1



Galega officinalis, a natural source of galegine. Metformin (a) structurally is a biguanide and it has link with guanidine (b) and galegine (c), which can both be extracted from the plant goat's rue.

treatment alone. The result was free of blood lipid enhancement or weight loss, while on average weight stay reduced with metformin–insulin remedy, whereas the average weight raised with insulin therapy alone.

Metformin for the management of type-2 diabetes mellitus

Metformin is the core of T-2DM therapy for many years. It is used for its glucose-lowering effect since 1957 in Europe and 1995 in USA. In addition, being highly efficient in improving glycemic control, metformin has also lowered the risk of hypoglycemia. Metformin remains at the top of treatment protocol for T-2DM, either as monotherapy or in combination with thiazolidinediones, sulfonylureas, and insulin. The molecular mechanism of metformin behind its valuable effect is complex and not completely recognized. Physiologically, metformin has reduced hepatic glucose production (gluconeogenesis). Gluconeogenesis is an energy-dependent course which need ATP to be brought from the mitochondria. Metformin accumulates within the mitochondria to concentrate up to 1000-fold higher than in the extracellular medium, because metformin bears a positive charge. Inside the mitochondria, metformin blocks complex I of the respiratory chain thereby inhibiting ATP formation and finally reducing gluconeogenesis [5].

Metformin for the management of polycystic ovary syndrome

PCOS is the common hormonal disorder among women of reproductive period and has a range of metabolic and reproductive consequences. Metformin is the first insulin sensitizing drug (ISD) that is used in PCOS to examine the responsibility of insulin resistance in the pathogenesis of the syndrome. Significant improvements in menstrual regularity and decrease in circulating androgen levels reduced the body weight [6]. Another ISD, troglitazone was used in the development of cycle regularity and serum androgen levels in spite of lack of change in body weight [7]. Numerous studies have reported contradictory facts concerning the effect of metformin in PCOS. In several meta-analyses, the available facts have been reported with contradictory results [8]. ISD acts in PCOS by lowering the moving insulin levels in the body. But, some contradictory facts as metformin be able to directly influence ovarian steroidogenesis [9,10]. Numerous results have exhibited the advantages of metformin in PCOS patients together with restoring ovulation, reducing weight, circulating androgen levels, risk of miscarriage, and risk of gestational diabetes mellitus. Metformin in ovarian stimulation regime in in-vitro reproduction gives better pregnancy results.

Effect of metformin on cholesterol level

Metformin is the preferential treatment for diabetes because it appears to be the most efficient drug of all FDA-approved diabetes drugs for reducing unhealthy low-density lipoprotein cholesterol level [11].

Role of metformin on the prevention of heart disease

Metformin reduced the risk of coronary heart disease in individuals with metabolic syndrome or T-2 DM; some studies have reported that metformin reduces

Table 1 Roles and mechanisms of metformin in different uses

Sl. no.	Role of metformin	Probable mechanism
1	For the treatment of risk for diabetes	The main action of the drug to recover insulin sensitivity and also somewhat by a decrease in body weight [22]
2	For the treatment of T1-DM	Obvious mechanism of action yet not reported. But possible mechanism suggested that metformin could decrease insulin dose necessities by its insuling-sparing effect in T1-DM [4]
3	For the treatment of T2-DM	1. Metformin slows down mitochondrial respiration at the level of respiratory chain complex I outcome; it raises imbalance of energy and AMP kinase action and promotes insulin activity and reduce hepatic gluconeogenesis [23] 2. Raise in circulating cyclic adenosine monophosphate (cAMP) also resists the hyperglycemic effect of glucagon [24] 3. Metformin also improves the action of dipeptidyl peptidase-4 (DPP4) inhibitors by either droping the activity of DPP4 or raising discharge of glucagon-like peptide-1 (GLP-1) [25]
4	In the treatment of PCOS	Metformin in the treatment of PCOS is uncertain and a major work is needed before a result can be made about its effectiveness [26]
5	Effect on cholesterol level	Metformin causes lowered LDL-C levels, an effect mediated via metformin-mediated reduction of FADS activity and thus reduction of PUFA levels, namely arachidonic acid (AA). The lower levels of AA lead to improved membrane fluidity and rising LDL-C receptor recycling. The mechanism is metformin-induced activation of AMPK and suppression of SREBP1c and FADS, with reduced levels of PUFA and LDL-C [27]
6	Effect on the prevention of heart disease	Clear mechanism is not known, long-term treatment with metformin decreased the levels of circulating markers of endothelial dysfunction; these remarks were steady with a defensive action on the vasculature, as endothelial dysfunction is a premature marker of atherosclerosis. Various other mechanisms also explained the defensive effect of metformin on the vasculature in the UKPDS, together with better hemostasis (decreased potential for atherothrombotic disorders), decreased vascular inflammation, amelioration of oxidative stress, reduction of advanced glycation end product formation, improved action of the microcirculation and alteration of the cellular process that happens during atherogenesis [28]
7	Prevention of cancer and cancer repetition	Metformin have two possible modes of action that has given it its antineoplastic activity 1. An indirect method related to its insulin-reducing effect, which may exhibit tumor proliferation in hyperinsulinemia individuals 2. Direct action against respiratory complex I of the electron (e^-) transport chain in the mitochondria of neoplastic cells and preneoplastic cells, reducing energy use in the cell in target tissues Both modes of action involve the activation of AMP-activated protein kinase (AMPK), which inhibits the mammalian target of the rapamycin (mTOR) pathway, reducing cell proliferation and inducing apoptosis and cell-cycle arrest [29]
8	Fights fat in the womb	Hyperglycemia along with infant hyperinsulinemia were the causes of obese women's tendency to have big babies. There stay some unanswered query about the efficiency and safety of metformin in women with GDM or preexisting diabetes. There is a need for more studies to ascertain the effect of metformin on the developing embryo and fetus and potential long-term inferences [30]
9	Improving aging outcomes	1. Mechanisms of aging by the prevention of DNA damage and inflammation. Metformin activates the AMP-activated protein kinase (AMPK) signaling pathway and reduced inflammatory-cytokine-mediated DNA translation 2. Metformin inhibited DNA damage from surplus production of superoxide by directly reducing ROS formation via reverse electron (e^-) flux, and by reducing mTOR signaling pathways that causes superoxide formation [15] 3. High amounts of ceramides in the skeletal muscle are involved in aging development. This leads to reduced myoblast proliferation, aberrant cell cycle regulation, and a senescent myoblast phenotype. Metformin can limit the negative effects of ceramides, inhibiting myoblast senescence [19]
10	Neuroprotective effects	Neuronal damage due to hyperglycemia followed by higher formation of advanced glycosylation end product (AGEs) in diabetes. Metformin causes activation of AMP-activated protein kinase (AMPK). Human neural stem cells (hNSCs) exposed to AGEs have reduced cell capability. Metformin reduced the AGE-mediated effects in hNSCs. Metformin inhibited AGE-induced cytochrome c release from the mitochondria into cytosol in hNSCs. Metformin rescued hNSCs from age-mediated mitochondrial deficiency. The cotreatment of hNSCs with metformin is considerably blocked. Age-mediated reductions in expression levels of various neuroprotective genes (PPARγ, Bcl-2 and CREB) [20]

GDM, gestational diabetes mellitus; ROS, reactive oxygen species.

heart disease risk as regular exercise. It also established its efficacy in avoiding heart disease in people without metabolic syndrome [12].

Prevention of cancer and cancer recurrence

Various epidemiological studies have reported associations between metformin, used to treat

Table 2 Metformin improved nonalcoholic fatty liver disease [31–36]

	Metformin actions and mechanisms
Tissue	Improvement in hepatocellular ballooning
	Reduced triglyceride (TG) accumulation
	Apolipoprotein A5 (ApoA5) decreased
	Phosphorylation of AMP-activated protein kinase (AMPK) increased
	Liver X receptorα (LXRα) increased
	Stearyl-coenzyme A desaturase 1 (SCD1) decreased
Plasma	Total cholesterol and TG reduced
	Hepatic very low-density lipoprotein-triglycerides (VLDL-TG) production reduced
	Brown adipose tissue VLDL-TG clearance increased

Table 3 Beneficial effects of metformin on energy metabolism and white-adipose-tissue remodeling [37–39]

Tissues	Metformin actions and mechanisms
Brown adipose tissue (BAT)	Uncoupling protein-1 (UCP-1) increased
Skeletal muscle	Uncoupling protein-1 (UCP-3) increased
Adipocyte	Lipogenic markers reduced activation of AMPK increased
Stromal vascular fraction	Transforming growth factor-β1 (TGF-β 1) reduced in humans and mice

T-2DM, and reduced cancer occurrence and mortality [2]. Some studies reported that smokers with diabetes who takes metformin are less expected to produce lung cancer. Oral use of metformin reduced tumor incidence in mice by 40-50 percent, and injected metformin reduced tumor incidence by 72% [13].

Fights fat in the womb

Some morbidly obese pregnant women are taking metformin to avoid their babies from being born overweight. The drug safely reduced the quantity of food going to the unborn babies, although it will not assist the mother to lose weight. This type of barrier is vital because critically overweight pregnant women often produce obese babies, which can cause troubles during labor and delivery and life-long health for the child [14].

Metformin improving aging outcomes

Metformin also affect ageing other than glycemic control. Like inflammatory markers, interleukins and tumor necrosis factor can activate different cellular processes that lead to cellular and tissue damage. The interleukin-6 can persuade fibroblast proliferation and collagen formation, leading to cardiac remodeling. It can promote depressed contractility, myocyte hypertrophy and apoptosis [15]. Metformin changes inflammatory responses via inhibition of nuclear factor-kB via AMP-activated protein kinase (AMPK)-dependent pathways [16].

Table 4 Metformin reduces inflammation [2,40,41]

Tissues	Metformin effects and mechanism
Hepatocyte	Phosphorylation of C-JUNK-1 decreased, AMPK activation increased
Adipocyte	6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFKFB3/iPFK2) increased 3T3L-1 cell
Macrophages	IL-1β, IL-6, and TNF-α decreased alteration of macrophage polarization

IL, interleukin; TNF-α, tumor necrosis factor-α.

Table 5 Cardiovascular protective effect of metformin [2,42–47]

Tissue	Metformin effects and mechanism
Vascular smooth muscle cells	Infarct size smaller
	Left-ventricular dilatation reduced
	Left-ventricular ejection fraction improved
	AMPK activation increased
	eNOS increased
	THAP-induced CHOP reduced
Aortic endothelial cell	TXNIP reduced
	ChREBP decreased
	FOXO-1 decreased
	TXNIP decreased
	AMPK increased
	ER stress markers reduced
	Adhesion molecules reduced
	Inflammatory cytokines reduced
	Atherosclerotic plaques decreased
	Macrophage content in lesions reduced
	Mitochondrial complex I suppression
	Inhibition of mitochondrial fission
	Inhibition of PKC-NAD(P)H oxidase

Metformin also reduces the formation of reactive oxygen species via reverse electron flux [17] and via the mechanistic target of rapamycin, leading to a drop in in superoxide, which may guide to DNA damage and mutations [18]. High levels of ceramides in the skeletal muscle are concerned in the aging process. This decreases myoblast proliferation, aberrant cell-cycle regulation, and a senescent myoblast phenotype. Cell studies have exhibited that metformin can reserve the negative result of ceramides, thus potentially avoiding myoblast senescence [19]. This may be helpful for the rising population of older adults with sarcopenic obesity, while possibly improving tissue fitness and functions.

Neuroprotective role of metformin

Some studies have exhibited that metformin exhibited neuroprotective actions, reducing neuronal damage and enhancing oxygen and glucose deficiency, ensuing in improved neuronal survival and avoiding

etoposide-induced apoptosis in the key neurons [20,21] (Tables 1–5).

Conclusion

Metformin is not completely free from side effects. Most often caused side effects are nausea, vomiting, and headache. Rarely, in few individuals, it causes an increase of lactic acid in the blood (lactic acidosis), a very severe side effect. Individuals with kidney problems are more vulnerable to lactic acidosis and should not take metformin. Hence, although there are a variety of assumed applications of metformin in an enormous spectrum of diseases, many mechanisms remain to be understood. More clinical data are needed before the beneficial application of metformin which can be wide-ranging to treat those diseases other than of diabetes.

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Conflicts of interest

There are no conflicts of interest.

References

1 Bailey CJ. Metformin: historical overview. Diabetologia 2017; 60:1566–1576.

2 Zhou J, Massey S, Story D, Li L. Metformin: an old drug with new applications. Int J Mol Sci 2018; 19:2863.

3 Salpeter SR, Buckley NS, Kahn JA, Salpeter EE. Meta-analysis: metformin treatment in persons at risk for diabetes mellitus. Am J Med 2008; 121:149–157.

4 Beysel S, Unsal IO, Kizilgul M, Caliskan M, Ucan B, Cakal E. The effects of metformin in type 1 diabetes mellitus. BMC Endocrine Disord 2018; 18:1.

5 Rena G, Hardie GD, Pearson ER. The mechanisms of action of metformin. Diabetologia 2017; 60:1577–1585.

6 Velazquez EM, Mendoza S, Hamer T, Sosa F, Glueck CJ. Metformin therapy in polycystic ovary syndrome reduces hyperinsulinemia, insulin resistance, hyperandrogenemia, and systolic blood pressure, while facilitating normal menses and pregnancy. Metabolism 1994; 43:647–654.

7 Diamanti-Kandarakis E, Dunaif A. New perspectives in polycystic ovary syndrome. Trend Endocrinol Metab 1996; 7:267–271.

8 Nieuwenhuis-Ruifrok AE, Kuchenbecker WK, Hoek A, Middleton P, Norman RJ. Insulin sensitizing drugs for weight loss in women of reproductive age who are overweight or obese: systematic review and meta-analysis. Hum Reprod Update 2009; 15:57–68.

9 Mansfield R, Galea R, Brincat M, Hole D, Mason H. Metformin has direct effects on human ovarian steroidogenesis. Fertil Steril 2003; 79:956–962.

10 Arlt W, Auchus RJ, Miller WL. Thiazolidinediones but not metformin directly inhibit the steroidogenic enzymes P450c17 and 3 beta-hydroxysteroid dehydrogenase. J Biol Chem 2001; 276:16767–16771.

11 Pentikäinen PJ, Voutilainen E, Aro A, Uusitupa M, Penttilä I, Vapaatalo H. Cholesterol lowering effect of metformin in combined hyperlipidemia: placebo controlled double blind trial. Ann Med 1990; 22:307–312.

12 Griffin SJ, Leaver JK, Irving GJ. Impact of metformin on cardiovascular disease: a meta-analysis of randomised trials among people with type 2 diabetes. Diabetologia 2017; 60:1620–1629.

13 Sakoda LC, Ferrara A, Achacoso NS, Peng T, Ehrlich SF, Quesenberry CP, Habel LA. Metformin use and lung cancer risk in patients with diabetes. Cancer Prev Res (Phila) 2015; 8:174–179.

14 Chiswick C, Reynolds RM, Denison F, Drake AJ, Forbes S, Newby DE, *et al.* Effect of metformin on maternal and fetal outcomes in obese pregnant women (EMPOWaR): a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol 2015; 3:778–786.

15 Valencia WM, Tamariz PAL, Florez H. Metformin and ageing: improving ageing outcomes beyond glycaemic control. Diabetologia 2017; 60:1630–1638.

16 Mancini SJ, White AD, Bijland S, Rutherford C, Graham D, Richter EA, *et al.* Activation of AMP-activated protein kinase rapidly suppresses multiple pro-inflammatory pathways in adipocytes including IL-1 receptor-associated kinase-4 phosphorylation. Mol Cell Endocrinol 2017; 440:44–56.

17 Batandier C, Guigas B, Detaille D, El-Mir MY, Fontaine E, Rigoulet M, Leverve XM. The ROS production induced by a reverse-electron flux at respiratory-chain complex 1 is hampered by metformin. J Bioenerg Biomembr 2006; 38:33–42.

18 Halicka HD, Zhao H, Li J, Traganos F, Studzinski GP, Darzynkiewicz Z. Attenuation of constitutive DNA damage signaling by 1, 25-dihydroxyvitamin D3. Aging 2012; 4:270–278.

19 Jadhav KS, Dungan CM, Williamson DL. Metformin limits ceramide-induced senescence in C2C12 myoblasts. Mech Ageing Dev 2013; 134:548–559.

20 Chung MM, Chen YL, Pei D, Cheng YC, Sun B, Nicol CJ, *et al.* The neuroprotective role of metformin in advanced glycation end product treated human neural stem cells is AMPK-dependent. Biochem Biophys Acta 2015; 1852:720–731.

21 El-Mir MY, Detaille D, R-Villanueva G, Delgado-Esteban M, Guigas B, Attia S, *et al.* Neuroprotective role of antidiabetic drug metformin against apoptotic cell death in primary cortical neurons. J Mol Neurosci, 2008; 34:77–87.

22 Snehalatha C, Priscilla S, Nanditha A, Arun R, Satheesh K, Ramachandran A. Metformin in Prevention of Type 2 Diabetes. J Assoc Phys India 2018; 66:55–58.

23 Viollet B, Guigas B, Sanz Garcia N, Leclerc J, Foretz M, Andreelli F. Cellular and molecular mechanisms of metformin: an overview. Clin Sci (Lond) 2012; 122:253–270.

24 Miller RA, Chu Q, Xie J, Foretz M, Viollet B, Birnbaum MJ. Biguanides suppress hepatic glucagon signalling by decreasing production of cyclic AMP. Nature 2013; 494:256–260.

25 Wu T, Thazhath SS, Bound MJ, Jones KL, Horowitz M, Rayner CK. Mechanism of increase in plasma intact GLP-1 by metformin in type 2 diabetes: stimulation of GLP-1 secretion or reduction in plasma DPP-4 activity?. Diabetes Res Clin Pract 2014; 106:e3–e6.

26 Lashen H. Role of metformin in the management of polycystic ovary syndrome. Ther Adv Endocrinol Metabol 2010; 1:117–128.

27 Xu T, Brandmaier S, Essias AC, Herder C, Draisma HHM, Demirkan A, *et al.* Effects of metformin on metabolite profiles and LDL cholesterol in patients with type 2 diabetes. Diabetes Care 2015; 38:1858–1867.

28 Hostalek U, Gwilt M, Hildemann S. Therapeutic use of metformin in prediabetes and diabetes prevention. Drugs 2015; 75:1071–1094.

29 Han G, Gong H, Wang Y, Guo S, Liu K. AMPK/mTOR-mediated inhibition of survivin partly contributes to metformin-induced apoptosis in human gastric cancer cell. Cancer Biol Ther 2015; 16:77–87.

30 Abd El Fattah EA. Can metformin limit weight gain in the obese with pregnancy?. Int J Reprod Contracept Obstet Gynecol 2016; 5:818–825.

31 Zhu X, Yan H, Xia M, Chang X, Xu X, Wang L, *et al.* Metformin attenuates triglyceride accumulation in HepG2 cells through decreasing stearyl-coenzyme A desaturase 1 expression. Lipids Health Dis. 2018; 17:114.

32 Lin MJ, Dai W, Scott MJ, Li R, Zhang YQ, Yang Y, *et al.* Metformin improves nonalcoholic fatty liver disease in obese mice via down-regulation of apolipoprotein A5 as part of the AMPK/LXR signaling pathway. Oncotarget 2017; 8:108802–108809.

33 Li R, Chen L, Zhao W, Zhao SP, Huang XS. Metformin ameliorates obesity-associated hypertriglyceridemia in mice partly through the apolipoprotein A5 pathway. Biochem Biophys Res Commun 2016; 478:1173–1178.

34 Woo SL, Xu H, Li H, Zhao Y, Hu X, Zhao J, *et al.* Metformin ameliorates hepatic steatosis and inflammation without altering adipose phenotype in diet-induced obesity. PLoS One 2014; 9:e91111.

35 Geerling JJ, Boon MR, van der Zon GC, van den Berg SA, van den Hoek AM, Lombès M, *et al.* Metformin lowers plasma triglycerides by promoting VLDL-triglyceride clearance by brown adipose tissue in mice. Diabetes 2014; 63:880–891.

36 Duseja A, Das A, Dhiman RK, Chawla YK, Thumburu KT, Bhadada S, Bhansali A. Metformin is effective in achieving biochemical response in patients with nonalcoholic fatty liver disease (NAFLD) not responding to lifestyle interventions. Ann Hepatol 2007; 6:222–226.

37 Tokubuchi I, Tajiri Y, Iwata S, Hara K, Wada N, Hashinaga T, *et al.* Beneficial effects of metformin on energy metabolism and visceral fat volume through a possible mechanism of fatty acid oxidation in human subjects and rats. PLoS One 2017; 12:e0171293.

38 Breining P, Jensen JB, Sundelin EI, Gormsen LC, Jakobsen S, Busk M, *et al.* Metformin targets brown adipose tissue in vivo and reduces oxygen consumption in vitro. Diabetes Obes Metab 2018; 20:2264–2273.

39 Luo T, Nocon A, Fry J, Sherban A, Rui X, Jiang B, *et al.* AMPK Activation by Metformin Suppresses Abnormal Extracellular Matrix Remodeling in Adipose Tissue and Ameliorates Insulin Resistance in Obesity. Diabetes 2016; 65:2295–2310.

40 Qi T, Chen Y, Li H, Pei Y, Woo SL, Guo X, *et al.* A role for FKFB3/iPFK2 in metformin suppression of adipocyte inflammatory responses. J Mol Endocrinol 2017; 59:49–59.

41 Jing Y, Wu F, Li D, Yang L, Li Q, Li R. Metformin improves obesity-associated inflammation by altering macrophages polarization. Mol Cell Endocrinol 2018; 461:256–264.

42 Calvert JW, Gundewar S, Jha S, Greer JJ, Bestermann WH, Tian R, Lefer DJ. Acute metformin therapy confers cardioprotection against myocardial infarction via AMPK-eNOS-mediated signaling. Diabetes 2008; 57:696–705.

43 Yin M, van der Horst IC, van Melle JP, Qian C, van Gilst WH, Silljé HH, de Boer RA. Metformin improves cardiac function in a nondiabetic rat model of post-MI heart failure. Am J Physiol Heart Circ Physiol 2011; 301: H459–H468.

44 Chen Q, Thompson J, Hu Y, Das A, Lesnefsky EJ. Metformin attenuates ER stress induced mitochondrial dysfunction. Transl Res 2017; 190:40–50.

45 Bridges HR, Jones AJ, Pollak MN, Hirst J. Effects of metformin and other biguanides on oxidative phosphorylation in mitochondria. Biochem J 2014; 462:475–487.

46 Yang Q, Yuan H, Chen M, Qu J, Wang H, Yu B, *et al.* Metformin ameliorates the progression of atherosclerosis via suppressing macrophage infiltration and inflammatory responses in rabbits. Life Sci 2018; 198:56–64.

47 Li X, Kover KL, Heruth DP, Watkins DJ, Moore WV, Jackson K, *et al.* New Insight Into Metformin Action: Regulation of ChREBP and FOXO1 Activities in Endothelial Cells. Mol Endocrinol 2015; 29:1184–1194.