

## Is Berberine Superior to Metformin in Management of Diabetes Mellitus and its Complications?

Tatyasaheb Patil<sup>1\*</sup>, Snehal Patil<sup>2</sup>, Anuprita Patil<sup>3</sup>, Shreedevi Patil<sup>4</sup>

<sup>1</sup>Dept of Pharmacology, Bharati Vidyapeeth Deemed University Medical College and Hospital, Sangli, Maharashtra, India

<sup>2</sup>Dept of Public Health Dentistry, School of Dental Sciences, Krishna Institute of Medical Sciences Deemed University, Karad, India

<sup>3</sup>Consultant oral pathologist, 'Gurukripa', Behind Hotel Brindavan, Station Road Miraj, Maharashtra, India

<sup>4</sup>Practising gynaecologist, 'Gurukripa', Behind Hotel Brindavan, Station Road Miraj, Maharashtra, India

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### ABSTRACT

Diabetes is a fast growing non infectious disease affecting people of both developed and developing countries across the globe. Treatment of diabetes mellitus requires multisystemic approach to control the disease and prevent complications. Existing oral antidiabetics though potent, exhibit multiple adverse drug reactions and side effects. Berberine would prove to be an effective alternative to these drugs as it offers protection from systemic complications and has minor side effects. This review attempts to compare the efficacy of berberine and metformin as antidiabetic and their role in deterrence of diabetic complications. Berberine scores over metformin as a antidiabetic by certain pharmacological mechanism like alpha glucosidase reductase inhibition, release of GLP 1, modification of gut microbiota, inhibition of enzyme dipeptidyl peptidase 4 and as a insulin mimetic. Lipid lowering action and effect on polycystic ovarian disease is more superior with berberine than metformin. Thus it can be concluded that berberine can be superior to metformin in management of diabetes and in prevention of its complications.

**Key words:** Beberine, Metformin, Diabetes.

### INTRODUCTION

Diabetes is a fast growing non infectious disease affecting people of both developed and developing countries across the globe. It is estimated that by 2025 there will be 380 million people with type 2 diabetes<sup>1</sup>. Type 2 diabetes mellitus is more common in occurrence than type 1 diabetes which is mainly treated with oral antidiabetics of which metformin forms the first line drug preferred among both obese and non obese diabetics<sup>2</sup>. Berberine hydrochloride is known as antidiabetic since long and can be labeled as 'herbal metformin'. Treatment of diabetes mellitus requires multisystemic coverage to control the disease and prevent complications. Existing oral antidiabetics though potent exhibit multiple adverse drug reactions and side effects<sup>3</sup>. Berberine would prove to be an effective alternative to these drugs as it offers protection from systemic complications and has minor side effects. This review attempts to compare the efficacy of berberine and metformin as antidiabetic and their role in deterrence of diabetic complications.

Articles in various national and international databases were searched with search terms like berberine and diabetes, metformin and diabetes, berberine and metformin in diabetes, berberine in diabetic complications and metformin in diabetic complications.

Various databases searched were pubmed, scopus, google scholar, NIH.gov, and Medscape.com and others.

### BERBERINE

*Antidiabetic mechanisms of Berberine*  
*Inhibition of hepatic neoglucogenesis*

Berberine improves glucose metabolism in type 2 diabetes mellitus by inhibition of hepatic neoglucogenesis by activating AMPK-Adenosine Monophosphate Activated Protein Kinase and also improve insulin sensitivity. Inhibition of hepatic neoglucogenesis reflects in to decreased fasting blood sugar levels. This is a insulin independent action and involves mitochondrial inhibition by berberine<sup>4</sup>.

*Promotion of glycolysis*

Berberine activates AMPK leading to its enhanced phosphorylation resulting into consistent elevation AMP/ATP ratio and reduces consumption of oxygen. Resulting glycolysis increases lactic acid production which suggests that stimulation of glycolysis is a mechanism to enhance glucose metabolism by berberine resulting in to decreased blood sugar. This is related to inhibition of glucose oxidation in mitochondria. Mitochondrial inhibition and increase in AMP/ATP ratio leads to AMPK activation by berberine<sup>5</sup>.

*Effects of berberine on incretins*

Glucagon like peptide 1 is released from intestinal L cells and is a potent glucose dependent insulinotropic hormone. This Incretin GLP 1 causes increased release of Insulin from pancreatic beta cells in response to postprandial hyperglycemia. It also inhibits pancreatic Glucagon release, delays gastric emptying and decreases appetite and enhances satiety by central action. Berberine has been shown to increase GLP 1 secretion, promote proglucagon mRNA expression and the proliferation of L cells in the intestine. Berberine also promoted prohormone convertase 3. This shows that berberine promotes GLP 1 biosynthesis and its release which is one of the contributory mechanisms for its antihyperglycemic action<sup>6,7</sup>. Incretins are less prone to induce hypoglycemia as their release is stimulated by meal dependent hyperglycemia. Hence Berberine is less prone to induce hypoglycemic episodes

*Berberine activates AMPK and improves insulin sensitivity*

Berberine activates AMPK. AMPK has a vital role to play in cellular energy homeostasis. It is expressed in various tissues like liver, skeletal muscles and brain. The net effect of AMPK activation is stimulation of fatty acid oxidation in liver and ketogenesis. It inhibits lipogenesis, cholesterol and triglycerides synthesis. It stimulates skeletal muscle fatty acid oxidation and also increases muscle glucose uptake. It enhances biogenesis of GLUT 4-Glucose transporter 4. It is also known to modulate insulin secretion by pancreatic beta cells<sup>8</sup>. Metabolic syndrome occurs when these AMPK regulated pathways are turned off and produce hyperglycemia, hyperlipidemia, hypertension, obesity and inflammation. Only a few chemicals are known to activate AMPK. Berberine is one of them and forms the basis for the treatment of metabolic syndrome<sup>9</sup>. Berberine also suppresses proinflammatory responses<sup>10</sup>. This action is mediated through AMPK activation.

*Berberine acts like insulin-Insulinomimetic action*

Berberine acts like insulin as it increases glucose uptake by fat cells-3T3 L1 adipocytes and muscle cells L 6 and Leptin signaling. Phosphorylation in 3T3 L1 adipocytes is also enhanced by berberine. It also inhibits protein tyrosine phosphatase 1 B activity which is a negative regulator of insulin and leptin<sup>11</sup>.

*Berberine reduces insulin resistance*

Berberine enhances the expression of insulin receptors in terms of their number and activity which translates into increased insulin efficiency. Berberine thus reduces insulin resistance. Berberine inhibits the enzyme Protein tyrosine phosphatase 1 B (PTP1B) which is known to inhibit insulin receptor. InsR gene expression was induced by berberine through protein kinase C (PKC) dependent activation of its promoter<sup>9, 12</sup>. Plasma fasting insulin and HOMA-IR values were reduced by 28.1% and 44.7% respectively as a result of berberine induced insulin sensitivity in patients of type 2 diabetes mellitus<sup>13</sup>. This effect may be related to decreased waist/hip ratio in absence of change in weight. Long term use of berberine improves insulin secretion<sup>14</sup>.

*Berberine inhibits enzyme Dipeptidyl Peptidase 4*

DPP 4-Enzyme DPP4 is responsible for metabolism of incretins. Hence the drug which inhibits enzyme DPP4 are bound to enhance endogenous GLP 1 incretin level which would contribute to their antihyperglycemic action. Berberine was found to inhibit enzyme DPP 4 which is one of the mechanisms for its antihyperglycemic action. Recent reports reveal that berberine inhibits prodiabetic target human protein Tyrosine phosphatase 1 B (H-PTP 1 B) which makes berberine a dual natural H-PTP 1 B and DPP 4 inhibitor<sup>15</sup>.

*Action of berberine on intestinal disaccharidases*

Berberine suppresses the synthesis of intestinal disaccharidases like alpha glucosidase which causes reduced conversion of sugar into glucose leading to reduced glucose absorption<sup>16</sup>. Probably this also contributes to its side effects like flatulence<sup>17,18</sup>.

*Modulation of gut microbiota*

Berberine by modulating gut microbiota helps to control hyperglycemia<sup>19</sup>.

*Berberine as Aldose reductase inhibitor*

Enzyme Aldose reductase and polyol pathway play an important role in the generation of sorbitol, the amount of which decides the complications of Diabetes mellitus, like diabetic retinopathy, diabetic neuropathy and nephropathy<sup>20</sup>. Aldose reductase as a rate limiting enzyme plays a role in the reduction of glucose to sorbitol by using NADPH (Nicotinamide adenine dinucleotide phosphate) as a co factor. This sorbitol with the help of sorbitol dehydrogenase gets metabolized to fructose. In the healthy normoglycemic people, very small amount of glucose about less than 3% is converted to sorbitol. But in the presence of severe hyperglycemia about 30% of glucose enters in the polyol pathway to generate sorbitol which leads to accumulation of large amounts of sorbitol. Sorbitol is the culprit which induces both oxidative and osmotic stress in the tissues wherever it accumulates and plays a pathological role in the onset of diabetic complications as mentioned above<sup>21</sup>. Berberine inhibits aldose reductase and thus prevents cataract formation<sup>22</sup>. Berberine is also known to reduce oxidative stress in the kidney<sup>23</sup>. Berberine being a known antihyperglycemic and also aldose reductase inhibitor controls hyperglycemia in diabetes mellitus and prevents diabetic complications arising out of sorbitol accumulation in the tissues<sup>24,25</sup>. Thus it plays an important role in the treatment of diabetes mellitus and prevention of its complications<sup>23</sup>.

*Effect of berberine on lipid profile*

Berberine lowers serum lipids (total serum cholesterol, LDL cholesterol and triglycerides) by its unique mechanism which differs from that of statins<sup>26</sup>. In a study conducted, berberine also lowered levels of free fatty acids which are known to be toxic to the pancreas and thus improved insulin resistance<sup>27,28</sup>. In hyperlipidemic hamsters, berberine reduced serum cholesterol and LDL-C. It also increased LDL receptors mRNA and protein in the liver<sup>29</sup>. These effects were mediated by the ERK signaling pathway and were partly due to stabilization of LDL receptor mRNA<sup>30</sup>. Berberine was reported to

upregulate LDL receptors and is also known to inhibit lipid synthesis through activation of AMPK in human hepatocytes<sup>31</sup>.

#### *Effect of berberine on weight gain and antiobesity effect*

Obesity is the major component of metabolic syndrome which is a net effect of hyperplasia and hypertrophy of adipocytes. Berberine was found to inhibit differentiation effect on adipocytes. Inhibition of mRNA and protein expression of PPAR gamma and CCAAT /enhancer binding protein-a(C/EBPa) was found to be due to berberine. C/EBPa is required for adipogenesis and also for adipocyte function. Berberine inhibits lipid accumulation in adipocytes by reducing the number as well as size of fat cells<sup>32,33</sup>.

#### *Berberine and polycystic ovarian disease*

Wei W Zhao et al published a study in 2012 which comprised of a clinical trial of berberine in the cases of polycystic ovarian syndrome and they found berberine being as effective as metformin<sup>14</sup> In the theca cells of ovary berberine reduced insulin resistance and also decreased the excessive production of testosterone<sup>34</sup>.

#### *Role of berberine in Non-alcoholic fatty liver disease*

##### *Possible mechanisms of berberine in reversing the dysfunction at cellular levels in NAFLD*

Berberine phosphorylates AMPK and its activation inhibits SREBPs-hepatic sterol regulatory element binding proteins-reduces lipogenesis, increases PPAR alpha expression which promotes fatty acid oxidation in liver<sup>35</sup>. Berberine improves insulin sensitivity, reduces production of proinflammatory cytokines and counteract ER stress<sup>35</sup>. Berberine blocks the entry of intestinal endotoxins in the liver by modifying gut cellular permeability and preventing endotoxemia in circulation<sup>35</sup>. Berberine promotes VLDL secretion<sup>35</sup>. Berberine systematically regulates hepatic gene expression and reverses the expression of several genes including 881mRNA & 538 lncRNA expression in steatotic liver and thus reverses the pathology of steatotic liver in NAFLD<sup>36</sup>.

#### *Antiinflammatory and Antioxidant property of Berberine*

Oxidative stress and inflammation are proved to be contributing factors of its aetiology as well as for its complications in diabetes mellitus. Studies revealed that berberine changed the oxidative stress markers, antioxidant enzymes and proinflammatory cytokines in diabetic animals. It reduced inflammation and oxidative stress in tissues like liver, pancreas, adipose tissue and kidney which are the most affected organs in diabetes mellitus. Mechanisms for these properties of berberine were complex and involved multiple cellular kinases and signaling pathways such as AMP activated protein kinase (AMPK), mitogen activated protein kinase (MAPKs), nuclear factor erythroid 2 related factor (Nrf2) pathway and nuclear factor kappa beta (Nf-kappa beta) pathway. Probably there may be other mechanisms for these properties of berberine which would need further studies<sup>37</sup>

#### *Protective effect of Berberine on diabetic nephropathy*

Berberine was found to have beneficial effects on renal injury in experimental diabetic animals. The possible

mechanisms by which berberine offers protective effects against diabetic nephropathy are as follows,

Sphingosine kinase- sphingosine 1 phosphate (SphK-S1P) signaling pathway plays an important role in the pathogenesis of diabetic nephropathy. Berberine partly exerts renoprotective effect in diabetic nephropathy by exerting inhibitory effect on the activation of SphK-S1P signaling pathway in kidneys of diabetic mice. Berberine ameliorates renal injury in diabetic C57BL/6 mice-involvement of suppression of SphK-S1P signaling pathway<sup>38</sup>. Renal fibrosis constitutes a main pathology of diabetic nephropathy. This includes glomerular sclerosis and tubulointerstitial fibrosis. In vivo and in vitro studies amelioration of renal dysfunction in rats with diabetic nephropathy was demonstrated with berberine. It inhibited the fibronectin expression in mesangial cells cultured under hyperglycemic states. Berberine reduced the degradation and partially restored the levels of I $\kappa$ B –  $\alpha$ . Berberine downregulated the expression of the protein levels of intercellular adhesion molecule-1, transforming growth factor-  $\beta$ 1 and fibronectin. Thus the ameliorating effects of berberine on extracellular matrix accumulation might be associated with its inhibitory action on NF- $\kappa$ B signal pathway<sup>39</sup>. Berberine ameliorated renal dysfunction in streptozotocin induced diabetic rats through the control of blood glucose, reduction of oxidative stress, inhibition of activation of polyol pathway and inhibition of aldose reductase, thus reducing overproduction of sorbitol which accumulates in intracellular compartments. Increased sorbitol causes rise in intracellular osmotic pressure which further depletes myo-inositol leading to cellular swelling, decreased activity of enzymes including ATPase and increased cellular membrane permeability<sup>40</sup>. Berberine has been used for treating kidney stones due to its antiurolithic effects. By its diuretic action berberine increases urinary sodium and potassium excretion while reducing that of calcium like hydrochlorothiazide<sup>41</sup>. Antiurolithic effect of berberine against calcium oxalate stones is mediated through multiple mechanisms like antioxidant, diuretic, hypocalciuric and urinary alkalinizing action<sup>42</sup>.

#### *Effect of Berberine on Cardiovascular system*

Endothelial dysfunction is an important feature of atherosclerosis. Obesity and insulin resistance alters gene expression and cell signaling in vascular endothelium resulting into increased secretion of proinflammatory cytokines, decreased secretion of adiponectin, increased circulating levels of free fatty acids and hyperglycemia. Endothelial dysfunction arising out of decreased NO release, increased expression of endothelin 1 and induction of adhesion molecules alters endothelial homeostasis which contributes for plaque formation and atherosclerosis. This results in hypertension, coronary and peripheral artery disease and diabetic nephropathy<sup>43</sup>. Endothelial AMPK has important role to play in the mediation of release of NO in response to shear stress<sup>44</sup> and protection from apoptosis<sup>45</sup>. It also regulates inflammation, angiogenesis and maintains perfusion<sup>46,47</sup>. Berberine has vasorelaxant and antiproliferative effect on endothelium and underlying vascular smooth muscles

which are mediated by activation of AMPK. It also inhibits cellular apoptosis, inflammation and vascular injury arising out of hyperglycemia induced reactive oxygen species<sup>48,49</sup>.

Berberine also decreases the number of adherent monocytes on endothelial cells. It suppresses activation of nuclear factor kappa beta (NF- $\kappa$ B), the expression of adhesion molecules (VCAM-1 and ICAM-1) arising out of hyperglycemia and by induction of proinflammatory cytokines and chemokines including tumor necrosis factor alpha, interleukin 1 B, interleukin 8 and MCP 1<sup>49</sup>.

Other mechanisms which contribute to vasorelaxant effect of berberine are inhibition of angiotensin converting enzyme (ACE)<sup>50</sup>, alpha adrenoceptor antagonism,<sup>51</sup> increased sensitivity to acetylcholine,<sup>52</sup> activation of K<sup>+</sup> channels, inhibition of intracellular Ca<sup>2+</sup> release and blocking of L type calcium channels in experimental studies.<sup>53</sup> AMPK activation by berberine inhibits platelet derived growth factor (PDGF) induced vascular smooth muscle cell growth and thus has antiproliferative effect<sup>54</sup>. In human studies berberine increased cardiac index, increased left ventricular ejection fraction and decreased left ventricular end diastolic pressure and also systemic and pulmonary vascular resistance<sup>55</sup>.

Berberine also decreased ventricular premature beats in congestive heart failure. It has antiplatelet activity arising out of inhibition of COX pathway and calcium influx and also by partial agonistic effect on platelet alpha 2 adrenoceptors<sup>56</sup>. Berberine also inhibited synthesis of thromboxane induced by collagen and adenosine diphosphate<sup>57</sup>. Antiinflammatory effect of berberine also contributes for its antiatherosclerotic potential, probably due to inhibition of cyclooxygenase -2 (COX -2) via ERK 1/2 or JNK pathway in peripheral blood monocytes<sup>58</sup>.

Berberine exerts anti-inflammatory action by inhibiting interleukin 6 and nuclear factor  $\kappa$ B activation and modulates transcription of genes coding for COX-2, matrix metalloproteinase-9, cyclin D-1 and survivin<sup>59</sup>. Berberine downregulates mRNA of TNF alpha, IL-6, C reactive protein and haptoglobin in 3T3L1 adipocytes<sup>60</sup>.

#### *Role of berberine in Alzheimer's disease and its mechanism of action*

Berberine suppresses amyloid induced inflammatory responses in microglia by inhibiting nuclear factor kappa beta and by blocking mitogen activated kinase signaling pathway resulting into decrease in production of interleukin 6-IL-6 and monocyte chemotactic protein. It also downregulated the expression of cyclooxygenase 2 and induction of nitric oxide synthetase in microglia<sup>61</sup>. Berberine is known to reduce amyloid precursor protein-APP and inhibits the generation of amyloid beta. Berberine also inhibits the alpha, beta and gamma secretases which play an important role in generation of amyloid beta<sup>42,62</sup>.

Berberine inhibits Tau phosphorylation and prevents the formation of NFTs- neurofibrillary tangles<sup>63</sup>.

Berberine has inhibitory effect on acetyl cholinesterase and butyl cholinesterase-AChE & BChE and enhances the brain acetyl choline levels resulting into improved neurotransmission and clinical picture of AD<sup>64-67</sup>.

MAO-B inhibition has potential role to play in neurodegenerative diseases. Berberine inhibits both MAO- A & MAO- B resulting in neuroprotection and elevation of mood by its antidepressant action<sup>68-72</sup>.

Lipid lowering effect of berberine contributes to better clinical recovery in AD patients. Its lipid lowering activity decreases neuronal cholesterol and can inhibit amyloid beta forming amyloidogenic pathway, possibly by removing APP from membrane microdomain.

Oxidative damage plays an important role in pathogenesis of AD. Antioxidant property of berberine enables it to scavenge reactive oxygen species (ROS) and reactive nitrogen species (RNS). Berberine also has protective effect against low density lipoprotein oxidation and also inhibits lipid peroxidation<sup>73,74</sup>.

GLP 1 activation by berberine –Diabetics have higher incidence of AD which is attributed to the impaired insulin signaling in the brain. GLP 1 is known to enhance insulin release. GLP 1 has been proved to be neuroprotective and is also proposed a new therapeutic target for AD. Berberine enhances GLP 1 and extends neuroprotection in AD<sup>75,76</sup>.

#### *Antimicrobial property of berberine*

Berberine is known to exert antimicrobial activity covering bacterial population, fungi, helminthic parasites and viruses. The possible mechanisms for these actions are

- 1) suppression of cell adhesion and migration e.g.- Streptococci and E.coli.
- 2) Inhibition of microbial enzymes
- 3) DNA binding property
- 4) Production of compounds which target the bacterial efflux mechanisms e.g.- Methoxyhydrinocarpine.
- 5) Production of inhibitors of multidrug resistant pumps and thus enhancing accumulation of berberine within the microbial cells.
- 6) Inhibiting FtSz protein regulated cell division by binding to C terminal interdomain cleft of FtSz projecting 9 methoxy group towards the outside of cavity<sup>77</sup>.

#### *Anticancer potential of berberine*

Berberine has inhibitory activity on the proliferation and multiplication of certain tumorigenic microorganisms and viruses like Helicobacter pylori<sup>78</sup> and hepatitis B virus respectively<sup>79</sup>. Transcriptional regulation of certain oncogenes and interactions with both DNA & RNA are also documented with berberine<sup>80,81</sup>.

Berberine is also a broad spectrum enzyme inhibitor affecting N-acetyl transferase,<sup>82-84</sup> cyclooxygenase 2<sup>85-90</sup> and topoisomerase activities. These actions together with the regulation of reactive oxygen species production,<sup>91-93</sup> mitochondrial transmembrane potential and nuclear factor kappa B activation<sup>94</sup> might underlie its antiproliferative and proapoptotic effects<sup>95-97</sup>. Berberine's effect on suppression of tumor growth and metastasis<sup>98</sup>

and efficacy to reduce multidrug resistance<sup>99,100</sup> promises its potential in anticancer therapy.

### METFORMIN

Metformin is considered as first line antidiabetic drug either a monotherapy or in combination with other drugs to treat type 2 diabetes mellitus and is devoid of weight gain like Sulfonylureas and Glitazones.

Antidiabetic action-Metformin is more of antihyperglycemic than hypoglycemic. It inhibits hepatic gluconeogenesis, reduces glucose output and also enhances peripheral glucose utilization by its increased uptake in peripheral tissues mainly skeletal muscles. Activation of AMPK<sup>101</sup> and inhibition of mitochondrial respiration both reduce gluconeogenesis<sup>102</sup>. Metformin reduces degradation of GLP 1 and helps in glycemic control<sup>103</sup>.

#### *Effect on weight gain and lipid profile*

Metformin induces weight loss mainly in overweight/obese diabetics by decreasing carbohydrate absorption from gastrointestinal tract and also by reducing insulin resistance<sup>104</sup>.

It acts on Glucagon like peptide 1 and induces anorectic and lipolytic effect<sup>105</sup>. It also reduces the levels of Ghrelin<sup>106</sup> and leptin in response to hyperglycemia<sup>104</sup>. Metformin improves lipoprotein metabolism and decreases LDL cholesterol<sup>104</sup>, triglycerides and free fatty acids<sup>107</sup>.

#### *Effect of Metformin on nonalcoholic fatty liver disease*

It induces weight loss, enhances insulin sensitivity and reduces visceral fat<sup>108</sup>. It decreases hepatic transaminases and fat content reflecting into improvement in NAFLD<sup>109</sup>. Effect on oxidative stress and inflammatory pathway – Metformin by inhibiting mitochondrial respiration reduces reactive oxygen species<sup>110</sup>. By controlling hyperglycemia and improving insulin response Metformin reduces advanced glycation end products (AGE).<sup>111</sup> By enhancing reduced glutathione<sup>110</sup> and by upregulation of uncoupled proteins 2 in adipose tissue it also contributes to antioxidant effect<sup>112</sup>. By blocking P13K-Akt pathway it inhibits NF-kB and proinflammatory responses<sup>113</sup>.

#### *Effect of metformin on haemostasis*

Metformin reduces circulating coagulation factors like tissue plasminogen activator, plasminogen activator inhibitor (PAI-1) and Von Willebrand factor and factor VII<sup>114</sup>. Structure and function of fibrin is affected directly by decreasing factor VIII<sup>115</sup>.

#### *Cardiovascular effects of metformin*

Metformin reduces macrovascular complications in DM<sup>116</sup>. This effect is in addition to glycemic control and reduces the incidence of IHD and myocardial infarction<sup>117-120</sup>. But this effect may get negated by decreased intestinal absorption of Vit B 12 leading to hyperhomocysteinemia and increasing incidence of atherosclerosis<sup>121</sup>. Congestive cardiac failure is a relative contraindication due to potential risk of developing lactic acidosis.

Metformin may offer vascular protection beyond glycemic control as a result of improved inflammatory pathway,<sup>113</sup> improved insulin resistance<sup>122</sup> and lipid

profile<sup>104,123</sup> with redistribution of fat<sup>124-125</sup>. It also improves haemostasis<sup>126-129</sup> coagulation<sup>130</sup> and endothelial dysfunction<sup>126,131,132</sup>. Both oxidative stress and glycation are reduced<sup>126,131,132,127,128</sup>.

Metformin and neuroprotection- When used alone Metformin increases the production of beta amyloid and enhances the chances of Alzheimers disease<sup>133</sup> but its combination with insulin reduces its incidence<sup>134</sup>.

#### *Metformin and cancer*

1) By correcting hyperinsulinemia and reducing levels of IGF 1 which has mitogenic and cells proliferating activity Metformin reduces tumorigenesis and growth of malignant cells<sup>135</sup>. 2) Anticancer property of metformin is also mediated through AMPK activation causing inhibition of mTOR pathway which is responsible for tumour cell nutrition and growth<sup>136</sup>. Action of metformin by AMPK activation needs LKB 1 which is an important tumour suppressor<sup>101</sup>. 3) Inhibition of angiogenesis and inflammation<sup>137</sup>. Activation of protein 53 (p53) and induction of apoptosis also contributes for its anticancer activity<sup>138</sup>. Arrest of cell cycle is also major contributor for its anticancer action<sup>139,140</sup>.

### CONCLUSION

Metformin is considered first line antidiabetic to treat diabetes mellitus type 2. Berberine has been used since many years as antidiabetic in Chinese herbal medicine. Regarding Glucose reducing capacity metformin and berberine share few common pharmacological actions hence berberine could be called as herbal metformin. But berberine scores over metformin as an antidiabetic by certain additional pharmacological mechanism like alpha glucosidase enzyme inhibition, release of GLP 1, modification of gut microbiota, inhibition of enzyme dipeptidyl peptidase 4 and as an insulin mimetic. Lipid lowering action and effect on polycystic ovarian disease is more superior in berberine than metformin. Cardiovascular protection, prevention of atherosclerosis, survival in CHF, inhibition of arrhythmias and antiplatelet action are more profound with berberine as against metformin which needs to be used with lots of caution in diabetics with CHF as it might precipitate lactic acidosis. Minor beneficial effects of metformin on cardiovascular system may get nullified by metformin induced decrease in intestinal Vit B 12 absorption causing hyperhomocysteinemia and progression of atherosclerosis and endothelial dysfunction. Berberine has neuroprotective action in Alzheimers and also has antidepressant property. But metformin when used alone without insulin deteriorates Alzheimers. Though berberine and metformin share anticancer potential, metformin lacks antimicrobial property of berberine. Inhibition of aldose reductase and prevention of complication of diabetes mellitus arising out of accumulation of sorbitol like cataract formation diabetic neuropathy and nephropathy are only reduced by berberine. Berberine has nephroprotective action by different mechanism and also bears anti-urolithic potential. Thus it can be concluded that berberine can be considered to be superior to

metformin in management of diabetes and in prevention of its complications

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